Attachment 1



DOES ABORTION PILL REVERSAL WORK?

1. Yes! While there are no guarantees, studies show that Abortion Pill Reversal succeeds about two-thirds of the time. The protocol has saved the lives of thousands of babies.

2. Abortion Pill Reversal provides a woman with supplemental progesterone—a natural hormone that is safe for moms and babies. According to the American Academy of Obstetricians and Gynecologists, there is no evidence that progesterone has harmful effects on an unborn child. Initial studies show no increase in the birth defect rate after Abortion Pill Reversal.

3. It's your decision: While some abortion providers insist that you have to complete the medication abortion process once you've taken the first pill, Abortion Pill Reversal is your choice!

Get Help Now!

Call 877-558-0333
or visit
abortionpillreversal.com

Brought to you by

40 DAYS FOR LIFE

More Resources

Pregnancy Help

Visit 40daysforlife.com/pregnancyhelp for a list of resources that can help empower you to choose life. Resources include:

- ✓ Free pregnancy counseling
- ✓ Parenting classes
- ✓ Material support
- ✓ Health care
- ✓ Housing
- ✓ Other essential needs

FREE Ultrasound

Be sure to get a qualified medical opinion and a free ultrasound—which can rule out ectopic pregnancy (a condition that can make the abortion pill extremely dangerous).

Contact

www.40daysforlife.com

info@40daysforlife.com

1 888-543-3316

WHAT IS THE ABORTION PILL?



What you should know before you—or a loved one—take the abortion pill**...and why there might still be hope if you've already taken it**

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WHAT IS "MEDICATION ABORTION"/ THE ABORTION PILL?

1. **A series of pills that kill a developing child:** Medication Abortion is a two-drug cocktail that ends the life of the developing child during the first trimester of pregnancy. The first pill (mifepristone/RU-486) blocks the pre-born baby from receiving the hormonal support[i] (progesterone) essential for the baby to develop, and the second pill (misoprostol) causes the uterus to contract and expels the baby from the uterus.[ii]

2. **Painful:** Side effects include vomiting, fever, nausea, chills, diarrhea, and headache.[iii] According to the Mayo Clinic, women might need painkillers to manage pain after a chemical abortion, and they might not be able to "go about [their] usual daily routine" after a chemical abortion.[iv] "I was amply prepared for the bleeding, but not for the pain," said one woman of her chemical abortion. "I…spent a few hours in enough pain to be incoherent."[v]

3. **Messy:** While abortion providers often describe pill-induced abortion as similar to having a period, former abortion worker Abby Johnson described her abortion experience as like "sitting in the middle of a crime scene…I sat there for hours bleeding, throwing up into the bathroom trash can, crying, and sweating."[vi]

> "I sat there for hours bleeding, throwing up into the bathroom trash can, crying, and sweating."
>
> ABBY JOHNSON

[i] https://www.newsweek.com/take-dangerous-abortion-drugs-off-market-opinion-1773043
[ii] https://www.newsweek.com/take-dangerous-abortion-drugs-off-market-opinion-1773043
[iii] https://www.mayoclinic.org/tests-procedures/medical-abortion/about/pac- 20394687
[iv] Ibid
[v] https://www.vogue.com/article/medication-abortion-5-people-share-their- stories
[vi] https://abbyj.com/tonsillectomy/



I TOOK THE FIRST ABORTION PILL; IS IT TOO LATE TO SAVE MY BABY?

1. If you've taken the first abortion pill, there's a chance you can reverse it. Abortion Pill Reversal might be possible—if you get help NOW!

2. Don't wait! The sooner you begin the Abortion Pill Reversal protocol, the more likely it is you'll be able to reverse the abortion.

3. How it works: The first abortion pill, mifepristone, blocks the hormone progesterone, which is necessary for providing nutrients to an unborn baby and sustaining pregnancy. Abortion Pill Reversal provides supplemental natural progesterone to overwhelm the mifepristone.

Get Help Now!

Call 877-558-0333
or visit
abortionpillreversal.com

WHAT "MEDICATION ABORTION" / THE ABORTION PILL IS NOT

- **NOT medication:** Medicine restores and preserves the healthy functioning of the human body. Abortion pills break a woman's healthy reproductive system.

- **NOT safe:** One woman described her medication abortion as "the most painful experience I've ever had in my life…I literally said to my boyfriend…'I just want to die.'"[i] Dozens of women have died after taking abortion pills.[ii] According to the Mayo Clinic, a woman who undergoes a pill-induced abortion needs "access to emergency services."[iii] Abortion pill complications include hemorrhage, infection, isoimmunization, and death.[iv]

- **NOT contraception:** Abortion doesn't prevent a woman from becoming a mother. The moment she conceives, she becomes the mother of a new, distinct, and unique human being. From that point on, the unborn child is growing, moving, and processing nutrition—all with his or her own personal human DNA code. By the time a woman takes an abortion pill, her child's heart is already beating!

- **NOT your only option:** Countless women regret their abortions[v], so if you're considering terminating a pregnancy, find out about abortion alternatives before you make a decision that will end your baby's life and change your life forever.

[i] https://l9thnews.org/2022/05/medication-abortion-pill-self-managed-home- experience/
[ii] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifepristone-medical-termination-pregnancy- through-ten-weeks-gestation
[iii] https://www.mayoclinic.org/tests-procedures/medical-abortion/about/pac- 20394687
[iv] https://lozierinstitute.org/fact-sheet-risks-and-complications-of-chemical- abortion/
[v] https://silentnomoreawareness.org/testimonies/

Attachment 2

Syllabus

BUCKMAN CO. *v.* PLAINTIFFS' LEGAL COMMITTEE

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

No. 98–1768. Argued December 4, 2000—Decided February 21, 2001

Respondent represents plaintiffs claiming injuries caused by the use of orthopedic bone screws in the pedicles of their spines. Petitioner assisted the screws' manufacturer in securing approval for the devices from the Food and Drug Administration (FDA or Administration), which has regulatory authority under the Federal Food, Drug, and Cosmetic Act (FDCA), as amended by the Medical Devices Amendments of 1976 (MDA). While the screws are in a class that normally must go through a time-consuming process to receive premarket approval (PMA), they were approved under an exception, known as the § 510(k) process, for predicate devices—devices that were already on the market when the MDA was enacted—and for devices that are "substantially equivalent" to predicate devices. The § 510(k) application filed by petitioner and the manufacturer sought clearance to market the screws for use in arm and leg bones, not the spine. Claiming that the FDA would not have approved the screws had petitioner not made fraudulent representations regarding their intended use, plaintiffs sought damages under state tort law. The District Court dismissed these fraud-on-the-FDA claims on, *inter alia*, the ground that they were pre-empted by the MDA. The Third Circuit reversed.

Held: The plaintiffs' state-law fraud-on-the-FDA claims conflict with, and are therefore impliedly pre-empted by, the FDCA, as amended by the MDA. Pp. 347–353.

(a) The relationship between a federal agency and the entity it regulates is inherently federal because it originates from, is governed by, and terminates according to federal law. Because petitioner's FDA dealings were prompted by the MDA and the very subject matter of petitioner's statements were dictated by that statute—and in contrast to situations implicating "federalism concerns and the historic primacy of state regulation of [health and safety matters]," *Medtronic, Inc.* v. *Lohr*, 518 U. S. 470, 485—no presumption against pre-emption obtains in this case. The conflict here stems from the fact that the federal statutory scheme amply empowers the FDA to punish and deter fraud against the Administration, and the Administration uses this authority to achieve a delicate balance of statutory objectives that can be skewed by allowing state-law fraud-on-the-FDA claims. While the § 510(k)

Syllabus

process lacks the PMA review's rigor, the former does set forth a comprehensive scheme for determining substantial equivalence with a predicate device. Other provisions give the FDA enforcement options that allow it to make a measured response to suspected fraud upon the Administration. This flexibility is a critical component of the framework under which the FDA pursues its difficult (and often competing) objectives of regulating medical device marketing and distribution without intruding upon decisions committed by the FDCA to health care professionals. Pp. 347–350.

(b) State-law fraud-on-the-FDA claims inevitably conflict with the FDA's responsibility to police fraud consistently with the Administration's judgment and objectives. Complying with the FDA's detailed regulatory regime in the shadow of 50 States' tort regimes will dramatically increase the burdens facing potential applicants, who might be deterred from seeking approval of devices with potentially beneficial off-label uses—an accepted medical practice in which a device is used for some other purpose than that for which the FDA approved it—for fear of being exposed to unpredictable civil liability. Conversely, applicants' fear that their disclosures to the FDA will later be judged insufficient in state court might lead them to submit information that the Administration neither needs nor wants, thus delaying the comparatively speedy § 510(k) process, and, in turn, impeding competition and delaying the prescription of appropriate off-label uses. Respondent's reliance on *Silkwood* v. *Kerr-McGee Corp.*, 464 U. S. 238, is misplaced. *Silkwood* was based on traditional state tort law principles, not on a fraud-on-the-agency theory, and, unlike *Silkwood*, there is clear evidence here that Congress intended that the MDA be enforced exclusively by the Federal Government. In addition, the MDA's express pre-emption provision does not bar the ordinary working of conflict pre-emption principles. *Geier* v. *American Honda Motor Co.*, 529 U. S. 861, 869. And although *Medtronic* can be read to allow certain state-law causes of actions that parallel federal safety requirements, it does not stand for the proposition that any FDCA violation will support a state-law claim. Pp. 350–353.

159 F. 3d 817, reversed.

REHNQUIST, C. J., delivered the opinion of the Court, in which O'CONNOR, SCALIA, KENNEDY, SOUTER, GINSBURG, and BREYER, JJ., joined. STEVENS, J., filed an opinion concurring in the judgment, in which THOMAS, J., joined, *post*, p. 353.

Kenneth S. Geller argued the cause for petitioner. With him on the briefs were *Alan E. Untereiner* and *Sharon Swingle.*

Irving L. Gornstein argued the cause for the United States as *amicus curiae* urging reversal. With him on the brief were *Solicitor General Waxman*, *Assistant Attorney General Ogden*, *Deputy Solicitor General Kneedler*, *Douglas N. Letter*, *Peter J. Smith*, *Margaret Jane Porter*, and *Patricia J. Kaeding*.

Michael D. Fishbein argued the cause for respondent. With him on the brief were *Arnold Levin*, *Sandra L. Duggan*, and *John J. Cummings III*.*

CHIEF JUSTICE REHNQUIST delivered the opinion of the Court.

Respondent represents plaintiffs who claim injuries resulting from the use of orthopedic bone screws in the pedicles of their spines. Petitioner is a consulting company that assisted the screws' manufacturer, AcroMed Corporation, in navigating the federal regulatory process for these devices. Plaintiffs say petitioner made fraudulent representations to the Food and Drug Administration (FDA or Administration) in the course of obtaining approval to market the screws. Plaintiffs further claim that such representations were at least a "but for" cause of injuries that plaintiffs sustained from the implantation of these devices: Had the representations not been made, the FDA would not have approved the devices, and plaintiffs would not have been injured. Plaintiffs sought damages from petitioner under state tort law.

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*Briefs of *amici curiae* urging reversal were filed for the Medical Device Manufacturers Association by *Daniel G. Jarcho*, *Donald R. Stone*, and *Larry R. Pilot;* for Medtronic Sofamor Danek, Inc., by *James M. Beck* and *Stephen S. Phillips;* for Pharmaceutical Research and Manufacturers of America by *Bert W. Rein*, *Daniel E. Troy*, and *Jennifer A. Shah;* for the Product Liability Advisory Council, Inc., by *Malcolm E. Wheeler;* and for the Washington Legal Foundation by *Daniel J. Popeo* and *Richard A. Samp*.

Briefs of *amici curiae* urging affirmance were filed for the Association of Trial Lawyers of America by *Jeffrey Robert White* and *Frederick M. Baron;* and for Public Citizen by *Allison M. Zieve*, *Brian Wolfman*, and *Alan Morrison*.

We hold that such claims are pre-empted by the Federal Food, Drug, and Cosmetic Act (FDCA), 52 Stat. 1040, as amended by the Medical Device Amendments of 1976 (MDA), 90 Stat. 539, 21 U. S. C. § 301 (1994 ed. and Supp. V).

I

Regulation of medical devices is governed by the two Acts just named. The MDA separates devices into three categories: Class I devices are those that present no unreasonable risk of illness or injury and therefore require only general manufacturing controls; Class II devices are those possessing a greater potential dangerousness and thus warranting more stringent controls; Class III devices "presen[t] a potential unreasonable risk of illness or injury" and therefore incur the FDA's strictest regulation. § 360c(a)(1)(C)(ii)(II). It is not disputed that the bone screws manufactured by AcroMed are Class III devices.

Class III devices must complete a thorough review process with the FDA before they may be marketed. This premarket approval (PMA) process requires the applicant to demonstrate a "reasonable assurance" that the device is both "safe . . . [and] effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." §§ 360e(d)(2)(A), (B). Among other information, an application must include all known reports pertaining to the device's safety and efficacy, see § 360e(c)(1)(A); "a full statement of the components, ingredients, and properties and of the principle or principles of operation of such device," § 360e(c)(1)(B); "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such device," § 360e(c)(1)(C); samples of the device (when practicable), see § 360e(c)(1)(E); and "specimens of the labeling proposed to be used for such device," § 360e(c)(1)(F). The PMA process is ordinarily quite time consuming because

the FDA's review requires an "average of 1,200 hours [for] each submission." *Medtronic, Inc.* v. *Lohr*, 518 U. S. 470, 477 (1996) (citing Hearings before the Subcommittee on Health and the Environment of the House Committee on Energy & Commerce, 100th Cong., 1st Sess. (Ser. No. 100–34), p. 384 (1987); Kahan, Premarket Approval Versus Premarket Notification: Different Routes to the Same Market, 39 Food Drug Cosm. L. J. 510, 512–514 (1984)).

An exception to the PMA requirement exists for devices that were already on the market prior to the MDA's enactment in 1976. See 21 U. S. C. § 360e(b)(1)(A). The MDA allows these "predicate" devices to remain available until the FDA initiates and completes the PMA process. In order to avoid the potentially monopolistic consequences of this predicate-device exception, the MDA allows other manufacturers to distribute (also pending completion of the predicate device's PMA review) devices that are shown to be "substantially equivalent" to a predicate device. § 360e(b)(1)(B).

Demonstrating that a device qualifies for this exception is known as the "§ 510(k) process," which refers to the section of the original MDA containing this provision. Section 510(k) submissions must include the following: "Proposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use," 21 CFR § 807.87(e) (2000); "[a] statement indicating the device is similar to and/or different from other products of comparable type in commercial distribution, accompanied by data to support the statement," § 807.87(f); "[a] statement that the submitter believes, to the best of his or her knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted," § 807.87(k); and "[a]ny additional information regarding the device requested by the [FDA] Commissioner that is necessary for the Commissioner to make a finding as to whether or not the device is substan-

tially equivalent to a device in commercial distribution," § 807.87(l).

In 1984, AcroMed sought § 510(k) approval for its bone screw device, indicating it for use in spinal surgery. See *In re Orthopedic Bone Screw Products Liability Litigation*, 159 F. 3d 817, 820 (CA3 1998). The FDA denied approval on the grounds that the Class III device lacked substantial equivalence to a predicate device. See *ibid.* In September 1985, with the assistance of petitioner, AcroMed filed another § 510(k) application. "The application provided additional information about the . . . device and again indicated its intended use in spinal surgery. The FDA again rejected the application, determining that the device was not substantially equivalent to a predicate device and that it posed potential risks not exhibited by other spinal-fixation systems." *Ibid.* In December 1985, AcroMed and petitioner filed a third § 510(k) application.

> "AcroMed and [petitioner] split the . . . device into its component parts, renamed them 'nested bone plates' and '[cancellous] bone screws' and filed a separate § 510(k) application for each component. In both applications, a new intended use was specified: rather than seeking clearance for spinal applications, they sought clearance to market the plates and screws for use in the long bones of the arms and legs. AcroMed and Buckman claimed that the two components were substantially equivalent to predicate devices used in long bone surgery. The FDA approved the devices for this purpose in February 1986." *Ibid.*

Pursuant to its designation by the Judicial Panel on Multidistrict Litigation as the transferee court for *In re: Orthopedic Bone Screw Liability Litigation*, MDL No. 1014, the District Court for the Eastern District of Pennsylvania has been the recipient of some 2,300 civil actions related to these medical devices. Many of these actions include state-law

causes of action claiming that petitioner and AcroMed made fraudulent representations to the FDA as to the intended use of the bone screws and that, as a result, the devices were improperly given market clearance and were subsequently used to the plaintiffs' detriment. The District Court dismissed these "fraud-on-the-FDA" claims, first on the ground that they were expressly pre-empted by the MDA, and then, after our decision in *Medtronic*, on the ground that these claims amounted to an improper assertion of a private right of action under the MDA.[1] See 159 F. 3d, at 821.

A divided panel of the United States Court of Appeals for the Third Circuit reversed, concluding that plaintiffs' fraud claims were neither expressly nor impliedly pre-empted. We granted certiorari, 530 U. S. 1273 (2000), to resolve a split among the Courts of Appeals on this question, see *Kemp* v. *Medtronic, Inc.*, 231 F. 3d 216, 233–236 (CA6 2000) (identifying split and holding such claims expressly pre-empted), and we now reverse.

II

Policing fraud against federal agencies is hardly "a field which the States have traditionally occupied," *Rice* v. *Santa Fe Elevator Corp.*, 331 U. S. 218, 230 (1947), such as to warrant a presumption against finding federal pre-emption of a state-law cause of action. To the contrary, the relationship between a federal agency and the entity it regulates is inherently federal in character because the relationship originates from, is governed by, and terminates according to federal law. Cf. *Boyle* v. *United Technologies Corp.*, 487 U. S. 500, 504–505 (1988) (allowing pre-emption of state law by federal common law where the interests at stake are "uniquely federal" in nature). Here, petitioner's dealings with the FDA were prompted by the MDA, and the very subject matter

[1] The District Court also determined that the plaintiffs' fraud claims failed for lack of proximate cause, see *In re Orthopedic Bone Screw Products Liability Litigation*, 159 F. 3d 817, 821 (CA3 1998), but that question is not presently before us.

of petitioner's statements were dictated by that statute's provisions. Accordingly—and in contrast to situations implicating "federalism concerns and the historic primacy of state regulation of matters of health and safety," *Medtronic*, 518 U. S., at 485—no presumption against pre-emption obtains in this case.

Given this analytical framework, we hold that the plaintiffs' state-law fraud-on-the-FDA claims conflict with, and are therefore impliedly pre-empted by, federal law.[2] The conflict stems from the fact that the federal statutory scheme amply empowers the FDA to punish and deter fraud against the Administration, and that this authority is used by the Administration to achieve a somewhat delicate balance of statutory objectives. The balance sought by the Administration can be skewed by allowing fraud-on-the-FDA claims under state tort law.

As described in greater detail above, the § 510(k) process sets forth a comprehensive scheme for determining whether an applicant has demonstrated that a product is substantially equivalent to a predicate device. Among other information, the applicant must submit to the FDA "[p]roposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use," 21 CFR § 807.87(e) (2000), and a statement attesting to and explaining the similarities to and/or differences from similar devices (along with supporting data), see § 807.87(f). The FDA is also empowered to require additional necessary information. See § 807.87(l). Admittedly, the § 510(k) process lacks the PMA review's rigor: The former requires only a showing of substantial equivalence to a predicate device, while the latter involves a time-consuming inquiry into the risks and efficacy of each device. Nevertheless, to achieve its limited purpose, the § 510(k) process imposes upon applicants a variety of requirements that are designed to enable the FDA to

[2] In light of this conclusion, we express no view on whether these claims are subject to express pre-emption under 21 U. S. C. § 360k.

make its statutorily required judgment as to whether the device qualifies under this exception.

Accompanying these disclosure requirements are various provisions aimed at detecting, deterring, and punishing false statements made during this and related approval processes. The FDA is empowered to investigate suspected fraud, see 21 U. S. C. § 372; 21 CFR § 5.35 (2000), and citizens may report wrongdoing and petition the agency to take action, § 10.30. In addition to the general criminal proscription on making false statements to the Federal Government, 18 U. S. C. § 1001 (1994 ed., Supp. V),[3] the FDA may respond to fraud by seeking injunctive relief, 21 U. S. C. § 332, and civil penalties, 21 U. S. C. § 333(f)(1)(A); seizing the device, § 334(a)(2)(D); and pursuing criminal prosecutions, § 333(a). The FDA[4] thus has at its disposal a variety of enforcement options that allow it to make a measured response to suspected fraud upon the Administration.

This flexibility is a critical component of the statutory and regulatory framework under which the FDA pursues difficult (and often competing) objectives. For example, with respect to Class III devices, the FDA simultaneously maintains the exhaustive PMA and the more limited § 510(k) processes in order to ensure both that medical devices are

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[3] Title 18 U. S. C. § 1001(a) (1994 ed., Supp. V) provides: "[W]hoever, in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States, knowingly and willfully falsifies, conceals or covers up by any trick, scheme, or device a material fact; [or] makes any materially false, fictitious or fraudulent statement or representation; or makes or uses any false writing or document knowing the same to contain any materially false, fictitious or fraudulent statement or entry; shall be fined under this title or imprisoned not more than 5 years, or both."

[4] The FDCA leaves no doubt that it is the Federal Government rather than private litigants who are authorized to file suit for noncompliance with the medical device provisions: "[A]ll such proceedings for the enforcement, or to restrain violations, of this chapter shall be by and in the name of the United States." 21 U. S. C. § 337(a).

reasonably safe and effective and that, if the device qualifies under the § 510(k) exception, it is on the market within a relatively short period of time. Similarly, "off-label" usage of medical devices (use of a device for some other purpose than that for which it has been approved by the FDA) is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine. See, *e. g.*, Beck & Azari, FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions, 53 Food & Drug L. J. 71, 76–77 (1998) (noting that courts, several States, and the "FDA itself recogniz[e] the value and propriety of off-label use"). Indeed, a recent amendment to the FDCA expressly states in part that "[n]othing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship." 21 U. S. C. § 396 (1994 ed., Supp. V). Thus, the FDA is charged with the difficult task of regulating the marketing and distribution of medical devices without intruding upon decisions statutorily committed to the discretion of health care professionals.

State-law fraud-on-the-FDA claims inevitably conflict with the FDA's responsibility to police fraud consistently with the Administration's judgment and objectives. As a practical matter, complying with the FDA's detailed regulatory regime in the shadow of 50 States' tort regimes will dramatically increase the burdens facing potential applicants—burdens not contemplated by Congress in enacting the FDCA and the MDA. Would-be applicants may be discouraged from seeking § 510(k) approval of devices with potentially beneficial off-label uses for fear that such use might expose the manufacturer or its associates (such as petitioner) to unpredictable civil liability. In effect, then, fraud-on-the-FDA claims could cause the Administration's reporting requirements to deter off-label use despite the fact that the FDCA

expressly disclaims any intent to directly regulate the practice of medicine, see 21 U. S. C. § 396 (1994 ed., Supp. V), and even though off-label use is generally accepted.[5]

Conversely, fraud-on-the-FDA claims would also cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient in state court. Applicants would then have an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA's evaluation of an application. As a result, the comparatively speedy § 510(k) process could encounter delays, which would, in turn, impede competition among predicate devices and delay health care professionals' ability to prescribe appropriate off-label uses.[6]

Respondent relies heavily on *Silkwood* v. *Kerr-McGee Corp.*, 464 U. S. 238 (1984), which it reads to "creat[e] a virtually irrefutable presumption against implied preemption of private damage remedies predicated on an alleged conflict with a federal remedial scheme." Brief for Respondent 34.

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[5] See Green & Schultz, Tort Law Deference to FDA Regulation of Medical Devices, 88 Geo. L. J. 2119, 2133 (2000) ("Physicians may prescribe drugs and devices for off-label uses"); Smith, Physician Modification of Legally Marketed Medical Devices: Regulatory Implications Under the Federal Food, Drug, and Cosmetic Act, 55 Food & Drug L. J. 245, 251–252 (2000) (discussing off-label use in terms of the "practice of medicine doctrine[, which] stands firmly for the proposition that regulatory efforts are directed primarily at device marketing by manufacturers, not device use by physicians"); Beck & Azari, FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions, 53 Food & Drug L. J. 71, 72 (1998) ("Off-label use is widespread in the medical community and often is essential to giving patients optimal medical care, both of which medical ethics, FDA, and most courts recognize").

[6] In light of the likely impact that the fraud-on-the-FDA claims would have on the administration of the Administration's duties, we must reject respondent's contention that these claims "will . . . affect only the litigants and will not have the kind of direct impact on the United States, which preemption is designed to protect from undue incursion." Brief for Respondent 30 (citing *Miree* v. *DeKalb County*, 433 U. S. 25 (1977)).

Silkwood is different from the present case, however, in several respects. Silkwood's claim was not based on any sort of fraud-on-the-agency theory, but on traditional state tort law principles of the duty of care owed by the producer of plutonium fuel pins to an employee working in its plant. See 464 U. S., at 241. Moreover, our decision there turned on specific statutory evidence that Congress "disclaimed any interest in promoting the development and utilization of atomic energy by means that fail to provide adequate remedies for those who are injured by exposure to hazardous nuclear materials." *Id.*, at 257. In the present case, by contrast, we have clear evidence that Congress intended that the MDA be enforced exclusively by the Federal Government. 21 U. S. C. § 337(a).

Respondent also suggests that we should be reluctant to find a pre-emptive conflict here because Congress included an express pre-emption provision in the MDA. See Brief for Respondent 37. To the extent respondent posits that anything other than our ordinary pre-emption principles apply under these circumstances, that contention must fail in light of our conclusion last Term in *Geier* v. *American Honda Motor Co.*, 529 U. S. 861 (2000), that neither an express pre-emption provision nor a saving clause "bar[s] the ordinary working of conflict pre-emption principles." *Id.*, at 869.

We must also reject respondent's attempt to characterize both the claims at issue in *Medtronic* (common-law negligence action against the manufacturer of an allegedly defective pacemaker lead) and the fraud claims here as "claims arising from violations of FDCA requirements." Brief for Respondent 38. Notwithstanding the fact that *Medtronic* did not squarely address the question of implied pre-emption, it is clear that the *Medtronic* claims arose from the manufacturer's alleged failure to use reasonable care in the production of the product, not solely from the violation of FDCA requirements. See 518 U. S., at 481. In the present case,

however, the fraud claims exist solely by virtue of the FDCA disclosure requirements. Thus, although *Medtronic* can be read to allow certain state-law causes of actions that parallel federal safety requirements, it does not and cannot stand for the proposition that any violation of the FDCA will support a state-law claim.

In sum, were plaintiffs to maintain their fraud-on-the-agency claims here, they would not be relying on traditional state tort law which had predated the federal enactments in questions. On the contrary, the existence of these federal enactments is a critical element in their case. For the reasons stated above, we think this sort of litigation would exert an extraneous pull on the scheme established by Congress, and it is therefore pre-empted by that scheme.

The judgment of the Court of Appeals is reversed.

It is so ordered.

JUSTICE STEVENS, with whom JUSTICE THOMAS joins, concurring in the judgment.

As the Court points out, an essential link in the chain of causation that respondent must prove in order to prevail is that, but for petitioner's fraud, the allegedly defective orthopedic bone screws would not have reached the market. The fact that the Food and Drug Administration (FDA) has done nothing to remove the devices from the market, even though it is aware of the basis for the fraud allegations, convinces me that this essential element of the claim cannot be proved. I therefore agree that the case should not proceed.[1]

[1] Though my analysis focuses on the failure of the plaintiffs to establish a necessary element of their claim, that failure is grounded not in the minutiae of state law but in the details of the federal regulatory system for medical devices. Therefore, while this case does not fit neatly into our pre-existing pre-emption jurisprudence, it is accurate, in a sense, to say that federal law "pre-empts" this state-law fraud-on-the-FDA claim because the FDA has not acknowledged such a fraud and taken steps to remove the device from the market.

This would be a different case if, prior to the instant litigation, the FDA had determined that petitioner had committed fraud during the § 510(k) process and had then taken the necessary steps to remove the harm-causing product from the market. Under those circumstances, respondent's state-law fraud claim would not depend upon speculation as to the FDA's behavior in a counterfactual situation but would be grounded in the agency's explicit actions. In such a case, a plaintiff would be able to establish causation without second-guessing the FDA's decisionmaking or overburdening its personnel, thereby alleviating the Government's central concerns regarding fraud-on-the-agency claims.

If the FDA determines both that fraud has occurred and that such fraud requires the removal of a product from the market, state damages remedies would not encroach upon, but rather would supplement and facilitate, the federal enforcement scheme. Cf. *Medtronic, Inc.* v. *Lohr*, 518 U. S. 470, 495 (1996) (holding that the presence of a state-law damages remedy for violations of FDA requirements does not impose an additional requirement upon medical device manufacturers but "merely provides another reason for manufacturers to comply with . . . federal law"); *id.*, at 513 (O'CONNOR, J., concurring in part and dissenting in part) (same).[2]

[2] Though the United States in this case appears to take the position that fraud-on-the-FDA claims conflict with the federal enforcement scheme even when the FDA has publicly concluded that it was defrauded and taken all the necessary steps to remove a device from the market, see Brief for United States as *Amicus Curiae* 24, 30, that has not always been its position. As recently as 1994, the United States took the position that state-law tort suits alleging fraud in FDA applications for medical devices do not conflict with federal law where the FDA has "subsequently concluded" that the device in question never met the appropriate federal requirements and "initiated enforcement actions" against those responsible for fraudulently obtaining its approval. Brief for United States as *Amicus Curiae* in *Talbott* v. *C. R. Bard, Inc.*, No. 94–1951 (CA1), reprinted in App. to Pet. for Cert. in *Talbott* v. *C. R. Bard., Inc.*, O. T. 1995, No. 95–1321, p. 84a.

Under the pre-emption analysis the Court offers today, however, parties injured by fraudulent representations to federal agencies would have no remedy even if recognizing such a remedy would have no adverse consequences upon the operation or integrity of the regulatory process. I do not believe the reasons advanced in the Court's opinion support the conclusion that Congress intended such a harsh result. Cf. *Silkwood* v. *Kerr-McGee Corp.*, 464 U. S. 238, 251 (1984) (declining to infer that a federal statutory scheme that affords no alternative means of seeking redress pre-empted traditional state-law remedies). For that reason, although I concur in the Court's disposition of this case, I do not join its opinion.

Attachment 3

VIRGINIA STATE BOARD OF PHARMACY ET AL. *v.* VIRGINIA CITIZENS CONSUMER COUNCIL, INC., ET AL.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF VIRGINIA

No. 74-895. Argued November 11, 1975—Decided May 24, 1976

Appellees, as consumers of prescription drugs, brought suit against the Virginia State Board of Pharmacy and its individual members, appellants herein, challenging the validity under the First and Fourteenth Amendments of a Virginia statute declaring it unprofessional conduct for a licensed pharmacist to advertise the prices of prescription drugs. A three-judge District Court declared the statute void and enjoined appellants from enforcing it. *Held:*

1. Any First Amendment protection enjoyed by advertisers seeking to disseminate prescription drug price information is also enjoyed, and thus may be asserted, by appellees as recipients of such information. Pp. 756–757.

2. "Commercial speech" is not wholly outside the protection of the First and Fourteenth Amendments, and the Virginia statute is therefore invalid. Pp. 761–773.

(a) That the advertiser's interest in a commercial advertisement is purely economic does not disqualify him from protection under the First and Fourteenth Amendments. Both the individual consumer and society in general may have strong interests in the free flow of commercial information. Pp. 762–765.

(b) The ban on advertising prescription drug prices cannot be justified on the basis of the State's interest in maintaining the professionalism of its licensed pharmacists; the State is free to require whatever professional standards it wishes of its pharmacists, and may subsidize them or protect them from competition in other ways, but it may not do so by keeping the public in ignorance of the lawful terms that competing pharmacists are offering. Pp. 766–770.

(c) Whatever may be the bounds of time, place, and manner restrictions on commercial speech, they are plainly exceeded by

the Virginia statute, which singles out speech of a particular content and seeks to prevent its dissemination completely. Pp. 770–771.

(d) No claim is made that the prohibited prescription drug advertisements are false, misleading, or propose illegal transactions, and a State may not suppress the dissemination of concededly truthful information about entirely lawful activity, fearful of that information's effect upon its disseminators and its recipients. Pp. 771–773.

373 F. Supp. 683, affirmed.

BLACKMUN, J., delivered the opinion of the Court, in which BURGER, C. J., and BRENNAN, STEWART, WHITE, MARSHALL, and POWELL, JJ., joined. BURGER, C. J., *post*, p. 773, and STEWART, J., *post*, p. 775, filed concurring opinions. REHNQUIST, J., filed a dissenting opinion, *post*, p. 781. STEVENS, J., took no part in the consideration or decision of the case.

Anthony F. Troy, Chief Deputy Attorney General of Virginia, argued the cause for appellants. With him on the brief were *Andrew P. Miller,* Attorney General, and *D. Patrick Lacy, Jr.,* Deputy Attorney General.

Alan B. Morrison argued the cause and filed a brief for appellees.*

MR. JUSTICE BLACKMUN delivered the opinion of the Court.

The plaintiff-appellees in this case attack, as violative of the First and Fourteenth Amendments,[1] that portion of § 54–524.35 of Va. Code Ann. (1974), which provides that a pharmacist licensed in Virginia is guilty of unpro-

*Briefs of *amici curiae* urging affirmance were filed by *Alfred Miller* and *Stephen L. Solomon* for the American Association of Retired Persons et al.; by *Gilbert H. Weil, Philip B. Kurland,* and *Alan L. Unikel* for the Association of National Advertisers, Inc.; and by *Harold Rosenwald* for Osco Drug, Inc.

[1] The First Amendment is applicable to the States through the Due Process Clause of the Fourteenth Amendment. See, *e. g., Bigelow* v. *Virginia,* 421 U. S. 809, 811 (1975); *Schneider* v. *State,* 308 U. S. 147, 160 (1939).

fessional conduct if he "(3) publishes, advertises or promotes, directly or indirectly, in any manner whatsoever, any amount, price, fee, premium, discount, rebate or credit terms . . . for any drugs which may be dispensed only by prescription." [2] The three-judge District Court declared the quoted portion of the statute "void and of no effect," Jurisdictional Statement, App. 1, and enjoined the defendant-appellants, the Virginia State Board of Pharmacy and the individual members of that Board, from enforcing it. 373 F. Supp. 683 (ED Va. 1974). We noted probable jurisdiction of the appeal. 420 U. S. 971 (1975).

I

Since the challenged restraint is one that peculiarly concerns the licensed pharmacist in Virginia, we begin with a description of that profession as it exists under Virginia law.

The "practice of pharmacy" is statutorily declared to be "a professional practice affecting the public health, safety and welfare," and to be "subject to regulation and control in the public interest." Va. Code Ann. § 54–524.2 (a) (1974).[3] Indeed, the practice is subject to ex-

[2] Section 54–524.35 provides in full:

"Any pharmacist shall be considered guilty of unprofessional conduct who (1) is found guilty of any crime involving grave moral turpitude, or is guilty of fraud or deceit in obtaining a certificate of registration; or (2) issues, publishes, broadcasts by radio, or otherwise, or distributes or uses in any way whatsoever advertising matter in which statements are made about his professional service which have a tendency to deceive or defraud the public, contrary to the public health and welfare; or (3) publishes, advertises or promotes, directly or indirectly, in any manner whatsoever, any amount, price, fee, premium, discount, rebate or credit terms for professional services or for drugs containing narcotics or for any drugs which may be dispensed only by prescription."

[3] The parties, also, have stipulated that pharmacy "is a profession." Stipulation of Facts ¶ 11, App. 11.

tensive regulation aimed at preserving high professional standards. The regulatory body is the appellant Virginia State Board of Pharmacy. The Board is broadly charged by statute with various responsibilities, including the "[m]aintenance of the quality, quantity, integrity, safety and efficacy of drugs or devices distributed, dispensed or administered." § 54–524.16 (a). It also is to concern itself with "[m]aintaining the integrity of, and public confidence in, the profession and improving the delivery of quality pharmaceutical services to the citizens of Virginia." § 54–524.16 (d). The Board is empowered to "make such bylaws, rules and regulations . . . as may be necessary for the lawful exercise of its powers." § 54–524.17.

The Board is also the licensing authority. It may issue a license, necessary for the practice of pharmacy in the State, only upon evidence that the applicant is "of good moral character," is a graduate in pharmacy of a school approved by the Board, and has had "a suitable period of experience [the period required not to exceed 12 months] acceptable to the Board." § 54–524.21. The applicant must pass the examination prescribed by the Board. *Ibid.* One approved school is the School of Pharmacy of the Medical College of Virginia, where the curriculum is for three years following two years of college. Prescribed prepharmacy courses, such as biology and chemistry, are to be taken in college, and study requirements at the school itself include courses in organic chemistry, biochemistry, comparative anatomy, physiology, and pharmacology. Students are also trained in the ethics of the profession, and there is some clinical experience in the school's hospital pharmacies and in the medical center operated by the Medical College. This

is "a rigid, demanding curriculum in terms of what the pharmacy student is expected to know about drugs." [4]

Once licensed, a pharmacist is subject to a civil monetary penalty, or to revocation or suspension of his license, if the Board finds that he "is not of good moral character," or has violated any of a number of stated professional standards (among them that he not be "negligent in the practice of pharmacy" or have engaged in "fraud or deceit upon the consumer . . . in connection with the practice of pharmacy"), or is guilty of "unprofessional conduct." § 54–524.22:1. "Unprofessional conduct" is specifically defined in § 54–524.35, n. 2, *supra,* the third numbered phrase of which relates to advertising of the price for any prescription drug, and is the subject of this litigation.

Inasmuch as only a licensed pharmacist may dispense prescription drugs in Virginia, § 54–524.48,[5] advertising or other affirmative dissemination of prescription drug price information is effectively forbidden in the State. Some pharmacies refuse even to quote prescription drug prices over the telephone. The Board's position, however, is that this would not constitute an unprofessional publication.[6] It is clear, nonetheless, that all advertising of such prices, in the normal sense, is forbidden. The prohibition does not extend to nonprescription drugs, but neither is it confined to prescriptions that the pharmacist compounds himself. Indeed, about 95% of all prescriptions now are filled with dosage forms prepared by the pharmaceutical manufacturer.[7]

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[4] *Id.,* ¶ 8, App. 11. See generally *id.,* ¶¶ 6–16, App. 10–12.

[5] Exception is made for "legally qualified" practitioners of medicine, dentistry, osteopathy, chiropody, and veterinary medicine. § 54–524.53.

[6] Stipulation of Facts ¶ 25, App. 15.

[7] *Id.,* ¶ 18, App. 13.

II

This is not the first challenge to the constitutionality of § 54–524.35 and what is now its third-numbered phrase. Shortly after the phrase was added to the statute in 1968,[8] a suit seeking to enjoin its operation was instituted by a drug retailing company and one of its pharmacists. Although the First Amendment was invoked, the challenge appears to have been based primarily on the Due Process and Equal Protection Clauses of the Fourteenth Amendment. In any event, the prohibition on drug price advertising was upheld. *Patterson Drug Co.* v. *Kingery,* 305 F. Supp. 821 (WD Va. 1969). The three-judge court did find that the dispensation of prescription drugs "affects the public health, safety and welfare." *Id.,* at 824–825. No appeal was taken.

The present, and second, attack on the statute is one made not by one directly subject to its prohibition, that is, a pharmacist, but by prescription drug consumers who claim that they would greatly benefit if the prohibition were lifted and advertising freely allowed. The plaintiffs are an individual Virginia resident who suffers from diseases that require her to take prescription drugs on a daily basis,[9] and two nonprofit organizations.[10] Their

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[8] Theretofore an administrative regulation to the same effect had been outstanding. The Board, however, in 1967 was advised by the State Attorney General's office that the regulation was unauthorized. The challenged phrase was added to the statute the following year. See *Patterson Drug Co.* v. *Kingery,* 305 F. Supp. 821, 823 n. 1 (WD Va. 1969).

[9] Stipulation of Facts ¶ 3, App. 9.

[10] The organizations are the Virginia Citizens Consumer Council, Inc., and the Virginia State AFL–CIO. Each has a substantial membership (approximately 150,000 and 69,000, respectively) many of whom are users of prescription drugs. *Id.,* ¶¶ 1 and 2, App. 9. The American Association of Retired Persons and the National Retired Teachers Association, also claiming many members who "de-

claim is that the First Amendment entitles the user of prescription drugs to receive information that pharmacists wish to communicate to them through advertising and other promotional means, concerning the prices of such drugs.

Certainly that information may be of value. Drug prices in Virginia, for both prescription and nonprescription items, strikingly vary from outlet to outlet even within the same locality. It is stipulated, for example, that in Richmond "the cost of 40 Achromycin tablets ranges from $2.59 to $6.00, a difference of 140% [*sic*]," and that in the Newport News-Hampton area the cost of tetracycline ranges from $1.20 to $9.00, a difference of 650%.[11]

The District Court seized on the identity of the plaintiff-appellees as consumers as a feature distinguishing the

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pend substantially on prescription drugs for their well-being," Brief 2, are among those who have filed briefs *amici curiae* in support of the appellees.

[11] Stipulation of Facts ¶¶ 22 (b) and (c), App. 14. The phenomenon of widely varying drug prices is apparently national in scope. The American Medical Association conducted a survey in Chicago that showed price differentials in that city of up to 1200% for the same amounts of a specific drug. A study undertaken by the Consumers Union in New York found that prices for the same amount of one drug ranged from 79¢ to $7.45, and for another from $1.25 to $11.50. *Id.*, ¶¶ 22 (d) and (e), App. 14. *Amici* American Association of Retired Persons and National Retired Teachers Association state that in 1974 they participated in a survey of three prescription drug prices at 28 pharmacies in Washington, D. C., and found pharmacy-to-pharmacy variances in the price of identical drugs as great as 245%. Brief as *Amici Curiae* 10. The prevalence of such discrepancies "throughout the United States" is documented in a recent report. Staff Report to the Federal Trade Commission, Prescription Drug Price Disclosures 119 (1975). The same report indicates that 34 States impose significant restrictions on dissemination of drug price information and, thus, make the problem a national one. *Id.*, at 34.

present case from *Patterson Drug Co.* v. *Kingery, supra.* Because the unsuccessful plaintiffs in that earlier case were pharmacists, the court said, "theirs was a prima facie commercial approach," 373 F. Supp., at 686. The present plaintiffs, on the other hand, were asserting an interest in their own health that was "fundamentally deeper than a trade consideration." *Ibid.* In the District Court's view, the expression in *Valentine* v. *Chrestensen,* 316 U. S. 52, 54–55 (1942), to the effect that "purely commercial advertising" is not protected had been tempered, by later decisions of this Court, to the point that First Amendment interests in the free flow of price information could be found to outweigh the countervailing interests of the State. The strength of the interest in the free flow of drug price information was borne out, the court felt, by the fact that three States by court decision had struck down their prohibitions on drug price advertising. *Florida Board of Pharmacy* v. *Webb's City, Inc.,* 219 So. 2d 681 (Fla. 1969); *Maryland Board of Pharmacy* v. *Sav-A-Lot, Inc.,* 270 Md. 103, 311 A. 2d 242 (1973); *Pennsylvania State Board of Pharmacy* v. *Pastor,* 441 Pa. 186, 272 A. 2d 487 (1971).[12] The District Court recognized that this Court had upheld—against federal constitutional challenges other than on First Amendment grounds—state restric-

[12] The Florida and Pennsylvania decisions appear to rest on state constitutional grounds. The Maryland decision was based on the Due Process Clause of the Fourteenth Amendment as well as on provisions of the State Constitution.

Accord: *Terry* v. *California State Board of Pharmacy,* 395 F. Supp. 94 (ND Cal. 1975), appeal docketed, No. 75-336. Contra: *Urowsky* v. *Board of Regents,* 38 N. Y. 2d 364, 342 N. E. 2d 583 (1975); *Supermarkets General Corp.* v. *Sills,* 93 N. J. Super. 326, 225 A. 2d 728 (1966).

See Note: Commercial Speech—An End in Sight to *Chrestensen?* 23 De Paul L. Rev. 1258 (1974); Comment, 37 Brooklyn L. Rev. 617 (1971); Comment, 24 Wash. and Lee L. Rev. 299 (1967).

tions on the advertisement of prices for optometrists' services, *Head* v. *New Mexico Board,* 374 U. S. 424 (1963), for eyeglass frames, *Williamson* v. *Lee Optical Co.,* 348 U. S. 483 (1955), and for dentists' services, *Semler* v. *Dental Examiners,* 294 U. S. 608 (1935).[13] The same dangers of abuse and deception were not thought to be present, however, when the advertised commodity was prescribed by a physician for his individual patient and was dispensed by a licensed pharmacist. The Board failed to justify the statute adequately, and it had to fall. 373 F. Supp., at 686–687.

III

The question first arises whether, even assuming that First Amendment protection attaches to the flow of drug price information, it is a protection enjoyed by the appellees as recipients of the information, and not solely, if at all, by the advertisers themselves who seek to disseminate that information.

Freedom of speech presupposes a willing speaker. But where a speaker exists, as is the case here,[14] the protection afforded is to the communication, to its source and to its recipients both. This is clear from the decided cases. In *Lamont* v. *Postmaster General,* 381 U. S. 301 (1965), the Court upheld the First Amendment rights of citizens to receive political publications sent from abroad.

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[13] In *Head* v. *New Mexico Board,* the First Amendment issue was raised. This Court refused to consider it, however, because it had not been presented to the state courts, nor reserved in the notice of appeal here. 374 U. S., at 432 n. 12. The Court's action to this effect was noted in *Pittsburgh Press Co.* v. *Human Relations Comm'n,* 413 U. S. 376, 387 n. 10 (1973). The appellants at the oral argument recognized that *Head* was a due process case. Tr. of Oral Arg. 10.

[14] "In the absence of Section 54–524.35 (3), some pharmacies in Virginia would advertise, publish and promote price information regarding prescription drugs." Stipulation of Facts ¶ 26, App. 15.

More recently, in *Kleindienst* v. *Mandel,* 408 U. S. 753, 762–763 (1972), we acknowledged that this Court has referred to a First Amendment right to "receive information and ideas," and that freedom of speech " 'necessarily protects the right to receive.' " And in *Procunier* v. *Martinez,* 416 U. S. 396, 408–409 (1974), where censorship of prison inmates' mail was under examination, we thought it unnecessary to assess the First Amendment rights of the inmates themselves, for it was reasoned that such censorship equally infringed the rights of noninmates to whom the correspondence was addressed. There are numerous other expressions to the same effect in the Court's decisions. See, *e. g., Red Lion Broadcasting Co.* v. *FCC,* 395 U. S. 367, 390 (1969); *Stanley* v. *Georgia,* 394 U. S. 557, 564 (1969); *Griswold* v. *Connecticut,* 381 U. S. 479, 482 (1965); *Marsh* v. *Alabama,* 326 U. S. 501, 505 (1946); *Thomas* v. *Collins,* 323 U. S. 516, 534 (1945); *Martin* v. *Struthers,* 319 U. S. 141, 143 (1943). If there is a right to advertise, there is a reciprocal right to receive the advertising, and it may be asserted by these appellees.[15]

[15] The dissent contends that there is no such right to receive the information that another seeks to disseminate, at least not when the person objecting could obtain the information in another way, and could himself disseminate it. Our prior decisions, cited above, are said to have been limited to situations in which the information sought to be received "would not be otherwise reasonably available," see *post,* at 782; emphasis is also placed on the appellees' great need for the information, which need, assertedly, should cause them to take advantage of the alternative of digging it up themselves. We are aware of no general principle that freedom of speech may be abridged when the speaker's listeners could come by his message by some other means, such as seeking him out and asking him what it is. Nor have we recognized any such limitation on the independent right of the listener to receive the information sought to be communicated. Certainly, the recipients of the political publications in *Lamont* could have gone abroad and thereafter disseminated them

IV

The appellants contend that the advertisement of prescription drug prices is outside the protection of the First Amendment because it is "commercial speech." There can be no question that in past decisions the Court has given some indication that commercial speech is unprotected. In *Valentine* v. *Chrestensen, supra,* the Court upheld a New York statute that prohibited the distribution of any "handbill, circular . . . or other advertising matter whatsoever in or upon any street." The Court concluded that, although the First Amendment would forbid the banning of all communication by handbill in the public thoroughfares, it imposed "no such restraint on government as respects purely commercial advertising." 316 U. S., at 54. Further support for a "commercial speech" exception to the First Amendment may perhaps be found in *Breard* v. *Alexandria,* 341 U. S. 622 (1951), where the Court upheld a conviction for violation of an ordinance prohibiting door-to-door solicitation of magazine subscriptions. The Court reasoned: "The selling . . . brings into the transaction a commercial feature," and it distinguished *Martin* v. *Struthers, supra,* where it had reversed a conviction for door-to-door distribution of leaflets publicizing a religious meeting, as a case involving "no element of the commercial." 341 U. S., at 642–643. Moreover, the Court several times has stressed that communications to which First Amendment protection was given were *not* "purely commercial." *New York Times Co.* v. *Sullivan,* 376 U. S. 254, 266

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themselves. Those in *Kleindienst* who organized the lecture tour by a foreign Marxist could have done the same. And the addressees of the inmate correspondence in *Procunier* could have visited the prison themselves. As for the recipients' great need for the information sought to be disseminated, if it distinguishes our prior cases at all, it makes the appellees' First Amendment claim a stronger rather than a weaker one.

(1964); *Thomas* v. *Collins,* 323 U. S., at 533; *Murdock* v. *Pennsylvania,* 319 U. S. 105, 111 (1943); *Jamison* v. *Texas,* 318 U. S. 413, 417 (1943).

Since the decision in *Breard,* however, the Court has never *denied* protection on the ground that the speech in issue was "commercial speech." That simplistic approach, which by then had come under criticism or was regarded as of doubtful validity by Members of the Court,[16] was avoided in *Pittsburgh Press Co.* v. *Human Relations Comm'n,* 413 U. S. 376 (1973). There the Court upheld an ordinance prohibiting newspapers from listing employment advertisements in columns according to whether male or female employees were sought to be hired. The Court, to be sure, characterized the advertisements as "classic examples of commercial speech," *id.,* at 385, and a newspaper's printing of the advertisements as of the same character. The Court, however, upheld the ordinance on the ground that the restriction it imposed was permissible because the discriminatory hirings proposed by the advertisements, and by their newspaper layout, were themselves illegal.

Last Term, in *Bigelow* v. *Virginia,* 421 U. S. 809 (1975), the notion of unprotected "commercial speech" all but passed from the scene. We reversed a conviction for violation of a Virginia statute that made the circulation of any publication to encourage or promote the

[16] See *Bigelow* v. *Virginia,* 421 U. S., at 820 n. 6, citing Mr. Justice Douglas' observation in *Cammarano* v. *United States,* 358 U. S. 498, 514 (1959) (concurring opinion), that the *Chrestensen* ruling "was casual, almost offhand. And it has not survived reflection"; the similar observation of four Justices in dissent in *Lehman* v. *City of Shaker Heights,* 418 U. S. 298, 314 n. 6 (1974); and expressions of three Justices in separate dissents in *Pittsburgh Press Co.* v. *Human Relations Comm'n,* 413 U. S., at 393, 398, and 401. See also Mr. Justice Douglas' comment, dissenting from the denial of certiorari in *Dun & Bradstreet, Inc.* v. *Grove,* 404 U. S. 898, 904–906 (1971).

processing of an abortion in Virginia a misdemeanor. The defendant had published in his newspaper the availability of abortions in New York. The advertisement in question, in addition to announcing that abortions were legal in New York, offered the services of a referral agency in that State. We rejected the contention that the publication was unprotected because it was commercial. *Chrestensen*'s continued validity was questioned, and its holding was described as "distinctly a limited one" that merely upheld "a reasonable regulation of the manner in which commercial advertising could be distributed." 421 U. S., at 819. We concluded that "the Virginia courts erred in their assumptions that advertising, as such, was entitled to no First Amendment protection," and we observed that the "relationship of speech to the marketplace of products or of services does not make it valueless in the marketplace of ideas." *Id.*, at 825–826.

Some fragment of hope for the continuing validity of a "commercial speech" exception arguably might have persisted because of the subject matter of the advertisement in *Bigelow*. We noted that in announcing the availability of legal abortions in New York, the advertisement "did more than simply propose a commercial transaction. It contained factual material of clear 'public interest.'" *Id.*, at 822. And, of course, the advertisement related to activity with which, at least in some respects, the State could not interfere. See *Roe* v. *Wade*, 410 U. S. 113 (1973); *Doe* v. *Bolton*, 410 U. S. 179 (1973). Indeed, we observed: "We need not decide in this case the precise extent to which the First Amendment permits regulation of advertising that is related to activities the State may legitimately regulate or even prohibit." 421 U. S., at 825.

Here, in contrast, the question whether there is a First Amendment exception for "commercial speech" is

squarely before us. Our pharmacist does not wish to editorialize on any subject, cultural, philosophical, or political. He does not wish to report any particularly newsworthy fact, or to make generalized observations even about commercial matters. The "idea" he wishes to communicate is simply this: "I will sell you the X prescription drug at the Y price." Our question, then, is whether this communication is wholly outside the protection of the First Amendment.

V

We begin with several propositions that already are settled or beyond serious dispute. It is clear, for example, that speech does not lose its First Amendment protection because money is spent to project it, as in a paid advertisement of one form or another. *Buckley* v. *Valeo,* 424 U. S. 1, 35–59 (1976); *Pittsburgh Press Co.* v. *Human Relations Comm'n,* 413 U. S., at 384; *New York Times Co.* v. *Sullivan,* 376 U. S., at 266. Speech likewise is protected even though it is carried in a form that is "sold" for profit, *Smith* v. *California,* 361 U. S. 147, 150 (1959) (books); *Joseph Burstyn, Inc.* v. *Wilson,* 343 U. S. 495, 501 (1952) (motion pictures); *Murdock* v. *Pennsylvania,* 319 U. S., at 111 (religious literature), and even though it may involve a solicitation to purchase or otherwise pay or contribute money. *New York Times Co.* v. *Sullivan, supra; NAACP* v. *Button,* 371 U. S. 415, 429 (1963); *Jamison* v. *Texas,* 318 U. S., at 417; *Cantwell* v. *Connecticut,* 310 U. S. 296, 306–307 (1940).

If there is a kind of commercial speech that lacks all First Amendment protection, therefore, it must be distinguished by its content. Yet the speech whose content deprives it of protection cannot simply be speech on a commercial subject. No one would contend that our pharmacist may be prevented from being heard on

the subject of whether, in general, pharmaceutical prices should be regulated, or their advertisement forbidden. Nor can it be dispositive that a commercial advertisement is noneditorial, and merely reports a fact. Purely factual matter of public interest may claim protection. *Bigelow* v. *Virginia,* 421 U. S., at 822; *Thornhill* v. *Alabama,* 310 U. S. 88, 102 (1940).

Our question is whether speech which does "no more than propose a commercial transaction," *Pittsburgh Press Co.* v. *Human Relations Comm'n,* 413 U. S., at 385, is so removed from any "exposition of ideas," *Chaplinsky* v. *New Hampshire,* 315 U. S. 568, 572 (1942), and from " 'truth, science, morality, and arts in general, in its diffusion of liberal sentiments on the administration of Government,' " *Roth* v. *United States,* 354 U. S. 476, 484 (1957), that it lacks all protection. Our answer is that it is not.

Focusing first on the individual parties to the transaction that is proposed in the commercial advertisement, we may assume that the advertiser's interest is a purely economic one. That hardly disqualifies him from protection under the First Amendment. The interests of the contestants in a labor dispute are primarily economic, but it has long been settled that both the employee and the employer are protected by the First Amendment when they express themselves on the merits of the dispute in order to influence its outcome. See, *e. g., NLRB* v. *Gissel Packing Co.,* 395 U. S. 575, 617–618 (1969); *NLRB* v. *Virginia Electric & Power Co.,* 314 U. S. 469, 477 (1941); *AFL* v. *Swing,* 312 U. S. 321, 325–326 (1941); *Thornhill* v. *Alabama,* 310 U. S., at 102. We know of no requirement that, in order to avail themselves of First Amendment protection, the parties to a labor dispute need address themselves to the merits of unionism in general

or to any subject beyond their immediate dispute.[17] It was observed in *Thornhill* that "the practices in a single factory may have economic repercussions upon a whole region and affect widespread systems of marketing." *Id.*, at 103. Since the fate of such a "single factory" could as well turn on its ability to advertise its product as on the resolution of its labor difficulties, we see no satisfactory distinction between the two kinds of speech.

As to the particular consumer's interest in the free flow of commercial information, that interest may be as keen, if not keener by far, than his interest in the day's most urgent political debate. Appellees' case in this respect is a convincing one. Those whom the suppression of prescription drug price information hits the hardest are the poor, the sick, and particularly the aged. A disproportionate amount of their income tends to be spent on prescription drugs; yet they are the least able to learn, by shopping from pharmacist to pharmacist, where their scarce dollars are best spent.[18] When drug prices

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[17] The speech of labor disputants, of course, is subject to a number of restrictions. The Court stated in *NLRB* v. *Gissel Packing Co.*, 395 U. S., at 618, for example, that an employer's threats of retaliation for the labor actions of his employees are "without the protection of the First Amendment." The constitutionality of restrictions upon speech in the special context of labor disputes is not before us here. We express no views on that complex subject, and advert to cases in the labor field only to note that in some circumstances speech of an entirely private and economic character enjoys the protection of the First Amendment.

[18] The point hardly needs citation, but a few figures are illustrative. It has been estimated, for example, that in 1973 and 1974 per capita drug expenditures of persons age 65 and over were $97.27 and $103.17, respectively, more than twice the figures of $41.18 and $45.14 for all age groups. Cooper & Piro, Age Differences in Medical Care Spending, Fiscal Year 1973, 37 Social Security Bull., No. 5, p. 6 (1974); Mueller & Gibson, Age Differences in Health Care Spending, Fiscal Year 1974, 38 Social Security Bull., No.

vary as strikingly as they do, information as to who is charging what becomes more than a convenience. It could mean the alleviation of physical pain or the enjoyment of basic necessities.

Generalizing, society also may have a strong interest in the free flow of commercial information. Even an individual advertisement, though entirely "commercial," may be of general public interest. The facts of decided cases furnish illustrations: advertisements stating that referral services for legal abortions are available, *Bigelow* v. *Virginia, supra;* that a manufacturer of artificial furs promotes his product as an alternative to the extinction by his competitors of fur-bearing mammals, see *Fur Information & Fashion Council, Inc.* v. *E. F. Timme & Son,* 364 F. Supp. 16 (SDNY 1973); and that a domestic producer advertises his product as an alternative to imports that tend to deprive American residents of their jobs, cf. *Chicago Joint Board* v. *Chicago Tribune Co.,* 435 F. 2d 470 (CA7 1970), cert. denied, 402 U. S. 973 (1971). Obviously, not all commercial messages contain the same or even a very great public interest element. There are few to which such an element, however, could not be added. Our pharmacist, for example, could cast himself as a commentator on store-to-store dispari-

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6, p. 5 (1975). These figures, of course, reflect the higher rate of illness among the aged. In 1971, 16.9% of all Americans 65 years and over were unable to carry on major activities because of some chronic condition, the figure for all ages being only 2.9%. Statistical Policy Division, Office of Management and Budget, Social Indicators 1973, p. 36. These figures eloquently suggest the diminished capacity of the aged for the kind of active comparison shopping that a ban on advertising makes necessary or desirable. Diminished resources are also the general rule for those 65 and over; their income averages about half that for all age groups. *Id.,* at 176.

The parties have stipulated that a "significant portion of income of elderly persons is spent on medicine." Stipulation of Facts ¶ 27, App. 15.

ties in drug prices, giving his own and those of a competitor as proof. We see little point in requiring him to do so, and little difference if he does not.

Moreover, there is another consideration that suggests that no line between publicly "interesting" or "important" commercial advertising and the opposite kind could ever be drawn. Advertising, however tasteless and excessive it sometimes may seem, is nonetheless dissemination of information as to who is producing and selling what product, for what reason, and at what price. So long as we preserve a predominantly free enterprise economy, the allocation of our resources in large measure will be made through numerous private economic decisions. It is a matter of public interest that those decisions, in the aggregate, be intelligent and well informed. To this end, the free flow of commercial information is indispensable. See *Dun & Bradstreet, Inc.* v. *Grove,* 404 U. S. 898, 904–906 (1971) (Douglas, J., dissenting from denial of certiorari). See also *FTC* v. *Procter & Gamble Co.,* 386 U. S. 568, 603–604 (1967) (Harlan, J., concurring). And if it is indispensable to the proper allocation of resources in a free enterprise system, it is also indispensable to the formation of intelligent opinions as to how that system ought to be regulated or altered. Therefore, even if the First Amendment were thought to be primarily an instrument to enlighten public decisionmaking in a democracy,[19] we could not say that the free flow of information does not serve that goal.[20]

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[19] For the views of a leading exponent of this position, see A. Meiklejohn, Free Speech And Its Relation to Self-Government (1948). This Court likewise has emphasized the role of the First Amendment in guaranteeing our capacity for democratic self-government. See *New York Times Co.* v. *Sullivan,* 376 U. S. 254, 269–270 (1964), and cases cited therein.

[20] Pharmaceuticals themselves provide a not insignificant illustra-

Arrayed against these substantial individual and societal interests are a number of justifications for the advertising ban. These have to do principally with maintaining a high degree of professionalism on the part of licensed pharmacists.[21] Indisputably, the State has a strong interest in maintaining that professionalism. It is exercised in a number of ways for the consumer's benefit. There is the clinical skill involved in the compounding of drugs, although, as has been noted, these now make up only a small percentage of the prescriptions filled. Yet, even with respect to manufacturer-prepared compounds, there is room for the pharmacist

tion. The parties have stipulated that expenditures for prescription drugs in the United States in 1970 were estimated at $9.14 billion. Stipulation of Facts ¶ 17, App. 12. It has been said that the figure for drugs and drug sundries in 1974 was $9.695 billion, with that amount estimated to be increasing about $700 million per year. Worthington, National Health Expenditures 1929–1974, 38 Social Security Bull., No. 2, p. 9 (1975). The task of predicting the effect that a free flow of drug price information would have on the production and consumption of drugs obviously is a hazardous and speculative one. It was recently undertaken, however, by the staff of the Federal Trade Commission in the course of its report, see n. 11, *supra,* on the merits of a possible Commission rule that would outlaw drug price advertising restrictions. The staff concluded that consumer savings would be "of a very substantial magnitude, amounting to many millions of dollars per year." Staff Report, *supra,* n. 11, at 181.

[21] An argument not advanced by the Board, either in its brief or in the testimony proffered prior to summary judgment, but which on occasion has been made to other courts, see, *e. g., Pennsylvania State Board of Pharmacy* v. *Pastor,* 441 Pa. 186, 272 A. 2d 487 (1971), is that the advertisement of low drug prices will result in overconsumption and in abuse of the advertised drugs. The argument prudently has been omitted. By definition, the drugs at issue here may be sold only on a physician's prescription. We do not assume, as apparently the dissent does, that simply because low prices will be freely advertised, physicians will overprescribe, or that pharmacists will ignore the prescription requirement.

to serve his customer well or badly. Drugs kept too long on the shelf may lose their efficacy or become adulterated. They can be packaged for the user in such a way that the same results occur. The expertise of the pharmacist may supplement that of the prescribing physician, if the latter has not specified the amount to be dispensed or the directions that are to appear on the label. The pharmacist, a specialist in the potencies and dangers of drugs, may even be consulted by the physician as to what to prescribe. He may know of a particular antagonism between the prescribed drug and another that the customer is or might be taking, or with an allergy the customer may suffer. The pharmacist himself may have supplied the other drug or treated the allergy. Some pharmacists, concededly not a large number, "monitor" the health problems and drug consumptions of customers who come to them repeatedly.[22] A pharmacist who has a continuous relationship with his customer is in the best position, of course, to exert professional skill for the customer's protection.

Price advertising, it is argued, will place in jeopardy the pharmacist's expertise and, with it, the customer's health. It is claimed that the aggressive price competition that will result from unlimited advertising will make it impossible for the pharmacist to supply professional services in the compounding, handling, and dispensing

[22] Monitoring, even if pursued, is not fully effective. It is complicated by the mobility of the patient; by his patronizing more than one pharmacist; by his being treated by more than one prescriber; by the availability of over-the-counter drugs; and by the antagonism of certain foods and drinks. Stipulation of Facts ¶¶ 30–47, App. 16–19. Neither the Code of Ethics of the American Pharmaceutical Association nor that of the Virginia Pharmaceutical Association requires a pharmacist to maintain family prescription records. *Id.*, ¶ 42, App. 18. The appellant Board has never promulgated a regulation requiring such records. *Id.*, ¶ 43, App. 18.

of prescription drugs. Such services are time consuming and expensive; if competitors who economize by eliminating them are permitted to advertise their resulting lower prices, the more painstaking and conscientious pharmacist will be forced either to follow suit or to go out of business. It is also claimed that prices might not necessarily fall as a result of advertising. If one pharmacist advertises, others must, and the resulting expense will inflate the cost of drugs. It is further claimed that advertising will lead people to shop for their prescription drugs among the various pharmacists who offer the lowest prices, and the loss of stable pharmacist-customer relationships will make individual attention—and certainly the practice of monitoring—impossible. Finally, it is argued that damage will be done to the professional image of the pharmacist. This image, that of a skilled and specialized craftsman, attracts talent to the profession and reinforces the better habits of those who are in it. Price advertising, it is said, will reduce the pharmacist's status to that of a mere retailer.[23]

The strength of these proffered justifications is greatly undermined by the fact that high professional standards, to a substantial extent, are guaranteed by the close regulation to which pharmacists in Virginia are subject. And this case concerns the retail sale by the pharmacist more than it does his professional standards. Surely, any pharmacist guilty of professional dereliction that actually endangers his customer will promptly lose his

[23] Descriptions of the pharmacist's expertise, its importance to the consumer, and its alleged jeopardization by price advertising are set forth at length in the numerous summaries of testimony of proposed witnesses for the Board, and objections to testimony of proposed witnesses for the plaintiffs, that the Board filed with the District Court prior to summary judgment, the substance of which appellees did not contest. App. 4, 27–48, 52–53; Brief for Appellants 4–5, and n. 2.

license. At the same time, we cannot discount the Board's justifications entirely. The Court regarded justifications of this type sufficient to sustain the advertising bans challenged on due process and equal protection grounds in *Head* v. *New Mexico Board, supra; Williamson* v. *Lee Optical Co., supra;* and *Semler* v. *Dental Examiners, supra.*

The challenge now made, however, is based on the First Amendment. This casts the Board's justifications in a different light, for on close inspection it is seen that the State's protectiveness of its citizens rests in large measure on the advantages of their being kept in ignorance. The advertising ban does not directly affect professional standards one way or the other. It affects them only through the reactions it is assumed people will have to the free flow of drug price information. There is no claim that the advertising ban in any way prevents the cutting of corners by the pharmacist who is so inclined. That pharmacist is likely to cut corners in any event. The only effect the advertising ban has on him is to insulate him from price competition and to open the way for him to make a substantial, and perhaps even excessive, profit in addition to providing an inferior service. The more painstaking pharmacist is also protected but, again, it is a protection based in large part on public ignorance.

It appears to be feared that if the pharmacist who wishes to provide low cost, and assertedly low quality, services is permitted to advertise, he will be taken up on his offer by too many unwitting customers. They will choose the low-cost, low-quality service and drive the "professional" pharmacist out of business. They will respond only to costly and excessive advertising, and end up paying the price. They will go from one pharmacist to another, following the discount, and destroy the pharmacist-customer relationship. They will lose respect for

the profession because it advertises. All this is not in their best interests, and all this can be avoided if they are not permitted to know who is charging what.

There is, of course, an alternative to this highly paternalistic approach. That alternative is to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them. If they are truly open, nothing prevents the "professional" pharmacist from marketing his own assertedly superior product, and contrasting it with that of the low-cost, high-volume prescription drug retailer. But the choice among these alternative approaches is not ours to make or the Virginia General Assembly's. It is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us. Virginia is free to require whatever professional standards it wishes of its pharmacists; it may subsidize them or protect them from competition in other ways. Cf. *Parker* v. *Brown*, 317 U. S. 341 (1943). But it may not do so by keeping the public in ignorance of the entirely lawful terms that competing pharmacists are offering. In this sense, the justifications Virginia has offered for suppressing the flow of prescription drug price information, far from persuading us that the flow is not protected by the First Amendment, have reinforced our view that it is. We so hold.

VI

In concluding that commercial speech, like other varieties, is protected, we of course do not hold that it can never be regulated in any way. Some forms of commercial speech regulation are surely permissible. We mention a few only to make clear that they are not before us and therefore are not foreclosed by this case.

There is no claim, for example, that the prohibition on prescription drug price advertising is a mere time, place, and manner restriction. We have often approved restrictions of that kind provided that they are justified without reference to the content of the regulated speech, that they serve a significant governmental interest, and that in so doing they leave open ample alternative channels for communication of the information. Compare *Grayned* v. *City of Rockford,* 408 U. S. 104, 116 (1972); *United States* v. *O'Brien,* 391 U. S. 367, 377 (1968); and *Kovacs* v. *Cooper,* 336 U. S. 77, 85–87 (1949), with *Buckley* v. *Valeo,* 424 U. S. 1; *Erznoznik* v. *City of Jacksonville,* 422 U. S. 205, 209 (1975); *Cantwell* v. *Connecticut,* 310 U. S., at 304–308; and *Saia* v. *New York,* 334 U. S. 558, 562 (1948). Whatever may be the proper bounds of time, place, and manner restrictions on commercial speech, they are plainly exceeded by this Virginia statute, which singles out speech of a particular content and seeks to prevent its dissemination completely.

Nor is there any claim that prescription drug price advertisements are forbidden because they are false or misleading in any way. Untruthful speech, commercial or otherwise, has never been protected for its own sake. *Gertz* v. *Robert Welch, Inc.,* 418 U. S. 323, 340 (1974); *Konigsberg* v. *State Bar,* 366 U. S. 36, 49, and n. 10 (1961). Obviously, much commercial speech is not provably false, or even wholly false, but only deceptive or misleading. We foresee no obstacle to a State's dealing effectively with this problem.[24] The First Amendment,

[24] In concluding that commercial speech enjoys First Amendment protection, we have not held that it is wholly undifferentiable from other forms. There are commonsense differences between speech that does "no more than propose a commercial transaction," *Pittsburgh Press Co.* v. *Human Relations Comm'n,* 413 U. S., at 385, and other varieties. Even if the differences do not justify the conclusion

as we construe it today, does not prohibit the State from insuring that the stream of commercial information flow cleanly as well as freely. See, for example, Va. Code Ann. § 18.2-216 (1975).

Also, there is no claim that the transactions proposed in the forbidden advertisements are themselves illegal in any way. Cf. *Pittsburgh Press Co.* v. *Human Relations Comm'n,* 413 U. S. 376 (1973); *United States*

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that commercial speech is valueless, and thus subject to complete suppression by the State, they nonetheless suggest that a different degree of protection is necessary to insure that the flow of truthful and legitimate commercial information is unimpaired. The truth of commercial speech, for example, may be more easily verifiable by its disseminator than, let us say, news reporting or political commentary, in that ordinarily the advertiser seeks to disseminate information about a specific product or service that he himself provides and presumably knows more about than anyone else. Also, commercial speech may be more durable than other kinds. Since advertising is the *sine qua non* of commercial profits, there is little likelihood of its being chilled by proper regulation and forgone entirely.

Attributes such as these, the greater objectivity and hardiness of commercial speech, may make it less necessary to tolerate inaccurate statements for fear of silencing the speaker. Compare *New York Times Co.* v. *Sullivan,* 376 U. S. 254 (1964), with *Dun & Bradstreet, Inc.* v. *Grove,* 404 U. S. 898 (1971). They may also make it appropriate to require that a commercial message appear in such a form, or include such additional information, warnings, and disclaimers, as are necessary to prevent its being deceptive. Compare *Miami Herald Publishing Co.* v. *Tornillo,* 418 U. S. 241 (1974), with *Banzhaf* v. *FCC,* 132 U. S. App. D. C. 14, 405 F. 2d 1082 (1968), cert. denied *sub nom. Tobacco Institute, Inc.* v. *FCC,* 396 U. S. 842 (1969). Cf. *United States* v. *95 Barrels of Vinegar,* 265 U. S. 438, 443 (1924) ("It is not difficult to choose statements, designs and devices which will not deceive"). They may also make inapplicable the prohibition against prior restraints. Compare *New York Times Co.* v. *United States,* 403 U. S. 713 (1971), with *Donaldson* v. *Read Magazine,* 333 U. S. 178, 189–191 (1948); *FTC* v. *Standard Education Society,* 302 U. S. 112 (1937); *E. F. Drew & Co.* v. *FTC,* 235 F. 2d 735, 739–740 (CA2 1956), cert. denied, 352 U. S. 969 (1957).

v. *Hunter,* 459 F. 2d 205 (CA4), cert. denied, 409 U. S. 934 (1972). Finally, the special problems of the electronic broadcast media are likewise not in this case. Cf. *Capitol Broadcasting Co.* v. *Mitchell,* 333 F. Supp. 582 (DC 1971), aff'd *sub nom. Capitol Broadcasting Co.* v. *Acting Attorney General,* 405 U. S. 1000 (1972).

What is at issue is whether a State may completely suppress the dissemination of concededly truthful information about entirely lawful activity, fearful of that information's effect upon its disseminators and its recipients. Reserving other questions,[25] we conclude that the answer to this one is in the negative.

The judgment of the District Court is affirmed.

It is so ordered.

MR. JUSTICE STEVENS took no part in the consideration or decision of this case.

MR. CHIEF JUSTICE BURGER, concurring.

The Court notes that roughly 95% of all prescriptions are filled with dosage units already prepared by the manufacturer and sold to the pharmacy in that form. These are the drugs that have a market large enough to make their preparation profitable to the manufacturer; for the same reason, they are the drugs that it is profitable for the pharmacist to advertise. In dispensing

[25] We stress that we have considered in this case the regulation of commercial advertising by pharmacists. Although we express no opinion as to other professions, the distinctions, historical and functional, between professions, may require consideration of quite different factors. Physicians and lawyers, for example, do not dispense standardized products; they render professional *services* of almost infinite variety and nature, with the consequent enhanced possibility for confusion and deception if they were to undertake certain kinds of advertising.

these *prepackaged* items, the pharmacist performs largely a packaging rather than a compounding function of former times. Our decision today, therefore, deals largely with the State's power to prohibit pharmacists from advertising the retail price of *prepackaged drugs.* As the Court notes, *ante,* at 773 n. 25, quite different factors would govern were we faced with a law regulating or even prohibiting advertising by the traditional learned professions of medicine or law. "The interest of the States in regulating lawyers is especially great since lawyers are essential to the primary governmental function of administering justice, and have historically been 'officers of the courts.'" *Goldfarb* v. *Virginia State Bar,* 421 U. S. 773, 792 (1975). See also *Cohen* v. *Hurley,* 366 U. S. 117, 123–124 (1961). We have also recognized the State's substantial interest in regulating physicians. See, *e. g., United States* v. *Oregon Medical Society,* 343 U. S. 326, 336 (1952); *Semler* v. *Oregon State Board of Dental Examiners,* 294 U. S. 608, 612 (1935). Attorneys and physicians are engaged *primarily* in providing services in which professional judgment is a large component, a matter very different from the retail *sale* of labeled drugs already prepared by others.

MR. JUSTICE STEWART aptly observes that the "differences between commercial price and product advertising . . . and ideological communication" allow the State a scope in regulating the former that would be unacceptable under the First Amendment with respect to the latter. I think it important to note also that the advertisement of professional services carries with it quite different risks from the advertisement of standard products. The Court took note of this in *Semler, supra,* at 612, in upholding a state statute prohibiting entirely certain types of advertisement by dentists:

"The legislature was not dealing with traders in

> commodities, but with the vital interest of public health, and with a profession treating bodily ills and demanding different standards of conduct from those which are traditional in the competition of the market place. The community is concerned with the maintenance of professional standards which will insure not only competency in individual practitioners, but protection against those who would prey upon a public peculiarly susceptible to imposition through alluring promises of physical relief. And the community is concerned in providing safeguards not only against deception, but against practices which would tend to demoralize the profession by forcing its members into an unseemly rivalry which would enlarge the opportunities of the least scrupulous."

I doubt that we know enough about evaluating the quality of medical and legal services to know which claims of superiority are "misleading" and which are justifiable. Nor am I sure that even advertising the price of certain professional services is not inherently misleading, since what the professional must do will vary greatly in individual cases. It is important to note that the Court wisely leaves these issues to another day.

MR. JUSTICE STEWART, concurring.

In *Thornhill* v. *Alabama,* 310 U. S. 88, the Court observed that "[f]reedom of discussion, if it would fulfill its historic function in this nation, must embrace all issues about which information is needed or appropriate to enable the members of society to cope with the exigencies of their period." *Id.,* at 102. Shortly after the *Thornhill* decision, the Court identified a single category of communications that is constitutionally unprotected: communications "which by their very utterance inflict

injury." *Chaplinsky* v. *New Hampshire,* 315 U. S. 568, 572. Yet only a month after *Chaplinsky,* and without reference to that decision, the Court stated in *Valentine* v. *Chrestensen,* 316 U. S. 52, 54, that "the Constitution imposes no such restraint on government as respects purely commercial advertising." For more than 30 years this "casual, almost offhand" statement in *Chrestensen* has operated to exclude commercial speech from the protection afforded by the First Amendment to other types of communication. *Cammarano* v. *United States,* 358 U. S. 498, 514 (Douglas, J., concurring).[1]

Today the Court ends the anomalous situation created by *Chrestensen* and holds that a communication which does no more than propose a commercial transaction is not "wholly outside the protection of the First Amendment." *Ante,* at 761. But since it is a cardinal principle of the First Amendment that "government has no power to restrict expression because of its message, its ideas, its subject matter, or its content," [2] the Court's decision calls into immediate question the constitutional legitimacy of every state and federal law regulating false or deceptive advertising. I write separately to explain why I think today's decision does not preclude such governmental regulation.

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[1] In recent years the soundness of the sweeping language of the *Chrestensen* opinion has been repeatedly questioned. See *Bigelow* v. *Virginia,* 421 U. S. 809, 819–821; *Lehman* v. *City of Shaker Heights,* 418 U. S. 298, 314–315, and n. 6 (BRENNAN, J., dissenting); *Pittsburgh Press Co.* v. *Human Relations Comm'n,* 413 U. S. 376, 398 (Douglas, J., dissenting); *id.,* at 401, and n. 6 (STEWART, J., dissenting); *Dun & Bradstreet, Inc.* v. *Grove,* 404 U. S. 898, 904–906 (Douglas, J., dissenting from denial of certiorari).

[2] *Police Dept. of Chicago* v. *Mosley,* 408 U. S. 92, 95. See, *e. g., Hudgens* v. *NLRB,* 424 U. S. 507, 520; *Erznoznik* v. *City of Jacksonville,* 422 U. S. 205, 209; *Pell* v. *Procunier,* 417 U. S. 817, 828; *Grayned* v. *City of Rockford,* 408 U. S. 104, 115.

The Court has on several occasions addressed the problem posed by false statements of fact in libel cases. Those cases demonstrate that even with respect to expression at the core of the First Amendment, the Constitution does not provide absolute protection for false factual statements that cause private injury. In *Gertz* v. *Robert Welch, Inc.*, 418 U. S. 323, 340, the Court concluded that "there is no constitutional value in false statements of fact." As the Court had previously recognized in *New York Times Co.* v. *Sullivan*, 376 U. S. 254, however, factual errors are inevitable in free debate, and the imposition of liability for erroneous factual assertions can "dampe[n] the vigor and limi[t] the variety of public debate" by inducing "self-censorship." *Id.*, at 279. In order to provide ample "breathing space" for free expression, the Constitution places substantial limitations on the discretion of government to permit recovery for libelous communications. See *Gertz* v. *Robert Welch, Inc., supra*, at 347–349.

The principles recognized in the libel decisions suggest that government may take broader action to protect the public from injury produced by false or deceptive price or product advertising than from harm caused by defamation. In contrast to the press, which must often attempt to assemble the true facts from sketchy and sometimes conflicting sources under the pressure of publication deadlines, the commercial advertiser generally knows the product or service he seeks to sell and is in a position to verify the accuracy of his factual representations before he disseminates them. The advertiser's access to the truth about his product and its price substantially eliminates any danger that governmental regulation of false or misleading price or product advertising will chill accurate and nondeceptive commercial expression. There

is, therefore, little need to sanction "some falsehood in order to protect speech that matters." *Id.*, at 341.

The scope of constitutional protection of communicative expression is not universally inelastic. In the area of labor relations, for example, the Court has recognized that "an employer's free speech right to communicate his views to his employees is firmly established and cannot be infringed by a union or the National Labor Relations Board." *NLRB* v. *Gissel Packing Co.*, 395 U. S. 575, 617. See *NLRB* v. *Virginia Electric & Power Co.*, 314 U. S. 469. Yet, in that context, the Court has concluded that the employer's freedom to communicate his views to his employees may be restricted by the requirement that any predictions "be carefully phrased on the basis of objective fact." [3] 395 U. S., at 618. In response to the contention that the "line between so-called permitted predictions and proscribed threats is too vague to stand up under traditional First Amendment analysis," the Court relied on the employer's intimate knowledge of the employer-employee relationship and his ability to "avoid coercive speech simply by avoiding conscious overstatements he has reason to believe will mislead his em-

[3] Speech by an employer or a labor union organizer that contains material misrepresentations of fact or appeals to racial prejudice may form the basis of an unfair labor practice or warrant the invalidation of a certification election. See, *e. g.*, *Sewell Mfg. Co.*, 138 N. L. R. B. 66; *United States Gypsum Co.*, 130 N. L. R. B. 901; *Gummed Products Co.*, 112 N. L. R. B. 1092. Such restrictions would clearly violate First Amendment guarantees if applied to political expression concerning the election of candidates to public office. See *Vanasco* v. *Schwartz*, 401 F. Supp. 87 (EDNY) (three-judge court), summarily aff'd *sub nom. Schwartz* v. *Postel*, 423 U. S. 1041. Other restrictions designed to promote antiseptic conditions in the labor relations context, such as the prohibition of certain campaigning during the 24-hour period preceding the election, would be constitutionally intolerable if applied in the political arena. Compare *Peerless Plywood Co.*, 107 N. L. R. B. 427, with *Mills* v. *Alabama*, 384 U. S. 214.

ployees." *Id.*, at 620. Cf. *United States* v. *95 Barrels of Vinegar*, 265 U. S. 438, 443 ("It is not difficult to choose statements, designs and devices which will not deceive"). Although speech in the labor relations setting may be distinguished from commercial advertising,[4] the *Gissel Packing Co.* opinion is highly significant in the present context because it underscores the constitutional importance of the speaker's specific and unique knowledge of the relevant facts and establishes that a regulatory scheme monitoring "the impact of utterances" is not invariably inconsistent with the First Amendment.[5] See 395 U. S., at 620.

The Court's determination that commercial advertising of the kind at issue here is not "wholly outside the protection of" the First Amendment indicates by its very phrasing that there are important differences between commercial price and product advertising, on the one hand, and ideological communication on the other. See *ante*, at 771–772, n. 24. Ideological expression, be it oral, literary, pictorial, or theatrical, is integrally related to the exposition of thought—thought that may shape our concepts of the whole universe of man. Although such expression may convey factual information relevant to social and individual decisionmaking, it is protected by

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[4] In the labor relations area, governmental regulation of expression by employers has been justified in part by the competing First Amendment associational interests of employees and by the economic dependence of employees on their employers. See *NLRB* v. *Gissel Packing Co.*, 395 U. S., at 617–618; *NLRB* v. *Virginia Electric & Power Co.*, 314 U. S. 469, 477.

[5] The Court in *Gissel Packing Co.* emphasized the NLRB's expertise in determining whether statements by employers would tend to mislead or coerce employees. 395 U. S., at 620. The NLRB's armamentarium for responding to material misrepresentations and deceptive tactics includes the issuance of cease-and-desist orders and the securing of restraining orders. See 29 U. S. C. §§ 160 (c), (j).

the Constitution, whether or not it contains factual representations and even if it includes inaccurate assertions of fact. Indeed, disregard of the "truth" may be employed to give force to the underlying idea expressed by the speaker.[6] "Under the First Amendment there is no such thing as a false idea," and the only way that ideas can be suppressed is through "the competition of other ideas," *Gertz* v. *Robert Welch, Inc.*, 418 U. S., at 339–340.

Commercial price and product advertising differs markedly from ideological expression because it is confined to the promotion of specific goods or services.[7] The First Amendment protects the advertisement because of the "information of potential interest and value" conveyed, *Bigelow* v. *Virginia*, 421 U. S. 809, 822, rather than because of any direct contribution to the interchange of ideas. See *ante*, at 762–765, 770.[8] Since the factual claims contained in commercial price or product advertisements relate to tangible goods or services, they may be tested empirically and corrected to reflect the truth without in any manner jeopardizing the free dis-

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[6] As the Court observed in *Cantwell* v. *Connecticut*, 310 U. S. 296, 310:

"To persuade others to his own point of view, the pleader, as we know, at times, resorts to exaggeration, to vilification of men who have been, or are, prominent in church or state, and even to false statement. But the people of this nation have ordained in the light of history, that, in spite of the probability of excesses and abuses, these liberties are, in the long view, essential to enlightened opinion and right conduct on the part of the citizens of a democracy."

[7] See Developments in the Law—Deceptive Advertising, 80 Harv. L. Rev. 1005, 1030–1031 (1967).

[8] The information about price and product conveyed by commercial advertisements may, of course, stimulate thought and debate about political questions. The drug price information at issue in the present case might well have an impact, for instance, on a person's views concerning price control issues, government subsidy proposals, or special health care, consumer protection, or tax legislation.

semination of thought. Indeed, the elimination of false and deceptive claims serves to promote the one facet of commercial price and product advertising that warrants First Amendment protection—its contribution to the flow of accurate and reliable information relevant to public and private decisionmaking.

MR. JUSTICE REHNQUIST, dissenting.

The logical consequences of the Court's decision in this case, a decision which elevates commercial intercourse between a seller hawking his wares and a buyer seeking to strike a bargain to the same plane as has been previously reserved for the free marketplace of ideas, are far reaching indeed. Under the Court's opinion the way will be open not only for dissemination of price information but for active promotion of prescription drugs, liquor, cigarettes, and other products the use of which it has previously been thought desirable to discourage. Now, however, such promotion is protected by the First Amendment so long as it is not misleading or does not promote an illegal product or enterprise. In coming to this conclusion, the Court has overruled a legislative determination that such advertising should not be allowed and has done so on behalf of a consumer group which is not directly disadvantaged by the statute in question. This effort to reach a result which the Court obviously considers desirable is a troublesome one, for two reasons. It extends standing to raise First Amendment claims beyond the previous decisions of this Court. It also extends the protection of that Amendment to purely commercial endeavors which its most vigorous champions on this Court had thought to be beyond its pale.

I

I do not find the question of the appellees' standing to urge the claim which the Court decides quite as easy

as the Court does. The Court finds standing on the part of the consumer appellees based upon a "right to 'receive information.' " *Ante,* at 757. Yet it has been stipulated in this case that the challenged statute does not prohibit anyone from receiving this information either in person or by phone. *Ante,* at 752, and n. 6. The statute forbids "only publish[ing], advertis[ing] or promot[ing]" prescription drugs.

While it may be generally true that publication of information by its source is essential to effective communication, it is surely less true, where, as here, the potential recipients of the information have, in the Court's own words, a "keen, if not keener by far," interest in it than "in the day's most urgent political debate." *Ante,* at 763. Appellees who have felt so strongly about their right to receive information as to litigate the issue in this lawsuit must also have enough residual interest in the matter to call their pharmacy and inquire.

The statute, in addition, only forbids *pharmacists* to publish this price information. There is no prohibition against a consumer group, such as appellees, collecting and publishing comparative price information as to various pharmacies in an area. Indeed they have done as much in their briefs in this case. Yet, though appellees could both receive and publish the information in question the Court finds that they have standing to protest that pharmacists are not allowed to advertise. Thus, contrary to the assertion of the Court, appellees are not asserting their "right to receive information" at all but rather the right of some third party to publish. In the cases relied upon by the Court, *ante,* at 756–757, the plaintiffs asserted their right to receive information which would not be otherwise reasonably available to them.* They did not seek to assert the right of a third

*The Court contends, *ante,* at 757–758, n. 15, that this case is indistinguishable from *Procunier, Kleindienst,* and *Lamont,* in that in all

party, not before the Court, to disseminate information. Here, the only group truly restricted by this statute, the pharmacists, have not even troubled to join in this litigation and may well feel that the expense and competition of advertising is not in their interest.

II

Thus the issue on the merits is not, as the Court phrases it, whether "[o]ur pharmacist" may communicate the fact that he "will sell you the X prescription drug at the Y price." No pharmacist is asserting any such claim to so communicate. The issue is rather whether appellee consumers may override the legislative determination that pharmacists should not advertise even though the pharmacists themselves do not object. In deciding that they may do so, the Court necessarily adopts a rule which cannot be limited merely to dissemination of price alone, and which cannot possibly be confined to pharmacists but must likewise extend to lawyers, doctors, and all other professions.

The Court speaks of the consumer's interest in the free flow of commercial information, particularly in the case of the poor, the sick, and the aged. It goes on to observe that "society also may have a strong interest in the free flow of commercial information." *Ante,* at 764. One need not disagree with either of these statements in order to feel that they should presumptively be the concern of the Virginia Legislature, which sits to balance these and other claims in the process of making laws such as the one here under attack. The Court speaks of the

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of those cases it was possible for the parties to obtain the information on their own. In *Procunier* this would have entailed traveling to a state prison; in *Kleindienst* and *Lamont,* traveling abroad. Obviously such measures would limit access to information in a way that the requirement of a phone call or a trip to the corner drugstore would not.

importance in a "predominantly free enterprise economy" of intelligent and well-informed decisions as to allocation of resources. *Ante,* at 765. While there is again much to be said for the Court's observation as a matter of desirable public policy, there is certainly nothing in the United States Constitution which requires the Virginia Legislature to hew to the teachings of Adam Smith in its legislative decisions regulating the pharmacy profession. *E. g., Nebbia* v. *New York,* 291 U. S. 502 (1934); *Olsen* v. *Nebraska,* 313 U. S. 236 (1941).

As Mr. Justice Black, writing for the Court, observed in *Ferguson* v. *Skrupa,* 372 U. S. 726, 730 (1963):

> "The doctrine . . . that due process authorizes courts to hold laws unconstitutional when they believe the legislature has acted unwisely—has long since been discarded. We have returned to the original constitutional proposition that courts do not substitute their social and economic beliefs for the judgment of legislative bodies who are elected to pass laws."

Similarly in *Williamson* v. *Lee Optical Co.,* 348 U. S. 483 (1955), the Court, in dealing with a state prohibition against the advertisement of eyeglass frames, held: "We see no constitutional reason why a State may not treat all who deal with the human eye as members of a profession who should use no merchandising methods for obtaining customers." *Id.,* at 490.

The Court addresses itself to the valid justifications which may be found for the Virginia statute, and apparently discounts them because it feels they embody a "highly paternalistic approach." *Ante,* at 770. It concludes that the First Amendment requires that channels of advertising communication with respect to prescription drugs must be opened, and that Virginia may not

keep "the public in ignorance of the entirely lawful terms that competing pharmacists are offering." *Ibid.*

The Court concedes that legislatures may prohibit false and misleading advertisements, and may likewise prohibit advertisements seeking to induce transactions which are themselves illegal. In a final footnote the opinion tosses a bone to the traditionalists in the legal and medical professions by suggesting that because they sell services rather than drugs the holding of this case is not automatically applicable to advertising in those professions. But if the sole limitation on permissible state proscription of advertising is that it may not be false or misleading, surely the difference between pharmacists' advertising and lawyers' and doctors' advertising can be only one of degree and not of kind. I cannot distinguish between the public's right to know the price of drugs and its right to know the price of title searches or physical examinations or other professional services for which standardized fees are charged. Nor is it apparent how the pharmacists in this case are less engaged in a regulatable profession than were the opticians in *Williamson, supra.*

Nor will the impact of the Court's decision on existing commercial and industrial practice be limited to allowing advertising by the professions. The Court comments that in labor disputes "it has long been settled that both the employee and the employer are protected by the First Amendment when they express themselves on the merits of the dispute in order to influence its outcome." *Ante,* at 762. But the first case cited by the Court in support of this proposition, *NLRB* v. *Gissel Packing Co.,* 395 U. S. 575, 617–618 (1969), falls a good deal short of supporting this general statement. The Court there said that "an employer is free to communicate to his employees any of his general views about unionism or any of his specific views about a particular union, so long as the

communications do not contain a 'threat of reprisal or force or promise of benefit.'" *Id.*, at 618. This carefully guarded language is scarcely a ringing endorsement of even the second-class First Amendment rights which the Court has today created in commercial speech.

It is hard to see why an employer's right to publicize a promise of benefit may be prohibited by federal law, so long as the promise is neither false nor deceptive, if pharmacists' price advertising may not be prohibited by the Virginia Legislature. Yet such a result would be wholly inconsistent with established labor law.

Both the Courts of Appeals and the National Labor Relations Board have not hesitated to set aside representation elections in which the employer made statements which were undoubtedly truthful but which were found to be implicitly coercive. For instance, in *NLRB* v. *Realist, Inc.*, 328 F. 2d 840 (CA7 1964), an election was set aside when the employer, in a concededly non-threatening manner, raised the specter of plant closings which would result from unionism. In *Oak Mfg. Co.*, 141 N. L. R. B. 1323, 1328–1330 (1963), the Board set aside an election where the employer stated "categorically" that the union "cannot and will not obtain any wage increase for you," and with respect to seniority said that it could "assure" the employees that the union's program "will be worse" than the present system. In *Freeman Mfg. Co.*, 148 N. L. R. B. 577 (1964), the employer sent letters to employees in which he urged that unionization might cause customers to cease buying the company's product because of delays and higher prices. The Board found this to be ground for invalidating the election. Presumably all of these holdings will require re-evaluation in the light of today's decision with a view toward allowing the employer's speech because it is now protected by the First Amendment, as expanded by this decision.

There are undoubted difficulties with an effort to draw a bright line between "commercial speech" on the one hand and "protected speech" on the other, and the Court does better to face up to these difficulties than to attempt to hide them under labels. In this case, however, the Court has unfortunately substituted for the wavering line previously thought to exist between commercial speech and protected speech a no more satisfactory line of its own—that between "truthful" commercial speech, on the one hand, and that which is "false and misleading" on the other. The difficulty with this line is not that it wavers, but on the contrary that it is simply too Procrustean to take into account the congeries of factors which I believe could, quite consistently with the First and Fourteenth Amendments, properly influence a legislative decision with respect to commercial advertising.

The Court insists that the rule it lays down is consistent even with the view that the First Amendment is "primarily an instrument to enlighten public decisionmaking in a democracy." *Ante,* at 765. I had understood this view to relate to public decisionmaking as to political, social, and other public issues, rather than the decision of a particular individual as to whether to purchase one or another kind of shampoo. It is undoubtedly arguable that many people in the country regard the choice of shampoo as just as important as who may be elected to local, state, or national political office, but that does not automatically bring information about competing shampoos within the protection of the First Amendment. It is one thing to say that the line between strictly ideological and political commentaries and other kinds of commentary is difficult to draw, and that the mere fact that the former may have in it an element of commercialism does not strip it of First Amendment protection. See *New York Times Co.* v. *Sullivan,* 376 U. S. 254 (1964). But it is another thing to say that because that

line is difficult to draw, we will stand at the other end of the spectrum and reject out of hand the observation of so dedicated a champion of the First Amendment as Mr. Justice Black that the protections of that Amendment do not apply to a " 'merchant' who goes from door to door 'selling pots.' " *Breard* v. *City of Alexandria,* 341 U. S. 622, 650 (1951) (dissenting).

In the case of "our" hypothetical pharmacist, he may now presumably advertise not only the prices of prescription drugs, but may attempt to energetically promote their sale so long as he does so truthfully. Quite consistently with Virginia law requiring prescription drugs to be available only through a physician, "our" pharmacist might run any of the following representative advertisements in a local newspaper:

> "Pain getting you down? Insist that your physician prescribe Demerol. You pay a little more than for aspirin, but you get a lot more relief."
>
> "Can't shake the flu? Get a prescription for Tetracycline from your doctor today."
>
> "Don't spend another sleepless night. Ask your doctor to prescribe Seconal without delay."

Unless the State can show that these advertisements are either actually untruthful or misleading, it presumably is not free to restrict in any way commercial efforts on the part of those who profit from the sale of prescription drugs to put them in the widest possible circulation. But such a line simply makes no allowance whatever for what appears to have been a considered legislative judgment in most States that while prescription drugs are a necessary and vital part of medical care and treatment, there are sufficient dangers attending their widespread use that they simply may not be promoted in the same manner as hair creams, deodorants, and toothpaste. The very real dangers that general advertising for such drugs

might create in terms of encouraging, even though not sanctioning, illicit use of them by individuals for whom they have not been prescribed, or by generating patient pressure upon physicians to prescribe them, are simply not dealt with in the Court's opinion. If prescription drugs may be advertised, they may be advertised on television during family viewing time. Nothing we know about the acquisitive instincts of those who inhabit every business and profession to a greater or lesser extent gives any reason to think that such persons will not do everything they can to generate demand for these products in much the same manner and to much the same degree as demand for other commodities has been generated.

Both Congress and state legislatures have by law sharply limited the permissible dissemination of information about some commodities because of the potential harm resulting from those commodities, even though they were not thought to be sufficiently demonstrably harmful to warrant outright prohibition of their sale. Current prohibitions on television advertising of liquor and cigarettes are prominent in this category, but apparently under the Court's holding so long as the advertisements are not deceptive they may no longer be prohibited.

This case presents a fairly typical First Amendment problem—that of balancing interests in individual free speech against public welfare determinations embodied in a legislative enactment. As the Court noted in *American Communications Assn.* v. *Douds,* 339 U. S. 382, 399 (1950):

> "[L]egitimate attempts to protect the public, not from the remote possible effects of noxious ideologies, but from the present excesses of direct, active conduct, are not presumptively bad because they

> interfere with and, in some of its manifestations, restrain the exercise of First Amendment rights."

Here the rights of the appellees seem to me to be marginal at best. There is no ideological content to the information which they seek and it is freely available to them—they may even publish it if they so desire. The only persons directly affected by this statute are not parties to this lawsuit. On the other hand, the societal interest against the promotion of drug use for every ill, real or imaginary, seems to me extremely strong. I do not believe that the First Amendment mandates the Court's "open door policy" toward such commercial advertising.

Attachment 4

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SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF ALAMEDA

THE PEOPLE OF THE STATE OF CALIFORNIA,

Plaintiff,

v.

HEARTBEAT INTERNATIONAL, INC., REALOPTIONS, DOES 1-100, INCLUSIVE,

Defendants.

Case No. 23CV044940

COMPLAINT FOR PERMANENT INJUNCTION, CIVIL PENALTIES, AND OTHER EQUITABLE RELIEF

(Bus. & Prof. Code §§ 17200, et seq., 17500, et seq.)

[VERIFIED ANSWER REQUIRED PURSUANT TO CODE CIV. PROC. § 446]

Plaintiff, the People of the State of California, by and through Attorney General Rob Bonta ("Plaintiff" or "the People"), alleges the following, on information and belief:

INTRODUCTION

1. For the vast majority of pregnant people who choose to undergo an abortion, their most common emotion is relief.[1] For a significant percentage of those people, medication abortion is their preferred method of exercising their reproductive choice. The standard medication abortion regime, consisting of two medications, mifepristone and misoprostol, has been proven to be incredibly safe—safer than Penicillin, Viagra, and even some over-the-counter drugs like Tylenol.[2] It is also incredibly effective, with more than 95% of individuals who take the standard two-dose regime completing their abortion without need for any further intervention.[3]

2. A vast majority, however, is not everyone. A small percentage of pregnant people—0.004%—may reconsider their decision while in the midst of a medication abortion.[4] As

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[1] (Corinne H. Rocca et al., *Emotions & Decision Rightness over Five Years Following an Abortion: An Examination of Decision Difficulty & Abortion Stigma* (2020) 248 Soc. Sci. & Med. 112704, https://www.sciencedirect.com/science/article/pii/S0277953619306999?via%3Dihub; *see also* Lauren Ralph et al., *Measuring decisional certainty among women seeking abortion* (2017) 95 Contraception 269-78; Diana Greene Foster, The Turnaway Study: Ten Years, A Thousand Women, and the Consequences of Having—or Being Denied—an Abortion (2021) pp. 124 [describing the seminal study regarding emotions and decision rightness following abortion, which provides that "at every interview over the five years after their abortion, 95% of women reported that having the abortion was the right decision for them."].)

[2] (Annette Choi & Will Muller, *How Safe Is the Abortion Pill Compared with Other Common Drugs*, CNN (Apr. 21, 2023), https://www.cnn.com/2023/03/15/health/abortion-pill-safety-dg/index.html; Amy Schoenfeld Walker et al., *Are Abortion Pills Safe? Here's the Evidence*, N.Y. Times (Apr. 7, 2023), https://www.nytimes.com/interactive/2023/04/01/health/abortion-pill-safety.html.)

[3] (FDA, Full Prescribing Info.: Mifeprex, p. 12, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf [as of Aug. 16, 2023].)

[4] (See Daniel Grossman et al., *Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: a systematic review* (2015) 92 Contraception 206-11 ["According to data obtained from Danco Laboratories, the U.S. manufacturer of mifepristone, less than 0.004% of patients who took mifepristone between 2000 and 2012 ended up deciding to

part of that change of heart, these people likely face emotional turmoil—anxious and unsure about what choices remain open to them. In such a vulnerable state, they need and deserve accurate, scientifically sound information about their options, including the risks involved with those options.

3. Instead of offering vulnerable pregnant people accurate information, Defendants Heartbeat International, Inc. ("HBI") and RealOptions provide them with false and misleading statements. They claim that there is a way to "reverse" the effects of mifepristone, which they call "abortion pill reversal" or "APR." They further claim—falsely—that through APR "thousands of lives" have been "saved."[5] But, there is no evidence showing that mifepristone can be "reversed" or that the APR "protocol" contributes to the continuation of a pregnancy.

4. Defendants know this. Nevertheless, they regularly continue to advertise and promote APR, and they cite flawed and misleading reports to support their claims.

5. Defendants further misrepresent that APR can be safe and effective if initiated after a pregnant person has taken misoprostol (i.e., the second abortion drug in the two-drug abortion regime), or after taking a different medication abortion drug, methotrexate, or when initiated longer than 72 hours after taking the mifepristone dose. There are **no studies** suggesting APR is effective or safe in those situations.

6. Defendants falsely imply to patients that APR is safe, even though the only credible study on APR suggests potentially significant health risks. Defendants fail to disclose these potential risks, which can arise from stopping a medication abortion midway. They also fail to disclose the potential for unknown risks, which, given the absence of long-term data, may not be evident for many years. This information is crucial for pregnant individuals and their families as they decide their next steps in this time-sensitive situation.

7. In essence, Defendants use emotionally vulnerable individuals who come to them in the midst of a gut-wrenching life choice as subjects in experiments to determine whether APR

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continue their pregnancies."].)

[5] (Heartbeat International, *Abortion Pill Rescue Network*, https://www.heartbeatinternational.org/our-work/apr [as of Aug. 21, 2023].)

is safe and effective. Defendants attract these individuals through multiple misrepresentations and pressure them by claiming they must start treatment as quickly as possible, further exploiting these individuals' heightened emotional state.

8. The People of the State of California bring this suit to end this misconduct.

PARTIES

9. Plaintiff is the People of the State of California. The People bring this action by and through Rob Bonta, Attorney General of the State of California ("Attorney General"). The Attorney General is the chief law officer of the State and has authority to file civil actions to protect public rights and interests. (Const., art. V, § 13; Bus. & Prof. Code, § 321.)[6] The Attorney General is authorized by Business and Professions Code sections 17204 and 17535 to obtain injunctive relief to halt violations of, and enforce compliance with, Business and Professions Code section 17200 et seq., and Business and Professions Code section 17500 et seq., respectively. The Attorney General is authorized by Business and Professions Code sections 17206 and 17536 to obtain civil penalties of up to $2,500 for each violation of sections 17200 et seq. and 17500 et seq., respectively. The Attorney General brings this challenge pursuant to his independent constitutional, statutory, and common law authority to represent the public interest.

10. Defendant Heartbeat International, Inc. ("HBI") is a 501(c)(3) charitable organization that operates the "most expansive network" of "pro-life pregnancy resource centers" and has "over 3,000 affiliated pregnancy help locations," including over 2,000 locations throughout the United States.[7] HBI is incorporated and has its principal place of business in Columbus, Ohio. HBI owns and operates the Abortion Pill Rescue Network ("APRN") as well as the Abortion Pill Reversal ("APR") hotline.

11. Defendant RealOptions ("RealOptions") is a 501(c)(3) non-profit organization that is incorporated in California, has a principal place of business in San Jose, and operates five clinics in California. RealOptions operates the clinics under the name "RealOptions Obria

[6] All further statutory references are to California statutes.

[7] (Heartbeat International, *Our Mission & Vision*, https://www.heartbeatinternational.org/about/our-passion [as of Aug. 21, 2023].)

Medical Clinics." Two of RealOptions' clinics are located in San Jose; one clinic is located in Union City; one clinic is located in Oakland; and one clinic is located in Redwood City. RealOptions advertises APR as a service available at all five of its clinics.

12. The true names and capacities of Defendants sued herein as DOES 1 through 100, inclusive, are unknown to the People, who therefore sue said Defendants by such fictitious names. When the true names and capacities of said Defendants have been ascertained, the People will ask leave of the court to amend this Complaint to insert in lieu of such fictitious names the true names and capacities of said fictitiously named Defendants.

13. At all relevant times, Defendants have controlled, directed, formulated, known, and/or approved of, and/or agreed to the various acts and practices of each of the Defendants.

14. Whenever reference is made in this Complaint to any act of any Defendant or Defendants, such allegation means that such Defendant or Defendants did the acts alleged in this Complaint either personally or through the Defendant's officers, directors, employees, agents, and/or representatives acting within the actual or ostensible scope of their authority.

15. Defendants have engaged in a conspiracy, common enterprise, and common course of conduct, the purpose of which is and was to engage in the violations of law alleged in this Complaint. The conspiracy, common enterprise, and common course of conduct continue to the present.

JURISDICTION AND VENUE

16. This Court has jurisdiction over the People's claims pursuant to article VI, section 10 of the California Constitution and Business and Professions Code sections 17204, 17206, 17535, and 17536.

17. This Court has personal jurisdiction over Defendants because each Defendant intentionally avails itself of the California market so as to render the exercise of jurisdiction by California courts consistent with traditional notions of fair play and substantial justice. Defendant RealOptions additionally is incorporated in and has a principal place of business in California and therefore resides in the state. Since 2008, defendant HBI has been registered with the California Secretary of State as doing business in the state. HBI has multiple affiliated clinics in California,

and a number of those affiliates, including RealOptions, offer APR as a medical service. On information and belief, HBI refers pregnant individuals who contact its APR hotline or livechat to its California-based affiliates that offer APR services.

18. The violations of law alleged in this Complaint occurred in the Counties of San Mateo, San Jose, Alameda, and throughout California.

19. Venue is proper in Alameda County pursuant to Code of Civil Procedure section 393, subdivision (a) because Defendant RealOptions operates a medical clinic offering APR within this county, in Oakland, and HBI advertises APR to the public and Abortion Pill Rescue Network Training to potential affiliates within the county. Accordingly, at least some part of the cause of action arose within this county. (See Code Civ. Proc., § 393, subd. (a).)

FACTUAL ALLEGATIONS

I. "ABORTION PILL REVERSAL"

20. Abortion pill reversal ("APR") is an experimental protocol that Defendants claim is "safe" and "effective" for "reversing" a medication abortion when a pregnant person has taken the first drug, mifepristone, but before having taken the second drug, misoprostol, in the standard two-drug medication abortion regime. Mifepristone blocks the effects of progesterone and thereby inhibits the continuation of the pregnancy. Misoprostol, which is taken 24-48 hours after the mifepristone, causes the uterus to contract and expel the remaining pregnancy tissue, completing the abortion.

21. As HBI explains the process, the APR "protocol" directs a patient to take high doses of progesterone within 72 hours of taking mifepristone to try to "reverse" the effects of the mifepristone. Although HBI uses the term "reverse" and "reversal," the theory underlying APR is more akin to a "competition" between progesterone and mifepristone. Even APR's proponents acknowledge that APR cannot truly "reverse" mifepristone, such as by acting as an antidote.

22. As of the date of this filing, not a single credibly designed medical study has verified HBI's claims.

23. According to HBI, the APR "protocol" requires the pregnant person who has taken mifepristone to be administered a high dose of progesterone in one of three ways: orally,

vaginally, or through intramuscular injection. The pregnant person is also advised not to take the second drug in the medication abortion regimen, misoprostol. The "protocol" calls for treatment with progesterone to be tapered after the first three days, and then to continue until the end of the first trimester. Under this "protocol," the dosage and frequency of progesterone differs depending on the route of administration.

24. HBI offers similar "protocols" of high-dose progesterone administration for pregnant individuals who have taken both drugs in the standard medication abortion regime (mifepristone and misoprostol). As of the date of this filing, no medical study has verified this protocol.

25. HBI also offers similar "protocols" of high-dose progesterone administration for those pregnant individuals who have taken methotrexate, a separate drug that can be used to induce an abortion. Unlike mifepristone, however, methotrexate inhibits folic acid rather than progesterone. For the "attempted reversal of methotrexate" "protocol," HBI advises providers to also administer leucovorin and folic acid to counteract the effects of the methotrexate—another "protocol" which has never been studied.

II. 2012 CASE SERIES AND 2018 REPORT

26. The original APR "protocol" for pregnant people who have completed only the first step in a medication abortion (i.e., taken only mifepristone) was conceptualized by two providers, Dr. George Delgado and Dr. Matthew Harrison. Harrison purportedly first used progesterone in 2006 on a pregnant patient who had taken mifepristone but did not want to continue with a medication abortion. In 2008, Delgado, a California-based family physician and HBI's medical advisor, devised the APR "protocol" described above.

27. To support the APR "protocol," in 2012, Delgado and Dr. Mary Davenport, a California-licensed physician and the current medical director of RealOptions' Redwood City and Oakland locations, published a case series review ("2012 Case Series").[8] In the 2012 Case Series, they described the administration of progesterone to seven pregnant women who had taken

[8] (George Delgado & Mary Davenport, *Progesterone Use to Reverse the Effects of Mifepristone* (2012) 46 Pharmacotherapy 1723.)

mifepristone, six of whom were included in the case series' analysis and four of whom carried their pregnancies to full-term, reportedly with no birth defects. The progesterone route of administration and dosage varied among the women included in the case series, and there was no control group.

28. Despite the small sample size, the presence of confounding variables, and the lack of control group, Delgado nevertheless concluded that "[t]he experience of these patients suggests that medical abortion can be arrested by progesterone injection after mifepristone ingestion prior to misoprostol" and that further research was necessary only "to have an evidence basis for the best protocol."[9] The 2012 Case Series, however, was insufficient evidence for these conclusions.

29. In May 2012, Delgado created the Abortion Pill Reversal Network, consisting of an APR website (www.abortionpillreversal.com) and a telephone hotline (1-800-712-HELP), through which he promoted APR and sought to connect pregnant people who have initiated a medication abortion with providers willing to administer the APR protocol. He collected data on individuals who contacted the hotline, especially those individuals who opted to pursue APR.

30. Using this hotline patient data, in 2018, Delgado, Davenport, and others wrote an article ("2018 Report"), labeling it "an observational case series of 754 patients."[10] According to the 2018 Report, 1,668 calls were received by the hotline from June 24, 2012 to June 21, 2016. Of these 1,668 callers, 754 pregnant individuals initiated the experimental progesterone treatment. The 2018 Report claimed to have tracked the pregnancy outcomes to ultimately conclude, "[t]he reversal effects of Mifepristone using progesterone is safe and effective."[11]

31. As an AMA Journal of Ethics article explained, case series like the 2012 Case Series and the 2018 Report (which claimed to be a case series), "describe characteristics of patients with certain diseases and may help identify questions for future research" but "are ranked lower than other [study] designs because of associated bias, lack of random sampling, the absence

[9] (*Ibid.*)

[10] (George Delgado et al., *A case series detailing the successful reversal of the effects of mifepristone using progesterone* (2018) 33 Issues L. Med. 21-31.)

[11] (*Ibid.*)

of controls or a comparison group, and heterogeneity of subjects."[12] Because case series provide only weak scientific evidence, they are not commonly used to make changes in how medications are used. Instead, they are used to inform further studies with more rigorous methodologies.

32. As Delgado and Davenport have acknowledged, the 2018 Report has serious design flaws that undermine classifying it even as a "case series," further underscoring that the report is not credible scientific evidence to support a conclusion that APR is either safe or effective as a treatment for the continuation of a pregnancy after administration of mifepristone. These design flaws include, but are not limited to, the following:

a. The 2018 Report did not report outcomes on all participants. This is a key failing. The Report purported to observe "754 patients," but only included 547 patients in the analysis. The Report explains that three groups were excluded: (1) those who had taken misoprostol prior to taking progesterone or who had taken mifepristone more than 72 hours prior to initiating progesterone; (2) those with whom Delgado lost contact; and (3) those who ultimately chose to complete the medication abortion or opt for surgical abortion. The Report did not observe or study the outcomes of these excluded groups (i.e. 207 patients). That constitutes nearly *a third* of the total pregnant people observed.

b. The Report used flawed data. To show that APR was effective, the Report needed to show a more successful embryo survival rate with the use of progesterone than without the use of progesterone. But, the Report used flawed data that made the rate of embryo survival without progesterone look artificially low, which in turn made the embryo survival rate with progesterone look misleadingly high.

[12] (Opeyemi Daramola & John Rhee, *Rating Evidence in Medical Literature* (Jan. 2011) AMA J. Ethics, https://journalofethics.ama-assn.org/article/rating-evidence-medical-literature/2011-01.)

c. The Report says nothing about whether APR had negative health effects on the pregnant person. Nothing in the Report suggests that Delgado tracked patients to see if they had such adverse effects. Without that tracking, the Report says nothing about—and therefore cannot be used to tout—the safety of the APR "protocol."

d. The Report has misleading results. The Report differentiated the APR "success rates" based on the dosage of progesterone and how the drug was administered. The "success rates" range from an overall rate of 48% to 68% for oral progesterone to 64% for progesterone injections.[13] None of those rates account for different gestational ages of the pregnancies (i.e., pregnancy length determined by the number of weeks following the pregnant person's last menstrual period).[14] Mifepristone becomes less effective the longer an individual is pregnant, meaning that for further-along pregnancies, progesterone may not have made a difference to the embryo surviving. In short, it is misleading to lump into one "success rate" pregnancies that were at different stages.

33. Due to its flaws and weaknesses, the 2018 Report does not establish causation between the APR protocol and the continuation of pregnancies for the women tracked in the Report. In other words, the study does not show whether their pregnancies were just as likely to have continued without the APR protocol as with it.

34. In addition, Delgado and Davenport appear not to have timely secured the necessary institutional oversight to conduct their research on human subjects. Delgado and Davenport appear to have obtained institutional review board ("IRB") approval only *after* they

[13] The 68% statistic is from the highest dosage of oral progesterone, which only 31 individuals received out of the total 119 who received oral progesterone. The 64% statistic is from progesterone injections and was calculated by combining all individuals who received intramuscular injections into one category, regardless of the dosage received.

[14] The 2018 Report did track embryo survival rates by gestational age, but it did not factor gestational age into the survival rates attributed to each method of administering progesterone.

conducted their research, meaning there was no institutional oversight during the course of their experiment.[15] Such oversight is important to secure *before* beginning medical experiments on human subjects because an IRB helps ensure ethical treatment of and reduction of risks to those human subjects.[16]

35. The 2018 Report failed to adequately disclose Delgado's potential conflicts of interest. The sources of the data in the 2018 Report were patient contacts to Delgado's Abortion Pill Reversal Network hotline and live chat, but the 2018 Report does not disclose that fact. Instead, it states only that "[s]ubjects called an informational hotline linked to an informational website and staffed by nurses and a physician assistant," with no disclosure of Delgado's connection.[17]

36. Delgado and Davenport knew about the flaws and weaknesses in the 2018 Report. Even after Davenport and Delgado had collected the data from incoming calls to Delgado's hotline, Davenport acknowledged that a rat study provided stronger evidence than the hotline data. That Davenport made this assessment after completing the data collection demonstrates that even the Report's authors understood that their data was not sufficient to make the claims in the Report.

37. As a reflection of these flaws, three journals—the Annals of Emergency Medicine, the Journal of the American Board of Family Medicine, and the Annals of Pharmacotherapy—rejected the 2018 Report for publication. The medical journal that ultimately published the 2018 Report—Issues in Law & Medicine—is a publication sponsored by two anti-abortion organizations and, as Delgado has admitted, is "not particularly well-known in the medical field."

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[15] (Daniel Grossman & Kari White, *Abortion "Reversal" — Legislating without Evidence* (Oct. 18, 2018) 379 N. Eng. J. Med. 1491-93.)

[16] (See Off. for Human Res. Protections, U.S. Dept. of Health & Human Servs. (June 28, 2021) Human Research Protection Training, Lesson 3: What Are IRBs?, https://www.hhs.gov/ohrp/education-and-outreach/online-education/human-research-protection-training/lesson-3-what-are-irbs/index.html#:~:text=Membership%20%3E%20Quiz%20Questions-,Purpose%20of%20IRBs,and%20adequately%20protect%20research%20participants.)

[17] (George Delgado et al., *A case series detailing the successful reversal of the effects of mifepristone using progesterone* (2018) 33 Issues L. Med. 21-31.)

(*Planned Parenthood of Tenn. & N. Mississ. v. Slatery* (M.D. Tenn. 2021) 523 F.Supp.3d 985, 994.)

38. Despite these acknowledged flaws and its failure to establish causation between the APR protocol and pregnancy continuation, the 2018 Report is the seminal "study" cited in support of the safety and efficacy of APR by Defendants HBI and RealOptions.

39. Given its substantial deficiencies, the 2018 Report cannot be considered a study by any stretch. It is certainly not a rigorous scientific study of the effectiveness and safety of APR. As described more fully below, the only rigorous study on APR suggested potentially significant health risks arising from stopping a medication abortion after taking mifepristone, an essential step in the APR "protocol."

III. SAFETY CONCERNS, CONTRARY EVIDENCE, AND CRITICISMS OF ABORTION PILL REVERSAL PROTOCOL

40. Further underscoring the lack of credibility of Delgado and Davenport's 2012 Case Series and 2018 Report are multiple articles using rigorous scientific methodology, which call into question the conclusions that the 2012 Case Series and 2018 Report reached about the safety and effectiveness of APR.

41. For example, a 2015 systematic literature review ("2015 Literature Review") published in *Contraception*, a peer-reviewed medical journal, found that there was a lack of evidence that pregnancy continuation after administration of mifepristone was more likely after treatment with progesterone as compared with expectant management (i.e., not administering misoprostol and monitoring the pregnancy). The 2015 Literature Review further found that in published studies the percentage of pregnancies that continued after only mifepristone administration (but no progesterone) ranged from 8-46%.[18] This review, authored by experts in obstetrics, gynecology, and public health at the University of California, San Francisco, University of Alabama at Birmingham, University of Michigan, Johns Hopkins, Stanford University, and the University of North Carolina, concluded that "[i]n the rare case that a woman

[18] (Daniel Grossman et al., *Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: a systematic review* (2015) 92 Contraception 206-11.)

changes her mind after starting medical abortion, evidence is insufficient to determine whether treatment with progesterone after mifepristone results in a higher proportion of continuing pregnancies compared to expectant treatment [i.e., waiting for spontaneous miscarriage]."

42. The 2015 Literature Review also included analysis of the 2012 Case Series, finding that the 2012 Case Series "was of poor quality and lacked clear information on patient selection."[19]

43. A 2018 article published in the New England Journal of Medicine analyzed the 2018 Report in detail in the context of commenting on state laws requiring physicians to discuss APR with patients. That article described APR as an "unmonitored research experiment" and observed: "It is difficult to compare the results from [the 2018 Report] with data on mifepristone alone for several reasons," including the exclusions of patients by some of the providers because the embryo had died following the pregnant patient taking mifepristone and exclusions of patients who were lost to follow up before 20 weeks, both of which "probably exaggerated the treatment's reported success."[20]

44. A 2019 comment published in *Contraception*, a peer-reviewed medical journal, by Dr. Mitchell Creinin, identified numerous flaws in the 2018 Report: "lack of control groups, no confirmation of mifepristone ingestion, failure to establish viability prior to progesterone treatment, and providing experimental treatment without patient consent or institutional review board oversight."[21]

45. In light of the lack of credible evidence on its safety and effectiveness, medical associations have highlighted concerns about APR:

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[19] (*Ibid*.)

[20] (Daniel Grossman & Kari White, *Abortion "Reversal" — Legislating without Evidence* (Oct. 18, 2018) 379 N. Eng. J. Med. 1491-93.)

[21] (Mitchell D. Creinin & Melissa J. Chen, *Mifepristone antagonization requires real studies to evaluate safety and efficacy* (Nov. 14, 2019) 100 Contraception 427-29, https://www.contraceptionjournal.org/article/S0010-7824(19)30450-0/fulltext.)

a. The American College of Obstetricians and Gynecologists ("ACOG") stated: "Claims regarding abortion 'reversal' treatment are not based on science and do not meet clinical standards. The American College of Obstetricians and Gynecologists (ACOG) ranks its recommendations on the strength of the evidence, and does not support prescribing progesterone to stop a medical abortion."[22]

b. In a challenge to North Dakota's law requiring physicians to tell patients that medication abortion may be "reversible," the American Medical Association ("AMA") stated that "[t]he Compelled Reversal Mandate forces physicians to tell their patients that medication abortions may be reversible, a claim wholly unsupported by the best, most reliable scientific evidence, contravening their ethical and legal obligations as medical providers."[23]

c. The Society of Obstetricians and Gynaecologists of Canada has stated that it "does not support prescribing progesterone to stop a medical abortion" and that "[t]he claims regarding so-called abortion 'reversal' treatments are not based on scientific evidence."[24]

d. The Royal College of Obstetricians and Gynaecologists, the Faculty of Sexual and Reproductive Healthcare, the Royal College of Midwives, and the British Society of Abortion Care Providers have stated that "[t]here are **no reputable national or international clinical guidelines that**

[22] (ACOG, Facts are Important: Medication Abortion "Reversal" Is Not Supported by Science, https://www.acog.org/advocacy/facts-are-important/medication-abortion-reversal-is-not-supported-by-science [as of Jan. 31, 2022, 2:29 PM].)

[23] (*Am. Med. Ass'n v. Stenehjem* (June 25, 2019, No. 1:19-cv-125) [412 F. Supp. 3d 1134] [complaint at 2], https://www.ama-assn.org/system/files/2019-06/ND-mife-reversal-complaint.pdf.)

[24] (Soc. Obstetricians and Gynaecologists of Canada, SOGC Statement on Abortion Medication "Reversal" (Mar. 19, 2021), https://sogc.org/en/content/featured-news/SOGC_Statement_on_Abortion_Medication_Reversal.aspx.)

> **recommend the use of progesterone to reverse the effect of mifepristone**, and no evidence that it increases the likelihood of continuing pregnancy, compared to expectant management alone."[25]

46. The first (and only) randomized clinical study to attempt to test the safety and efficacy of APR was initiated at the University of California, Davis in 2019 but had to be halted due to serious "safety concerns" after 3 of the 12 enrolled study participants "experienced severe bleeding, requiring ambulance transport to an emergency department."[26] Because the study was cut short, the researchers were unable to "quantify the full extent of the hemorrhage risk."[27] The lead researcher, however, has cautioned that "[w]omen who use mifepristone for a medical abortion should be advised that not following up with misoprostol could result in severe hemorrhage, even with progesterone treatment."[28]

47. In addition to the medical community's criticisms, three federal district courts, having evaluated expert evidence from APR proponents and critics, have found that the 2018 Report does not establish causation between the APR protocol and pregnancy continuation. (*See All-Options, Inc. v. Atty. Gen. of Ind.* (D. Ind. 2021) 546 F.Supp.3d 754, 766; *Planned Parenthood of Tenn. & N. Mississ.*, 523 F.Supp.3d at 1003-04; *Am. Med. Ass'n v. Stenehjem* (D.N.D. 2019) 412 F.Supp.3d 1134, 1150.)

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[25] (Royal College of Obstetricians & Gynaecologists, et al., Joint Statement on "Abortion Reversal" (July 7, 2022), https://www.rcog.org.uk/media/nbahkgvo/rcog-fsrh-abortion-reversal-position-statement.pdf.)

[26] (UC Davis Health, Can the abortion pill be reversed? A novel search for answers (Dec. 4, 2019), https://providervideos.ucdavis.edu/news/can-the-abortion-pill-be-reversed-a-novel-search-for-answers; see also Jessica Washington, *Study of "Abortion Reversal" Pill Halted Because It's Too Dangerous*, Mother Jones (Dec. 6, 2019), https://www.motherjones.com/politics/2019/12/study-of-abortion-reversal-pill-halted-because-its-too-dangerous/; Kayla Epstein, *Some lawmakers push 'abortion reversal' treatments. A study shows how dangerous they are*, Wash. Post (Dec. 24, 2019), https://www.washingtonpost.com/health/2019/12/24/some-lawmakers-push-abortion-reversal-treatments-new-study-shows-how-dangerous-they-are/.)

[27] (UC Davis Health, Can the abortion pill be reversed? A novel search for answers (Dec. 4, 2019), https://providervideos.ucdavis.edu/news/can-the-abortion-pill-be-reversed-a-novel-search-for-answers.)

[28] (*Ibid.*)

48. The 2012 Case Series' and 2018 Report's failure to establish the efficacy of APR is even more problematic in light of the potential—albeit small—risks from the administration of supplemental progesterone. As an expert in *American Medical Association v. Stenehjem* explained, supplemental progesterone is associated with maternal depression, cholestatic jaundice, and hypertension. That expert also noted that certain studies have raised concerns (though not conclusively) about possible associations between certain progesterone preparations and second trimester miscarriages and stillbirths. With no credible evidence showing that APR is effective, the treatment essentially exposes pregnant individuals to the risks of supplemental progesterone without any benefits.

IV. HBI'S MISLEADING REPRESENTATIONS

49. In April 2018, HBI acquired Delgado's Abortion Pill Reversal Network, including the www.abortionpillreversal.com website and the APR hotline. Since then, HBI has operated both as part of its Abortion Pill Rescue Network ("APRN"). Delgado currently is a member of HBI's medical advisory team.

50. HBI continues to operate the website and the hotline and to advertise and promote APR, despite long having knowledge of the unreliable scientific evidence supporting Delgado's "protocol." In its April 2018 press release announcing its acquisition of the Abortion Pill Reversal Network, HBI acknowledged the existence of (and voiced its opposition to) criticisms of APR as being unproven and not backed by credible science. And, in August 2019, HBI intervened in a federal lawsuit challenging a law mandating that abortion providers make disclosures about APR, where it received notice of the September 2019 preliminary injunction order outlining the flaws in the 2018 Report.

51. HBI also has knowledge of the more recent studies and statements about the unreliability and potential risks of stopping a medication abortion halfway, an essential step in APR. In September 2021, HBI issued a press release about a Center for Countering Digital Hate report that included excerpts from the American College of Obstetricians and Gynecologist's statement about APR; information about the 2018 New England Journal of Medicine article criticizing the 2018 Report; and information about the 2019 U.C. Davis study that was halted.

Also, in September 2021, APRN's medical director, Brent Boles, posted an entry on the HBI website about Google's restrictions of advertisements about APR because the claims were "unreliable." In short, for years now, HBI has been fully aware of APR's lack of credible scientific support as well as its risks.

A. Website Representations

52. In addition to www.abortionpillreversal.com ("APR Website"), HBI also operates the website www.heartbeatinternational.org/our-work/apr ("HBI Webpage"). On both websites, HBI uses misleading statements as it seeks to persuade pregnant people who have started the medication abortion process to undergo APR.

Abortionpillreversal.com

53. The purpose of the APR Website is to advertise APR to pregnant people, stating: "Have you taken the first dose of the abortion pill? Do you regret your decision and wish you could reverse the effects of the abortion pill? ***We're here for you!***" (emphasis in original). HBI encourages potential patients to call its hotline and/or message through its live chat and explains that its hotline and live chat will connect potential patients with medical professionals who will "guide [the patient] towards reversing the effects of the abortion pill."

54. Throughout its website, HBI misleadingly uses the terms "reverse" and "reversal." The use of these terms is false and misleading because there is no credible scientific evidence showing that APR "reverses" medication abortions. The terms are also false and misleading because "reverse" and "reversal" do not accurately convey even the theory underlying APR.

55. Amidst its advertisements and attempts to persuade potential patients to undergo APR, HBI makes additional misleading statements. For example, on multiple pages, HBI states that APR is an "effective process" because "APR has been shown to increase the chances of allowing the pregnancy to continue." HBI touts on multiple webpages that "initial studies have shown" that the success rate for APR is 64-68%. In its drop-down Frequently Asked Questions page ("FAQs"), HBI also touts that "initial studies have found that the birth defect rate in babies born after the APR is less or equal to the rate in the general population."

56. These statements are misleading because, as described above, there is no credible support for them.

57. HBI also misleadingly presents information about the risks from APR. HBI does not provide an FAQ about the possible side effects from APR, such as the risk of severe bleeding. Instead, HBI provides a response to a question about the "possible side effects of progesterone" and lists only mild effects, such as "sleepiness, lack of energy, lightheadedness, dizziness, gastrointestinal discomfort and headaches." The only location where HBI provides any warning about the potential risks of severe bleeding from stopping a medication abortion halfway—an essential step in APR—is in response to two FAQs about "cramping and spotting."

58. This information is presented misleadingly because it does not adequately warn individuals of the risks from APR.

59. As detailed above, HBI has known or should have known that these statements and presentation of information were misleading.

60. HBI further advertises that potential patients should contact the hotline or live chat even if more than 72 hours have passed since they took mifepristone, stating "We are here to help. It may not be too late." This statement is likely to create the impression among potential patients that APR is effective and safe beyond the 72-hour window.

61. This statement is misleading because there is no evidence to support it. To the extent HBI relies on the 2012 Case Series and the 2018 Report, those publications looked only at the use of progesterone within a 72-hour window following administration of mifepristone, specifically excluding pregnant individuals who had taken progesterone more than 72 hours after taking mifepristone.

Heartbeatinternational.org/our-work/apr

62. HBI also advertises APR on the Abortion Pill Rescue Network page on HBI's www.heartbeatinternational.org website ("HBI Webpage"). HBI encourages viewers to call its hotline and visit www.abortionpillreversal.com to obtain more information about APR. HBI further touts "women can reach out to the Abortion Pill Rescue Network and be connected with a local medical provider who starts" APR.

63. Throughout its website, HBI misleadingly uses the terms "reverse" and "reversal." The use of these terms is false and misleading because there is no credible scientific evidence showing that APR "reverses" medication abortions. The terms are also false and misleading because "reverse" and "reversal" do not accurately convey even the theory underlying APR.

64. HBI includes additional misleading statements within these advertisements. For example, similar to its misleading statements on its APR Website, HBI touts that a "2018 peer-reviewed study showed positive results" and then repeats the 64-68% success rate statistic and that there was "no increase in birth defects." HBI also claims that the referenced study showed "lower preterm delivery rate than the general population."

65. Once again, HBI's statements are misleading because there is no evidence to support them.

66. As detailed above, HBI has known or should have known that there was no credible support for its statements and that the statements were therefore misleading.

67. HBI makes an additional misrepresentation that "thousands of lives have been saved" through the use of APR. This statement is based primarily on two numbers. First, HBI includes the number of pregnant people who undertook APR and that HBI can confirm remained pregnant at 13 weeks. For those individuals that started APR but HBI cannot confirm remained pregnant at 13 weeks, HBI multiplies the number of those individuals by a 64% success rate, which it obtained from the 2018 Report, and which, as detailed above, is not a reliable statistic.[29] In other words, HBI's statement is speculation, not evidence. As a result, HBI's statements are misleading.

B. Hotline and Live Chat

68. HBI has a "policies and procedures manual" that it provides to volunteers and employees that staff its APR hotline and live chat, through which HBI also advertises APR. The manual includes outlines of information that hotline staff must provide to people who have called,

[29] The 64% statistic is unreliable for the additional fact that it relies on providers using oral or intramuscular administration of progesterone. Many providers appear to use vaginal administration, which even the 2018 Report shows has a lower chance of a pregnancy continuing.

such as explanations of APR and potential side effects, information about misoprostol, the risk of birth defects, and APR success rates.

69. In this manual, HBI instructs APR hotline staff to make several misleading statements when talking with hotline callers. For example, HBI instructs hotline staff to use the term "reverse" or "reversal" to describe APR. HBI further instructs hotline staff to state that "[i]nitial studies have shown that APR may have a 64-68% success rate." HBI also instructs hotline staff to state that "APR has been shown to increase the chances of allowing the pregnancy to continue." HBI further instructs hotline staff to state that "[i]nitial studies have found that the birth defect rate in babies born after the APR is less than or equal to the rate in the general population." As explained above, however, there is no credible support for any of these statements, and as a result, these statements are misleading.

70. HBI also instructs its hotline staff to recommend APR for callers who have already taken both mifepristone and misoprostol or who have taken methotrexate. HBI includes this instruction even though no study has even considered the use of APR for pregnant individuals who had already taken misoprostol or methotrexate. As a result, these statements advertising the use of APR for pregnant people who have taken methotrexate or misoprostol are misleading.

C. Training Kits

71. HBI sells to its affiliates an "APR Healthcare Professional Kit" that will allow those affiliates to advertise and administer APR. The kit consists of an overview of the APR procedure; the progesterone protocols used in APR; frequently asked questions and answers about APR for healthcare professionals and patients; and form templates, including consent forms and outcome report forms. HBI includes several misleading representations within this kit that it encourages its affiliates to use in their advertisements about and administration of APR.

Protocols

72. HBI provides a "protocol" to attempt reversing a methotrexate medication abortion. In that "protocol," HBI represents that "for women who have taken methotrexate, prescribed progesterone may also be beneficial to support the pregnancy even though it is not an antidote to methotrexate." HBI includes this statement and encourages its affiliates to advertise

and administer APR in these circumstances even though no evidence supports the use of APR for pregnant individuals who have taken methotrexate. HBI includes this protocol even as it acknowledges that the APR "is designed to serve women who have taken mifepristone (Mifeprex)," which shows that HBI knows that APR was not developed for pregnant people who have taken methotrexate.

73. HBI also provides a "protocol" to attempt reversing a medication abortion after a pregnant person has taken both mifepristone and misoprostol. In that protocol, HBI states that "progesterone may be beneficial to support the pregnancy even though it is not an antidote to misoprostol." HBI includes this statement and encourages its affiliates to advertise and administer APR in these circumstances even though no evidence supports the use of APR for pregnant individuals who have taken misoprostol. HBI includes this protocol even as it acknowledges that APR "is designed to serve women who have taken mifepristone (Mifeprex)," which shows that HBI knows that APR was not contemplated for pregnant people who have taken misoprostol.

Patient FAQs

74. In the kit, HBI also provides "APR Patient FAQs," with answers from Delgado, which are nearly identical to the "Reversal FAQs" appearing on HBI's website. Like the "Reversal FAQs" on HBI's website, the "APR Patient FAQs" include several misleading statements.

75. Similar to the APR Webpage, the APR Patient FAQs use the term "reverse" and "reversal" to describe APR. The APR Patient FAQs also state that "[i]nitial studies of APR have shown that APR has a 64-68% success rate" and that "APR has been shown to increase the chances of allowing the pregnancy to continue." The APR Patient FAQs also represent that "[i]nitial studies have found that the birth defect rate in babies born after the APR is less than or equal to the rate in the general population." As explained above, these statements are misleading because there is no credible evidence to support them.

76. Like the APR Website, the APR Patient FAQs state in response to the question "[i]s it too late to reverse the abortion pill," that "[t]here have been many successful reversals

when treatment was started within 72 hours of taking the first abortion pill. **Even if 72 hours have passed, it may not be too late.**" (emphasis added). This statement implies that APR is effective and safe after a 72-hour window following mifepristone administration. This statement is misleading because no evidence supports the use of APR for pregnant individuals after 72 hours have passed.

77. Like the APR Website, the APR Patient FAQs misleadingly present the risks associated with APR. These FAQs do not provide an FAQ about the side effects of APR, instead only providing the potential (minor) side effects from progesterone. The FAQs misleadingly present the risk of severe bleeding only under a question about cramping and spotting.

"Informed" Consent Templates

78. As part of its training kit, HBI provides template forms for use in securing consent from patients. HBI also provides consent forms based on these templates to pregnant individuals who contact HBI and decide to pursue APR. These consent forms include several misleading statements.

79. For example, the "Consent for Patients who took Mifepristone Only" form uses the misleading terms "reverse" and "reversal" and includes the misleading statements that "[i]nitial studies have found that the birth defect rate in babies born after the APR is less than or equal to the rate in the general population"; that "[i]nitial studies of APR have shown that APR has a 64-68% success rate"; and that "APR has been shown to increase the chances of allowing the pregnancy to continue." These statements are misleading because there is no credible evidence supporting any of these statements.

80. The "Consent for Patients who took both Mifepristone and Misoprostol" form uses the misleading terms "reverse" and "reversal" and includes the misleading statement that "**for women who have taken the first and second drugs of the medical abortion regimen, mifepristone on day one and misoprostol (Cytotec) 12-48 hours later, progesterone may be beneficial to support the pregnancy even though it is not an antidote to misoprostol.**" (emphasis in original). These statements are misleading because no evidence supports the use of APR for pregnant individuals who have already taken misoprostol.

81. The "Consent for Patients who took Methotrexate" form uses the misleading terms "reverse" and "reversal" and includes the misleading statement that "**for women who have taken methotrexate, prescribing progesterone may also be beneficial to support the pregnancy even though it is not an antidote to methotrexate.**" (emphasis in original). These statements are misleading because no evidence supports the use of APR for pregnant individuals who have taken methotrexate.

D. Media Appearances

82. HBI executives have made multiple media appearances within the course of their employment in which the executives advertised and made misleading statements about APR.

83. For example, on or around May 28, 2020, during the course of their employment, HBI's Director of Medical Impact, Christa Brown, and HBI's Director of Communications and Marketing, Andrea Trudee, appeared on an episode of the Ohio Right to Life: The Push for the Abortion Pill. During their appearance, Brown and Trudee regularly used the terms "reverse" and "reversal" and touted APR and encouraged pregnant people to visit the APR Website to "connect" them to providers. Brown stated that APR is a "cutting edge application of a time-tested FDA-approved treatment that's been used for decades to help women who are at risk for preterm delivery or miscarriage." HBI's statement—made through Brown in the course of her employment—misleadingly implies that APR is an FDA-approved treatment, which it is not, and which Brown knew it was not.

84. For her part, Truddee stated that APR has resulted in over 1,000 lives "saved." As explained above, however, representations about the number of lives "saved" are inherently misleading given the method HBI uses to reach that number. In short, HBI's statements are based on speculation, not evidence. As a result, HBI's statements—made through Trudee in the course of her employment—are misleading.

85. In another example, on or around September 21, 2021, during the course of his employment, HBI President Jor-El Godsey appeared on an episode of the Help Her Be Brave podcast. Multiple times during his appearance, Godsey advertised APR by encouraging listeners to visit the APR Website and to call HBI's hotline to speak with "a number of nurses" and

"hopefully connect [the pregnant person] to a local pregnancy center." As he was advertising APR, Godsey repeatedly used the terms "reverse" and "reversal," and cited the 2018 Report and repeated the claim that APR has a 64-68% success rate, going so far as to say "so almost 70, 7 out of 10 women that seek [APR] and get that progesterone in a timely fashion are able to reverse the effects of the abortion pill." As explained above, however, these statements are misleading because there is no credible evidence to support these statements.

86. Godsey also made the misleading statement that "over 2,000 babies [] have been saved" via APR. As explained above, however, representations about the number of lives "saved" are based on speculation, not evidence. As a result, HBI's statements—made through Godsey in the course of his employment—are misleading.

V. REALOPTIONS' MISLEADING REPRESENTATIONS

87. RealOptions advertises and administers APR. RealOptions uses HBI-created materials for its APR advertisements.

88. Whereas HBI engages in widespread promotion of APR and equips its affiliates and providers with training and materials to administer it, RealOptions is an on-the-ground provider. Through its five clinics, RealOptions is advertising that it will provide APR to pregnant people.

89. In the course of those advertisements and during its administration of APR, RealOptions has made and continues to make misleading statements.

A. Website Representations

90. RealOptions operates the website www.realoptions.net, on which it advertises APR. Through its website, RealOptions seeks to persuade pregnant people who have started the medication abortion process to undergo APR, and in so doing, it makes multiple misleading statements.

91. Like HBI does on its websites, RealOptions advertises on its website that APR can "reverse" a medication abortion, that "[i]nitial studies of APR have shown it has a 64-68% success rate," and that "APR has been shown to increase the chances of allowing the pregnancy to

continue." As explained above, however, these statements are misleading because no credible evidence supports these statements.

92. RealOptions similarly implies that APR is effective for continuing a pregnancy after a 72-hour window following mifepristone administration. In response to two different FAQs about timing for APR, RealOptions states that potential patients should nevertheless call because "[i]t may not be too late," misleadingly implying that APR is effective past the 72-hour period. This statement is misleading because there is no evidence supporting this statement.

93. RealOptions licenses all five of its clinics with the California Department of Health. Dr. Mary Davenport, who is the medical director for two of RealOptions' clinics, was Delgado's co-author for both the 2012 Case Series and the 2018 Report. Davenport acknowledged that the data collected for the 2018 Report was insufficient for its ultimate conclusions.

B. Consent Forms

94. In its form to obtain consent for what it calls "pregnancy sustaining progesterone therapy," RealOptions misleadingly omits that APR patients may experience severe bleeding as a result of undergoing the process, even though the 2019 U.C. Davis study found that there was a risk of that outcome. RealOptions instead states that patients may experience "side effects such as pain or swelling at the injection site, an increase in pregnancy/hormone symptoms (breast tenderness, nausea, and/or increased body or facial hair), weight loss, weight gain, acne, loss of scalp hair, drowsiness and/or dizziness." The failure to include the possibility of severe bleeding makes this statement materially misleading, in that patients are likely to believe that the side effects from APR are minor, when in fact they could be life threatening.

95. In a June 2020 podcast, Davenport and Delgado spoke about APR, including discussing the 2019 U.C. Davis study, thereby demonstrating Davenport's knowledge of that study and the potentially life-threatening severe bleeding that resulted.[30] Given her role as a RealOptions' medical director, it is appropriate to impute her knowledge to RealOptions.

[30] (Mises Inst., *Mary Davenport and George Delgado on Reversing Medical Abortion* (June 18, 2020), https://mises.org/library/mary-davenport-and-george-delgado-reversing-medical-abortion.)

CAUSES OF ACTION

FIRST CAUSE OF ACTION

(False or Misleading Statements)

(Bus. & Prof. Code, § 17500 et seq.)

96. The People reallege all paragraphs set forth above and incorporate them by reference as though they were fully set forth in this cause of action.

97. From a date unknown to the People and continuing to the present, Defendants have engaged in and continue to engage in, aided and abetted and continue to aid and abet, and conspired to and continue to conspire to engage in acts or practices that constitute violations of Business and Professions Code section 17500 et seq., by making or causing to be made untrue or misleading statements with the intent to induce members of the public to undergo APR. Defendants' untrue and misleading representations include, but are not limited to, the following:

a. that APR can "reverse" a medication abortion, as well as an "effective" process that "has been shown to increase the chances of allowing the pregnancy to continue," and that APR has a 64-68% success rate, even though no credible scientific evidence supports these claims;

b. that APR may be effective after a 72-hour window following administration of mifepristone by encouraging pregnant people to contact them "even if more than 72 hours have passed," even though no credible scientific evidence supports this claim;

c. that the rate of birth defects following APR "is less or equal to the rate in the general population," even though no credible scientific evidence supports these claims;

d. that "thousands of lives" have been saved via APR, even though no credible evidence supports this claim;

e. that APR may be effective following administration of misoprostol and methotrexate, even though no credible scientific evidence supports this claim; and

f. that APR can cause only non-life-threatening side effects, when in fact APR can cause severe, life-threatening bleeding.

98. Defendants knew or should have known that these statements were misleading.

SECOND CAUSE OF ACTION

(Unlawful, Unfair, and Fraudulent Business Practices)

(Bus. & Prof. Code, § 17200 et seq.)

99. The People reallege all paragraphs set forth above and incorporate them by reference as though they were fully set forth in this cause of action.

100. From a date unknown to the People and continuing to the present, Defendants have engaged in and continue to engage in, aided and abetted and continue to aid and abet, and conspired to and continue to conspire to engage in unlawful, unfair, and/or fraudulent acts or practices, which constitute unfair competition within the meaning of section 17200 of the Business and Professions Code. Defendants' acts or practices include, but are not limited to, the following:

a. Violating Business and Professions Code section 17500 et seq., as alleged in the First Cause of Action;

b. Fraudulently representing the following:

i. Via HBI and RealOptions, that APR can "reverse" medication abortions, is an "effective" process that "has been shown to increase the chances of allowing the pregnancy to continue," and that APR has a 64-68% success rate, even though no credible scientific evidence supports these claims;

ii. Via HBI and RealOptions, that APR may be effective after a 72-hour window following administration of mifepristone by encouraging pregnant people to contact them "even if more than 72 hours have passed," even though no credible scientific evidence supports this claim;

iii. Via HBI, that the rate of birth defects following APR "is less or

equal to the rate in the general population," even though no credible scientific evidence supports this claim;

iv. Via HBI, that "thousands of lives" have been saved via APR, even though no credible evidence supports that statement;

v. Via HBI, that APR may be effective following administration of misoprostol or methotrexate, even though no evidence supports this claim; and

vi. Via RealOptions, that APR can cause only non-life-threatening side effects and omitting that APR can cause severe, life-threatening bleeding.

101. Each and every separate act, including, but not limited to: each call to the APR hotline and each chat initiated on the live chat, each training kit sold to affiliates, and each consent form provided to pregnant individuals, constitutes an unlawful, unfair, and/or fraudulent business practice. Each time that the Defendants engaged in each separate unlawful, unfair, and/or fraudulent act, omission, or practice is a separate and distinct violation of Business and Professions Code section 17200.

PRAYER FOR RELIEF

WHEREFORE, the People respectfully request that the Court enter judgment in favor of the People and against Defendants, jointly and severally, as follows:

1. That Defendants, their successors, agents, representatives, employees, assigns, and all persons who act in concert with Defendants be permanently or preliminarily enjoined from making any untrue or misleading statements in violation of Business and Professions Code section 17500, including, but not limited to, the untrue or misleading statements alleged in this Complaint, under the authority of Business and Professions Code section 17535;

2. That Defendants, their successors, agents, representatives, employees, assigns, and all persons who act in concert with Defendants be permanently or preliminarily enjoined from engaging in unfair competition as defined in Business and Professions Code section 17200, including, but not limited to, the acts and practices alleged in this Complaint, under the authority

of Business and Professions Code section 17203;

3. That the Court make such orders or judgments as may be necessary, including preliminary injunctive and ancillary relief, to prevent the use or employment by any Defendant of any practice which violates Business and Professions Code section 17500, or which may be necessary to restore to any person in interest any money or property, real or personal, which may have been acquired by means of any such practice, under the authority of Business and Professions Code section 17535;

4. That the Court make such orders or judgments as may be necessary, including preliminary injunctive and ancillary relief, to prevent the use or employment by any Defendant of any practice which constitutes unfair competition or as may be necessary to restore to any person in interest any money or property, real or personal, which may have been acquired by means of such unfair competition, under the authority of Business and Professions Code section 17203;

5. That the Court assess a civil penalty of up to $2,500 against each Defendant for each violation of Business and Professions Code section 17500, in an amount according to proof, under the authority of Business and Professions Code section 17536;

6. That the Court assess a civil penalty of up to $2,500 against each Defendant for each violation of Business and Professions Code section 17200, in an amount according to proof, under the authority of Business and Professions Code section 17206;

7. That the People recover their costs of suit;

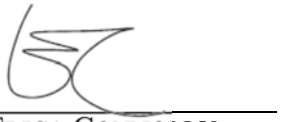
8. That the People receive all other relief to which they are legally entitled; and

That the Court award such other relief that it deems just, proper, and equitable.

Dated: September 21, 2023

Respectfully submitted,

ROB BONTA
Attorney General of California
RENU GEORGE
Senior Assistant Attorney General
KARLI EISENBERG
KATHLEEN BOERGERS
Supervising Deputy Attorneys General



ERICA CONNOLLY
HAYLEY PENAN
Deputy Attorneys General
Attorneys for Defendant Rob Bonta, in his official capacity as Attorney General of the State of California

Attachment 5

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SUPREME COURT OF THE STATE OF NEW YORK

COUNTY OF NEW YORK

THE PEOPLE OF THE STATE OF NEW YORK, by LETITIA JAMES, Attorney General of the State of New York,

Plaintiff,

-against-

HEARTBEAT INTERNATIONAL, INC.; ADIRONDACK PREGNANCY CENTER, INC. d/b/a AscentCare; CRISIS PREGNANCY SERVICES, INC. d/b/a CompassCare Pregnancy Services; THE CARE CENTER INC. d/b/a Soundview Pregnancy Services; NEW HOPE FAMILY SERVICES INC.; PREGNANCY CENTER OF PENN YAN, INC. d/b/a Care Net Penn Yan; STUDY THE OPTIONS PLEASE INC d/b/a Care Net of Wayne County; PREGNANCY CENTER OF CENTRAL NEW YORK d/b/a Willow Network; CRISIS PREGNANCY CENTER, INC. d/b/a Care Net Pregnancy Center of the Hudson Valley; 1ST WAY LIFE CENTER INC.; CARING CHOICES PREGNANCY HELP CENTER INC.; THE BRIDGE TO LIFE INC. d/b/a Bridge Women's Support Center,

Defendants.

SUMMONS

Index No. _____

IAS Part _____

TO THE ABOVE NAMED DEFENDANTS:

YOU ARE HERBY SUMMONED to answer the attached complaint in this action and to serve a copy of your answer or notice of appearance on attorneys for plaintiff.

If this summons and complaint was personally served upon you in the State of New York, you must serve your answer within twenty (20) days after such service, excluding the day of service. If this summons and complaint was not personally served upon you in the State of New York, you must serve your answer within thirty (30) days after the service of the summons is

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complete, as provided by law. In case of your failure to answer or appear in this action, judgment may be entered against you, by default, for the relief demanded in the complaint.

Plaintiff designates New York County as the venue for this action, pursuant to CPLR 503 and 505, because plaintiff resides here and this action was initiated out of plaintiff's office located in New York County at 28 Liberty Street, New York, NY.

Dated: New York, New York
May 6, 2024

Respectfully submitted,

LETITIA JAMES
Attorney General of the State of New York
Attorney for Plaintiff

By: /s/*Louisa Irving*
Louisa Irving
Assistant Attorney General
Civil Rights Bureau
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Galen Sherwin
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Eve Woodin
Assistant Attorney General
Health Care Bureau

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SUPREME COURT OF THE STATE OF NEW YORK

COUNTY OF NEW YORK

THE PEOPLE OF THE STATE OF NEW YORK, by LETITIA JAMES, Attorney General of the State of New York,

Plaintiff,

-against-

HEARTBEAT INTERNATIONAL, INC.; ADIRONDACK PREGNANCY CENTER, INC. d/b/a AscentCare; CRISIS PREGNANCY SERVICES, INC. d/b/a CompassCare Pregnancy Services; THE CARE CENTER INC. d/b/a Soundview Pregnancy Services; NEW HOPE FAMILY SERVICES INC.; PREGNANCY CENTER OF PENN YAN, INC. d/b/a Care Net Penn Yan; STUDY THE OPTIONS PLEASE INC d/b/a Care Net of Wayne County; PREGNANCY CENTER OF CENTRAL NEW YORK d/b/a Willow Network; CRISIS PREGNANCY CENTER, INC. d/b/a Care Net Pregnancy Center of the Hudson Valley; 1ST WAY LIFE CENTER INC.; CARING CHOICES PREGNANCY HELP CENTER INC.; THE BRIDGE TO LIFE INC. d/b/a Bridge Women's Support Center,

Defendants.

COMPLAINT

Index No. _____

IAS Part _____

Assigned to Justice

The People of the State of New York, by their attorney, Letitia James, Attorney General of the State of New York, respectfully allege, upon information and belief:

INTRODUCTION

1. Medication abortion is a safe and effective method for early termination of pregnancy approved by the U.S. Food and Drug Administration ("FDA"). The FDA-approved

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method for medication abortion is a two-drug regimen: first, the patient takes mifepristone, and second, between 24 to 48 hours after taking mifepristone, the patient takes misoprostol.

2. Since medication abortion first came on the market nearly a quarter of a century ago, nearly 5 million individuals across the United States have used it to terminate pregnancy. It is now used in the majority of abortions performed in the United States.

3. Medication abortion is an essential component of reproductive health care and has been an important tool in expanding abortion access in New York, particularly in rural and underserved communities where procedural abortion may be unavailable or more difficult to obtain.

4. In light of the increased use of medication abortion over the last two decades and its increasing importance in the reproductive health landscape, this safe and effective regimen for terminating early pregnancies has become a primary target for opponents of abortion, who not only seek to deter pregnant people from choosing to have a medication abortion in the first place, but also increasingly seek to deter pregnant individuals who have begun the process of a medication abortion from completing that process.

5. Defendants are an international organization, Heartbeat International, Inc. ("HBI"), and various not-for-profit organizations incorporated and located in New York ("New York Defendants") that are part of HBI's worldwide network of what it calls "pro-life pregnancy help organizations" ("PHOs") and share a central mission to deter people from having abortions. In furtherance of that goal, they advertise and widely promote an unproven protocol they refer to as "Abortion Pill Reversal" or "APR," a process through which they claim to be able to "reverse" a medication abortion or the effects of what they refer to as the "abortion pill."

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6. As will be explained, the terms "abortion pill reversal" or "abortion reversal" are misleading. Nonetheless, Defendants routinely employ these misleading terms in their advertising statements. Accordingly, to avoid unnecessary confusion, the terms "Abortion Pill Reversal" and "APR" are used herein in reference to the advertising and business practices challenged in this Complaint.

7. Defendant HBI is the architect of a strategic and coordinated marketing campaign through which local PHOs, including New York Defendants, promote APR in their communities using advertising schemes and materials, including those created by HBI. Defendants carry out this campaign by unlawfully advertising APR to consumers through misleading and/or false statements and omissions on their public websites and marketing materials, on various social media platforms, and through targeted advertising campaigns.

8. The APR protocol involves advising a pregnant person who has taken mifepristone not to take the second drug in the FDA-approved medication abortion regimen, misoprostol, thus disrupting that FDA-approved process before it is complete. In place of misoprostol, the APR protocol entails administering repeated doses of the hormone progesterone—although methods of administration and duration of treatment may vary. According to claims on Defendants' websites and in other promotional materials, this treatment can "reverse" the "abortion pill," and increase the chances of the pregnancy continuing without harmful effects.

9. In their websites and other promotional materials, Defendants have made repeated and persistent misleading and/or false claims and omissions about APR's efficacy and safety.[1]

[1] Defendants' websites and social media pages were last visited on May 4, 2024, and the allegations that they contain specific statements or images are accurate as of that date, unless otherwise indicated.

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Those claims and omissions stand in stark contrast to Defendants' numerous dire warnings about the purported dangers of medication abortion and about abortion in general.

10. The overall impression created by Defendants' websites and other promotional materials is likely to mislead consumers into believing:

a. that an abortion, "the abortion pill," or the "effects" of the abortion pill or mifepristone can be "reversed;"

b. that APR has been proven to be safe;

c. that APR has been proven to be effective, and specifically, that it has been proven to increase the chances of safely continuing a pregnancy after taking mifepristone; and

d. that APR is an accepted and uncontroversial medical treatment.

In fact, none of these things is true.

11. There is no competent and reliable scientific evidence to substantiate Defendants' claims about APR's efficacy and safety, including the central promise that APR can "reverse" the "abortion pill." The process has never been FDA approved, and researchers and major medical professional associations in the United States and abroad, including the American College of Obstetricians and Gynecologists ("ACOG"), have warned that it is unproven and unscientific.

12. No valid clinical trials have demonstrated the efficacy or safety of APR. The sole clinical trial to undertake such an evaluation had to be abruptly halted due to safety concerns after three participants experienced severe bleeding and sought emergency treatment, leading the trial's authors to warn that patients in early pregnancy who take only mifepristone, but not misoprostol, "may be at high risk of significant hemorrhage." The physicians who conducted this study warned that due to "the void in high-quality research addressing" APR's efficacy and safety, APR should

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be considered "experimental and should be offered only in institutional review board-approved human clinical trials to ensure proper oversight." Defendants do not mention this halted clinical trial in any of their advertising.

13. Instead, to the extent any Defendants point to any specific support for claims about APR, they rely almost exclusively on two "studies" that have been criticized in numerous scientific publications and by several preeminent medical organizations as so scientifically and ethically flawed as to be meaningless.

14. Defendants direct these misleading and/or false advertising statements about APR toward New York consumers who may be in the midst of a medication abortion, with the purpose of disrupting that process by inducing those consumers to undergo APR treatment in New York, either through their own facilities or with one of the local medical providers approved by HBI for membership in its "Abortion Pill Rescue Network" ("APRN").

15. Defendants are free to use lawful means to attempt to persuade pregnant individuals to continue their pregnancies rather than have an abortion, in furtherance of their mission and their beliefs. But in advertising APR to consumers for the purpose of inducing them to obtain this "treatment," Defendants must be held to the same standard as anyone else advertising health care services in the state—they cannot use misleading and/or false statements, including those that misrepresent the nature and strength of the scientific evidence substantiating the efficacy and safety of those services.

16. It is extremely difficult for the average consumer to verify the accuracy of claims concerning efficacy and safety made in health care marketing. False or misleading statements about the efficacy and safety of health care services interfere with consumers' ability to make

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informed decisions directly impacting their bodily integrity, wellbeing, and, as may be the case, pregnancy.

17. Obtaining accurate information can be especially difficult in the context of reproductive health care, where opponents of abortion intentionally distort and obfuscate facts to convince, scare, shame, or guilt people facing unintended pregnancy into deciding not to obtain or complete abortions at a moment when they are particularly vulnerable.

18. In the case of APR, Defendants' consumer-oriented statements distort the evidence and mislead New Yorkers to undergo this experimental "treatment," believing that it has been proven safe and effective, when it has not.

19. Therefore, the People of the State of New York, by Attorney General Letitia James (the "NYAG"), bring this action for an injunction to stop Defendants' misleading advertising; equitable relief to redress Defendants' fraudulent and unlawful conduct; and the imposition of civil penalties and costs.

PARTIES

20. Plaintiff is the People of the State of New York, by their attorney, Letitia James, Attorney General of the State of New York.

Heartbeat International, Inc.

21. **Defendant Heartbeat International, Inc.** ("HBI") is a 501(c)(3) charitable organization incorporated in 1973 under Ohio law with its principal place of business located at 8405 Pulsar Place, Columbus, Ohio 43240. HBI is registered as a charity in New York and as doing business in the state under the name "Heartbeat International of Ohio." HBI operates an extensive network of "pro-life pregnancy help organizations" ("PHOs"), some of which pay an

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annual fee of $300 to be a Heartbeat International Affiliate ("HBI Affiliate" or "Affiliate"). HBI owns and maintains a searchable directory of its network, Worldwide Directory of Pregnancy Help ("Worldwide Directory"), on its website, heartbeatinternational.org/worldwide-directory. HBI also owns and operates the Abortion Pill Rescue Network ("APRN"), as well as the Abortion Pill Reversal website, abortionpillreversal.com, which advertises APR treatment to consumers, and the Abortion Pill Reversal hotline ("APR Hotline"), which connects those consumers to medical providers and PHOs in the APRN that provide that treatment.

New York Defendants

22. **Defendant Adirondack Pregnancy Center, Inc. d/b/a AscentCare** ("AscentCare") is a 501(c)(3) charitable organization that is incorporated in New York and is located at 20 Academy Street, Saranac Lake, New York 12983. AscentCare has been operating since at least 2020. AscentCare is listed in HBI's Worldwide Directory.

23. **Defendant Crisis Pregnancy Services, Inc. d/b/a CompassCare Pregnancy Services** ("CompassCare") is a 501(c)(3) charitable organization that is incorporated in New York and has its principal place of business in Rochester, New York. CompassCare has been operating since at least 1980. CompassCare operates four locations in New York: Rochester, Buffalo, Albany, and Brooklyn. CompassCare is listed in HBI's Worldwide Directory and is an HBI Affiliate.

24. **Defendant The Care Center Inc. d/b/a Soundview Pregnancy Services** ("Soundview") is a 501(c)(3) charitable organization that is incorporated in New York and has its principal place of business in Centereach, New York. Soundview has been operating since at least 1991. Soundview operates three locations in New York: Centereach, East Meadow, and Riverhead. Soundview is listed in HBI's Worldwide Directory and is an HBI Affiliate.

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25. **Defendant New Hope Family Services Inc.** ("New Hope") is a 501(c)(3) charitable organization that is incorporated in New York and is located at 3519 James Street, Syracuse, New York 13206. New Hope has been operating since at least 1973. New Hope is listed in HBI's Worldwide Directory and is an HBI Affiliate.

26. **Defendant Pregnancy Center of Penn Yan, Inc. d/b/a Care Net Penn Yan** ("Care Net Penn Yan") is a 501(c)(3) charitable organization that is incorporated in New York and is located at 162 Main Street, Penn Yan, New York 14527. Care Net Penn Yan has been operating since at least 2014. Care Net Penn Yan is listed in HBI's Worldwide Directory and is an HBI Affiliate.

27. **Defendant Study the Options Please Inc. d/b/a Care Net of Wayne County** ("Care Net of Wayne County") is a 501(c)(3) charitable organization that is incorporated in New York and is located at 1141 E. Union Street, Newark, New York 14513. Care Net of Wayne County has been operating since at least 1992. Care Net of Wayne County is listed in HBI's Worldwide Directory and is an HBI Affiliate.

28. **Defendant Care Net Pregnancy Center of Central New York d/b/a Willow Network** ("Willow Network") is a 501(c)(3) charitable organization that is incorporated in New York and has its principal place of business in Utica, New York. Willow Network has been operating since at least 1988. Willow Network operates eight locations in New York: Boonville, Camden, Ilion, Liverpool, Morrisville, Oneida, Rome, and Utica. Willow Network is listed in HBI's Worldwide Directory and is an HBI Affiliate.

29. **Defendant Alternative Crisis Pregnancy Center, Inc. d/b/a Care Net Pregnancy Center of the Hudson Valley** ("Care Net Pregnancy Center of the Hudson Valley") is a 501(c)(3) charitable organization that is incorporated in New York and is located at 226 Church

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Street, Poughkeepsie, New York 12601. Care Net Pregnancy Center of the Hudson Valley has been operating since at least 1987. Care Net Pregnancy Center of the Hudson Valley is listed in HBI's Worldwide Directory and is an HBI Affiliate.

30. **Defendant 1st Way Life Center Inc.** ("1st Way Life Center") is a 501(c)(3) charitable organization that is incorporated in New York and is located at 481 Broadway #3, Monticello, New York 12701. 1st Way Life Center has been operating since at least 2010. 1st Way Life Center is listed in HBI's Worldwide Directory.

31. **Defendant Caring Choices Pregnancy Help Center Inc.,** which appears to do business as Caring Choices Pregnancy Help Community ("Caring Choices") is a 501(c)(3) charitable organization that is incorporated in New York and has its principal place of business in Rochester, New York. Caring Choices has been operating since at least 2020. Caring Choices operates two locations in New York: Rochester and Webster. Caring Choices is listed in HBI's Worldwide Directory and is an HBI Affiliate.

32. **Defendant The Bridge to Life Inc. d/b/a Bridge Women's Support Center** ("Bridge Women's Support Center") is a 501(c)(3) charitable organization that is incorporated in New York and is located at 14-02 124th Street, College Point, New York 11356. Bridge Women's Support Center has been operating since at least 1993. Bridge Women's Support Center is listed in HBI's Worldwide Directory and is an HBI Affiliate.

33. All Defendants other than HBI are herein collectively referred to as "New York Defendants."

Heartbeat International, Inc.'s Contacts with New York

34. Since January 13, 2003, HBI has been registered as a charity in New York.

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35. Since July 5, 2023, HBI has been registered with the New York State Department of State as doing business in New York under the name "Heartbeat International of Ohio."

36. In its March 17, 2023, application to do business in the state, HBI stated that its purpose in New York is to, in part, "REACH people and organizations to empower them through services, products and education that provides true reproductive healthcare and ministry," and that its activities in New York will include staffing a hotline with health care professionals and providing services directly to Affiliate organizations. HBI also stated that its New York-based office would be located in Albany County.

37. On its website, heartbeatinternational.org, HBI's Worldwide Directory includes 196 PHO locations across New York, heartbeatinternational.org/index.php?option=com_civicrm&task=civicrm/profile&reset=1&force=1&gid=11&state_province-9=1031.

38. All New York Defendants are listed in HBI's Worldwide Directory.

39. HBI sells various services and products to PHOs through another of its websites, heartbeatservices.org. For example, HBI offers (1) on-site trainings and consultations (typically $1,200.00/day); (2) a subscription (ranging from $30.00 to $150.00, monthly, to $324.00 to $1,600.00, annually) to a proprietary client management software program, HBI's Next Level™, which allows PHOs to, among other things, manage client intake, appointment, and medical information; and (3) services from HBI's Extend Web Services team, "experts at making sure" a PHO's "marketing plan is attracting the abortion-minded client," which include website development, design, and operation (ranging from $300/year to $1,620/year, plus one-time set up fee), management of social media content and Google advertising campaigns, graphic design for

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promotional materials, local search marketing, custom blog content, video commercials, and targeted display ads.

40. HBI also sells products and training resources related to APR on heartbeatservices.org/resources/store/abortion-pill-rescue, such as *Abortion Pill Rescue Network Training* ($119.95), *Abortion Pill Reversal: The Science, The Strategy, & The Opposition* ($19.95), *Introduction to Abortion Pill Reversal* training ($19.95), and *The Latest Updates on Abortion Pill Reversal* webinar ($19.95).

41. Of the 196 New York PHO locations listed in HBI's Worldwide Directory, approximately 80 are designated as HBI Affiliates. This designation means that, for an annual fee of $300.00, these Affiliates receive HBI's "Comprehensive Support." Nine of the New York Defendants are HBI Affiliates.

42. HBI supports and "nurtures all aspects of" its Affiliates, offering assistance by phone, through on-site visits, and via "personalized training and consultations." In addition, Affiliates receive back-up support from HBI's 24/7 pregnancy helpline and website, Option Line, which fields forwarded calls from Affiliates during afterhours and schedules appointments with callers on behalf of Affiliates.

43. HBI Affiliates have access to exclusive benefits, such as: discounts on on-site consultations, Extend Web Services, and most HBI training, manuals, and webinars; the option to participate in HBI's 403(b) retirement plan or IRA program; and the opportunity to receive HBI grants to fund everything from on-site operations to specialized training programs.

44. In addition to doing business with and purposefully cultivating contacts with New York-based PHOs and Affiliates, HBI also advertises APR treatment to New York consumers through its website, abortionpillreversal.com.

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45. On one of its website pages, heartbeatinternational.org/advertising-abortion-pill-reversal-in-your-community, HBI asks PHOs, Affiliate or otherwise, to "include our website (abortionpillreversal.com) and [hotline] number (877.558.0333) in advertising so the women know where to immediately reach out anytime, day or night." HBI explains that if PHOs direct consumers to abortionpillreversal.com and the APR Hotline, then HBI's "medical staff" will "answer[] questions," "explain[] reversal," "assess health concerns," and "quickly connect women with an [APRN] provider and to your center for support as quickly as possible."

46. New York Defendants all direct consumers to abortionpillreversal.com, via a direct hyperlink, and/or to the APR Hotline, to obtain APR treatment.

47. Some New York Defendants also provide or facilitate APR treatment onsite.

48. HBI maintains a non-public directory of medical providers and PHOs that it has vetted, trained, and approved for membership in the APRN; this non-public directory includes medical providers and PHOs located in New York. Through abortionpillreversal.com and the APR Hotline, HBI directs consumers located in or near New York to those New York-based medical providers and PHOs to receive APR treatment and related medical services.

JURISDICTION AND VENUE

49. Plaintiff brings this action pursuant to New York Executive Law § 63(12) and General Business Law ("GBL") Article 22-A, §§ 349 and 350. Executive Law § 63(12) empowers the NYAG to seek injunctive relief, restitution, disgorgement, damages, and costs when any person or entity has engaged in or otherwise demonstrated repeated or persistent fraudulent or illegal acts in the transaction of business. GBL Article 22-A, §§ 349 and 350, authorize the NYAG to seek injunctive relief, restitution and civil penalties for deceptive acts or practices and false advertising.

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50. This Court may exercise personal jurisdiction over HBI because HBI regularly conducts business in New York with New York consumers, has purposefully established contacts with New York, has availed itself of the New York market, and the exercise of jurisdiction does not offend traditional norms of fair play and substantial justice.

51. This Court may exercise personal jurisdiction over all other Defendants because they are each incorporated in New York, have their principal places of business in New York, and therefore reside in the state.

52. Venue is properly laid in New York County because the NYAG resides here, and because this action was initiated by the NYAG's Executive Office, Civil Rights Bureau, and Health Care Bureau, which are located in New York County at 28 Liberty Street, New York, NY.

53. The NYAG has provided pre-litigation notice pursuant to GBL Article 22-A, §§ 349(c) and 350-c.

FACTS

Background on Medication Abortion

54. Abortion is basic and necessary health care and has been legal in New York since 1970. It is the policy of the state that "[e]very individual who becomes pregnant has the fundamental right to choose to carry the pregnancy to term, to give birth to a child, or to have an abortion." N.Y. Pub. Health Law § 2599-aa (McKinney).

55. There are two principal methods available for abortion—procedural abortion and medication abortion, also known as "the abortion pill."

56. Procedural abortion is a medical procedure whereby suction and/or surgical instruments are used to empty the contents of the uterus. Procedural abortion is conducted in a clinical setting, such as an outpatient clinic.

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57. Medication abortion is accomplished by the patient taking an oral medication to terminate the pregnancy, typically using a combination of the drug mifepristone, sold under the brand name Mifeprex, followed by the drug misoprostol 24 to 48 hours later.

58. The term "the abortion pill" generally refers to the regimen involving these two drugs.

59. The mifepristone-misoprostol combination has been approved by the Food and Drug Administration (FDA) since 2000 as a safe and effective way to end a pregnancy through 10 weeks gestation (70 days or less since the first day of the last menstrual period).

60. The FDA maintains a website with information about medication abortion, Questions and Answers on Mifepristone for Medical Termination of Pregnancy Through Ten Weeks Gestation, U.S. FDA, Sept. 1, 2023, fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation.

61. A pregnant person undergoing a medication abortion first takes mifepristone. Mifepristone works by blocking the body's progesterone receptors.

62. Progesterone is a hormone produced by the body that is essential to maintaining the endometrium (uterine lining) for a fertilized egg to implant and grow. The body increases progesterone production during pregnancy, and progesterone levels generally remain high to maintain a pregnancy. By blocking the progesterone receptors, mifepristone inhibits the biological effects of progesterone and prevents the pregnancy from continuing.

63. Then, between 24 and 48 hours after taking mifepristone, the pregnant person will take the second medicine in the medication abortion regimen, misoprostol. Misoprostol induces

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the uterus to contract (experienced as cramping) which causes the contents of the uterus to be expelled.

Background on APR

64. In light of the increase in medication abortions in the United States, Defendants, along with other organizations and individuals opposed to abortion, engaged in a coordinated effort to stigmatize medication abortion and deter people from using it, or to disrupt the process once it is already underway.

65. On their websites and in their promotional materials, Defendants attempt to reach pregnant people who have taken mifepristone, but not misoprostol, to convince them not to complete the second step in the medication abortion regimen. Their tactics include multiple statements suggesting that it is common for pregnant people to experience regret or change their minds after taking mifepristone and emphasizing purported safety risks of medication abortion, alongside heavy marketing of "Abortion Pill Reversal."

66. APR involves advising pregnant individuals not to take misoprostol following mifepristone and instead to undergo additional medical treatment intended to support the continuation of the pregnancy.

67. According to abortionpillreversal.com, the APR "treatment" involves performing an ultrasound "to confirm heart rate, placement, and dating of the pregnancy." A medical provider "will prescribe progesterone, given as a pill to be taken orally or vaginally or possibly by intramuscular injection," and the "treatment will usually continue through the first trimester of pregnancy."

68. The APR "treatment" or "protocol," as HBI refers to it, was developed in or around 2008 by Dr. George Delgado, a family physician based in California.

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69. In 2012, Delgado created a network of medical providers willing to perform the APR protocol, which he called the "Abortion Pill Reversal Network," as well as a helpline (877-558-0333) that operated 24 hours a day, 7 days a week, and website, abortionpillreversal.com, that would field questions about APR and connect pregnant people with network providers to receive APR treatment.

70. Delgado also co-authored, with Dr. Mary Davenport and others, several "studies," purporting to evaluate APR's efficacy and safety.

71. The first, a case series published in 2012 ("2012 Case Series"), looked at six pregnant women who were administered progesterone after taking mifepristone; found that four of them carried their pregnancies to full-term, reportedly with no birth defects; and concluded that "[t]he experience of these patients suggests that medical abortion can be arrested by progesterone injection after mifepristone ingestions prior to misoprostol."[2] Delgado and his co-authors suggested a specific protocol for administering progesterone after mifepristone, and "welcome[d] further clinical trials utilizing this protocol or others, in order to have an evidence basis for the best protocol."

72. The second of these studies, published in 2018 ("2018 Case Series"), is an "an observational case series of 754 patients" who were administered the APR protocol following calls

[2] George Delgado & Mary L. Davenport, *Progesterone Use to Reverse the Effects of Mifepristone*, 46 Annals of Pharmacotherapy e36 (2012), *available at* https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=406aec089e809942f4b58b6b16f0b0b4f038256b.

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to the hotline.[3] After excluding 207 (27%) of these patients for various reasons, including due to loss of contact before 20 weeks gestation and the decision to complete the abortion, the 2018 Case Series analyzed 547 patient outcomes and determined that the "overall rate of reversal of mifepristone was 48%." Despite acknowledging that the "study is limited in that it is not a randomized placebo-controlled trial," among other limitations, the authors concluded that "[t]he reversal of the effects of mifepristone using progesterone is safe and effective." They proposed further research "employing randomized controlled trials" to determine the most efficacious and least burdensome progesterone doses and routes of administration.

APR is Not Backed by Competent and Reliable Scientific Evidence

73. There is no competent and reliable scientific evidence proving that the APR protocol is safe or that it is effective in increasing the chances of the pregnancy continuing. The only clinical trial to evaluate APR's safety and efficacy had to be halted due to safety concerns.

74. HBI and other proponents of APR typically point to the 2012 and 2018 Case Series as support for statements about APR's efficacy. However, these studies have been criticized as scientifically and ethically flawed in several scientific publications and by several medical associations.

75. For example, a 2015 systematic literature review published in the peer-reviewed medical journal *Contraception* criticized the 2012 Case Series as presenting data from "anecdotal experiences of physicians who performed experimental treatment on pregnant women, without the

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[3] George Delgado et al., *A Case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone*, 33 Issues in Law & Medicine 1 (2018), *available at* https://www.heartbeatservices.org/images/pdf/Delgado_et_al__Revisions_-_FINAL_0919.pdf.

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usual safeguards."[4] The review characterized the 2012 Case Series as "of poor quality with few details," making it impossible to compare its results to the rates of continuing pregnancy after taking mifepristone alone, "which was as high as 46% in one of the clinical trials." The authors therefore concluded that the "evidence is insufficient to determine whether treatment with progesterone after mifepristone," i.e., following the APR protocol, "results in a higher proportion of continuing pregnancies compared to expectant treatment," i.e., doing nothing but monitoring the patient. In other words, there was not sufficient evidence to demonstrate that patients remained pregnant because they underwent APR. A 2018 commentary published in the *American Journal of Obstetrics & Gynecology* also described the "many limitations" of the 2012 Case Series, including "small sample size, lack of long-term follow-up, as well as no review or oversight by an institutional review board or ethics committee."[5]

76. A different 2018 commentary, published in the *New England Journal of Medicine,* criticized the 2018 Case Series on several bases including its failure to account for confounding variables such as gestational age, minimal safety data, and lack of clarity as to whether institutional review board approval was obtained prior to administering the "experimental treatment protocol" to patients.[6] The authors found that, even when the results of the 2018 Case Series were adjusted to account for significant methodological flaws, there was no statistically significant difference in outcomes between treatment with progesterone following mifepristone and doing nothing.

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[4] Daniel Grossman et al., *Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: a systematic review*, 92 Contraception 206-11 (2015).

[5] Khadijah Z. Bhatti et al., *Medical abortion reversal: science and politics meet*, Am. J. of Obstetrics & Gynecology at 317 (March 2018).

[6] Daniel Grossman and Kari White, *Abortion "Reversal"—Legislating without Evidence*, 379 New England J. of Med. 1491 (2018).

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77. Original research published in January 2020 in *Obstetrics & Gynecology* also criticized these case series as having "significant limitations," including "using investigational treatment (high-dose progesterone) after mifepristone ingestion without consenting patients for this experiment; incomplete reporting of outcomes; use of varying progesterone doses, routes and durations; and lack of control [i.e., comparison] groups to understand true efficacy."[7] The authors accordingly cautioned that those series are "not evidence of efficacy and do not address safety," and "[t]his level of evidence is inadequate to support or refute the benefits and risks of any treatment."

78. To date, the *only* double-blind, placebo-controlled, randomized clinical trial aimed at estimating the efficacy and safety of the APR protocol had to be halted after 3 of the 12 enrolled patients experienced "[s]evere hemorrhage requiring ambulance transport to the hospital."[8] The abrupt end of this clinical trial due to safety concerns foreclosed any estimate of the efficacy of progesterone at countering the effects of mifepristone. One of the few conclusions reached was that "patients in early pregnancy who use only mifepristone," as required by the APR protocol, "may be at high risk of significant hemorrhage." And so, the physicians who conducted this clinical trial cautioned: "Because of the potential dangers for patients who opt not to use misoprostol after mifepristone ingestion, any mifepristone antagonization treatment must be considered experimental."

Major Medical Associations Denounce APR

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[7] Mitchell D. Creinin et al., *Mifepristone Antagonization with Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial*, 135 Obst. & Gynecology 158, 159 (2020) [Herein "Mifepristone Antagonization with Progesterone Controlled Trial"].

[8] Creinin et al., *Mifepristone Antagonization with Progesterone Controlled Trial*, *supra*.

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79. The poor quality of the Case Series and absence of science substantiating APR have led major medical associations in the United States and abroad to denounce APR and to issue warnings against its use.

80. The American College of Obstetricians and Gynecologists ("ACOG"), the premier professional membership organization for obstetrician–gynecologists, criticized the limitations of the 2012 and 2018 Case Series in an opinion piece titled: "Facts Are Important: Medication Abortion 'Reversal' Is Not Supported by Science," noting that they had "no ethics approval, no control group, under-reporting of data, and no reported safety outcomes," and explaining further that "[c]ase series with no control groups are among the weakest forms of medical evidence."[9] ACOG accordingly warned that "[c]laims regarding abortion 'reversal' treatment are not based on science and do not meet clinical standards," and stated unequivocally that ACOG "does not support prescribing progesterone to stop a medication abortion."

81. Internationally, other major medical associations, including The Society of Obstetricians and Gynaecologists of Canada, The Royal College of Obstetricians and Gynaecologists, the Faculty of Sexual and Reproductive Healthcare, the Royal College of Midwives, and the British Society of Abortion Care Providers have similarly denounced APR as unproven and lacking any valid scientific basis.[10]

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[9] ACOG, *Facts Are Important: Medication Abortion "Reversal" Is Not Supported by Science*, https://www.acog.org/advocacy/facts-are-important/medication-abortion-reversal-is-not-supported-by-science (last visited May 2, 2024).

[10] SOGC, *SOGC Statement on Abortion Medication "Reversal,"* Mar. 19, 2021; The Royal College of Obstetricians and Gynaecologists (RCOG), The Faculty of Sexual and Reproductive Healthcare (FSRH), the Royal College of Midwives (RCM) and the British Society of Abortion Care Providers (BSACP), *Joint statement on 'Abortion reversal'*, July 6, 2022, *available at* https://www.rcog-fsrh-abortion-reversal-position-statement.pdf.

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82. The latter three groups in the United Kingdom released a joint statement in July 2022 that stated: "There are **no reputable national or international clinical guidelines that recommend the use of progesterone to reverse the effect of mifepristone**, and no evidence that it increases the likelihood of continuing pregnancy, compared to expectant management alone." (emphasis in original.)[11]

HBI Provides APR Through its Abortion Pill Rescue Network

83. In April 2018, just after the 2018 Case Series was published, HBI assumed ownership and operation of the Abortion Pill Rescue Network (then called Abortion Pill Reversal Network) ("APRN") from Delgado, as well as the website and hotline, with the goal of expanding its reach and making APR available to many more pregnant people.

84. Since HBI's takeover of the APRN, Delgado continues in a leadership role as one of the APRN's several medical advisors.

85. Delgado also founded and serves as the president of the board of directors of an organization called the Steno Institute. According to its website, stenoinstitute.org, the institute's purpose is "to serve as the platform for broader pro-life research, including abortion pill reversal."

86. The APRN consists of medical providers and PHOs. According to a 2022 "Impact Report," *available at* heartbeatinternational.org/images/ImpactReports/APRN_Impact_Report_2022.pdf, HBI claims that the APRN consists of 1,300 providers, clinics, and hospitals worldwide, and that the APRN has assisted women in all 50 states and in 86 countries.

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[11] The Royal College of Obstetricians and Gynaecologists (RCOG) et al., *supra.*

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87. According to the APRN website, aprnworldwide.com/about/medical-network, medical providers and PHOs join the APRN by submitting an enrollment form, successfully completing a vetting process, reviewing HBI's "approved Abortion Pill Rescue Network Provider Kit," and making themselves available to assist with providing the APR protocol to women having regret after starting chemical abortion" in their geographic area.

88. When HBI took over the APRN, it integrated the APR Hotline with its existing helpline called Option Line. According to the HBI website, heartbeatinternational.org, Option Line is "the only fully staffed, bilingual pro-life contact center in the U.S." and "offers compassionate, personalized guidance for all who reach out" via phone call, live chat, text, or email. Option Line is staffed by consultants who connect callers to local PHOs by scheduling appointments in real time and providing "consultation on abortion, adoption, and parenting."

89. If a caller expresses interest in APR, the Option Line consultant sends the caller to one of the APRN's "trained nurses," who serves as an APR Hotline "consultant." The nurse provides information about APR and connects the caller with a medical provider to perform the protocol.

90. According to the APRN website, aprnworldwide.com/abortion-pill-reversal, over the phone, the APRN "trained nurse" will review the patient's medical and pregnancy history, as well as the circumstances of their "attempted chemical abortion," and determine whether the patient is considered "an appropriate candidate for attempting reversal." If deemed appropriate, the patient's contact information will be given to an APRN provider in their geographic area who will contact them and confirm their information.

91. If the patient remains interested in "attempt[ing] reversal," the APRN provider will prescribe an "oral protocol of progesterone," which the provider will either call directly into a

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pharmacy of the patient's choosing or which will be "dispensed through a pregnancy help organization, clinic, or hospital." The patient will receive assistance locating a facility or provider who can see them for follow-up care. An ultrasound may or may not be performed before the patient begins taking progesterone.

92. The "trained nurses" who work as APR Hotline consultants are not volunteers. They work as contractors for HBI and are paid by HBI.

93. Although the hotline consultation is free, APR is not.

94. According to abortionpillreversal.com, the "[c]osts of the treatment varies depending on the progesterone used." Private insurance and Medicaid may cover these costs. However, HBI directs consumers of APR treatment who do not have insurance or financial means to pay, to "discuss this with their medical provider." For women facing "financial hardship," HBI states it will help "find ways to reduce the cost of the treatment."

HBI Promotes and Advertises APR to Consumers Through Coordinated and Strategic Marketing Involving Local PHOs

95. HBI has developed and employs a coordinated and strategic multi-media marketing scheme to advertise APR to potential consumers.

96. This scheme includes HBI's own advertising through its website, abortionpillreversal.com, and other promotional materials, as well as advertising by local PHOs that carry out HBI's marketing strategy using HBI's tips, templates, and ready-to-go materials to advertise APR in their own local communities.

97. These tips, published on HBI's website, heartbeatinternational.org/advertising-abortion-pill-reversal-in-your-community, include recommendations that PHOs "reach the masses through social media" posts and paid ads; purchase HBI's Extend Web Services to help with

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geofencing (i.e., location-based targeted advertising); launch APR billboard campaigns using HBI sample designs that direct consumers to abortionpillreversal.com; use a flyer with HBI's messaging, including a QR Code that hyperlinks directly to abortionpillreversal.com, for distribution at events and as bathroom advertisements; and add an "Abortion Pill Reversal™ page" to their website as it "increases your chance of appearing high in organic search results for searches related to the abortion pill."

98. HBI also asks PHOs to include its website, abortionpillreversal.com, and the APR Hotline number in their advertising so that consumers can be connected with an APRN medical provider who provides the APR protocol "as quickly as possible."

99. All New York Defendants include a direct hyperlink to abortionpillreversal.com and/or the APR Hotline on their own websites advertising APR treatment, as HBI requests.

100. In doing this, New York Defendants carry out HBI's coordinated marketing strategy for advertising APR in New York, and adopt and spread the content of abortionpillreversal.com, including all misleading and/or false statements and omissions.

101. Abortionpillreversal.com is the centerpiece of HBI's marketing scheme for APR because it is the hub to which local PHOs direct consumers to access APR treatment.

102. Abortionpillreversal.com uses a generic design. It does not have any HBI or APRN branding on it, allowing it to function as an extension of the website of any PHO that links to it.

103. None of the New York Defendants that include a direct hyperlink to abortionpillrevsal.com on their website clearly alerts consumers that they are being directed to a different organization's website or specifically disclaims the content and statements made on that website.

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104. The statements made on abortionpillreversal.com, and the strategic design through which they are presented, are aimed at inducing consumers who have taken mifepristone into not taking misoprostol, and instead, obtaining APR treatment through the APRN.

105. The landing page of abortionpillreversal.com (see Figure 1) pitches APR directly to consumers, asking, "Have you taken the first dose of the abortion pill? Do you regret your decision and wish you could reverse the effects of the abortion pill? ***We're here for you!***" An image of the complete landing page of abortionpillreversal.com is attached hereto as Exhibit A.

FIGURE 1



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106. Just as it suggests to its network of PHOs, HBI includes an "Abortion Pill Reversal™ page" on abortionpillreversal.com, to increase its visibility in internet searches for the abortion pill.

107. HBI also maximizes the advertising impact of abortionpillreversal.com by incorporating several of the design recommendations it makes to PHOs in connection with billboard campaigns on its website, heartbeatservices.org/billboard-campaigns. For example, the text "is printed in clean, bold font to ensure the best readability;" the website landing page uses both "bright colors," pink and blue, and a "bold image," of a woman, to "effortlessly attract eyes;" the website also includes "[c]ontrasting colors within the design," such as the blue button that states "I want to Reverse my Abortion*" and the pink text directing consumers to call the APR Hotline and promising "an effective process called Abortion Pill Reversal* that gives your unborn child a second chance at life," to "create an even bigger impact" to "help improve the retention" of the message.

108. Through abortionpillreversal.com, HBI advertises APR treatment directly to pregnant people who may be deciding whether to continue their pregnancy after taking mifepristone, with the aim of convincing them that their quandary is common or that they should feel regret; disrupting their medication abortion; and connecting them with an APRN medical provider to perform the protocol as soon as possible.

HBI Makes Misleading and/or False Statements about APR on Abortionpillreversal.com and on the APR Facebook Page

109. On abortionpillreversal.com and in other promotional materials, HBI makes numerous statements about APR and its efficacy and safety that are misleading and/or false and are not substantiated by competent and reliable scientific evidence.

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110. These statements about APR and its efficacy and safety are targeted at and are likely to mislead a consumer into believing that APR is widely-accepted, safe, effective, and uncontroversial and that it will increase their chances of continuing their pregnancy and delivering a healthy baby.

Misleading Claims that Abortion, the Abortion Pill, and its Effects can be "Reversed"

111. The name Abortion Pill *Reversal* is itself misleading and inaccurate, as are statements claiming that abortion and the effects of "the abortion pill" can be "reversed." Such statements are made repeatedly on abortionpillreversal.com, on HBI's "Abortion Pill Reversal" Facebook page, and in other promotional materials.

112. For example, as depicted in Figure 1 above, upon arriving at the landing page of abortionpill*reversal*.com (emphasis added), a potential consumer of APR treatment is immediately asked "Have you taken the first dose of the abortion pill? Do you regret your decision and wish you could reverse the effects of the abortion pill?" and presented the option to click a prominent blue button that reads "I want to **Reverse my Abortion***" (emphasis in original). (*See* Figure 1 and Exhibit A.)

113. This button directs the consumer to a separate page on abortionpillreversal.com that states: "**Can the abortion pill be reversed?** The simple answer is yes! If done in time." Then HBI elaborates: "There is an effective process called abortion pill reversal* that can reverse the effects of the abortion pill and allow you to continue your pregnancy, but time is of the essence."

114. HBI makes similar statements on a flyer it promotes and makes available for use by PHOs advertising APR in their local communities. The flyer states: "**Have you taken the first dose of the abortion pill?** Do you regret your decision and wish you could reverse the effects of the abortion pill? ***We're here for you!***" (emphasis in original.)

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115. HBI further includes numerous posts and graphics on the APR Facebook page referencing APR and claiming abortion can be "reversed" or "undone." For example:

a. A post from March 2, 2024, an image of which is attached hereto as Exhibit B, presents a dramatized text exchange between "Me" asking: "Can I undo my abortion? I've already taken the first pill," and "APR Hotline" answering: "It is possible. We can connect you with the help you need." Consumers are then directed to "Get in touch for free consultation with a nurse and a connection to start reversal" by contacting the APR Hotline or visiting abortionpillreversal.com.

b. A post from February 16, 2024, an image of which is attached hereto as Exhibit C, states: "Abortion Pill Reversal is Possible," and directs consumers who are "Having regret[]" to visit abortionpillreversal.com or call the APR Hotline.

c. A post from January 27, 2024, an image of which is attached hereto as Exhibit D, includes the statement, "Regrets? Want to undo the abortion? Call for info…" and directs consumers to the APR Hotline and abortionpillreversal.com.

d. A post from August 22, 2023, an image of which is attached hereto as Exhibit E, posits the question, "Can you undo the abortion after the first pill?," and directs consumers to the APR Hotline and abortionpillreversal.com.

e. An APR "promotional video," an image of which is attached hereto as Exhibit F, was posted September 10, 2015, with the caption: "IT IS POSSIBLE to reverse the abortion pill!" The video opens with the question: "Have you ever made a choice or decision that you wish you could reverse? What if I told you

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there is an option" (0:06-0:16) and later claims that as of 2015 "nearly 100 babies have been born to women who have successfully reversed the effects of mifepristone using progesterone." (2:40-2:49)

116. Statements like these, which use "reverse" and "reversal" to describe APR are misleading and inaccurate for several reasons.

117. First, statements claiming that an "abortion" can be reversed are misleading and inaccurate because they imply the impossible—that fetal tissue that has been expelled from the uterus due to a completed abortion can be returned to the uterus. It cannot.

118. Second, APR involves disrupting the approved medication abortion regimen *before the second step* in that regimen, misoprostol, has been taken, in order to *prevent* an abortion from occurring. In other words, a person whose pregnancy continues after taking mifepristone—i.e.., i.e., a person HBI would consider eligible for APR—has not had an abortion, so there is no "abortion" to be "reversed."

119. The way that HBI uses the words "reverse" and "reversal" in naming and advertising APR conveys information about APR and its effectiveness that is not accurate or backed by competent and reliable scientific evidence, and is likely to mislead a consumer into believing that APR will undo what has been done and save their pregnancy.

Misleading Claims about APR's Efficacy

120. HBI makes several different statements on abortionpillreversal.com and other promotional materials about APR's efficacy that are misleading and/or false. These statements, taken individually and together, are likely to mislead a consumer into believing that APR has been proven effective at continuing a pregnancy, even 72 hours after use of mifepristone, when it has not been so proven.

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Misleading Claims that APR is "Effective" and "Increases the Chances" of Pregnancy Continuation

121. HBI makes repeated statements on abortionpillreversal.com that APR is "effective" and "increases the chances" of a pregnancy continuing. For example, on the website landing page, HBI advertises APR as an "effective process" that "gives your unborn child a second chance at life." (*See* Exhibit A.)

122. In an overview of APR treatment, HBI claims that it "can reverse the effects of the abortion pill and allow you to continue your pregnancy."

123. HBI similarly claims in its "FAQs," abortionpillreversal.com/abortion-pill-reversal/faq, that although "your pregnancy may continue even without APR if you decide not to take the second abortion drug . . . APR has been shown to increase the chances of allowing the pregnancy to continue."

124. Such statements are misleading because they create the misimpression that a pregnant person who has taken mifepristone, but wants to continue their pregnancy, is *better off* obtaining APR treatment by submitting to supplemental progesterone doses than merely monitoring for miscarriage.

125. These statements are likely to mislead a consumer considering APR treatment because they address an issue that is at the heart of that consumer's decision-making—will APR increase the likelihood that my pregnancy will continue? HBI's website statements in the affirmative are not supported by any competent and reliable scientific evidence.

Misleading Claims that APR has a 64-68% Success Rate

126. HBI also specifically advertises APR's purported success rate on abortionpillreversal.com, claiming that "Using the natural hormone progesterone, medical

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professionals have been able to save 64-68% of pregnancies through abortion pill reversal" and "Initial studies of APR have shown it has a 64-68% success rate." No sources are cited to support these claims.

127. An APR "promotional video" that was posted to the APR Facebook page on September 10, 2015, similarly claims, without reference to any source, that the "APR success rate has been about 60%." (3:01–3:05) (*See* Exhibit F.)

128. No competent and reliable scientific evidence exists to substantiate these claimed success rates. To the extent these rates rely upon the 2018 Case Series, and even assuming the validity of that study, they significantly overstate and oversimplify the results, which actually reported a broader range of success rates based on several factors.

129. But more fundamentally, as discussed above, the 2018 Case Series is not competent and reliable evidence of APR's efficacy in light of significant flaws in the methodology used to evaluate outcomes. The 2018 case series, therefore, does not demonstrate that APR is effective at all, much less substantiate the claimed success rates.

130. Statements about specific success rates are likely to mislead consumers trying to determine just *how* effective APR treatment will be at saving a pregnancy. The purported 64-68% success rate is very compelling, and also very misleading.

Misleading Claims that APR may be Effective even 72 Hours After Mifepristone

131. On abortionpillreversal.com, HBI misleadingly implies that APR may be effective in reversing the effects of the abortion pill *more than* 72 hours after a pregnant person has taken mifepristone.

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132. In response to the "FAQ" "Is it too late to reverse the abortion pill?" HBI explains that "[e]ven if 72 hours have passed [since taking mifepristone], call our hotline 877.558.0333. We are here to help. It may not be too late."

133. There is no evidence, credible or otherwise, to support the use of APR more than 72 hours after a pregnant person has taken mifepristone.

134. Neither the 2012 nor 2018 Case Series examined the use of progesterone in these circumstances.

135. Therefore, HBI's statements are likely to mislead a consumer who is wondering if it is "too late" into thinking that APR treatment may be effective in increasing the chances of a pregnancy continuing, even after the 72-hour window has closed. There is no competent and reliable scientific evidence to substantiate this claim.

Misleading Statements and Omissions Regarding Health and Safety Risks

136. The information HBI provides on abortionpillreversal.com about potential side effects and risks of APR is incomplete, inaccurate, and taken out of context. This creates a misimpression that the APR protocol has been proven safe and essentially risk-free. It has not.

137. On abortionpillreversal.com, HBI addresses the possible side effect of "cramping or spotting," explaining in one "FAQ" that, "Spotting or bleeding is common during the reversal treatment," but that it is "important and safe to continue the progesterone" despite these symptoms "unless directed otherwise." In another "FAQ," HBI explains that, "Many women have experienced cramping or spotting and still go on to have successful reversals," but to "[b]e sure to let your doctor or medical provider know you are experiencing these symptoms." In both "FAQs," HBI warns, in bold letters, that in the event of "heavy bleeding, fainting, severe abdominal pain, or fever," consumers of APR medical services should "seek emergency medical attention

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immediately" as these symptoms "could be an *effect of the first abortion pill* [mifepristone] and would require immediate care." (emphasis added.)

138. HBI's warning is incomplete, and therefore misleading, because it attributes these risks as possible effects of "the first abortion pill," mifepristone. It does not explain that these serious, life-threatening complications could, in fact, be the result of complying with the APR protocol's direction to take only mifepristone—and not misoprostol.

139. HBI's reference to "heavy bleeding" is also incomplete, and therefore misleading, because HBI does not mention that the sole clinical trial that attempted to evaluate the safety and efficacy of the APR protocol had to be terminated due to three instances of severe hemorrhage, leading to the conclusion that "[p]atients in early pregnancy who use only mifepristone may be at high risk of significant hemorrhage." HBI does not include any information on the risk of significant hemorrhage.

140. In addition, in its "FAQs," HBI provides some information about "possible side effects of progesterone," such as sleepiness or dizziness, and warns consumers with peanut allergies that progesterone may contain peanut oil. However, HBI's statements about progesterone create the overall misimpression that its use in the context of the APR protocol is conclusively benign.

141. HBI states in one "FAQ" that progesterone is "the natural hormone in a woman's body that is necessary to nurture and sustain a pregnancy." And in answering another "FAQ" about possible birth defects, HBI states, without citation, that "[p]rogesterone, used in the reversal process, has been safely used in pregnancy for over 50 years." A reasonable reading of this statement would leave a consumer with the misimpression that progesterone as it is "used in the reversal process" is safe. In fact, established uses of progesterone during pregnancy for particular

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purposes are not directly applicable to the use of progesterone in the APR protocol and do not establish its safety in this context.

142. Birth defect rates are addressed on both abortionpillreversal.com and the APR Facebook page. On abortionpillreversal.com, HBI relies, at least in part on the flawed 2018 Case Series, to support its claim that APR treatment is safe, stating: "Initial studies have found that the birth defect rate in babies born after the APR is less or equal to the rate in the general population" (and hyperlinking to the 2018 Case Series).

143. The APR "promotional video" posted to Facebook on September 10, 2015, states that by 2015, nearly 100 babies born to women who successfully underwent APR treatment "have been healthy with no major birth defects," (2:50-2:53), and that for the 75 women who successfully underwent the APR in 2015 "all of those pregnancies appear[] to be healthy." (2:54–3:02) (*See* Exhibit F.) These health conclusions appear to be based solely on anecdote and self-reporting.

144. HBI's failure to directly address the side effects and risks of APR are all the more misleading when compared to its treatment of the side effects and risks associated with medication abortion.

145. HBI's webpage for "The Abortion Pill," abortionpillreversal.com/the-abortion-pill, contains grave warnings regarding the side effects and risks of medication abortion, stating that "[a]ll women considering the abortion pill deserve to know about the side effects and risks." HBI asks: "What are the side effects of the abortion pill?" It explains, in response, that "[t]he abortion pill includes very strong drugs, and with each, you may experience side effects after taking them," that "[s]ide effects vary from person to person and no two women's experiences are alike," and hyperlinks to the Mayo Clinic's website containing "a list of potential side effects" of medication abortion.

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146. No comparable statements directly address the side effects and risks of APR. As described above, any such statements relate only to the side effects and risks of mifepristone and progesterone, but not their use together, and, critically, in the absence of misoprostol. The contrast in HBI's discussion of side effects and risks associated with medication abortion versus APR furthers the misimpression that APR is without risk.

147. By misleadingly discussing the side effects of mifepristone and progesterone; omitting any reference to the clinical trial that was terminated for safety reasons; presenting anecdotes about healthy babies and pregnancies as conclusive evidence of safety; citing the flawed 2018 Case Series; and presenting a direct and grave discussion of the risks and side effects of medication abortion, HBI creates the misimpression that APR is a proven and safe treatment with minimal risks. However, no competent or reliable science has established this as a fact.

148. Further, information regarding APR's safety risks is not reasonably obtainable by a consumer who is making a decision about their reproductive health care in a landscape full of misinformation, and under the time crunch and stress of deciding whether to complete a medication abortion or obtain APR treatment.

149. Taken together, the various safety-related statements and omissions are likely to mislead consumers considering APR into believing APR has been proven safe when it has not.

Misleading Statements Implying FDA and ACOG Endorsement of APR

150. HBI incorporates misleading references to statements and actions by ACOG, the country's foremost professional membership organization for obstetricians and gynecologists, and by the FDA, the federal agency universally known for protecting public health by regulating the safety and efficacy of drugs, in a manner that misleadingly implies their endorsement or approval of APR.

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151. HBI explains in response to an "FAQ" about birth defects: "The American Academy [sic] of Obstetricians and Gynecologists stated in its Practice Bulletin Number 225 (reaffirmed 2023): 'No evidence exists to date of a teratogenic effect of mifepristone.' In other words, it does not appear that the abortion pill causes birth defects." HBI has embedded a hyperlink in this text directing the reader to the cited practice bulletin on ACOG's website.

152. Although this ACOG practice bulletin includes the quoted language, HBI's subsequent characterization of that language and of ACOG's position is incorrect and misleading. First, the quoted language pertains to the to the lack of teratogenic effect from mifepristone *alone*. It does not address or purport to evaluate any teratogenic effects of 1) mifepristone *followed by* the administration of multiple doses of progesterone, as required under the APR protocol, or of 2) "the abortion pill," which includes mifepristone *and* misoprostol. In fact, the ACOG practice bulletin states that "misoprostol can result in congenital anomalies." HBI's statement misleadingly creates the impression that ACOG has represented that the APR protocol will not cause birth defects, when it has made no such statement.

153. Second, HBI's invocation of ACOG's practice bulletin implies that ACOG approves of the use of APR. In fact, ACOG has warned that "so-called abortion 'reversal' procedures" are "unproven and unethical." HBI omits any mention of this unequivocal criticism, instead relying on ACOG's legitimacy to bolster its misleading statements.

154. In the same "FAQ" about birth defects associated with APR, HBI similarly invokes the FDA, stating: "A 1999 FDA review revealed no increased risk of birth defects in pregnant women taking progesterone." The embedded hyperlink currently leads to a "Page Not Found" on the FDA's website. It previously led to a 53-page highly technical FDA Briefing Document regarding a brand-name injectable form of progesterone called Makena—a drug whose approval

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the FDA subsequently *withdrew* in April 2023 because it was not shown to be effective at reducing the risk of preterm birth and there were known risks associated with the drug.

155. HBI's invocation of the FDA is false and misleading for several reasons. First, the APR protocol directly conflicts with the FDA's approved use of mifepristone, which the FDA has approved *together with* misoprostol to end a pregnancy. Instead, the APR protocol requires a patient who has taken mifepristone *to not take misoprostol*. HBI fails to disclose this conflict with the FDA's conditions for use and labeling for mifepristone.

156. Second, HBI's vague reference to an "FDA review" involving "pregnant women taking progesterone" creates the misimpression that the FDA has reviewed and approved the APR protocol, which also involves pregnant women taking progesterone. It has not. To the extent the FDA has evaluated and approved the use of progesterone for certain indications, that approval does not mean that the FDA has approved the use of progesterone in the context of APR.

157. HBI's misleading incorporation of statements by ACOG on the safety of mifepristone (outside the context of APR), and by the FDA on the safety of progesterone (outside the context of APR), are likely to mislead consumers into believing that these entities have granted their imprimatur on APR as safe, effective, and uncontroversial, when they have not.

New York Defendants Amplify Misleading and/or False Claims on Their Websites

158. Each New York Defendant operates its own consumer-oriented website.[12] All of these websites direct consumers to abortionpillreversal.com—without clearly notifying consumers

[12] As alleged in Paragraph 239, the website for NY Defendant 1st Way Life Center is currently unavailable but was available through at least March 2024. As alleged in Paragraph 184, the

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that they are being directed to an external website or specifically disclaiming the content and statements made on that website—and/or to the APR Hotline to obtain APR treatment. In doing this, New York Defendants carry out HBI's strategic marketing scheme for advertising APR treatment in New York and adopt and spread the content of abortionpillreversal.com, including all misleading and/or false claims and omissions contained therein, to an even wider audience of New York consumers.

159. New York Defendants' websites also advertise APR through many of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, none of which are substantiated by competent and reliable scientific evidence. New York Defendants each make these claims and omissions in order to direct consumers to medical services, specifically, the APR protocol, which is provided through Defendants' own facilities or through the APRN's medical providers.

160. These claims and omissions by New York Defendants are false and/or misleading for the same reasons discussed in paragraphs 54-157 above and are likely to mislead consumers to believe that APR reverses an abortion, the abortion pill, or the effects of the abortion pill or mifepristone, that it has been proven effective, and that it has been proven to pose little or no safety risk.

AscentCare

APR webpage for NY Defendant Soundview Pregnancy Services is currently unavailable but was available through at least April 15, 2024.The allegations in this complaint are based on the most recently available versions of this website and webpage.

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161. AscentCare advertises several pregnancy-related services, including APR treatment, through its website, ascentcare.org. AscentCare provides APR treatment to consumers directly on-site and makes misleading and/or false claims and omissions about APR.

162. AscentCare advertises its on-site APR treatment through its website, including through its webpage titled "Abortion Pill Reversal," ascentcare.org/services/abortion-pill-reversal.

163. AscentCare's website describes these services and the process through which consumers can obtain APR treatment directly from AscentCare. AscentCare states, "To connect with a healthcare professional for abortion pill reversal treatment, call [the APR Hotline] as soon as possible," and explains, "The [APR] hotline representative will contact AscentCare, *even if it's after hours or on the weekend*. AscentCare will then contact you to arrange your care. We work quickly to get you the necessary medication, a limited obstetric ultrasound, and the emotional support you need." (emphasis in original.) Elsewhere AscentCare urges consumers, "If you have taken RU486 (mifepristone), call the Abortion Pill Reversal Hotline now," and provides an embedded hyperlink to abortionpillreversal.com, so that AscentCare can be looped in to "arrange your care."

164. AscentCare's website includes some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, and AscentCare adopts and spreads HBI's misleading and/or false claims and omissions by directing consumers to abortionpillreversal.com.

165. AscentCare's website claims that APR will "reverse" a medication abortion and repeatedly uses the term "reverse." For example, the website states, "Is it possible to reverse medication abortion? Yes, it is possible!"

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166. AscentCare's website contains an additional informational page on APR, ascentcare.org/what-you-need-to-know-about-abortion-pill-reversal, that includes claims about APR's efficacy. The website states, "In one study, [APR] was successful up to 64-68% of the time." AscentCare cites and embeds a hyperlink to the abstract for the flawed 2018 Case Series as the basis for this claim about APR's success rate. AscentCare also states that this "study" "concluded" that progesterone is "effective in reversing mifepristone."

167. AscentCare's website does not include any information about potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen. In contrast, AscentCare's webpage on abortion, ascentcare.org/options/abortion, includes information about potential risks and side effects of medication abortion.

168. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and likely to mislead consumers to believe that APR reverses an abortion, has been proven effective, and poses little or no safety risks.

CompassCare

169. CompassCare advertises several pregnancy-related services, including APR treatment, through its website, compasscare.info, and its Facebook page. CompassCare provides APR treatment to consumers directly on-site and makes misleading and/or false claims and omissions about APR.

170. CompassCare advertises its on-site APR treatment through its webpage titled "Abortion Pill Reversal," compasscare.info/medical-services/abortion-pill-reversal.

171. CompassCare's website describes APR and the process through which consumers can obtain this treatment directly from CompassCare: "**If you have taken mifepristone in the last 72 hours, have NOT taken misoprostol and want to continue with a healthy pregnancy, it**

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may be possible to reverse the effects of a medical abortion. Call CompassCare immediately. We will perform an ultrasound to confirm that your baby is alive. If your baby is viable, your medical abortion reversal will involve natural progesterone treatments for about two and a half weeks." (emphasis in original.)

172. CompassCare's website directs consumers who are "Not from Western NY" to "call the [APR hotline] or visit abortionpillreversal.com."

173. CompassCare's website includes some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, and CompassCare adopts and spreads HBI's misleading and/or false claims and omissions by directing consumers to abortionpillreversal.com.

174. CompassCare's website claims that APR will "reverse" an abortion. For example, the website reads, "Can the abortion pill process be reversed? Yes, it is possible to reverse a medical abortion."

175. CompassCare's website includes an embedded video, apparently created by CompassCare, in which a CompassCare healthcare provider asks: "Can the abortion pill process be reversed?" and answers: "Yes, it can" (0:13-0:16).

176. CompassCare makes claims about APR's efficacy. For example, CompassCare's website claims, "If progesterone therapy is administered within 72 hours of taking mifepristone and before taking misoprostol, it is possible to reverse the effects of the abortion."

177. In support of this claim, CompassCare cites and embeds a hyperlink to a one-page document by Delgado titled, "The Reversal of Mifepristone with Progesterone." This document appears to be the first page of a 2015 summary article describing Delgado's APR protocol.

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178. CompassCare also states that through the APR protocol, "[b]y increasing the amount of progesterone present after taking mifepristone (the progesterone blocker), the baby can still receive pregnancy-sustaining progesterone and has a greater chance of continuing to develop." No citation is provided to support this claim.

179. CompassCare's website does not include any information about the potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen. Rather, in the embedded video discussed above, CompassCare claims that "progesterone therapy has been used to prevent spontaneous abortion, also known as miscarriage, since the 1950s. Now, progesterone therapy is also being used to prevent the completion of induced abortion." (0:22-0:35)

180. In contrast, CompassCare's website includes a separate webpage titled "Abortion Risks and Side Effects," compasscare.info/health-information/abortion/abortion-risks-and-side-effects, that includes extensive statements about the potential side effects, complications, and "future health risks" of abortion, including sepsis, infertility, and death. While these risks exist, they are exceedingly small, and abortion has been proven to be safe.

181. CompassCare's Facebook page also makes claims that APR will "reverse" an abortion. For example:

a. A post from November 27, 2017, an image of which is attached hereto as Exhibit G, includes the statement "So far, of the women that have come into CompassCare having started a medical abortion, it's been 100% successful in reversing the abortion and saving the baby."

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b. A post from May 3, 2013, an image of which is attached hereto as Exhibit H, includes the statement "CompassCare can now 'Reverse Abortion!' Truly ground breaking."

182. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and likely to mislead consumers to believe that APR reverses an abortion, has been proven effective, and poses little or no safety risks.

Soundview Pregnancy Services

183. Soundview Pregnancy Services has advertised several pregnancy-related services, including APR treatment, through its website, soundviewpregnancy.com. Soundview Pregnancy Services has provided APR treatment to consumers and has made misleading and/or false claims and omissions about APR.

184. Soundview Pregnancy Services has advertised the APR treatment it has provided through its affiliated medical providers on its webpage titled "Abortion Pill Reversal", soundviewpregnancy.com/abortion-pill-reversal. Although unavailable at the time of this filing, this APR-dedicated webpage was publicly accessible until at least April 15, 2024. An image of this complete webpage is attached hereto as Exhibit I.

185. Soundview Pregnancy Services' APR webpage has directed consumers to "[c]all the Abortion Pill Reversal Network Now at 1-877-558-0333. The Network Nurse will connect you with one of Soundview's affiliated Medical Providers . . . The medical provider will work quickly with you to arrange your care including the Progesterone Protocol, Diagnostic Ultrasound, and the emotional support and care you need and deserve."

186. Soundview Pregnancy Services' APR webpage has included some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com.

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187. Soundview Pregnancy Services' APR webpage has included claims that APR treatment will "reverse" an abortion. For example, the webpage asked, "CAN A MEDICAL ABORTION PROCESS BE REVERSED?" and answered, "Yes, a Progesterone protocol can help reverse the effects of a medical abortion."

188. Soundview Pregnancy Services' APR webpage has included claims about the efficacy of APR treatment. The webpage claimed, "IT MAY NOT BE TOO LATE TO SAVE YOUR PREGNANCY!" and that progesterone "can help reverse the effects of a medical abortion."

189. Soundview Pregnancy Services' website did not include any information about potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen. On its APR webpage, Soundview Pregnancy Services has described progesterone as the means for "reversing the effects of a medication abortion" and that progesterone is "a critical hormone for supporting pregnancy," thereby implying that the use of progesterone in APR is safe.

190. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and likely to mislead consumers to believe that APR reverses an abortion, has been proven effective, and poses little or no safety risks.

New Hope

191. New Hope advertises several pregnancy-related services, including APR treatment, through its website, newhopefamilyservices.com. New Hope directs consumers to APR treatment through abortionpillreversal.com and the APR Hotline and makes misleading and/or false claims and omissions about APR.

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192. On its webpage titled "Abortion Pill Reversal," newhopefamilyservices.com/abortion-pill-reversal, New Hope directs consumers "who took the abortion pill and need help" to "[c]ontact us or the Abortion Pill Reversal Network (APR) Immediately," and embeds a hyperlink to abortionpillreversal.com.

193. New Hope's website includes some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, and New Hope adopts and spreads HBI's misleading and/or false claims and omissions by directing consumers to abortionpillreversal.com.

194. New Hope's website also cites to abortionpillreversal.com as a reference for its own statements about APR.

195. New Hope's website states that APR will "reverse" medication abortion. For example, the website states, "Is abortion pill reversal possible? **Yes, reversal of the abortion pill is possible**." (emphasis in original.)

196. New Hope makes several claims about APR's efficacy. New Hope's website states that "[t]here is an effective process called Abortion Pill Reversal (Or Rescue) that can reverse the effects of the first drug given during a medication abortion," and embeds a hyperlink to abortionpillreversal.com in this text.

197. New Hope's website implies that the FDA approves of APR, by referencing the FDA's 1998 approval of progesterone. However, that approval was for its use in post-menopausal, i.e., *non*-pregnant, women.

198. New Hope's website does not include any information about potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen. New Hope also claims, "Is abortion pill reversal safe? Yes," and goes on to imply that the use of progesterone as part of APR "has an extensive safety record."

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199. In a February 6, 2024, blog post on its website titled "Is Abortion Pill Regret Real," newhopefamilyservices.com/post/is-abortion-pill-regret-real, New Hope directs consumers to APR medical services through abortionpillreversal.com, stating, "For immediate assistance, click here," and embeds a hyperlink to abortionpillreversal.com.

200. This blog post describes "successful reversals," and includes several other misleading statements about APR's efficacy. For example, it claims that the use of progesterone in APR provides "a renewed opportunity to continue the pregnancy." New Hope also claims that "[w]hile the optimal window for Abortion Pill Reversal is within 72 hours of taking the first abortion pill, successful reversals have been achieved outside this timeframe." The blog post references the flawed 2018 Case Series as a source for its statements about APR and APR's efficacy. This blog post also references anecdotal claims that other individuals successfully followed the APR protocol when they regretted their decision to begin a medication abortion: "this [regret] led them to explore a possible second chance, and through Abortion Pill Reversal, they received just that!" The reference to "Abortion Pill Reversal" embeds a hyperlink to abortionpillreversal.com.

201. This blog post also includes misleading statements and omissions about the risks of APR. The blog purports to tell consumers considering APR what they "Need to Know," including that progesterone "can induce side effects like sleepiness, fatigue, dizziness, gastrointestinal discomfort, and headaches," but assures consumers that "the potential second chance [APR] represents is priceless." The blog post does not include any other information about the health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen, thereby implying that the only risks are those enumerated.

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202. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and are likely to mislead consumers to believe that APR reverses an abortion, has been proven effective, and poses little or no safety risks.

Care Net Penn Yan

203. Care Net Penn Yan advertises several pregnancy-related services, including APR treatment, through its website, carenetpy.com. Care Net Penn Yan directs consumers to APR treatment through abortionpillreversal.com and the APR Hotline and makes misleading and/or false claims and omissions about APR.

204. On its webpage titled "Abortion Pill Reversal," carenetpy.com/be-informed/abortion-pill-reversal, Care Net Penn Yan repeatedly directs consumers to obtain APR treatment through the APRN by calling the APR Hotline or visiting abortionpillreversal.com. For example, Care Net Penn Yan's website directs consumers seeking "help" after starting the medication abortion process to "talk with someone about reversal," by calling 877-558-0333 or visiting "the Abortion Pill Reversal website" and embeds a hyperlink in that text to abortionpillreversal.com.

205. Care Net Penn Yan's website poses the question, "Where do I start the APR protocol?" and provides the following answer:

> "The APR Network is an international network with many medical professionals who are trained and ready to assist you with reversal. The hotline is staffed 24/7 and there is always a nurse ready to talk with you and provide the help you need. You can call the APR hotline at 877-558-0333 to speak with a nurse who will discuss the reversal process, answer your questions, and complete a medical intake with you. The nurse will then connect you with a medical professional in your area who is able to begin the reversal protocol."

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206. Care Net Penn Yan's website includes some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, and Care Net Penn Yan adopts and spreads HBI's misleading and/or false claims and omissions by directing consumers to abortionpillreversal.com.

207. Care Net Penn Yan's website also cites abortionpillreversal.com as a reference for its own statements about APR.

208. Care Net Penn Yan's website claims that APR will "reverse" a medication abortion. For example, the website states, "Even if you have started the chemical abortion process, reversal may still be a choice for you."

209. Care Net Penn Yan's website makes several claims about APR's efficacy. Care Net Penn Yan claims that the progesterone prescribed as part of APR will "restabilize the pregnancy" and that APR "increases the likelihood of continuing the pregnancy." Care Net Penn Yan also claims that "[i]nitial studies of APR have shown it is successful about 68% of the time."

210. Care Net Penn Yan's website implies that APR has been proven safe by claiming that "[n]either mifepristone nor progesterone is associated with birth defects" and referencing the ACOG Practice Bulletin discussed above (Paras. 150-157), as well as unidentified "initial studies" that it claims "have found that the birth defect rate in babies born after APR is less than or equal to the rate in the general population."

211. By citing to the ACOG Practice Bulletin, Care Net Penn Yan's website implies that ACOG approves of APR. It does not. To the extent the "initial studies" referenced by Care Net Penn Yan are the 2012 and 2018 Case Series, both are flawed for the reasons stated above (Paras. 54-157).

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212. Care Net Penn Yan's website does not include any information about potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen. In contrast, Care Net Penn Yan's webpage on abortion, carenetpy.com/be-informed/abortion-information, lists several potential health risks for medication abortion and instructs consumers to seek medical attention if they experience these symptoms.

213. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and likely to mislead consumers to believe that APR reverses an abortion, has been proven effective, and poses little or no safety risks.

Care Net of Wayne County

214. Care Net of Wayne County advertises several pregnancy-related services, including APR treatment, through its website, carenetofwaynecounty.com. Care Net of Wayne County directs consumers to APR treatment through abortionpillreversal.com and the APR Hotline and makes misleading and/or false claims and omissions about APR.

215. On its webpage titled "Abortion Pill Information," carenetofwaynecounty.com/newark-ny-abortion-pill-info, Care Net of Wayne County directs consumers to obtain APR treatment through the APRN by visiting abortionpillreversal.com. Care Net of Wayne County's website states, "If you have recently taken the first pill [mifepristone] and decided not to take the second [misoprostol], please contact Abortion Pill Reversal," and embeds a hyperlink to abortionpillreversal.com.

216. Care Net of Wayne County's website includes some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, and Care Net of Wayne County adopts and spreads HBI's misleading and/or false claims and omissions by directing consumers to abortionpillreversal.com.

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217. Care Net of Wayne County's website also cites abortionpillreversal.com as a reference for its own statement about APR.

218. Care Net of Wayne County's website claims that APR will "reverse" mifepristone and that APR is effective. The website states, "Reversal is possible if action is taken after the first dose."

219. Care Net of Wayne County's website does not include any information about potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen. In contrast, Care Net of Wayne County's website states that "certain health conditions" limit the use of medication abortion and invites consumers to learn more about the side effects of abortion.

220. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and likely to mislead consumers to believe that APR reverses mifepristone, has been proven effective, and poses little or no safety risks.

Willow Network

221. Willow Network advertises several pregnancy-related services, including APR treatment, on its website, willownetwork.org. Willow Network directs consumers to APR treatment through abortionpillreversal.com and the APR Hotline and makes misleading and/or false claims and omissions about APR.

222. On its webpage titled "The Abortion Pill Info," willownetwork.org/abortion-pill-info, Willow Network directs consumers to APR treatment through abortionpillreversal.com and the APR Hotline. The webpage states, "It may be possible to continue your pregnancy if only the first dose of the abortion pill has been taken. If you regret taking the abortion pill, contact the

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Abortion Pill Reversal hotline at 1-877-558-0333 immediately," and embeds a hyperlink to abortionpillreversal.com in that text.

223. Willow Network's website includes some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, and Willow Network adopts and spreads HBI's misleading and/or false claims and omissions by directing consumers to abortionpillreversal.com.

224. Willow Network also cites abortionpillreversal.com as a reference for the statements included on its own website regarding APR.

225. Willow Network's website claims that APR will "reverse" medication abortion.

226. For example, in a January 15, 2024, blog post on its website titled "Is Abortion Pill Regret Real," willownetwork.org/post/is-abortion-pill-regret-real, Willow Network describes "successful reversals," directs consumers to APR services through abortionpillreversal.com by stating, "For immediate assistance, click here," and embeds a hyperlink to abortionpillreversal.com.

227. This blog post also includes several statements about APR's efficacy. For example, it claims that the use of progesterone in APR provides "a renewed opportunity to continue the pregnancy." Willow Network also claims that "[w]hile the optimal window for Abortion Pill Reversal is within 72 hours of taking the first abortion pill, successful reversals have been achieved outside this timeframe." The blog post references the flawed 2018 Case Series as a source for its statements about APR and APR's efficacy. This blog post also references anecdotal claims that other individuals successfully followed the APR protocol when they regretted their decision to begin a medication abortion: "this [regret] led them to explore a possible second chance, and

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through Abortion Pill Reversal, they received just that!" The reference to "Abortion Pill Reversal" embeds a hyperlink to abortionpillreversal.com.

228. This blog post also includes misleading statements and omissions about the risks of APR. The blog post purports to tell consumers considering APR what they "Need to Know," including that progesterone "can induce side effects like sleepiness, fatigue, dizziness, gastrointestinal discomfort, and headaches," but assures consumers that "the potential second chance [APR] represents is priceless." The blog post does not include any other information about the health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen, thereby implying that the only risks are those enumerated.

229. Willow Network's website does not otherwise include any information about potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen.

230. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and likely to mislead consumers to believe that APR reverses an abortion, has been proven effective, and poses little or no safety risks.

Care Net Pregnancy Center of the Hudson Valley

231. Care Net Pregnancy Center of the Hudson Valley advertises several pregnancy-related services, including APR treatment, on its website, carenetpregnancycenter.com, and its Facebook page. Care Net Pregnancy Center of the Hudson Valley directs consumers to APR treatment through abortionpillreversal.com and the APR Hotline and makes misleading and/or false claims and omissions about APR.

232. On its webpage titled "Abortion Pill Reversal," carenetpregnancycenter.com/index.php/abortion-pill-reversal, Care Net Pregnancy Center of the

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Hudson Valley repeatedly directs consumers to obtain APR treatment through the APRN by calling the APR Hotline or visiting abortionpillreversal.com.

233. For example, Care Net Pregnancy Center of the Hudson Valley's website states, "CALL the 24/7 HOTLINE: (877) 558-0333" and lists "AbortionPillReversal.com" with a hyperlink to abortionpillreversal.com embedded in that text. The website further states, "Call right now, so they can talk with you and offer you help," and "**Please . . . talk with one of the nurses who can guide you towards reversing the effects of the abortion pill. They will help you every step of the way. Call now.**" (emphasis in original.)

234. Care Net Pregnancy Center of the Hudson Valley's website includes some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, and Care Net Pregnancy Center of the Hudson Valley adopts and spreads HBI's misleading and/or false claims and omissions by directing consumers to abortionpillreversal.com.

235. Care Net Pregnancy Center of the Hudson Valley's website claims that APR will "reverse" medication abortion and the effects of medication abortion. For example, Care Net Pregnancy Center of the Hudson Valley describes "reversing the abortion pill" and directs consumers to **"[p]lease . . . talk with one of the nurses who can guide you towards reversing the effects of the abortion pill. They will help you every step of the way. Call now."** (emphasis in original.)

236. Care Net Pregnancy Center of the Hudson Valley makes claims about APR's efficacy. For example, Care Net Pregnancy Center of the Hudson Valley's website states, "[t]here is an effective process for reversing the abortion pill, called ABORTION PILL REVERSAL, so call today!"

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237. Care Net Pregnancy Center of the Hudson Valley's website does not include any information about potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen. In contrast, Care Net Pregnancy Center of the Hudson Valley dedicates a webpage to possible risks of "abortion procedures," including organ damage, heavy bleeding, and embolism.

238. Care Net Pregnancy Center of the Hudson Valley's Facebook page makes similar misleading and/or false claims and directs consumers to use the APR Hotline for APR treatment. A post from November 12, 2020, attached hereto as Exhibit J, includes an image with the words "abortion pill" and "reverse," and the following text: "If you have taken the first dose of the abortion pill and regret your decision, time is of the essence. Call this hotline as soon as possible, and they will help you reverse your first pill: 877-558-0333."

239. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and likely to mislead consumers to believe that APR reverses "the abortion pill," has been proven effective, and poses little or no safety risks.

1st Way Life Center

240. 1st Way Life Center has advertised pregnancy-related services, including APR treatment, on its website, 1stwaylifecenter.org. Although unavailable at the time of this filing, this website was publicly accessible until at least March 2024. 1st Way Life Center has directed consumers to APR treatment through abortionpillreversal.com and the APR Hotline and has made misleading and/or false claims and omissions about APR.

241. 1st Way Life Center's website has directed consumers to access APR treatment through a hyperlink to abortionpillreversal.com. 1st Way Life Center's website has included an image comprised of several APR-related statements (Figure 2, below), such as "REVERSE YOUR

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ABORTION" and "IF YOU THINK YOU'VE MADE A MISTAKE THERE IS A WAY OUT!! PRESS HERE IMMEDIATELY!!" The image was embedded with a hyperlink to abortionpillreversal.com.

FIGURE 2



242. 1st Way Life Center's website has included some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, and 1st Way Life Center has adopted and spread HBI's misleading and/or false claims and omissions by directing consumers to abortionpillreversal.com.

243. 1st Way Life Center's website has included the claim that APR will "reverse" abortion. The website has stated "REVERSE YOUR ABORTION" and has included an embedded hyperlink to abortionpillreversal.com.

244. 1st Way Life Center's website has not include any information about potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen.

245. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and likely to mislead consumers to believe that APR reverses an abortion, has been proven effective, and poses little or no safety risks.

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Caring Choices

246. Caring Choices advertises several pregnancy-related services, including APR treatment, on its website, caringchoicesphc.com. Caring Choices directs consumers to APR treatment through abortionpillreversal.com and the APR Hotline and makes misleading and/or false claims and omissions about APR.

247. On its website caringchoicesphc.com/abortion-pill-webster-rochester-ny, Caring Choices directs consumers to obtain APR treatment by visiting abortionpillreversal.com. Caring Choices' website states, "If you have recently taken the first pill and decided not to take the second, please contact Abortion Pill Reversal," and embeds a hyperlink to abortionpillreversal.com in this text.

248. Caring Choices' website includes some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, and Caring Choices adopts and spreads HBI's misleading and/or false claims and omissions by directing consumers to abortionpillreversal.com. Caring Choices' website also cites abortionpillreversal.com as a reference for its own statements about APR.

249. Caring Choices' website claims that APR will "reverse" an abortion. Caring Choices' website asks: "Is reversal possible?" It states in response: "Reversal may be possible if action is taken after the first dose."

250. Caring Choices' website does not include any information about potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen. In contrast, the website mentions that "health conditions" and "medical conditions" may limit the use of mediation abortion.

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251. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and likely to mislead consumers to believe that APR reverses an abortion, has been proven effective, and poses little or no safety risks.

Bridge Women's Support Center

252. Bridge Women's Support Center advertises several pregnancy-related services, including APR treatment, on its website, bwscny.org. Bridge Women's Support Center directs consumers to APR treatment through abortionpillreversal.com and the APR Hotline and makes misleading and/or false claims and omissions about APR.

253. On its webpage titled "Taking Care of Yourself After Your Abortion," bwscny.org/post/taking-care-of-yourself-after-an-abortion, Bridge Women's Support Center instructs consumers to obtain APR treatment through the APRN by visiting abortionpillreversal.com. Bridge Women's Support Center's website states: "If you've recently taken the first dose of the abortion pill and change your mind about your decision, contact Abortion Pill Reversal today. It may be possible to continue a healthy pregnancy." It embeds a hyperlink to abortionpillreversal.com in this text.

254. On a different webpage, bwscny.org/post/at-home-abortion-info-flushing-ny, Bridge Women's Support Center states: "If you regret taking the pill, contact the Abortion Pill Reversal network immediately. They will discreetly connect you with a network of doctors and health professionals that can start the reversal process." It embeds a hyperlink to abortionpillreversal.com in this text.

255. Bridge Women's Support Center's website includes some of the same misleading and/or false claims and omissions that HBI makes on abortionpillreversal.com, and Bridge

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Women's Support Center adopts and spreads HBI's misleading and/or false claims and omissions by directing consumers to abortionpillreversal.com.

256. Bridge Women's Support Center's website claims that APR will "reverse" the abortion process. Bridge Women's Support Center website states, "The abortion process can often be reversed if you have only taken the first dose."

257. Bridge Women's Support Center's website does not include any information about potential health and safety risks associated with APR or failing to complete the two-drug medication abortion regimen. In contrast, the website includes warnings about the purported risks of medication abortion: "The abortion pill comes with a black box label, which is the highest level of caution assigned by the FDA. Taking the abortion pill without seeing a doctor or having an ultrasound is never recommended. The side effects range from unpleasant (cramping, bleeding, nausea, headache, fever) to life-threatening (sepsis, rupturing of the uterus, undiagnosed ectopic pregnancy, and more)."

258. These claims and omissions are misleading and/or false for the reasons stated above (Paras. 54-157) and likely to mislead reasonable consumers to believe that APR reverses an abortion, has been proven effective, and poses little or no safety risks.

FIRST CAUSE OF ACTION
VIOLATION OF GBL § 349

259. The NYAG repeats and re-alleges paragraphs 1 through 258 as if fully set forth herein.

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260. GBL § 349 prohibits deceptive acts or practices in the conduct of any business, trade, or commerce, or in the furnishing of any service, in the state of New York, including in the advertising of health care services to the public.

261. GBL § 349(b) authorizes the NYAG to bring an action to enjoin deceptive acts or practices in the conduct of any business, trade, or commerce, or in the furnishing of any service, in the state of New York, including in the advertising of health care services to the public.

262. At all relevant times, Defendants have been engaged in business, trade, or commerce, or in the furnishing of any service in New York within the meaning of GBL § 349.

263. Defendants have engaged in deceptive acts and practices in the conduct of their business, trade, or commerce or in the furnishing of any service by advertising APR services on their websites and other promotional materials, including but not limited to the following:

a. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that abortion, the abortion pill, and/or the abortion pill's effects can be "reversed;"

b. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been proven safe and risk-free;

c. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been proven effective and increases the chances of pregnancy continuation;

d. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has a 64-68% success rate;

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e. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR may be effective even 72 hours after mifepristone has been taken;

f. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been endorsed by ACOG and by the FDA as safe and effective.

264. These misrepresentations and omissions are targeted at convincing consumers not to complete their medication abortion and instead undergo APR treatment. Because these misrepresentations and omissions directly relate to the efficacy and safety of a medical treatment, they are likely to mislead a reasonable consumer deciding whether to obtain this treatment and are therefore material.

265. By their actions, Defendants have violated GBL § 349.

SECOND CAUSE OF ACTION
VIOLATION OF GBL § 350

266. The NYAG repeats and re-alleges paragraphs 1 through 258 as if fully set forth herein.

267. GBL § 350 prohibits false advertising in the conduct of any business, trade, or commerce, or in the furnishing of any service, in the State of New York.

268. At all relevant times, Defendants have been engaged in business, trade, or commerce or in the furnishing of any service in New York within the meaning of GBL § 350.

269. Defendants have engaged in false advertising in the conduct of their business, trade, or commerce or in the furnishing of any service by advertising APR services on their websites and

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other promotional materials through statements about APR that are materially misleading, including but not limited to the following:

a. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that abortion, the abortion pill, and/or the abortion pill's effects can be "reversed;"

b. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been proven safe and risk-free;

c. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been proven effective and increases the chances of pregnancy continuation;

d. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has a 64-68% success rate;

e. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply APR may be effective even 72 hours after mifepristone has been taken;

f. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been endorsed by ACOG and by the FDA as safe and effective.

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270. These misrepresentations and omissions are targeted at convincing consumers not to complete their medication abortion and instead undergo APR treatment. Because these misrepresentations and omissions directly relate to the efficacy and safety of a medical treatment, they are likely to mislead a reasonable consumer deciding whether to obtain this treatment and are therefore material.

271. By their actions, Defendants have violated GBL § 350.

THIRD CAUSE OF ACTION
PURSUANT TO EXECUTIVE LAW § 63(12)
VIOLATION OF GBL § 349

272. The NYAG repeats and re-alleges paragraphs 1 through 258 as if fully set forth herein.

273. Executive Law § 63(12) authorizes the NYAG to bring an action when any person or entity engages in repeated or persistent illegal acts in the carrying on, conducting, or transaction of a business.

274. GBL § 349 prohibits deceptive acts or practices in the conduct of any business, trade, or commerce, or in the furnishing of any service, in the state of New York, including in the advertising of health care services to the public.

275. At all relevant times, Defendants have engaged in the carrying on, conducting, or transaction of business in New York within the meaning of Executive Law § 63(12).

276. Defendants have engaged in repeated or persistent deceptive acts and practices in carrying on, conducting, or the transaction of their business, trade, or commerce, or in the furnishing of any service through the advertising of APR services on their websites and other promotional materials, including but not limited to the following:

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a. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that abortion, the abortion pill, and/or the abortion pill's effects can be "reversed;"

b. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been proven safe and risk-free;

c. Defendants have made misrepresentations and/or omissions and in the course of advertising APR services to the public that state or otherwise imply that APR has been proven effective and increases the chances of pregnancy continuation;

d. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has a 64-68% success rate;

e. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR may be effective even 72 hours after mifepristone has been taken;

f. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been endorsed by ACOG and by the FDA as safe and effective.

277. These misrepresentations and omissions are targeted at convincing consumers not to complete their medication abortion and instead undergo APR treatment. Because these misrepresentations and omissions directly relate to the efficacy and safety of a medical treatment, they are likely to mislead a reasonable consumer deciding whether to obtain this treatment and are therefore material.

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278. By engaging in the acts and practices alleged above, in violation of GBL § 349, Defendants have engaged in repeated or persistent illegal conduct in violation of Executive Law § 63(12).

FOURTH CAUSE OF ACTION
PURSUANT TO EXECUTIVE LAW § 63(12)
VIOLATION OF GBL § 350

279. The NYAG repeats and re-alleges paragraphs 1 through 258 as if fully set forth herein.

280. Executive Law § 63(12) authorizes the NYAG to bring an action when any person or entity engages in repeated or persistent illegal acts in the carrying on, conducting, or transaction of business.

281. GBL § 350 prohibits false advertising in the conduct of any business, trade, or commerce, or in the furnishing of any service, in the State of New York.

282. At all relevant times, Defendants have engaged in the carrying on, conducting, or transaction of business in New York within the meaning of Executive Law § 63(12).

283. Defendants have engaged in repeated or persistent false advertising in the carrying on, conducting, or the transaction of their business, trade, or commerce, or in the furnishing of any service through the advertising of APR services on their websites and other promotional materials through statements about APR that are materially misleading, including but not limited to the following:

a. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply

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that abortion, the abortion pill, and/or the abortion pill's effects can be "reversed;"

b. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been proven safe and risk-free;

c. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been proven effective and increases the chances of pregnancy continuation;

d. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has a 64-68% success rate;

e. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR may be effective even 72 hours after mifepristone has been taken;

f. Defendants have made material misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been endorsed by ACOG and by the FDA as safe and effective.

284. These misrepresentations and omissions are targeted at convincing consumers not to complete their medication abortion and instead undergo APR treatment. Because these misrepresentations and omissions directly relate to the efficacy and safety of a medical treatment, they are likely to mislead a reasonable consumer deciding whether to obtain this treatment and are therefore material.

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285. By engaging in the acts and practices alleged above, in violation of GBL § 350, Defendants have engaged in repeated or persistent illegal conduct in violation of Executive Law § 63(12).

FIFTH CAUSE OF ACTION
VIOLATION OF EXECUTIVE LAW § 63(12)
FRAUD

286. The NYAG repeats and re-alleges paragraphs 1 through 258 as if fully set forth herein.

287. Executive Law § 63(12) authorizes the NYAG to bring an action when any person or entity engages in repeated or persistent fraudulent acts in the carrying on, conducting, or transaction of business.

288. Executive Law § 63(12) broadly defines "fraud" or "fraudulent" to include "any device, scheme or artifice to defraud and any deception, misrepresentation, concealment, suppression, false pretense, false promise or unconscionable contractual provision."

289. At all relevant times, Defendants have engaged in carrying on, conducting, or transaction of business in New York within the meaning of Executive Law § 63(12).

290. Defendants have engaged in repeated or persistent fraudulent acts and practices in carrying on, conducting, or the transaction of their business through the advertising of APR services on their websites and other promotional materials, including but not limited to the following:

a. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that abortion, the abortion pill, and/or the abortion pill's effects can be "reversed;"

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b. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been proven safe and risk-free;

c. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been proven effective and increases the chances of pregnancy continuation;

d. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has a 64-68% success rate;

e. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR may be effective even 72 hours after mifepristone has been taken;

f. Defendants have made misrepresentations and/or omissions in the course of advertising APR services to the public that state or otherwise imply that APR has been endorsed by ACOG and by the FDA as safe and effective.

291. By engaging in the acts and practices alleged above, Defendants have engaged in repeated or persistent fraudulent conduct in violation of Executive Law § 63(12).

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests an order and judgment:

a. Declaring that Defendants' statements described in the Complaint violate New York Executive Law § 63(12) and General Business Law Article 22-A, §§ 349 and 350;

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b. Directing Defendants to remove from their websites, social media accounts, and other promotional materials, statements that violate New York Executive Law § 63(12) and General Business Law Article 22-A, §§ 349 and 350;

c. Permanently enjoining Defendants from violating New York Executive Law § 63(12) and General Business Law Article 22-A, §§ 349 and 350, and from engaging in the fraudulent, deceptive, and illegal acts or practices alleged in the Complaint;

d. Granting the State civil penalties of $5,000 per violation of General Business Law Article 22-A, pursuant to General Business Law § 350-d(a);

e. Awarding the State additional costs of $2,000.00 against each Defendant pursuant to CPLR § 8303(a)(6);

f. Ordering Defendants to pay the State's costs and reasonable attorney's fees;

g. Granting such other and further relief as the Court deems just and proper.

Dated: New York, New York
May 6, 2024

Respectfully submitted,

LETITIA JAMES
Attorney General of the State of New York
Attorney for Plaintiff

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Sudarsana Srinivasan
Bureau Chief
Health Care Bureau

Sandra Park
Bureau Chief
Civil Rights Bureau

Eve Woodin
Assistant Attorney General
Health Care Bureau

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Attachment 6

Syllabus

CENTRAL HUDSON GAS & ELECTRIC CORP. *v.* PUBLIC SERVICE COMMISSION OF NEW YORK

APPEAL FROM THE COURT OF APPEALS OF NEW YORK

No. 79–565. Argued March 17, 1980—Decided June 20, 1980

Held: A regulation of appellee New York Public Service Commission which completely bans an electric utility from advertising to promote the use of electricity violates the First and Fourteenth Amendments. Pp. 561–572.

(a) Although the Constitution accords a lesser protection to commercial speech than to other constitutionally guaranteed expression, nevertheless the First Amendment protects commercial speech from unwarranted governmental regulation. For commercial speech to come within the First Amendment, it at least must concern lawful activity and not be misleading. Next, it must be determined whether the asserted governmental interest to be served by the restriction on commercial speech is substantial. If both inquiries yield positive answers, it must then be decided whether the regulation directly advances the governmental interest asserted, and whether it is not more extensive than is necessary to serve that interest. Pp. 561–566.

(b) In this case, it is not claimed that the expression at issue is either inaccurate or relates to unlawful activity. Nor is appellant electrical utility's promotional advertising unprotected commercial speech merely because appellant holds a monopoly over the sale of electricity in its service area. Since monopoly over the supply of a product provides no protection from competition with substitutes for that product, advertising by utilities is just as valuable to consumers as advertising by unregulated firms, and there is no indication that appellant's decision to advertise was not based on the belief that consumers were interested in the advertising. Pp. 566–568.

(c) The State's interest in energy conservation is clearly substantial and is directly advanced by appellee's regulations. The State's further interest in preventing inequities in appellant's rates—based on the assertion that successful promotion of consumption in "off-peak" periods would create extra costs that would, because of appellant's rate structure, be borne by all consumers through higher overall rates—is also substantial. The latter interest does not, however, provide a constitutionally adequate reason for restricting protected speech because the link between the advertising prohibition and appellant's rate structure is, at most, tenuous. Pp. 568–569.

(d) Appellee's regulation, which reaches all promotional advertising regardless of the impact of the touted service on overall energy use, is more extensive than necessary to further the State's interest in energy conservation which, as important as it is, cannot justify suppressing information about electric devices or services that would cause no net increase in total energy use. In addition, no showing has been made that a more limited restriction on the content of promotional advertising would not serve adequately the State's interests. Pp. 569–571.

47 N. Y. 2d 94, 390 N. E. 2d 749, reversed.

POWELL, J., delivered the opinion of the Court, in which BURGER, C. J., and STEWART, WHITE, and MARSHALL, JJ., joined. BRENNAN, J., filed an opinion concurring in the judgment, *post*, p. 572. BLACKMUN, J., *post*, p. 573, and STEVENS, J., *post*, p. 579, filed opinions concurring in the judgment, in which BRENNAN, J., joined. REHNQUIST, J., filed a dissenting opinion, *post*, p. 583.

Telford Taylor argued the cause for appellant. With him on the briefs were *Walter A. Bossert, Jr.*, and *Davison W. Grant.*

Peter H. Schiff argued the cause for appellee. With him on the brief was *Howard J. Read.**

MR. JUSTICE POWELL delivered the opinion of the Court.

This case presents the question whether a regulation of the Public Service Commission of the State of New York violates the First and Fourteenth Amendments because it completely bans promotional advertising by an electrical utility.

I

In December 1973, the Commission, appellee here, ordered electric utilities in New York State to cease all advertising that "promot[es] the use of electricity." App. to Juris.

*Briefs of *amici curiae* urging reversal were filed by *Cameron F. MacRae* and *Robert L. Baum* for the Edison Electric Institute; by *Burt Neuborne* for Long Island Lighting Co.; by *Edward H. Dowd* and *Myrna P. Field* for the Mid-Atlantic Legal Foundation et al.; and by *Edwin P. Rome* and *William H. Roberts* for Mobil Corp.

Statement 31a. The order was based on the Commission's finding that "the interconnected utility system in New York State does not have sufficient fuel stocks or sources of supply to continue furnishing all customer demands for the 1973–1974 winter." *Id.*, at 26a.

Three years later, when the fuel shortage had eased, the Commission requested comments from the public on its proposal to continue the ban on promotional advertising. Central Hudson Gas & Electric Corp., the appellant in this case, opposed the ban on First Amendment grounds. App. A10. After reviewing the public comments, the Commission extended the prohibition in a Policy Statement issued on February 25, 1977.

The Policy Statement divided advertising expenses "into two broad categories: promotional—advertising intended to stimulate the purchase of utility services—and institutional and informational, a broad category inclusive of all advertising not clearly intended to promote sales." [1] App. to Juris. Statement 35a. The Commission declared all promotional advertising contrary to the national policy of conserving energy. It acknowledged that the ban is not a perfect vehicle for conserving energy. For example, the Commission's order prohibits promotional advertising to develop consumption during periods when demand for electricity is low. By limiting growth in "off-peak" consumption, the ban limits the "beneficial side effects" of such growth in terms of more efficient use of existing powerplants. *Id.*, at 37a. And since oil dealers are not under the Commission's jurisdiction and

[1] The dissenting opinion attempts to construe the Policy Statement to authorize advertising that would result "in a net energy savings" even if the advertising encouraged consumption of additional electricity. *Post,* at 604–605. The attempted construction fails, however, since the Policy Statement is phrased only in terms of advertising that promotes "the purchase of utility services" and "sales" of electricity. Plainly, the Commission did not intend to permit advertising that would enhance net energy efficiency by increasing consumption of electrical services.

thus remain free to advertise, it was recognized that the ban can achieve only "piecemeal conservationism." Still, the Commission adopted the restriction because it was deemed likely to "result in some dampening of unnecessary growth" in energy consumption. *Ibid.*

The Commission's order explicitly permitted "informational" advertising designed to encourage "*shifts* of consumption" from peak demand times to periods of low electricity demand. *Ibid.* (emphasis in orginal). Informational advertising would not seek to increase aggregate consumption, but would invite a leveling of demand throughout any given 24-hour period. The agency offered to review "specific proposals by the companies for specifically described [advertising] programs that meet these criteria." *Id.*, at 38a.

When it rejected requests for rehearing on the Policy Statement, the Commission supplemented its rationale for the advertising ban. The agency observed that additional electricity probably would be more expensive to produce than existing output. Because electricity rates in New York were not then based on marginal cost,[2] the Commission feared that additional power would be priced below the actual cost of generation. The additional electricity would be subsidized by all consumers through generally higher rates. *Id.*, at 57a–58a. The state agency also thought that promotional advertising would give "misleading signals" to the public by appearing to encourage energy consumption at a time when conservation is needed. *Id.*, at 59a.

Appellant challenged the order in state court, arguing that the Commission had restrained commercial speech in violation of the First and Fourteenth Amendments.[3] The Commis-

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[2] "Marginal cost" has been defined as the "*extra* or incremental cost of producing an *extra* unit of output." P. Samuelson, Economics 463 (10th ed. 1976) (emphasis in original).

[3] Central Hudson also alleged that the Commission's order reaches beyond the agency's statutory powers. This argument was rejected by the

sion's order was upheld by the trial court and at the intermediate appellate level.[4] The New York Court of Appeals affirmed. It found little value to advertising in "the noncompetitive market in which electric corporations operate." *Consolidated Edison Co.* v. *Public Service Comm'n,* 47 N. Y. 2d 94, 110, 390 N. E. 2d 749, 757 (1979). Since consumers "have no choice regarding the source of their electric power," the court denied that "promotional advertising of electricity might contribute to society's interest in 'informed and reliable' economic decisionmaking." *Ibid.* The court also observed that by encouraging consumption, promotional advertising would only exacerbate the current energy situation. *Id.,* at 110, 390 N. E. 2d, at 758. The court concluded that the governmental interest in the prohibition outweighed the limited constitutional value of the commercial speech at issue. We noted probable jurisdiction, 444 U. S. 962 (1979), and now reverse.

II

The Commission's order restricts only commercial speech, that is, expression related solely to the economic interests of the speaker and its audience. *Virginia Pharmacy Board* v. *Virginia Citizens Consumer Council,* 425 U. S. 748, 762 (1976); *Bates* v. *State Bar of Arizona,* 433 U. S. 350, 363–364 (1977); *Friedman* v. *Rogers,* 440 U. S. 1, 11 (1979). The First Amendment, as applied to the States through the Fourteenth Amendment, protects commercial speech from unwarranted governmental regulation. *Virginia Pharmacy Board,* 425 U. S., at 761–762. Commercial expression not only serves the economic interest of the speaker, but also assists consumers and furthers the societal interest in the fullest possible

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New York Court of Appeals, *Consolidated Edison Co.* v. *Public Service Comm'n,* 47 N. Y. 2d 94, 102–104, 390 N. E. 2d 749, 752–754 (1979), and was not argued to this Court.

[4] *Consolidated Edison Co.* v. *Public Service Comm'n,* 63 App. Div. 2d 364, 407 N. Y. S. 2d 735 (1978); App. to Juris. Statement 22a (N. Y. Sup. Ct., Feb. 17, 1978).

dissemination of information. In applying the First Amendment to this area, we have rejected the "highly paternalistic" view that government has complete power to suppress or regulate commercial speech. "[P]eople will perceive their own best interests if only they are well enough informed, and . . . the best means to that end is to open the channels of communication, rather than to close them. . . ." *Id.*, at 770; see *Linmark Associates, Inc.* v. *Willingboro,* 431 U. S. 85, 92 (1977). Even when advertising communicates only an incomplete version of the relevant facts, the First Amendment presumes that some accurate information is better than no information at all. *Bates* v. *State Bar of Arizona, supra,* at 374.

Nevertheless, our decisions have recognized "the 'commonsense' distinction between speech proposing a commercial transaction, which occurs in an area traditionally subject to government regulation, and other varieties of speech." *Ohralik* v. *Ohio State Bar Assn.*, 436 U. S. 447, 455–456 (1978); see *Bates* v. *State Bar of Arizona, supra,* at 381; see also Jackson & Jeffries, Commercial Speech: Economic Due Process and the First Amendment, 65 Va. L. Rev. 1, 38–39 (1979).[5] The

[5] In an opinion concurring in the judgment, MR. JUSTICE STEVENS suggests that the Commission's order reaches beyond commercial speech to suppress expression that is entitled to the full protection of the First Amendment. See *post,* at 580–581. We find no support for this claim in the record of this case. The Commission's Policy Statement excluded "institutional and informational" messages from the advertising ban, which was restricted to all advertising "clearly intended to promote sales." App. to Juris. Statement 35a. The complaint alleged only that the "prohibition of promotional advertising by Petitioner is not reasonable regulation of Petitioner's commercial speech. . . ." *Id.,* at 70a. Moreover, the state-court opinions and the arguments of the parties before this Court also viewed this litigation as involving only commercial speech. Nevertheless, the concurring opinion of MR. JUSTICE STEVENS views the Commission's order as suppressing more than commercial speech because it would outlaw, for example, advertising that promoted electricity consumption by touting the environmental benefits of such uses. See *post,* at 581. Ap-

Constitution therefore accords a lesser protection to commercial speech than to other constitutionally guaranteed expression. 436 U. S., at 456, 457. The protection available for particular commercial expression turns on the nature both of the expression and of the governmental interests served by its regulation.

The First Amendment's concern for commercial speech is based on the informational function of advertising. See *First National Bank of Boston* v. *Bellotti,* 435 U. S. 765, 783 (1978). Consequently, there can be no constitutional objection to the suppression of commercial messages that do not accurately inform the public about lawful activity. The government may ban forms of communication more likely to deceive the public than to inform it, *Friedman* v. *Rogers, supra,* at 13, 15–16; *Ohralik* v. *Ohio State Bar Assn., supra,* at 464–465, or

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parently the opinion would accord full First Amendment protection to all promotional advertising that includes claims "relating to . . . questions frequently discussed and debated by our political leaders." *Ibid.*

Although this approach responds to the serious issues surrounding our national energy policy as raised in this case, we think it would blur further the line the Court has sought to draw in commercial speech cases. It would grant broad constitutional protection to any advertising that links a product to a current public debate. But many, if not most, products may be tied to public concerns with the environment, energy, economic policy, or individual health and safety. We rule today in *Consolidated Edison Co.* v. *Public Service Comm'n, ante,* p. 530, that utilities enjoy the full panoply of First Amendment protections for their direct comments on public issues. There is no reason for providing similar constitutional protection when such statements are made only in the context of commercial transactions. In that context, for example, the State retains the power to "insur[e] that the stream of commercial information flow[s] cleanly as well as freely." *Virginia Pharmacy Board* v. *Virginia Citizens Consumer Council,* 425 U. S. 748, 772 (1975). This Court's decisions on commercial expression have rested on the premise that such speech, although meriting some protection, is of less constitutional moment than other forms of speech. As we stated in *Ohralik,* the failure to distinguish between commercial and noncommercial speech "could invite dilution, simply by a leveling process, of the force of the [First] Amendment's guarantee with respect to the latter kind of speech." 436 U. S., at 456.

commercial speech related to illegal activity, *Pittsburgh Press Co.* v. *Human Relations Comm'n,* 413 U. S. 376, 388 (1973).[6]

If the communication is neither misleading nor related to unlawful activity, the government's power is more circumscribed. The State must assert a substantial interest to be achieved by restrictions on commercial speech. Moreover, the regulatory technique must be in proportion to that interest. The limitation on expression must be designed carefully to achieve the State's goal. Compliance with this requirement may be measured by two criteria. First, the restriction must directly advance the state interest involved; the regulation may not be sustained if it provides only ineffective or remote support for the government's purpose. Second, if the governmental interest could be served as well by a more limited restriction on commercial speech, the excessive restrictions cannot survive.

Under the first criterion, the Court has declined to uphold regulations that only indirectly advance the state interest involved. In both *Bates* and *Virginia Pharmacy Board,* the Court concluded that an advertising ban could not be imposed to protect the ethical or performance standards of a profession. The Court noted in *Virginia Pharmacy Board* that "[t]he advertising ban does not directly affect professional standards one way or the other." 425 U. S., at 769. In *Bates,* the Court overturned an advertising prohibition that was designed to protect the "quality" of a lawyer's work.

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[6] In most other contexts, the First Amendment prohibits regulation based on the content of the message. *Consolidated Edison Co.* v. *Public Service Comm'n, ante,* at 537–540. Two features of commercial speech permit regulation of its content. First, commercial speakers have extensive knowledge of both the market and their products. Thus, they are well situated to evaluate the accuracy of their messages and the lawfulness of the underlying activity. *Bates* v. *State Bar of Arizona,* 433 U. S. 350, 381 (1977). In addition, commercial speech, the offspring of economic self-interest, is a hardy breed of expression that is not "particularly susceptible to being crushed by overbroad regulation." *Ibid.*

"Restraints on advertising . . . are an ineffective way of deterring shoddy work." 433 U. S., at 378.[7]

The second criterion recognizes that the First Amendment mandates that speech restrictions be "narrowly drawn." *In re Primus,* 436 U. S. 412, 438 (1978).[8] The regulatory technique may extend only as far as the interest it serves. The State cannot regulate speech that poses no danger to the asserted state interest, see *First National Bank of Boston* v. *Bellotti, supra,* at 794–795, nor can it completely suppress information when narrower restrictions on expression would serve its interest as well. For example, in *Bates* the Court explicitly did not "foreclose the possibility that some limited supplementation, by way of warning or disclaimer or the like, might be required" in promotional materials. 433 U. S., at 384. See *Virginia Pharmacy Board, supra,* at 773. And in *Carey* v. *Population Services International,* 431 U. S. 678, 701–702 (1977), we held that the State's "arguments . . . do not justify the total suppression of advertising concerning contraceptives." This holding left open the possibility that

[7] In *Linmark Associates, Inc.* v. *Willingboro,* 431 U. S. 85, 95–96 (1977), we observed that there was no definite connection between the township's goal of integrated housing and its ban on the use of "For Sale" signs in front of houses.

[8] This analysis is not an application of the "overbreadth" doctrine. The latter theory permits the invalidation of regulations on First Amendment grounds even when the litigant challenging the regulation has engaged in no constitutionally protected activity. *E. g., Kunz* v. *New York,* 340 U. S. 290 (1951). The overbreadth doctrine derives from the recognition that unconstitutional restriction of expression may deter protected speech by parties not before the court and thereby escape judicial review. *Broadrick* v. *Oklahoma,* 413 U. S. 601, 612–613 (1973); see Note, The First Amendment Overbreadth Doctrine, 83 Harv. L. Rev. 844, 853–858 (1970). This restraint is less likely where the expression is linked to "commercial well-being" and therefore is not easily deterred by "overbroad regulation." *Bates* v. *State Bar of Arizona, supra,* at 381.

In this case, the Commission's prohibition acts directly against the promotional activities of Central Hudson, and to the extent the limitations are unnecessary to serve the State's interest, they are invalid.

the State could implement more carefully drawn restrictions. See *id.*, at 712 (POWELL, J., concurring in part and in judgment); *id.*, at 716–717 (STEVENS, J., concurring in part and in judgment).[9]

In commercial speech cases, then, a four-part analysis has developed. At the outset, we must determine whether the expression is protected by the First Amendment. For commercial speech to come within that provision, it at least must concern lawful activity and not be misleading. Next, we ask whether the asserted governmental interest is substantial. If both inquiries yield positive answers, we must determine whether the regulation directly advances the governmental interest asserted, and whether it is not more extensive than is necessary to serve that interest.

III

We now apply this four-step analysis for commercial speech to the Commission's arguments in support of its ban on promotional advertising.

A

The Commission does not claim that the expression at issue either is inaccurate or relates to unlawful activity. Yet the New York Court of Appeals questioned whether Central Hudson's advertising is protected commercial speech. Because appellant holds a monopoly over the sale of electricity in its service area, the state court suggested that the Commission's order restricts no commercial speech of any worth. The court stated that advertising in a "noncompetitive market"

[9] We review with special care regulations that entirely suppress commercial speech in order to pursue a nonspeech-related policy. In those circumstances, a ban on speech could screen from public view the underlying governmental policy. See *Virginia Pharmacy Board*, 425 U. S., at 780, n. 8 (STEWART, J., concurring). Indeed, in recent years this Court has not approved a blanket ban on commercial speech unless the expression itself was flawed in some way, either because it was deceptive or related to unlawful activity.

could not improve the decisionmaking of consumers. 47 N. Y. 2d, at 110, 390 N. E. 2d, at 757. The court saw no constitutional problem with barring commercial speech that it viewed as conveying little useful information.

This reasoning falls short of establishing that appellant's advertising is not commercial speech protected by the First Amendment. Monopoly over the supply of a product provides no protection from competition with substitutes for that product. Electric utilities compete with suppliers of fuel oil and natural gas in several markets, such as those for home heating and industrial power. This Court noted the existence of interfuel competition 45 years ago, see *West Ohio Gas Co.* v. *Public Utilities Comm'n,* 294 U. S. 63, 72 (1935). Each energy source continues to offer peculiar advantages and disadvantages that may influence consumer choice. For consumers in those competitive markets, advertising by utilities is just as valuable as advertising by unregulated firms.[10]

Even in monopoly markets, the suppression of advertising reduces the information available for consumer decisions and thereby defeats the purpose of the First Amendment. The New York court's argument appears to assume that the providers of a monopoly service or product are willing to pay for wholly ineffective advertising. Most businesses—even regulated monopolies—are unlikely to underwrite promotional advertising that is of no interest or use to consumers. Indeed, a monopoly enterprise legitimately may wish to inform the public that it has developed new services or terms of doing business. A consumer may need information to aid his decision whether or not to use the monopoly service at all, or how much of the service he should purchase. In the absence of factors that would distort the decision to advertise, we

[10] Several commercial speech decisions have involved enterprises subject to extensive state regulation. *E. g., Friedman* v. *Rogers,* 440 U. S. 1, 4–5 (1979) (optometrists); *Bates* v. *State Bar of Arizona,* 433 U. S. 350 (1977) (lawyers); *Virginia Pharmacy Board* v. *Virginia Citizens Consumer Council, supra,* at 750–752 (pharmacists).

may assume that the willingness of a business to promote its products reflects a belief that consumers are interested in the advertising.[11] Since no such extraordinary conditions have been identified in this case, appellant's monopoly position does not alter the First Amendment's protection for its commercial speech.

B

The Commission offers two state interests as justifications for the ban on promotional advertising. The first concerns energy conservation. Any increase in demand for electricity—during peak or off-peak periods—means greater consumption of energy. The Commission argues, and the New York court agreed, that the State's interest in conserving energy is sufficient to support suppression of advertising designed to increase consumption of electricity. In view of our country's dependence on energy resources beyond our control, no one can doubt the importance of energy conservation. Plainly, therefore, the state interest asserted is substantial.

The Commission also argues that promotional advertising will aggravate inequities caused by the failure to base the utilities' rates on marginal cost. The utilities argued to the Commission that if they could promote the use of electricity in periods of low demand, they would improve their utilization of generating capacity. The Commission responded that promotion of off-peak consumption also would increase consumption during peak periods. If peak demand were to rise, the absence of marginal cost rates would mean that the rates charged for the additional power would not reflect the true costs of expanding production. Instead, the extra costs would

[11] There may be a greater incentive for a utility to advertise if it can use promotional expenses in determining its rate of return, rather than pass those costs on solely to shareholders. That practice, however, hardly distorts the economic decision whether to advertise. Unregulated businesses pass on promotional costs to consumers, and this Court expressly approved the practice for utilities in *West Ohio Gas Co.* v. *Public Utilities Comm'n*, 294 U. S. 63, 72 (1935).

be borne by all consumers through higher overall rates. Without promotional advertising, the Commission stated, this inequitable turn of events would be less likely to occur. The choice among rate structures involves difficult and important questions of economic supply and distributional fairness.[12] The State's concern that rates be fair and efficient represents a clear and substantial governmental interest.

C

Next, we focus on the relationship between the State's interests and the advertising ban. Under this criterion, the Commission's laudable concern over the equity and efficiency of appellant's rates does not provide a constitutionally adequate reason for restricting protected speech. The link between the advertising prohibition and appellant's rate structure is, at most, tenuous. The impact of promotional advertising on the equity of appellant's rates is highly speculative. Advertising to increase off-peak usage would have to increase peak usage, while other factors that directly affect the fairness and efficiency of appellant's rates remained constant. Such conditional and remote eventualities simply cannot justify silencing appellant's promotional advertising.

In contrast, the State's interest in energy conservation is directly advanced by the Commission order at issue here. There is an immediate connection between advertising and demand for electricity. Central Hudson would not contest the advertising ban unless it believed that promotion would increase its sales. Thus, we find a direct link between the state interest in conservation and the Commission's order.

D

We come finally to the critical inquiry in this case: whether the Commission's complete suppression of speech ordinarily protected by the First Amendment is no more extensive than

[12] See W. Jones, Regulated Industries 191–287 (2d ed. 1976).

necessary to further the State's interest in energy conservation. The Commission's order reaches all promotional advertising, regardless of the impact of the touted service on overall energy use. But the energy conservation rationale, as important as it is, cannot justify suppressing information about electric devices or services that would cause no net increase in total energy use. In addition, no showing has been made that a more limited restriction on the content of promotional advertising would not serve adequately the State's interests.

Appellant insists that but for the ban, it would advertise products and services that use energy efficiently. These include the "heat pump," which both parties acknowledge to be a major improvement in electric heating, and the use of electric heat as a "backup" to solar and other heat sources. Although the Commission has questioned the efficiency of electric heating before this Court, neither the Commission's Policy Statement nor its order denying rehearing made findings on this issue. In the absence of authoritative findings to the contrary, we must credit as within the realm of possibility the claim that electric heat can be an efficient alternative in some circumstances.

The Commission's order prevents appellant from promoting electric services that would reduce energy use by diverting demand from less efficient sources, or that would consume roughly the same amount of energy as do alternative sources. In neither situation would the utility's advertising endanger conservation or mislead the public. To the extent that the Commission's order suppresses speech that in no way impairs the State's interest in energy conservation, the Commission's order violates the First and Fourteenth Amendments and must be invalidated. See *First National Bank of Boston* v. *Bellotti*, 435 U. S. 765 (1978).

The Commission also has not demonstrated that its interest in conservation cannot be protected adequately by more limited regulation of appellant's commercial expression. To fur-

ther its policy of conservation, the Commission could attempt to restrict the format and content of Central Hudson's advertising. It might, for example, require that the advertisements include information about the relative efficiency and expense of the offered service, both under current conditions and for the foreseeable future. Cf. *Banzhaf* v. *FCC,* 132 U. S. App. D. C. 14, 405 F. 2d 1082 (1968), cert. denied *sub nom. Tobacco Institute, Inc.* v. *FCC,* 396 U. S. 842 (1969).[13] In the absence of a showing that more limited speech regulation would be ineffective, we cannot approve the complete suppression of Central Hudson's advertising.[14]

IV

Our decision today in no way disparages the national interest in energy conservation. We accept without reservation the argument that conservation, as well as the development of alternative energy sources, is an imperative national goal. Administrative bodies empowered to regulate electric utilities have the authority—and indeed the duty—to take appropriate action to further this goal. When, however, such action in-

[13] The Commission also might consider a system of previewing advertising campaigns to insure that they will not defeat conservation policy. It has instituted such a program for approving "informational" advertising under the Policy Statement challenged in this case. See *supra,* at 560. We have observed that commercial speech is such a sturdy brand of expression that traditional prior restraint doctrine may not apply to it. *Virginia Pharmacy Board* v. *Virginia Citizens Consumer Council,* 425 U. S., at 771–772, n. 24. And in other areas of speech regulation, such as obscenity, we have recognized that a prescreening arrangement can pass constitutional muster if it includes adequate procedural safeguards. *Freedman* v. *Maryland,* 380 U. S. 51 (1965).

[14] In view of our conclusion that the Commission's advertising policy violates the First and Fourteenth Amendments, we do not reach appellant's claims that the agency's order also violated the Equal Protection Clause of the Fourteenth Amendment, and that it is both overbroad and vague.

volves the suppression of speech, the First and Fourteenth Amendments require that the restriction be no more extensive than is necessary to serve the state interest. In this case, the record before us fails to show that the total ban on promotional advertising meets this requirement.[15]

Accordingly, the judgment of the New York Court of Appeals is

Reversed.

MR. JUSTICE BRENNAN, concurring in the judgment.

One of the major difficulties in this case is the proper characterization of the Commission's Policy Statement. I find it impossible to determine on the present record whether the Commission's ban on all "promotional" advertising, in contrast to "institutional and informational" advertising, see *ante,* at 559, is intended to encompass more than "commercial speech." I am inclined to think that MR. JUSTICE STEVENS is correct that the Commission's order prohibits more than mere proposals to engage in certain kinds of commercial transactions, and therefore I agree with his conclusion that the ban surely violates the First and Fourteenth Amendments. But even on the assumption that the Court is correct that the Commission's order reaches only commercial speech, I agree with MR. JUSTICE BLACKMUN that "[n]o differences between commercial speech and other protected speech justify suppression of commercial speech in order to influence public conduct through manipulation of the availability of information." *Post,* at 578.

Accordingly, with the qualifications implicit in the pre-

[15] The Commission order at issue here was not promulgated in response to an emergency situation. Although the advertising ban initially was prompted by critical fuel shortage in 1973, the Commission makes no claim that an emergency now exists. We do not consider the powers that the State might have over utility advertising in emergency circumstances. See *State* v. *Oklahoma Gas & Electric Co.,* 536 P. 2d 887, 895–896 (Okla. 1975).

ceding paragraph, I join the opinions of MR. JUSTICE BLACKMUN and MR. JUSTICE STEVENS concurring in the judgment.

MR. JUSTICE BLACKMUN, with whom MR. JUSTICE BRENNAN joins, concurring in the judgment.

I agree with the Court that the Public Service Commission's ban on promotional advertising of electricity by public utilities is inconsistent with the First and Fourteenth Amendments. I concur only in the Court's judgment, however, because I believe the test now evolved and applied by the Court is not consistent with our prior cases and does not provide adequate protection for truthful, nonmisleading, noncoercive commercial speech.

The Court asserts, *ante,* at 566, that "a four-part analysis has developed" from our decisions concerning commercial speech. Under this four-part test a restraint on commercial "communication [that] is neither misleading nor related to unlawful activity" is subject to an intermediate level of scrutiny, and suppression is permitted whenever it "directly advances" a "substantial" governmental interest and is "not more extensive than is necessary to serve that interest." *Ante,* at 564 and 566. I agree with the Court that this level of intermediate scrutiny is appropriate for a restraint on commercial speech designed to protect consumers from misleading or coercive speech, or a regulation related to the time, place, or manner of commercial speech. I do not agree, however, that the Court's four-part test is the proper one to be applied when a State seeks to suppress information about a product in order to manipulate a private economic decision that the State cannot or has not regulated or outlawed directly.

Since the Court, without citing empirical data or other authority, finds a "direct link" between advertising and energy consumption, it leaves open the possibility that the State may suppress advertising of electricity in order to lessen demand for electricity. I, of course, agree with the Court that,

in today's world, energy conservation is a goal of paramount national and local importance. I disagree with the Court, however, when it says that suppression of speech may be a permissible means to achieve that goal. MR. JUSTICE STEVENS appropriately notes: "The justification for the regulation is nothing more than the expressed fear that the audience may find the utility's message persuasive. Without the aid of any coercion, deception, or misinformation, truthful communication may persuade some citizens to consume more electricity than they otherwise would." *Post*, at 581.

The Court recognizes that we have never held that commercial speech may be suppressed in order to further the State's interest in discouraging purchases of the underlying product that is advertised. *Ante*, at 566, n. 9. Permissible restraints on commercial speech have been limited to measures designed to protect consumers from fraudulent, misleading, or coercive sales techniques.[1] Those designed to deprive consumers of information about products or services that are legally offered for sale consistently have been invalidated.[2]

I seriously doubt whether suppression of information concerning the availability and price of a legally offered product is ever a permissible way for the State to "dampen" demand for or use of the product. Even though "commercial" speech is involved, such a regulatory measure strikes at the heart of the First Amendment. This is because it is a covert attempt

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[1] See *Friedman* v. *Rogers*, 440 U. S. 1, 10 (1979) (Court upheld a ban on practice of optometry under a trade name as a permissible requirement that commercial information " 'appear in such a form . . . as [is] necessary to prevent its being deceptive,' " quoting from *Virginia Pharmacy Board* v. *Virginia Consumer Council*, 425 U. S. 748, 772, n. 24 (1976)); *Ohralik* v. *Ohio State Bar Assn.*, 436 U. S. 447 (1978).

[2] See *Bates* v. *State Bar of Arizona*, 433 U. S. 350 (1977); *Carey* v. *Population Services International*, 431 U. S. 678, 700–702 (1977); *Linmark Associates, Inc.* v. *Willingboro*, 431 U. S. 85 (1977); *Virginia Pharmacy Board* v. *Virginia Consumer Council*, 425 U. S. 748 (1976); *Bigelow* v. *Virginia*, 421 U. S. 809 (1975).

by the State to manipulate the choices of its citizens, not by persuasion or direct regulation, but by depriving the public of the information needed to make a free choice. As the Court recognizes, the State's policy choices are insulated from the visibility and scrutiny that direct regulation would entail and the conduct of citizens is molded by the information that government chooses to give them. *Ante,* at 566, n. 9 ("We review with special care regulations that entirely suppress commercial speech in order to pursue a nonspeech-related policy. In those circumstances, a ban on speech could screen from public view the underlying governmental policy"). See Rotunda, The Commercial Speech Doctrine in the Supreme Court, 1976 U. Ill. Law Forum 1080, 1080–1083.

If the First Amendment guarantee means anything, it means that, absent clear and present danger, government has no power to restrict expression because of the effect its message is likely to have on the public. See generally Comment, First Amendment Protection for Commercial Advertising: The New Constitutional Doctrine, 44 U. Chi. L. Rev. 205, 243–251 (1976). Our cases indicate that this guarantee applies even to commercial speech. In *Virginia Pharmacy Board* v. *Virginia Consumer Council,* 425 U. S. 748 (1976), we held that Virginia could not pursue its goal of encouraging the public to patronize the "professional pharmacist" (one who provided individual attention and a stable pharmacist-customer relationship) by "keeping the public in ignorance of the entirely lawful terms that competing pharmacists are offering." *Id.,* at 770. We noted that our decision left the State free to pursue its goal of maintaining high standards among its pharmacists by "requir[ing] whatever professional standards it wishes of its pharmacists." *Ibid.*

We went on in *Virginia Pharmacy Board* to discuss the types of regulation of commercial speech that, due to the "commonsense differences" between this form of speech and other forms, are or may be constitutionally permissible. We indicated that government may impose reasonable "time,

place, and manner" restrictions, and that it can deal with false, deceptive, and misleading commercial speech. We noted that the question of advertising of illegal transactions and the special problems of the electronic broadcast media were not presented.

Concluding with a restatement of the type of restraint that is not permitted, we said: "What is at issue is whether a State may completely suppress the dissemination of concededly truthful information about entirely lawful activity, fearful of that information's effect upon its disseminators and its recipients. . . . [W]e conclude that the answer to this [question] is in the negative." *Id.*, at 773.

Virginia Pharmacy Board did not analyze the State's interests to determine whether they were "substantial." Obviously, preventing professional dereliction and low quality health care are "substantial," legitimate, and important state goals. Nor did the opinion analyze the ban on speech to determine whether it "directly advance[d]," *ante,* at 566, 569, these goals. We also did not inquire whether a "more limited regulation of . . . commercial expression," *ante,* at 570, would adequately serve the State's interests. Rather, we held that the State "may *not* [pursue its goals] by keeping the public in ignorance." 425 U. S., at 770. (Emphasis supplied.)

Until today, this principle has governed. In *Linmark Associates, Inc.* v. *Willingboro,* 431 U. S. 85 (1977), we considered whether a town could ban "For Sale" signs on residential property to further its goal of promoting stable, racially integrated housing. We did note that the record did not establish that the ordinance was necessary to enable the State to achieve its goal. The holding of *Linmark,* however, was much broader.[3] We stated:

"The constitutional defect in this ordinance, however,

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[3] In my view, the Court today misconstrues the holdings of both *Virginia Pharmacy Board* and *Linmark Associates* by implying that those decisions were based on the fact that the restraints were not closely enough

> is far more basic. The Township Council here, like the Virginia Assembly in *Virginia Pharmacy Bd.*, acted to prevent its residents from obtaining certain information . . . which pertains to sales activity in Willingboro. . . . The Council has sought to restrict the free flow of these data because it fears that otherwise homeowners will make decisions inimical to what the Council views as the homeowners' self-interest and the corporate interest of the township: they will choose to leave town. The Council's concern, then, was not with any commercial aspect of "For Sale" signs—with offerors communicating offers to offerees—but with the substance of the information communicated to Willingboro citizens." *Id.*, at 96.

The Court in *Linmark* resolved beyond all doubt that a strict standard of review applies to suppression of commercial information, where the purpose of the restaint is to influence behavior by depriving citizens of information. The Court followed the strong statement above with an explicit adoption of the standard advocated by Mr. Justice Brandeis in his concurring opinion in *Whitney* v. *California,* 274 U. S. 357, 377 (1927): "If there be time to expose through discussion the falsehood and fallacies, to avert the evil by the processes of education, the remedy to be applied is more speech, not enforced silence. Only an emergency can justify repression." 431 U. S., at 97.

Carey v. *Population Services International,* 431 U. S. 678, 700–702 (1977), also applied to content-based restraints on commercial speech the same standard of review we have applied to other varieties of speech. There the Court held that a ban on advertising of contraceptives could not be justified

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related to the governmental interests asserted. See *ante,* at 564–565, and n. 7. Although the Court noted the lack of substantial relationship between the restraint and the governmental interest in each of those cases, the holding of each clearly rested on a much broader principle.

by the State's interest in avoiding " 'legitimation' of illicit sexual behavior" because the advertisements could not be characterized as " 'directed to inciting or producing imminent lawless action and . . . likely to incite or produce such action,' " *id.*, at 701, quoting *Brandenburg* v. *Ohio*, 395 U. S. 444, 447 (1969).

Our prior references to the " 'commonsense differences' " between commercial speech and other speech " 'suggest that a different degree of protection is necessary to insure that the flow of truthful and legitimate commercial information is unimpaired.' " *Linmark Associates*, 431 U. S., at 98, quoting *Virginia Pharmacy Board*, 425 U. S., at 771–772, n. 24. We have not suggested that the "commonsense differences" between commercial speech and other speech justify relaxed scrutiny of restraints that suppress truthful, nondeceptive, noncoercive commercial speech. The differences articulated by the Court, see *ante*, at 564, n. 6, justify a more permissive approach to regulation of the manner of commercial speech for the purpose of protecting consumers from deception or coercion, and these differences explain why doctrines designed to prevent "chilling" of protected speech are inapplicable to commercial speech. No differences between commercial speech and other protected speech justify suppression of commercial speech in order to influence public conduct through manipulation of the availability of information. The Court stated in *Carey* v. *Population Services International:*

> "Appellants suggest no distinction between commercial and noncommercial speech that would render these discredited arguments meritorious when offered to justify prohibitions on commercial speech. On the contrary, such arguments are clearly directed not at any commercial aspect of the prohibited advertising but at the ideas conveyed and form of expression—*the core of First Amendment values.*" 431 U. S., at 701, n. 28 (emphasis added).

It appears that the Court would permit the State to ban all direct advertising of air conditioning, assuming that a more limited restriction on such advertising would not effectively deter the public from cooling its homes. In my view, our cases do not support this type of suppression. If a governmental unit believes that use or overuse of air conditioning is a serious problem, it must attack that problem directly, by prohibiting air conditioning or regulating thermostat levels. Just as the Commonwealth of Virginia may promote professionalism of pharmacists directly, so too New York may *not* promote energy conservation "by keeping the public in ignorance." *Virginia Pharmacy Board,* 425 U. S., at 770.

MR. JUSTICE STEVENS, with whom MR. JUSTICE BRENNAN joins, concurring in the judgment.

Because "commercial speech" is afforded less constitutional protection than other forms of speech,[1] it is important that the commercial speech concept not be defined too broadly lest speech deserving of greater constitutional protection be inadvertently suppressed. The issue in this case is whether New York's prohibition on the promotion of the use of electricity through advertising is a ban on nothing but commercial speech.

In my judgment one of the two definitions the Court uses in addressing that issue is too broad and the other may be somewhat too narrow. The Court first describes commercial speech as "expression related solely to the economic interests of the speaker and its audience." *Ante,* at 561. Although it is not entirely clear whether this definition uses the subject matter of the speech or the motivation of the speaker as the limiting factor, it seems clear to me that it encompasses speech that is entitled to the maximum protection afforded by the First Amendment. Neither a labor leader's exhortation to

[1] See *Ohralik* v. *Ohio State Bar Assn.,* 436 U. S. 447, 456, quoted *ante,* at 563, n. 5. Cf. *Smith* v. *United States,* 431 U. S. 291, 318 (STEVENS, J., dissenting).

strike, nor an economist's dissertation on the money supply, should receive any lesser protection because the subject matter concerns only the economic interests of the audience. Nor should the economic motivation of a speaker qualify his constitutional protection; even Shakespeare may have been motivated by the prospect of pecuniary reward. Thus, the Court's first definition of commercial speech is unquestionably too broad.[2]

The Court's second definition refers to " 'speech proposing a commercial transaction.' " *Ante,* at 562. A saleman's solicitation, a broker's offer, and a manufacturer's publication of a price list or the terms of his standard warranty would unquestionably fit within this concept.[3] Presumably, the definition is intended to encompass advertising that advises possible buyers of the availability of specific products at specific prices and describes the advantages of purchasing such items. Perhaps it also extends to other communications that do little more than make the name of a product or a service more familiar to the general public. Whatever the precise contours of the concept, and perhaps it is too early to enunciate an exact formulation, I am persuaded that it should not include the entire range of communication that is embraced within the term "promotional advertising."

This case involves a governmental regulation that completely bans promotional advertising by an electric utility. This ban encompasses a great deal more than mere proposals to engage in certain kinds of commercial transactions. It prohibits all advocacy of the immediate or future use of elec-

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[2] See Farber, Commercial Speech and First Amendment Theory, 74 Nw. U. L. Rev. 372, 382–383 (1979):

"Economic motivation could not be made a disqualifying factor [from maximum protection] without enormous damage to the first amendment. Little purpose would be served by a first amendment which failed to protect newspapers, paid public speakers, political candidates with partially economic motives and professional authors." (Footnotes omitted.)

[3] See *id.,* at 386–387.

tricity. It curtails expression by an informed and interested group of persons of their point of view on questions relating to the production and consumption of electrical energy—questions frequently discussed and debated by our political leaders. For example, an electric company's advocacy of the use of electric heat for environmental reasons, as opposed to wood-burning stoves, would seem to fall squarely within New York's promotional advertising ban and also within the bounds of maximum First Amendment protection. The breadth of the ban thus exceeds the boundaries of the commercial speech concept, however that concept may be defined.[4]

The justification for the regulation is nothing more than the expressed fear that the audience may find the utility's message persuasive. Without the aid of any coercion, deception, or misinformation, truthful communication may persuade some citizens to consume more electricity than they otherwise would. I assume that such a consequence would be undesirable and that government may therefore prohibit and punish the unnecessary or excessive use of electricity. But if the perceived harm associated with greater electrical usage is not sufficiently serious to justify direct regulation, surely it does not constitute the kind of clear and present danger that can justify the suppression of speech.

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[4] The utility's characterization of the Commission's ban in its complaint as involving commercial speech clearly does not bind this Court's consideration of the First Amendment issues in this new and evolving area of constitutional law.

Nor does the Commission's intention not to suppress "institutional and informational" speech insure that only "commercial speech" will be suppressed. The blurry line between the two categories of speech has the practical effect of requiring that the utilities either refrain from speech that is close to the line, or seek advice from the Public Service Commission. But the Commission does not possess the necessary expertise in dealing with these sensitive free speech questions; and, in any event, ordinarily speech entitled to maximum First Amendment protection may not be subjected to a prior clearance procedure with a government agency.

Although they were written in a different context, the words used by Mr. Justice Brandeis in his concurring opinion in *Whitney* v. *California,* 274 U. S. 357, 376–377, explain my reaction to the prohibition against advocacy involved in this case:

> "But even advocacy of violation, however reprehensible morally, is not a justification for denying free speech where the advocacy falls short of incitement and there is nothing to indicate that the advocacy would be immediately acted on. The wide difference between advocacy and incitement, between preparation and attempt, between assembling and conspiracy, must be borne in mind. In order to support a finding of clear and present danger it must be shown either that immediate serious violence was to be expected or was advocated, or that the past conduct furnished reason to believe that such advocacy was then contemplated.
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> "Those who won our independence by revolution were not cowards. They did not fear political change. They did not exalt order at the cost of liberty. To courageous, self-reliant men, with confidence in the power of free and fearless reasoning applied through the processes of popular government, no danger flowing from speech can be deemed clear and present, unless the incidence of the evil apprehended is so imminent that it may befall before there is opportunity for full discussion. If there be time to expose through discussion the falsehood and fallacies, to avert the evil by the processes of education, the remedy to be applied is more speech, not enforced silence. Only an emergency can justify repression. Such must be the rule if authority is to be reconciled with freedom. Such, in my opinion, is the command of the Constitution." (Footnote omitted.) [5]

[5] Mr. Justice Brandeis quoted Lord Justice Scrutton's comment in *King* v. *Secretary of State for Home Affairs ex parte O'Brien,* [1923] 2 K. B. 361, 382: " 'You really believe in freedom of speech, if you are willing to

In sum, I concur in the result because I do not consider this to be a "commercial speech" case. Accordingly, I see no need to decide whether the Court's four-part analysis, *ante*, at 566, adequately protects commercial speech—as properly defined—in the face of a blanket ban of the sort involved in this case.

MR. JUSTICE REHNQUIST, dissenting.

The Court today invalidates an order issued by the New York Public Service Commission designed to promote a policy that has been declared to be of critical national concern. The order was issued by the Commission in 1973 in response to the Mideastern oil embargo crisis. It prohibits electric corporations "from *promoting* the use of electricity through the use of advertising, subsidy payments . . . , or employee incentives." State of New York Public Service Commission, Case No. 26532 (Dec. 5, 1973), App. to Juris. Statement 31a (emphasis added). Although the immediate crisis created by the oil embargo has subsided, the ban on promotional advertising remains in effect. The regulation was re-examined by the New York Public Service Commission in 1977. Its constitutionality was subsequently upheld by the New York Court of Appeals, which concluded that the paramount national interest in energy conservation justified its retention.[1]

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allow it to men whose opinions seem to you wrong and even dangerous. . . .'" 274 U. S., at 377, n. 4.

See also *Young* v. *American Mini Theatres, Inc.*, 427 U. S. 50, 63 (opinion of STEVENS, J.).

[1] The New York Court of Appeals stated:

"In light of current exigencies, one of the policies of any public service legislation must be the conservation of our vital and irreplaceable resources. The Legislature has but recently imposed upon the commission a duty 'to encourage all persons and corporations . . . to formulate and carry out long-range programs . . . [for] the preservation of environmental values and the conservation of natural resources' (Public Service Law, § 5, subd. 2). Implicit in this amendment is a legislative recognition of the serious situation which confronts our State and Nation. More important, conservation of resources has become an avowed legislative

The Court's asserted justification for invalidating the New York law is the public interest discerned by the Court to underlie the First Amendment in the free flow of commercial information. Prior to this Court's recent decision in *Virginia Pharmacy Board* v. *Virginia Citizens Consumer Council,* 425 U. S. 748 (1976), however, commercial speech was afforded no protection under the First Amendment whatsoever. See, *e. g., Breard* v. *Alexandria,* 341 U. S. 622 (1951); *Valentine* v. *Chrestensen,* 316 U. S. 52 (1942). Given what seems to me full recognition of the holding of *Virginia Pharmacy Board* that commercial speech is entitled to some degree of First Amendment protection, I think the Court is nonetheless incorrect in invalidating the carefully considered state ban on promotional advertising in light of pressing national and state energy needs.

The Court's analysis in my view is wrong in several respects. Initially, I disagree with the Court's conclusion that the speech of a state-created monopoly, which is the subject of a comprehensive regulatory scheme, is entitled to protection under the First Amendment. I also think that the Court errs here in failing to recognize that the state law is most accurately viewed as an economic regulation and that the speech involved (if it falls within the scope of the First Amendment at all) occupies a significantly more subordinate position in the hierarchy of First Amendment values than the Court gives it today. Finally, the Court in reaching its decision improperly substitutes its own judgment for that of the State in deciding how a proper ban on promotional advertising should be drafted. With regard to this latter point, the Court adopts as its final part of a four-part test a "no more

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policy embodied in the commission's enabling act (see also, *Matter of New York State Council of Retail Merchants* v. *Public Serv. Comm. of State of N. Y.,* 45 N. Y. 2d 661, 673–674)." *Consolidated Edison Co.* v. *Public Service Comm'n,* 47 N. Y. 2d 94, 102–103, 390 N. E. 2d 749, 753 (1979).

extensive than necessary" analysis that will unduly impair a state legislature's ability to adopt legislation reasonably designed to promote interests that have always been rightly thought to be of great importance to the State.

I

In concluding that appellant's promotional advertising constitutes protected speech, the Court reasons that speech by electric utilities is valuable to consumers who must decide whether to use the monopoly service or turn to an alternative energy source, and if they decide to use the service how much of it to purchase. *Ante,* at 567. The Court in so doing "assume[s] that the willingness of a business to promote its products reflects a belief that consumers are interested in the advertising." *Ante,* at 568. The Court's analysis ignores the fact that the monopoly here is entirely state-created and subject to an extensive state regulatory scheme from which it derives benefits as well as burdens.

While this Court has stated that the "capacity [of speech] for informing the public does not depend upon the identity of its source," *First National Bank of Boston* v. *Bellotti,* 435 U. S. 765, 777 (1978), the source of the speech nevertheless may be relevant in determining whether a given message is protected under the First Amendment.[2] When the source of the speech is a state-created monopoly such as this, traditional First Amendment concerns, if they come into play at all, certainly do not justify the broad interventionist role adopted by the Court today. In *Consolidated Edison Co.* v.

[2] In *Brown* v. *Glines,* 444 U. S. 348 (1980), for example, we recently upheld Air Force regulations that imposed restrictions on the free speech and petition rights of Air Force personnel. See also, *e. g., Parker* v. *Levy,* 417 U. S. 733 (1974) (commissioned officer may be prohibited from publicly urging enlisted personnel to disobey orders that might send them into combat); *Snepp* v. *United States,* 444 U. S. 507 (1980) (employees of intelligence agency may be required to submit publications relating to agency activity for prepublication review by the agency).

Public Service Comm'n, ante, at 549–550, MR. JUSTICE BLACKMUN observed:

> "A public utility is a state-created monopoly. See, *e. g.,* N. Y. Pub. Serv. Law § 68 (McKinney 1955); Jones, Origins of the Certificate of Public Convenience and Necessity; Developments in the States 1870–1920, 79 Colum. L. Rev. 426, 458–461 (1979); Comment, Utility Rates, Consumers, and the New York State Public Service Commission, 39 Albany L. Rev. 707, 709–714 (1975). Although monopolies generally are against the public policies of the United States and of the State of New York, see, *e. g.,* N. Y. Gen. Bus. Law § 340 (McKinney 1968 and Supp. 1979–1980), . . . utilities are permitted to operate as monopolies because of a determination by the State that the public interest is better served by protecting them from competition. See 2 A. Kahn, The Economics of Regulation 113–171 (1971).
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> "This exceptional grant of power to private enterprises justifies extensive oversight on the part of the State to protect the ratepayers from exploitation of the monopoly power through excessive rates and other forms of overreaching. . . . New York law gives its Public Service Commission plenary supervisory powers over all property, real and personal, 'used or to be used for or in connection with or to facilitate the . . . sale or furnishing of electricity for light, heat or power.' N. Y. Pub. Serv. Law §§ 2 (12) and 66 (1) (McKinney 1955)."

Thus, although *First National Bank of Boston* v. *Bellotti, supra,* holds that speech of a corporation is entitled to some First Amendment protection, it by no means follows that a utility with monopoly power conferred by a State is also entitled to such protection.

The state-created monopoly status of a utility arises from the unique characteristics of the services that a utility provides. As recognized in *Cantor* v. *Detroit Edison Co.,* 428 U. S. 579, 595–596 (1976), "public utility regulation typically

assumes that the private firm is a natural monopoly and that public controls are necessary to protect the consumer from exploitation." The consequences of this natural monopoly in my view justify much more wide-ranging supervision and control of a utility under the First Amendment than this Court held in *Bellotti* to be permissible with regard to ordinary corporations. Corporate status is generally conferred as a result of a State's determination that the corporate characteristics "enhance its efficiency as an economic entity." *First National Bank of Boston* v. *Bellotti, supra,* at 825–826 (REHNQUIST, J., dissenting). A utility, by contrast, fulfills a function that serves special public interests as a result of the natural monopoly of the service provided. Indeed, the extensive regulations governing decisionmaking by public utilities suggest that for purposes of First Amendment analysis, a utility is far closer to a state-controlled enterprise than is an ordinary corporation.[3] Accordingly, I think a State has broad discretion in determining the statements that a utility may make in that such statements emanate from the entity created by the State to provide important and unique public services. And a state regulatory body charged with the oversight of these types of services may reasonably decide to impose on the utility a special duty to conform its conduct to

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[3] In this regard the New York Court of Appeals stated:

"Public utilities, from the earliest days in this State, have been regulated and franchised to serve the commonweal. Our policy is 'to withdraw the unrestricted right of competition between corporations occupying . . . the public streets . . . and supplying the public with their products or utilities which are well nigh necessities' (*People ex rel. New York Edison Co.* v. *Willcox,* 207 N. Y. 86, 99; *Matter of New York Elec. Lines Co.,* 201 N. Y. 321). The realities of the situation all but dictate that a utility be granted monopoly status (see *People ex rel. New York Elec. Lines Co.* v. *Squire,* 107 N. Y. 593, 603–605). To protect against abuse of this superior economic position extensive governmental regulation has been deemed a necessary coordinate (see *People ex rel. New York Edison Co.* v. *Willcox, supra,* at pp. 93–94)." 47 N. Y. 2d, at 109–110, 390 N. E. 2d, at 757.

the agency's conception of the public interest. Thus I think it is constitutionally permissible for it to decide that promotional advertising is inconsistent with the public interest in energy conservation. I also think New York's ban on such advertising falls within the scope of permissible state regulation of an economic activity by an entity that could not exist in corporate form, say nothing of enjoy monopoly status, were it not for the laws of New York.[4]

II

This Court has previously recognized that although commercial speech may be entitled to First Amendment protection, that protection is not as extensive as that accorded to the advocacy of ideas. Thus, we stated in *Ohralik* v. *Ohio State Bar Assn.*, 436 U. S. 447, 455–456 (1978):

> "Expression concerning purely commercial transactions has come within the ambit of the Amendment's protec-

[4] The Commission's restrictions on promotional advertising are grounded in its concern that electric utilities fulfill their obligation under the New York Public Service Law to provide "adequate" service at "just and reasonable" rates. N. Y. Pub. Serv. Law § 65 (1) (McKinney 1955). The Commission, under state law, is required to set reasonable rates. N. Y. Pub. Serv. Law §§ 66 (2) and 72 (McKinney 1955); § 66 (12) (McKinney Supp. 1979). The Commission has also been authorized by the legislature to prescribe "such reasonable improvements [in electric utilities' practices] as will best promote the public interest. . . ." § 66 (2). And in the performance of its duties the Commission is required to "encourage all persons and corporations subject to its jurisdiction to formulate and carry out long-range programs, individually or cooperatively, for the performance of their public service responsibilities with economy, efficiency, and care for the public safety, the preservation of environmental values, and the conservation of natural resources." N. Y. Pub. Serv. Law § 5 (2) (McKinney Supp. 1979). Here I think it was quite reasonable for the State Public Service Commission to conclude that the ban on promotional advertising was necessary to prevent utilities from using their broad state-conferred monopoly power to promote their own economic well-being at the expense of the state interest in energy conservation—an interest that could reasonably be found to be inconsistent with the promotion of greater profits for utilities.

> tion only recently. In rejecting the notion that such speech 'is wholly outside the protection of the First Amendment,' *Virginia Pharmacy, supra,* at 761, we were careful not to hold 'that it is wholly undifferentiable from other forms' of speech. 425 U. S., at 771, n. 24. We have not discarded the 'common-sense' distinction between speech proposing a commercial transaction, which occurs in an area traditionally subject to government regulation, and other varieties of speech. *Ibid.* To require a parity of constitutional protection for commercial and noncommercial speech alike could invite dilution, simply by a leveling process, of the force of the Amendment's guarantee with respect to the latter kind of speech. Rather than subject the First Amendment to such a devitalization, we instead have afforded commercial speech a limited measure of protection, commensurate with its subordinate position in the scale of First Amendment values, while allowing modes of regulation that might be impermissible in the realm of noncommercial expression." (Footnote omitted.)

The Court's decision today fails to give due deference to this subordinate position of commercial speech. The Court in so doing returns to the bygone era of *Lochner* v. *New York,* 198 U. S. 45 (1905), in which it was common practice for this Court to strike down economic regulations adopted by a State based on the Court's own notions of the most appropriate means for the State to implement its considered policies.

I had thought by now it had become well established that a State has broad discretion in imposing economic regulations. As this Court stated in *Nebbia* v. *New York,* 291 U. S. 502, 537 (1934):

> "[T]here can be no doubt that upon proper occasion and by appropriate measures the state may regulate a business in any of its aspects. . . .

> "So far as the requirement of due process is concerned, and in the absence of other constitutional restriction, a state is free to adopt whatever economic policy may reasonably be deemed to promote public welfare, and to enforce that policy by legislation adapted to its purpose. The courts are without authority either to declare such policy, or, when it is declared by the legislature, to override it. If the laws passed are seen to have a reasonable relation to a proper legislative purpose, and are neither arbitrary nor discriminatory, the requirements of due process are satisfied, and judicial determination to that effect renders a court *functus officio*. . . . [I]t does not lie with the courts to determine that the rule is unwise."

And Mr. Justice Black, writing for the Court, observed more recently in *Ferguson* v. *Skrupa,* 372 U. S. 726, 730 (1963):

> "The doctrine . . . that due process authorizes courts to hold laws unconstitutional when they believe the legislature has acted unwisely—has long since been discarded. We have returned to the original constitutional proposition that courts do not substitute their social and economic beliefs for the judgment of legislative bodies, who are elected to pass laws."

The State of New York has determined here that economic realities require the grant of monopoly status to public utilities in order to distribute efficiently the services they provide, and in granting utilities such status it has made them subject to an extensive regulatory scheme. When the State adopted this scheme and when its Public Service Commission issued its initial ban on promotional advertising in 1973, commercial speech had not been held to fall within the scope of the First Amendment at all. *Virginia Pharmacy Board* v. *Virginia Citizens Consumer Council,* 425 U. S. 748 (1976), however, subsequently accorded commercial speech a limited measure of First Amendment protection.

The Court today holds not only that commercial speech is entitled to First Amendment protection, but also that when it is protected a State may not regulate it unless its reason for doing so amounts to a "substantial" governmental interest, its regulation "directly advances" that interest, and its manner of regulation is "not more extensive than necessary" to serve the interest. *Ante,* at 566. The test adopted by the Court thus elevates the protection accorded commercial speech that falls within the scope of the First Amendment to a level that is virtually indistinguishable from that of noncommercial speech. I think the Court in so doing has effectively accomplished the "devitalization" of the First Amendment that it counseled against in *Ohralik.* I think it has also, by labeling economic regulation of business conduct as a restraint on "free speech," gone far to resurrect the discredited doctrine of cases such as *Lochner* and *Tyson & Brother* v. *Banton,* 273 U. S. 418 (1927). New York's order here is in my view more akin to an economic regulation to which virtually complete deference should be accorded by this Court.

I doubt there would be any question as to the constitutionality of New York's conservation effort if the Public Service Commission had chosen to raise the price of electricity, see, *e. g., Sunshine Anthracite Coal Co.* v. *Adkins,* 310 U. S. 381 (1940); *Old Dearborn Distributing Co.* v. *Seagram-Distillers Corp.,* 299 U. S. 183 (1936), to condition its sale on specified terms, see, *e. g., Nebbia* v. *New York, supra,* at 527–528, or to restrict its production, see, *e. g., Wickard* v. *Filburn,* 317 U. S. 111 (1942). In terms of constitutional values, I think that such controls are virtually indistinguishable from the State's ban on promotional advertising.

An ostensible justification for striking down New York's ban on promotional advertising is that this Court has previously "rejected the 'highly paternalistic' view that government has complete power to suppress or regulate commercial speech. '[P]eople will perceive their own best interests if

only they are well enough informed and . . . the best means to that end is to open the channels of communication, rather than to close them. . . .' " *Ante,* at 562. Whatever the merits of this view, I think the Court has carried its logic too far here.

The view apparently derives from the Court's frequent reference to the "marketplace of ideas," which was deemed analogous to the commercial market in which a laissez-faire policy would lead to optimum economic decisionmaking under the guidance of the "invisible hand." See, *e. g.,* Adam Smith, Wealth of Nations (1776). This notion was expressed by Mr. Justice Holmes in his dissenting opinion in *Abrams* v. *United States,* 250 U. S. 616, 630 (1919), wherein he stated that "the best test of truth is the power of the thought to get itself accepted in the competition of the market. . . ." See also, *e. g., Consolidated Edison* v. *Public Service Comm'n, ante,* at 534; J. Mill, On Liberty (1858); J. Milton, Areopagitica, A Speech for the Liberty of Unlicensed Printing (1644).

While it is true that an important objective of the First Amendment is to foster the free flow of information, identification of speech that falls within its protection is not aided by the metaphorical reference to a "marketplace of ideas." There is no reason for believing that the marketplace of ideas is free from market imperfections any more than there is to believe that the invisible hand will always lead to optimum economic decisions in the commercial market. See, *e. g.,* Baker, Scope of the First Amendment, Freedom of Speech, 25 UCLA L. Rev. 964, 967–981 (1978). Indeed, many types of speech have been held to fall outside the scope of the First Amendment, thereby subject to governmental regulation, despite this Court's references to a marketplace of ideas. See, *e. g., Chaplinsky* v. *New Hampshire,* 315 U. S. 568 (1942) (fighting words); *Beauharnais* v. *Illinois.* 343 U. S. 250 (1952) (group libel); *Roth* v. *United States,* 354 U. S. 476 (1957) (obscenity). It also has been held that the government has

a greater interest in regulating some types of protected speech than others. See, *e. g., FCC* v. *Pacifica Foundation,* 438 U. S. 726 (1978) (indecent speech); *Virginia Pharmacy Board* v. *Virginia Citizens Consumer Council, supra* (commercial speech). And as this Court stated in *Gertz* v. *Robert Welch, Inc.,* 418 U. S. 323, 344, n. 9 (1974): "Of course, an opportunity for rebuttal seldom suffices to undo [the] harm of a defamatory falsehood. Indeed the law of defamation is rooted in our experience that the truth rarely catches up with a lie." The Court similarly has recognized that false and misleading commercial speech is not entitled to any First Amendment protection. See, *e. g., ante,* at 566.

The above examples illustrate that in a number of instances government may constitutionally decide that societal interests justify the imposition of restrictions on the free flow of information. When the question is whether a given commercial message is protected, I do not think this Court's determination that the information will "assist" consumers justifies judicial invalidation of a reasonably drafted state restriction on such speech when the restriction is designed to promote a concededly substantial state interest. I consequently disagree with the Court's conclusion that the societal interest in the dissemination of commercial information is sufficient to justify a restriction on the State's authority to regulate promotional advertising by utilities; indeed, in the case of a regulated monopoly, it is difficult for me to distinguish "society" from the state legislature and the Public Service Commission. Nor do I think there is any basis for concluding that individual citizens of the State will recognize the need for and act to promote energy conservation to the extent the government deems appropriate, if only the channels of communication are left open.[5] Thus, even if I were

[5] Although the Constitution attaches great importance to freedom of speech under the First Amendment so that individuals will be better informed and their thoughts and ideas will be uninhibited, it does not follow that "people will perceive their own best interests," or that if they do

to agree that commercial speech is entitled to some First Amendment protection, I would hold here that the State's decision to ban promotional advertising, in light of the substantial state interest at stake, is a constitutionally permissible exercise of its power to adopt regulations designed to promote the interests of its citizens.

The plethora of opinions filed in this case highlights the doctrinal difficulties that emerge from this Court's decisions granting First Amendment protection to commercial speech. My Brother STEVENS, quoting Mr. Justice Brandeis in *Whitney* v. *California*, 274 U. S. 357, 376–377 (1927), includes Mr. Justice Brandeis' statement that "[t]hose who won our independence by revolution were not cowards. They did not fear political change. They did not exalt order at the cost of liberty." *Ante*, at 582. MR. JUSTICE BLACKMUN, in his separate opinion, joins only in the Court's judgment because he believes that the Court's opinion "does not provide adequate protection for truthful, nonmisleading, noncoercive commercial speech." *Ante*, at 573. Both MR. JUSTICE STEVENS, *ante*, at 582, and MR. JUSTICE BLACKMUN, *ante*, at 577, would apply the following formulation by Mr. Justice Brandeis of the clear-and-present-danger test to the regulation of speech at issue in this case:

"If there be time to expose through discussion the false-

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they will act to promote them. With respect to governmental policies that do not offer immediate tangible benefits and the success of which depends on incremental contributions by all members of society, such as would seem to be the case with energy conservation, a strong argument can be made that while a policy may be in the longrun interest of all members of society, some rational individuals will perceive it to their own shortrun advantage to not act in accordance with that policy. When the regulation of commercial speech is at issue, I think this is a consideration that the government may properly take into account. As was observed in *Townsend* v. *Yeomans*, 301 U. S. 441, 451 (1937), "the legislature, acting within its sphere, is presumed to know the needs of the people of the State." This observation in my view is applicable to the determination of the State Public Service Commission here.

> hood and fallacies, to avert the evil by the processes of education, the remedy to be applied is more speech, not enforced silence. Only an emergency can justify repression." *Whitney* v. *California, supra,* at 377 (concurring opinion).

Although the Court today does not go so far as to adopt this position, its reasons for invalidating New York's ban on promotional advertising make it quite difficult for a legislature to draft a statute regulating promotional advertising that will satisfy the First Amendment requirements established by the Court in this context. See Part III, *infra.*

Two ideas are here at war with one another, and their resolution, although it be on a judicial battlefield, will be a very difficult one. The sort of "advocacy" of which Mr. Justice Brandeis spoke was not the advocacy on the part of a utility to use more of its product. Nor do I think those who won our independence, while declining to "exalt order at the cost of liberty," would have viewed a merchant's unfettered freedom to advertise in hawking his wares as a "liberty" not subject to extensive regulation in light of the government's substantial interest in attaining "order" in the economic sphere.

While I agree that when the government attempts to regulate speech of those expressing views on public issues, the speech is protected by the First Amendment unless it presents "a clear and present danger" of a substantive evil that the government has a right to prohibit, see, *e. g., Schenck* v. *United States,* 249 U. S. 47, 52 (1919), I think it is important to recognize that this test is appropriate in the political context in light of the central importance of such speech to our system of self-government. As observed in *Buckley* v. *Valeo,* 424 U. S. 1, 14 (1976):

> "Discussion of public issues and debate on the qualifications of candidates are integral to the operation of the system of government established by our Constitution. The First Amendment affords the broadest protection to

> such political expression in order 'to assure [the] unfettered interchange of ideas for the bringing about of political and social changes desired by the people.' "

And in *Garrison* v. *Louisiana,* 379 U. S. 64, 74–75 (1964), this Court stated that "speech concerning public affairs is more than self-expression; it is the essence of self-government."

The First Amendment, however, does not always require a clear and present danger to be present before the government may regulate speech. Although First Amendment protection is not limited to the "exposition of ideas" on public issues, see, *e. g., Winters* v. *New York,* 333 U. S. 507, 510 (1948)—both because the line between the informing and the entertaining is elusive and because art, literature, and the like may contribute to important First Amendment interests of the individual in freedom of speech—it is well established that the government may regulate obscenity even though its does not present a clear and present danger. Compare, *e. g., Paris Adult Theatre I* v. *Slaton,* 413 U. S. 49, 57–58 (1973), with *Brandenburg* v. *Ohio,* 395 U. S. 444, 447 (1969). Indecent speech, at least when broadcast over the airwaves, also may be regulated absent a clear and present danger of the type described by Mr. Justice Brandeis and required by this Court in *Brandenburg. FCC* v. *Pacifica Foundation,* 438 U. S. 726 (1978). And in a slightly different context this Court declined to apply the clear-and-present-danger test to a conspiracy among members of the press in violation of the Sherman Act because to do so would "degrade" that doctrine. *Associated Press* v. *United States,* 326 U. S. 1, 7 (1945). Nor does the Court today apply the clear-and-present-danger test in invalidating New York's ban on promotional advertising. As noted above, in these and other contexts the Court has clearly rejected the notion that there must be a free "marketplace of ideas."

If the complaint of those who feel the Court's opinion does not go far enough is that the "only test of truth is its ability

to get itself accepted in the marketplace of ideas"—the test advocated by Thomas Jefferson in his first inaugural address, and by Mr. Justice Holmes in *Abrams* v. *United States,* 250 U. S. 616, 630 (1919) (dissenting opinion)—there is no reason whatsoever to limit the protection accorded commercial speech to "truthful, nonmisleading, noncoercive" speech. See *ante,* at 573 (BLACKMUN, J., concurring in judgment). If the "commercial speech" is in fact misleading, the "marketplace of ideas" will in time reveal that fact. It may not reveal it sufficiently soon to avoid harm to numerous people, but if the reasoning of Brandeis and Holmes is applied in this context, that was one of the risks we took in protecting free speech in a democratic society.

Unfortunately, although the "marketplace of ideas" has a historically and sensibly defined context in the world of political speech, it has virtually none in the realm of business transactions. Even so staunch a defender of the First Amendment as Mr. Justice Black, in his dissent in *Breard* v. *Alexandria,* 341 U. S., at 650, n., stated:

> "Of course I believe that the present ordinance could constitutionally be applied to a 'merchant' who goes from door to door 'selling pots.' "

And yet, with the change in solicitation and advertising techniques, the line between what Central Hudson did here and the peddler selling pots in Alexandria a generation ago is difficult, if not impossible to fix. Doubtless that was why Mr. Justice Black joined the unanimous opinion of the Court in *Valentine* v. *Chrestensen,* 316 U. S., at 54, in which the Court stated:

> "This court has unequivocally held that the streets are proper places for the exercise of the freedom of communicating information and disseminating opinion and that, though the states and municipalities may appropriately regulate the privilege in the public interest, they may not unduly burden or proscribe its employment in these pub-

lic thoroughfares. *We are equally clear that the Constitution imposes no such restraint on government as respects purely commercial advertising.* Whether, and to what extent, one may promote or pursue a gainful occupation in the streets, to what extent such activity shall be adjudged a derogation of the public right of user, are matters for legislative judgment." (Emphasis added.)

I remain of the view that the Court unlocked a Pandora's Box when it "elevated" commercial speech to the level of traditional political speech by according it First Amendment protection in *Virginia Pharmacy Board* v. *Virginia Citizens Consumer Council,* 425 U. S. 748 (1976). The line between "commercial speech," and the kind of speech that those who drafted the First Amendment had in mind, may not be a technically or intellectually easy one to draw, but it surely produced far fewer problems than has the development of judicial doctrine in this area since *Virginia Pharmacy Board.* For in the world of political advocacy and *its* marketplace of ideas, there is no such thing as a "fraudulent" idea: there may be useless proposals, totally unworkable schemes, as well as very sound proposals that will receive the imprimatur of the "marketplace of ideas" through our majoritarian system of election and representative government. The free flow of information is important in this context not because it will lead to the discovery of any objective "truth," but because it is essential to our system of self-government.

The notion that more speech is the remedy to expose falsehood and fallacies is wholly out of place in the commercial bazaar, where if applied logically the remedy of one who was defrauded would be merely a statement, available upon request, reciting the Latin maxim *"caveat emptor."* But since "fraudulent speech" in this area is to be remediable under *Virginia Pharmacy Board, supra,* the remedy of one defrauded is a lawsuit or an agency proceeding based on common-law notions of fraud that are separated by a world of difference

from the realm of politics and government. What time, legal decisions, and common sense have so widely severed, I declined to join in *Virginia Pharmacy Board,* and regret now to see the Court reaping the seeds that it there sowed. For in a democracy, the economic is subordinate to the political, a lesson that our ancestors learned long ago, and that our descendants will undoubtedly have to relearn many years hence.

III

The Court concedes that the state interest in energy conservation is plainly substantial, *ante,* at 568, as is the State's concern that its rates be fair and efficient. *Ante,* at 569. It also concedes that there is a direct link between the Commission's ban on promotional advertising and the State's interest in conservation. *Ibid.* The Court nonetheless strikes down the ban on promotional advertising because the Commission has failed to demonstrate, under the final part of the Court's four-part test, that its regulation is no more extensive than necessary to serve the State's interest. *Ante,* at 569–571. In reaching this conclusion, the Court conjures up potential advertisements that a utility might make that conceivably would result in net energy savings. The Court does not indicate that the New York Public Service Commission has in fact construed its ban on "promotional" advertising to preclude the dissemination of information that clearly would result in a net energy savings, nor does it even suggest that the Commission has been confronted with and rejected such an advertising proposal.[6] The final part of the Court's test

[6] Indeed appellee in its brief states:

"[N]either Central Hudson nor any other party made an attempt before the Commission to demonstrate or argue for a specific advertising strategy that would avoid the difficulties that the Commission found inherent in electric utility promotional advertising. The Commission, therefore, continued to enforce its ban on promotion which it had instituted in 1973." Brief for Appellee 15.

The Court makes no attempt to address this statement, or to explain why,

thus leaves room for so many hypothetical "better" ways that any ingenious lawyer will surely seize on one of them to secure the invalidation of what the state agency actually did. As MR. JUSTICE BLACKMUN observed in *Illinois Elections Bd.* v. *Socialist Workers Party,* 440 U. S. 173, 188–189 (1979) (concurring opinion):

> "A judge would be unimaginative indeed if he could not come up with something a little less 'drastic' or a little less 'restrictive' in almost any situation, and thereby enable himself to vote to strike legislation down."

Here the Court concludes that the State's interest in energy conservation cannot justify a blanket ban on promotional advertising. In its statement of the facts, the Court observes that the Commission's ban on promotional advertising is not "a perfect vehicle for conserving energy." It states:

> "[T]he Commission's order prohibits promotional advertising to develop consumption during periods when demand for electricity is low. By limiting growth in 'off-peak' consumption, the ban limits the 'beneficial side effects' of such growth in terms of more efficient use of existing powerplants. [App. to Juris. Statement] 37a." *Ante,* at 559.

The Court's analysis in this regard is in my view fundamentally misguided because it fails to recognize that the beneficial side effects of "more efficient use" may be inconsistent with the goal of energy conservation. Indeed, the Commission explicitly found that the promotion of off-peak consumption would impair conservation efforts.[7] The Commission stated:

> "Increased off-peak generation, . . . while conferring

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when no state body has addressed the issue, the Court should nonetheless resolve it by invalidating the state regulation.

[7] In making this finding, the Commission distinguished "between promotional advertising designed to shift existing consumption from peak to off-peak hours and advertising designed to promote additional consump-

> some beneficial side effects, also consumes valuable energy resources and, if it is the result of increased sales, necessarily creates incremental air pollution and thermal discharges to waterways. More important, any increase in off-peak generation from most of the major companies producing electricity in this State would not, at this time, be produced from coal or nuclear resources, but would require the use of oil-fired generating facilities. The increased requirement for fuel oil to serve the incremental off-peak load created by promotional advertising would aggravate the nation's already unacceptably high level of dependence on foreign sources of supply and would, in addition, frustrate rather than encourage conservation efforts." App. to Juris. Statement 37a.[8]

The Court also observes, as the Commission acknowledged, that the ban on promotional advertising can achieve only "piecemeal conservationism" because oil dealers are not under the Commission's jurisdiction, and they remain free to advertise. Until I have mastered electrical engineering and marketing, I am not prepared to contradict by virtue of my judicial office those who assume that the ban will be successful in making a substantial contribution to conservation efforts.

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tion during off-peak hours." App. to Juris. Statement 58a, n. 2. It proscribed only the latter. *Ibid.*

[8] And in denying appellant's petition for rehearing, the Commission again stated:

"While promotion of off-peak usage, particularly electric space heating, is touted by some as desirable because it might increase off-peak usage and thereby improve a summer-peaking company's load factor, we are convinced that off-peak promotion, especially in the context of imperfectly structured electric rates, is inconsistent with the public interest, even if it could be divorced in the public mind from promoting electric usage generally. As we pointed out in our Policy Statement, increases in generation, even off-peak generation, at this time, requires the burning of scarce oil resources. This increased requirement for fuel oil aggravates the nation's already high level of dependence on foreign sources of supply." *Id.*, at 58a (footnotes omitted).

And I doubt that any of this Court's First Amendment decisions justify striking down the Commission's order because more steps toward conservation could have been made This is especially true when, as here, the Commission lacks authority over oil dealers.

The Court concludes that the Commission's ban on promotional advertising must be struck down because it is more extensive than necessary: it may result in the suppression of advertising by utilities that promotes the use of electrical devices or services that cause no net increase in total energy use. The Court's reasoning in this regard, however, is highly speculative. The Court provides two examples that it claims support its conclusion. It first states that both parties acknowledge that the "heat pump" will be "a major improvement in electric heating," and that but for the ban the utilities would advertise this type of "energy efficien[t]" product.[9] The New York Public Service Commission, however, considered the merits of the heat pump and concluded that it would most likely result in an overall increase in electric energy consumption. The Commission stated:

> "[I]nstallation of a heat pump means also installation of central air-conditioning. To this extent, promotion of off-peak electric space heating involves promotion of on-peak summer air-conditioning as well as on-peak usage

[9] As previously discussed, however, it does not follow that because a product is "energy efficient" it is also consistent with the goal of energy conservation. Thus, with regard to the heat pump, counsel for appellees stated at oral argument that "Central Hudson says there are some [heat pumps] without air conditioning, but . . . they have never advised us of that." Tr. of Oral Arg. 32–33. The electric heat pump, he continued, "normally carr[ies] with it air conditioning in the summer, and the commission found that this would result in air conditioning that would not otherwise happen." *Id.*, at 33. This is but one example of the veritable Sargasso Sea of difficult nonlegal issues that we wade into by adopting a rule that requires judges to evaluate highly complex and often controversial questions arising in disciplines quite foreign to ours.

> of electricity for water heating. And the price of electricity to most consumers in the State does not now fully reflect the much higher marginal costs of on-peak consumption in summer peaking markets. In these circumstances, there would be a subsidization of consumption on-peak, and consequently, higher rates for all consumers." App. to Juris. Statement 58a.

Subsidization of peak consumption not only may encourage the use of scarce energy resources during peak periods, but also may lead to larger reserve generating capacity requirements for the State.

The Court next asserts that electric heating as a backup to solar and other heat may be an efficient alternative energy source. *Ante,* at 570. The Court fails to establish, however, that an advertising proposal of this sort was properly presented to the Commission. Indeed, the Court's concession that the Commission did not make findings on this issue suggests that the Commission did not even consider it. Nor does the Court rely on any support for its assertion other than the assertion of appellant. Rather, it speculates that "[i]n the absence of authoritative findings to the contrary, we must credit as within the realm of possibility the claim that electric heat can be an efficient alternative in some circumstances." *Ibid.*[10]

Ordinarily it is the role of the State Public Service Commission to make factual determinations concerning whether a device or service will result in a net energy savings and, if so, whether and to what extent state law permits dissemination of information about the device or service. Otherwise,

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[10] Even assuming the Court's speculation is correct, it has shown too little. For the regulation to truly be "no more extensive than necessary," it must be established that a more efficient energy source will serve only as a means for saving energy, rather than as an inducement to consume more energy because the cost has decreased or because other energy using products will be used in conjunction with the more efficient one.

as here, this Court will have no factual basis for its assertions. And the State will never have an opportunity to consider the issue and thus to construe its law in a manner consistent with the Federal Constitution. As stated in *Barrows* v. *Jackson*, 346 U. S. 249, 256–257 (1953):

> "It would indeed be undesirable for this Court to consider every conceivable situation which might possibly arise in the application of complex and comprehensive legislation. Nor are we so ready to frustrate the expressed will of Congress or that of the state legislatures. Cf. *Southern Pacific Co.* v. *Gallagher*, 306 U. S. 167, 172."

I think the Court would do well to heed the admonition in *Barrows* here. The terms of the order of the New York Public Service Commission in my view indicate that advertising designed to promote net savings in energy use does not fall within the scope of the ban. The order prohibits electric corporations "from *promoting the use of electricity* through the use of advertising, subsidy payments . . . , or employee incentives." App. to Juris. Statement 31a (emphasis added). It is not clear to me that advertising that is likely to result in net savings of energy is advertising that "promot[es] the use of electricity," nor does the Court point to any language in the Commission order that suggests it has adopted this construction. Rather, it would seem more accurate to characterize such advertising as designed to "discourage" the use of electricity.[11] Indeed, I think it is quite likely that the Com-

[11] This characterization is supported by the reasoning of the New York Court of Appeals, which stated:

"[P]romotional advertising . . . seeks . . . to encourage the increased consumption of electricity, whether during peak hours or off-peak hours. Thus, not only does such communication lack any beneficial informative content, but it may be affirmatively detrimental to the society. . . . Conserving diminishing resources is a matter of vital State concern and increased use of electrical energy is inimical to our interests. Promotional advertising, if permitted, would only serve to exacerbate the crisis." 47 N. Y. 2d, at 110, 390 N. E. 2d, at 757–758.

mission would view advertising that would clearly result in a net savings in energy as consistent with the objectives of its order and therefore permissible.[12] The Commission, for example, has authorized the dissemination of information that would result in *shifts* in electrical energy demand, thereby reducing the demand for electricity during peak periods. *Id.*, at 37a.[13] It has also indicated a willingness to consider at least some other types of "specific proposals" submitted by utilities. *Id.*, at 37a–38a. And it clearly permits informational as opposed to promotional dissemination of information. *Id.*, at 43a–46a. Even if the Commission were ultimately to reject the view that its ban on promotional advertising does not include advertising that results in net energy savings, I think the Commission should at least be given an opportunity to consider it.

It is in my view inappropriate for the Court to invalidate the State's ban on commercial advertising here, based on its speculation that in some cases the advertising may result in a net savings in electrical energy use, and in the cases in which it is clear a net energy savings would result from utility advertising, the Public Service Commission would apply its

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[12] At oral argument counsel for appellant conceded that the ban would not apply to utility advertising promoting the nonuse of electricity. Tr. of Oral Arg. 6. Indeed, counsel stated: "If the use reduces the amount of electricity used, it is not within the ban. The promotional ban is defined as anything which might be expected to increase the use of electricity." *Ibid.* And counsel for appellee stated that "the only thing that is involved here is the promotion by advertising of electric usage." *Id.*, at 30. "And if a showing can be made that promotion in fact is going to conserve energy," counsel for appellee continued, "which . . . has never been made to us, the commission's order says we are ready to relax our ban, we're not interested in banning for the sake of banning it. We think that is basically a bad idea, if we can avoid it. In gas, we have been relaxing it as more gas has become available." *Id.*, at 40.

[13] By contrast, as previously discussed, the Public Service Commission does not permit the promotion of off-peak consumption alone. *Supra*, at 600–601, and n. 8.

ban so as to proscribe such advertising. Even assuming that the Court's speculation is correct, I do not think it follows that facial invalidation of the ban is the appropriate course. As stated in *Parker* v. *Levy,* 417 U. S. 733, 760 (1974), "even if there are marginal applications in which a statute would infringe on First Amendment values, facial invalidation is inappropriate if the 'remainder of the statute . . . covers a whole range of easily identifiable and constitutionally proscribable . . . conduct. . . .' *CSC* v. *Letter Carriers,* 413 U. S. 548, 580–581 (1973)." This is clearly the case here.

For the foregoing reasons, I would affirm the judgment of the New York Court of Appeals.

Attachment 7

New York Consolidated Laws, Executive Law - EXC § 63. General duties

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The attorney-general shall:

1. Prosecute and defend all actions and proceedings in which the state is interested, and have charge and control of all the legal business of the departments and bureaus of the state, or of any office thereof which requires the services of attorney or counsel, in order to protect the interest of the state, but this section shall not apply to any of the military department bureaus or military offices of the state. No action or proceeding affecting the property or interests of the state shall be instituted, defended or conducted by any department, bureau, board, council, officer, agency or instrumentality of the state, without a notice to the attorney-general apprising him of the said action or proceeding, the nature and purpose thereof, so that he may participate or join therein if in his opinion the interests of the state so warrant.

2. Whenever required by the governor, attend in person, or by one of his deputies, any term of the supreme court or appear before the grand jury thereof for the purpose of managing and conducting in such court or before such jury criminal actions or proceedings as shall be specified in such requirement; in which case the attorney-general or his deputy so attending shall exercise all the powers and perform all the duties in respect of such actions or proceedings, which the district attorney would otherwise be authorized or required to exercise or perform; and in any of such actions or proceedings the district attorney shall only exercise such powers and perform such duties as are required of him by the attorney-general or the deputy attorney-general so attending. In all such cases all expenses incurred by the attorney-general, including the salary or other compensation of all deputies employed, shall be a county charge.

3. Upon request of the governor, comptroller, secretary of state, commissioner of transportation, superintendent of financial services, commissioner of taxation and finance, commissioner of motor vehicles, or the state inspector general, or the head of any other department, authority, division or

agency of the state, investigate the alleged commission of any indictable offense or offenses in violation of the law which the officer making the request is especially required to execute or in relation to any matters connected with such department, and to prosecute the person or persons believed to have committed the same and any crime or offense arising out of such investigation or prosecution or both, including but not limited to appearing before and presenting all such matters to a grand jury.

4. Cause all persons indicted for corrupting or attempting to corrupt any member or member-elect of the legislature, or the commissioner of general services, to be brought to trial.

5. When required by the comptroller or the superintendent of public works, [1] prepare proper drafts for contracts, obligations and other instruments for the use of the state.

6. Upon receipt thereof, pay into the treasury all moneys received by him for debts due or penalties forfeited to the people of the state.

7. He may, on behalf of the state, agree upon a case containing a statement of the facts and submit a controversy for decision to a court of record which would have jurisdiction of an action brought on the same case. He may agree that a referee, to be appointed in an action to which the state is a party, shall receive such compensation at such rate per day as the court in the order of reference may specify. He may with the approval of the governor retain counsel to recover moneys or property belonging to the state, or to the possession of which the state is entitled, upon an agreement that such counsel shall receive reasonable compensation, to be fixed by the attorney-general, out of the property recovered, and not otherwise.

8. Whenever in his judgment the public interest requires it, the attorney-general may, with the approval of the governor, and when directed by the governor, shall, inquire into matters concerning the public peace, public safety and public justice. For such purpose he may, in his discretion, and without civil service examination, appoint and employ, and at pleasure remove, such deputies, officers and other persons as he deems necessary, determine their duties and, with the approval of the governor, fix their compensation. All appointments made pursuant to this subdivision shall be immediately reported to the governor, and shall not be reported to any other state officer or department. Payments of salaries and compensation of officers and employees and of the expenses of the inquiry shall be made out of funds provided by the legislature for such purposes, which shall be deposited in a bank or trust company in the names of the governor and the attorney-general, payable only on the draft or check of the attorney-general, countersigned by the governor, and such disbursements shall be subject to no audit except by the governor and the attorney-general. The attorney-general, his deputy, or other officer, designated by him, is empowered to subpoena witnesses, compel their attendance, examine them under oath before himself or a magistrate and require that any books, records, documents or papers relevant or material to the inquiry be turned over to him for inspection, examination or audit, pursuant to the civil practice law and rules. If a person subpoenaed to attend upon such inquiry fails

to obey the command of a subpoena without reasonable cause, or if a person in attendance upon such inquiry shall, without reasonable cause, refuse to be sworn or to be examined or to answer a question or to produce a book or paper, when ordered so to do by the officer conducting such inquiry, he shall be guilty of a misdemeanor. It shall be the duty of all public officers, their deputies, assistants and subordinates, clerks and employees, and all other persons, to render and furnish to the attorney-general, his deputy or other designated officer, when requested, all information and assistance in their possession and within their power. Each deputy or other officer appointed or designated to conduct such inquiry shall make a weekly report in detail to the attorney-general, in form to be approved by the governor and the attorney-general, which report shall be in duplicate, one copy of which shall be forthwith, upon its receipt by the attorney-general, transmitted by him to the governor. Any officer participating in such inquiry and any person examined as a witness upon such inquiry who shall disclose to any person other than the governor or the attorney-general the name of any witness examined or any information obtained upon such inquiry, except as directed by the governor or the attorney-general, shall be guilty of a misdemeanor.

9. Bring and prosecute or defend upon request of the commissioner of labor or the state division of human rights, any civil action or proceeding, the institution or defense of which in his judgment is necessary for effective enforcement of the laws of this state against discrimination by reason of age, race, sex, creed, color, national origin, sexual orientation, gender identity or expression, military status, disability, predisposing genetic characteristics, familial status, marital status, citizenship or immigration status, or domestic violence victim status, or for enforcement of any order or determination of such commissioner or division made pursuant to such laws.

10. Prosecute every person charged with the commission of a criminal offense in violation of any of the laws of this state against discrimination because of age, race, sex, creed, color, national origin, sexual orientation, gender identity or expression, military status, disability, predisposing genetic characteristics, familial status, marital status, citizenship or immigration status, or domestic violence victim status, in any case where in his judgment, because of the extent of the offense, such prosecution cannot be effectively carried on by the district attorney of the county wherein the offense or a portion thereof is alleged to have been committed, or where in his judgment the district attorney has erroneously failed or refused to prosecute. In all such proceedings, the attorney-general may appear in person or by his deputy or assistant before any court or any grand jury and exercise all the powers and perform all the duties in respect of such actions or proceedings which the district attorney would otherwise be authorized or required to exercise or perform.

11. Prosecute and defend all actions and proceedings in connection with safeguarding and enforcing the state's remainder interest in any trust which meets the requirements of subparagraph two of paragraph (b) of subdivision two of section three hundred sixty-six of the social services law.

12. Whenever any person shall engage in repeated fraudulent or illegal acts or otherwise demonstrate persistent fraud or illegality in the carrying on, conducting or transaction of business, the attorney general may apply, in the name of the people of the state of New York, to the supreme court of the state of New York, on notice of five days, for an order enjoining the continuance of such business activity or of any fraudulent or illegal acts, directing restitution and damages and, in an appropriate case, cancelling any certificate filed under and by virtue of the provisions of section four hundred forty of the former penal law [2] or section one hundred thirty of the general business law, and the court may award the relief applied for or so much thereof as it may deem proper. The word “fraud” or “fraudulent” as used herein shall include any device, scheme or artifice to defraud and any deception, misrepresentation, concealment, suppression, false pretense, false promise or unconscionable contractual provisions. The term “persistent fraud” or “illegality” as used herein shall include continuance or carrying on of any fraudulent or illegal act or conduct. The term “repeated” as used herein shall include repetition of any separate and distinct fraudulent or illegal act, or conduct which affects more than one person. Notwithstanding any law to the contrary, all monies recovered or obtained under this subdivision by a state agency or state official or employee acting in their official capacity shall be subject to subdivision eleven of section four of the state finance law.

In connection with any such application, the attorney general is authorized to take proof and make a determination of the relevant facts and to issue subpoenas in accordance with the civil practice law and rules. Such authorization shall not abate or terminate by reason of any action or proceeding brought by the attorney general under this section.

13. Prosecute any person for perjury committed during the course of any investigation conducted by the attorney-general pursuant to statute. In all such proceedings, the attorney-general may appear in person or by his deputy or assistant before any court or any grand jury and exercise all the powers and perform all the duties necessary or required to be exercised or performed in prosecuting any such person for such offense.

15. [3] In any case where the attorney general has authority to institute a civil action or proceeding in connection with the enforcement of a law of this state, in lieu thereof he may accept an assurance of discontinuance of any act or practice in violation of such law from any person engaged or who has engaged in such act or practice. Such assurance may include a stipulation for the voluntary payment by the alleged violator of the reasonable costs and disbursements incurred by the attorney general during the course of his investigation. Evidence of a violation of such assurance shall constitute prima facie proof of violation of the applicable law in any civil action or proceeding thereafter commenced by the attorney general.

16. (a) Notwithstanding any other law to the contrary, in resolving, by agreed judgment, stipulation, decree, agreement to settle, assurance of discontinuance or otherwise, any claim or cause of

action, whether filed or unfiled, actual or potential, and whether arising under common law, equity, or any provision of law, a state agency or a state official or employee acting in their official capacity shall not have the authority to include or agree to include in such resolution any term or condition that would provide the state agency, official, or employee, their agent or designee, the settling party, or any third party with control or discretion over how any moneys to be paid by the settling party would be used, spent, or allocated.

(b) Paragraph (a) of this subdivision shall not apply to any provision in the resolution of a claim or cause of action providing (1) moneys to be distributed to the federal government, to a local government, or to any holder of a bond or other debt instrument issued by the state, any public authority, or any public benefit corporation; (2) moneys to be distributed solely or exclusively as a payment of damages or restitution to individuals or entities that were specifically injured or harmed by the defendant's or settling party's conduct and that are identified in, or can be identified by the terms of, the relevant judgment, stipulation, decree, agreement to settle, assurance of discontinuance, or relevant instrument resolving the claim or cause of action; (3) moneys recovered or obtained by the attorney general where application of paragraph (a) of this subdivision is prohibited by federal law, rule, or regulation, or would result in the reduction or loss of federal funds or eligibility for federal benefits pursuant to federal law, rule, or regulation; (4) moneys recovered or obtained by or on behalf of a public authority, a public benefit corporation, the department of taxation and finance, the workers' compensation board, the New York state higher education services corporation, the tobacco settlement financing corporation, a state or local retirement system, an employee health benefit program administered by the New York state department of civil service, the Title IV-D child support fund, the lottery prize fund, the abandoned property fund, or an endowment of the state university of New York or any unit thereof or any state agency, provided that all of the moneys received or recovered are immediately transferred to the relevant public authority, public benefit corporation, department, fund, program, or endowment; (5) moneys to be refunded to an individual or entity as (i) an overpayment of a tax, fine, penalty, fee, insurance premium, loan payment, charge or surcharge; (ii) a return of seized assets; or (iii) a payment made in error; (6) moneys to be used to prevent, abate, restore, mitigate or control any identifiable instance of prior or ongoing water, land or air pollution; and/or (7) state moneys received as part of any statewide opioid settlement agreements as defined in section 25.18 of the mental hygiene law, to be spent on eligible expenditures as defined in section 25.18 of the mental hygiene law.

(c) Where an agreed judgment, stipulation, decree, agreement to settle, assurance of discontinuance or other legal instrument resolves (1) any claim or any cause of action asserted by a state agency or a state official or employee acting in their official capacity and (2) any claim or cause of action asserted by one or more foreign jurisdictions or third parties, paragraph (a) of this

subdivision shall only apply to the resolution of the claim or cause of action asserted by the state agency, official, or employee.

17. Expired and deemed repealed Feb. 1, 2022, pursuant to L.2021, c. 55, pt. L, § 2.

1 Now commissioner of transportation. See Transportation Law § 267.

2 Now General Business Law § 130.

3 So in original. There is no subd. 14.

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Attachment 8



SENATE BILL 23-190

BY SENATOR(S) Winter F. and Marchman, Cutter, Gonzales, Jaquez Lewis, Moreno, Buckner, Coleman, Danielson, Fields, Ginal, Hinrichsen, Kolker, Sullivan, Fenberg;
also REPRESENTATIVE(S) McCormick and Epps, Froelich, Titone, Amabile, Bacon, Bird, Boesenecker, Brown, Daugherty, deGruy Kennedy, Dickson, Garcia, Gonzales-Gutierrez, Herod, Joseph, Kipp, Lieder, Lindsay, Lindstedt, Lukens, Mabrey, McLachlan, Parenti, Ricks, Sharbini, Sirota, Story, Valdez, Velasco, Vigil, Willford, Woodrow, McCluskie, Michaelson Jenet.

CONCERNING POLICIES TO MAKE PUNISHABLE DECEPTIVE ACTIONS REGARDING PREGNANCY-RELATED SERVICES.

Be it enacted by the General Assembly of the State of Colorado:

SECTION 1. Legislative declaration. (1) The general assembly finds and declares that:

(a) In Colorado, a pregnant individual has a fundamental right to continue a pregnancy or to terminate a pregnancy by abortion;

(b) Pregnant individuals need timely and accurate information from

---

Capital letters or bold & italic numbers indicate new material added to existing law; dashes through words or numbers indicate deletions from existing law and such material is not part of the act.

qualified medical professionals to make informed decisions about their health and well-being;

(c) According to the American Medical Association's Journal of Ethics, anti-abortion centers, also known as "crisis pregnancy centers", aim "to prevent abortions by persuading people that adoption or parenting is a better option";

(d) Anti-abortion centers are the ground-level presence of a well-coordinated anti-choice movement;

(e) Some anti-abortion centers use deceptive advertising tactics to target and acquire clients from historically marginalized groups, including Black, Indigenous, and other people of color; those who live in rural areas; LGBTQ+ communities; students; people with lower incomes; and people for whom English is not their first language;

(f) Some anti-abortion centers go so far as to advertise medication abortion reversal, a dangerous and deceptive practice that is not supported by science or clinical standards, according to the American College of Obstetricians and Gynecologists, or by the United States food and drug administration;

(g) The American Medical Association states, "[Physicians] do not and cannot, without misleading them, tell their patients that it may be possible to reverse a medication abortion";

(h) Time is a critical factor for individuals seeking abortion care; and

(i) No one should be deceived, manipulated, or face unnecessary delays when seeking support or health care during pregnancy.

(2) Therefore, the general assembly finds and declares that it is imperative that Colorado stop deceptive trade practices and unprofessional conduct with respect to the provision of abortion services and medication abortion reversal, and accordingly, the following issues are matters of statewide concern:

(a) Stopping deceptive trade practices relating to access to timely

abortion and emergency contraceptives, as described in section 6-1-734, Colorado Revised Statutes, and medication abortion reversal; and

(b) Declaring that it is unprofessional conduct for a person regulated pursuant to title 12, Colorado Revised Statutes, to provide, prescribe, administer, or attempt medication abortion reversal, as described in section 12-30-120, Colorado Revised Statutes.

(3) The general assembly further finds and declares that:

(a) Section 6-1-105 (1)(e) and (1)(rrr), Colorado Revised Statutes, declare, in part, that it is a deceptive trade practice to knowingly or recklessly make a false representation as to the characteristics, uses, or benefits of products or services or to knowingly or recklessly engage in any unfair, unconscionable, deceptive, deliberately misleading, false, or fraudulent act or practice; and

(b) This prohibition on deceptive trade practices applies to disseminating or causing to be disseminated false advertising relating to the provision of abortion or emergency contraceptive services, or referrals for those services, and advertising for or providing or offering to provide or make available medication abortion reversal.

SECTION 2. In Colorado Revised Statutes, **add** 6-1-734 as follows:

6-1-734. Access to abortion services and emergency contraception - deceptive trade practice - definitions. (1) AS USED IN THIS SECTION, UNLESS THE CONTEXT OTHERWISE REQUIRES:

(a) "ABORTION" HAS THE MEANING SET FORTH IN SECTION 25-6-402 (1).

(b) "EMERGENCY CONTRACEPTIVE" MEANS A DRUG OR DEVICE APPROVED BY THE FOOD AND DRUG ADMINISTRATION TO SIGNIFICANTLY REDUCE THE RISK OF PREGNANCY IF TAKEN OR ADMINISTERED WITHIN A SPECIFIED PERIOD OF TIME AFTER SEXUAL INTERCOURSE, INCLUDING EMERGENCY CONTRACEPTIVE PILLS AND INTRAUTERINE DEVICES.

(c) "FOOD AND DRUG ADMINISTRATION" MEANS THE FOOD AND DRUG

ADMINISTRATION IN THE UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, OR ANY SUCCESSOR ENTITY.

(2) A PERSON ENGAGES IN A DECEPTIVE TRADE PRACTICE WHEN THE PERSON MAKES OR DISSEMINATES TO THE PUBLIC OR CAUSES TO BE MADE OR DISSEMINATED TO THE PUBLIC ANY ADVERTISEMENT THAT INDICATES THAT THE PERSON PROVIDES ABORTIONS OR EMERGENCY CONTRACEPTIVES, OR REFERRALS FOR ABORTIONS OR EMERGENCY CONTRACEPTIVES, WHEN THE PERSON KNOWS OR REASONABLY SHOULD HAVE KNOWN, AT THE TIME OF PUBLICATION OR DISSEMINATION TO THE PUBLIC OF THE ADVERTISEMENT, THAT THE PERSON DOES NOT PROVIDE THOSE SPECIFIC SERVICES.

SECTION 3. In Colorado Revised Statutes, **add** 12-30-120 as follows:

12-30-120. Unprofessional conduct - grounds for discipline - offering medication abortion reversal - definitions. (1) AS USED IN THIS SECTION:

(a) "ABORTION" HAS THE MEANING SET FORTH IN SECTION 25-6-402 (1).

(b) "MEDICATION ABORTION" MEANS AN ABORTION CONDUCTED SOLELY THROUGH THE USE OF ONE OR MORE PRESCRIPTION DRUGS.

(c) "MEDICATION ABORTION REVERSAL" MEANS ADMINISTERING, DISPENSING, DISTRIBUTING, OR DELIVERING A DRUG WITH THE INTENT TO INTERFERE WITH, REVERSE, OR HALT A MEDICATION ABORTION.

(2) (a) A LICENSEE, REGISTRANT, OR CERTIFICANT ENGAGES IN UNPROFESSIONAL CONDUCT OR IS SUBJECT TO DISCIPLINE PURSUANT TO THIS TITLE 12 IF THE LICENSEE, REGISTRANT, OR CERTIFICANT PROVIDES, PRESCRIBES, ADMINISTERS, OR ATTEMPTS MEDICATION ABORTION REVERSAL IN THIS STATE, UNLESS THE COLORADO MEDICAL BOARD CREATED IN SECTION 12-240-105 (1), THE STATE BOARD OF PHARMACY CREATED IN SECTION 12-280-104 (1), AND THE STATE BOARD OF NURSING CREATED IN SECTION 12-255-105 (1), IN CONSULTATION WITH EACH OTHER, EACH HAVE IN EFFECT RULES FINDING THAT IT IS A GENERALLY ACCEPTED STANDARD OF PRACTICE TO ENGAGE IN MEDICATION ABORTION REVERSAL.

(b) THE BOARDS SPECIFIED IN SUBSECTION (2)(a) OF THIS SECTION SHALL PROMULGATE APPLICABLE RULES NO LATER THAN OCTOBER 1, 2023, IN CONSULTATION WITH EACH OTHER, CONCERNING WHETHER ENGAGING IN MEDICATION ABORTION REVERSAL IS A GENERALLY ACCEPTED STANDARD OF PRACTICE.

SECTION 4. Safety clause. The general assembly hereby finds, determines, and declares that this act is necessary for the immediate preservation of the public peace, health, or safety.

Steve Fenberg
PRESIDENT OF
THE SENATE

Julie McCluskie
SPEAKER OF THE HOUSE
OF REPRESENTATIVES

Cindi L. Markwell
SECRETARY OF
THE SENATE

Robin Jones
CHIEF CLERK OF THE HOUSE
OF REPRESENTATIVES

APPROVED Friday April 14th 2023 at 2:05 pm
(Date and Time)

Jared S. Polis
GOVERNOR OF THE STATE OF COLORADO

Attachment 9

ORIGINAL ARTICLE

A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy

A. Coomarasamy, A.J. Devall, V. Cheed, H. Harb, L.J. Middleton, I.D. Gallos, H. Williams, A.K. Eapen, T. Roberts, C.C. Ogwulu, I. Goranitis, J.P. Daniels, A. Ahmed, R. Bender-Atik, K. Bhatia, C. Bottomley, J. Brewin, M. Choudhary, F. Crosfill, S. Deb, W.C. Duncan, A. Ewer, K. Hinshaw, T. Holland, F. Izzat, J. Johns, K. Kriedt, M.-A. Lumsden, P. Manda, J.E. Norman, N. Nunes, C.E. Overton, S. Quenby, S. Rao, J. Ross, A. Shahid, M. Underwood, N. Vaithilingam, L. Watkins, C. Wykes, A. Horne, and D. Jurkovic

ABSTRACT

BACKGROUND

Bleeding in early pregnancy is strongly associated with pregnancy loss. Progesterone is essential for the maintenance of pregnancy. Several small trials have suggested that progesterone therapy may improve pregnancy outcomes in women who have bleeding in early pregnancy.

METHODS

We conducted a multicenter, randomized, double-blind, placebo-controlled trial to evaluate progesterone, as compared with placebo, in women with vaginal bleeding in early pregnancy. Women were randomly assigned to receive vaginal suppositories containing either 400 mg of progesterone or matching placebo twice daily, from the time at which they presented with bleeding through 16 weeks of gestation. The primary outcome was the birth of a live-born baby after at least 34 weeks of gestation. The primary analysis was performed in all participants for whom data on the primary outcome were available. A sensitivity analysis of the primary outcome that included all the participants was performed with the use of multiple imputation to account for missing data.

RESULTS

A total of 4153 women, recruited at 48 hospitals in the United Kingdom, were randomly assigned to receive progesterone (2079 women) or placebo (2074 women). The percentage of women with available data for the primary outcome was 97% (4038 of 4153 women). The incidence of live births after at least 34 weeks of gestation was 75% (1513 of 2025 women) in the progesterone group and 72% (1459 of 2013 women) in the placebo group (relative rate, 1.03; 95% confidence interval [CI], 1.00 to 1.07; P=0.08). The sensitivity analysis, in which missing primary outcome data were imputed, resulted in a similar finding (relative rate, 1.03; 95% CI, 1.00 to 1.07; P=0.08). The incidence of adverse events did not differ significantly between the groups.

CONCLUSIONS

Among women with bleeding in early pregnancy, progesterone therapy administered during the first trimester did not result in a significantly higher incidence of live births than placebo. (Funded by the United Kingdom National Institute for Health Research Health Technology Assessment program; PRISM Current Controlled Trials number, ISRCTN14163439.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Coomarasamy at the Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham Edgbaston, Birmingham B15 2TT, United Kingdom, or at a.coomarasamy@bham.ac.uk.

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Miscarriage affects one in five pregnancies.[1] Miscarriage can cause excessive bleeding, infection, and complications associated with surgical treatment,[2] as well as substantial psychological harm, including anxiety, depression, and post-traumatic stress disorder.[3,4]

Progesterone, which is produced by the corpus luteum in the ovary, is necessary to prepare the endometrium for implantation of the embryo and thus is an essential hormone for a successful pregnancy. Additional progesterone is produced when an embryo implants in the endometrium and during early placental development. Subsequently, beginning at approximately 12 weeks of pregnancy, the placenta becomes the dominant source of progesterone.[5]

The physiological importance of progesterone has prompted researchers, physicians, and patients to consider progesterone supplementation during early pregnancy to prevent miscarriages. Progesterone supplementation in early pregnancy has been attempted in two contexts: the first is to prevent miscarriages in asymptomatic women who have a history of recurrent miscarriages, and the second is to rescue a pregnancy in women who have started to bleed during early pregnancy.[6] We addressed the first scenario in a previous issue of the *Journal*[7] and found no beneficial effect of progesterone in women with a history of unexplained recurrent miscarriages. The current trial focuses on women with vaginal bleeding in early pregnancy.

A Cochrane review (originally published in 2007 and last updated in 2018)[6] of 7 randomized trials of progestational agents that involved women with bleeding in early pregnancy showed a significantly lower risk of miscarriages among women who received progesterone than among those who received placebo or no treatment (odds ratio, 0.64; 95% confidence interval [CI], 0.47 to 0.87) but noted that the trials were small (the largest trial had a sample size of 191) and had methodologic weaknesses. Another Cochrane review of 13 trials of progestational agents that involved women with recurrent miscarriages was originally published in 2003 and was last updated in 2018.[8] The American College of Obstetricians and Gynecologists reviewed the evidence and concluded, "For threatened early pregnancy loss, the use of progestins is controversial, and conclusive evidence supporting their use is lacking. Women who have experienced at least three prior pregnancy losses, however, may benefit from progesterone therapy in the first trimester."[9] We conducted the multicenter, randomized, parallel-group, double-blind, placebo-controlled PRISM (Progesterone in Spontaneous Miscarriage) trial to investigate whether treatment with progesterone would result in a higher incidence of live births among women with bleeding in early pregnancy than placebo.

METHODS

TRIAL OVERSIGHT

The PRISM trial was approved by the United Kingdom Medicines and Healthcare Products Regulatory Agency, the United Kingdom National Research Ethics Service Committee (South Central Oxford), and the National Health Service research and development department at each participating hospital. The trial was conducted at clinics that are part of the trial research network of the Tommy's National Centre for Miscarriage Research, which is funded by Tommy's Charity. Progesterone and placebo were purchased from Besins Healthcare. This company had no role in the design of the trial; in the collection, analysis, or interpretation of the data; or in the preparation of the manuscript. Trial oversight and monitoring were provided by a trial steering committee and by an independent data and safety monitoring committee. The first, second, and last authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

TRIAL PARTICIPANTS

The participants in the PRISM trial were recruited at 48 hospitals in the United Kingdom. Women were eligible for enrollment in the trial if they were 16 to 39 years of age, if they had completed less than 12 weeks of pregnancy, if they presented with vaginal bleeding, and if they had an intrauterine gestational sac that was visible on ultrasonography. The upper threshold of 39 years for maternal age was chosen because the probability of miscarriages due to chromosomal abnormalities increases with advancing age,[10] and progesterone treatment could not be expected to prevent such miscarriages. Participants were excluded if at the time of presenta-

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tion the fetal crown–rump length was 7 mm or longer with no visible heartbeat; if the gestational sac was a mean of 25 mm or greater in diameter with no visible fetal pole on ultrasonography; if they had evidence of ectopic pregnancy; if they had life-threatening bleeding; if they had current or recent use of progesterone supplementation; if they had contraindications to progesterone therapy (i.e., a history of liver tumors; current genital or breast cancer, severe arterial disease, or acute porphyria; or a history during pregnancy of idiopathic jaundice, severe pruritus, or pemphigoid gestationis); or if they were participating in any other blinded, placebo-controlled trials of medicinal products in pregnancy. All the participants provided written informed consent.

TRIAL ASSIGNMENTS

Participants were randomly assigned, in a 1:1 ratio, to administer to themselves vaginal suppositories containing either 400 mg of micronized progesterone (Utrogestan, Besins Healthcare) or matching placebo twice daily, from the time of randomization through 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks). If vaginal administration was not preferred, participants could administer the suppositories rectally. Randomization was performed through a secure, centralized Internet facility with the use of minimization to balance the trial-group assignments according to maternal age (<35 years vs. ≥35 years), body-mass index (BMI [the weight in kilograms divided by the square of the height in meters], <30 vs. ≥30), fetal heart activity (present vs. absent), estimated gestation at presentation (<42 days vs. ≥42 days), and amount of vaginal bleeding (pictorial blood-loss assessment chart [PBAC] score of ≤2 vs. score of ≥3; scores range from 1 to 4, with higher scores indicating greater vaginal blood loss).[11] The appearance, route, and timing of administration of progesterone and placebo were identical. Participants, physicians, and trial nurses were unaware of the trial-group assignments throughout the course of the trial.

OUTCOME MEASURES

The primary outcome was the birth of a live-born baby after at least 34 completed weeks of gestation. Secondary outcomes included the time from conception to the end date of pregnancy, ongoing pregnancy at 12 weeks of gestation, miscarriage (defined as loss of pregnancy before 24 weeks of gestation), live birth before 34 weeks of gestation, ectopic pregnancy, stillbirth (defined as intrauterine death after at least 24 weeks of gestation), termination of pregnancy, the week of gestation at delivery, birth weight, size (small or large) for gestational age, preeclampsia, Apgar scores, survival at 28 days of neonatal life, and congenital abnormalities, as well as other antenatal, intrapartum, postpartum, and neonatal outcomes. A detailed list of all secondary outcomes is provided in the Supplementary Appendix, available at NEJM.org. We attempted to collect outcome data for all participants who underwent randomization, regardless of adherence to the trial-group assignment.

STATISTICAL ANALYSIS

We calculated that 1972 women would need to be included in each trial group to provide 90% power to detect a minimally important absolute difference of 5 percentage points between the progesterone group and the placebo group in the incidence of live births after at least 34 weeks of gestation (65% vs. 60%), at a two-sided alpha level of 0.05. This minimally important difference was chosen on the basis of a national survey of clinical practitioners in the United Kingdom. We planned to include 4150 women in the trial to account for an expected 5% loss to follow-up.

The analysis of the primary outcome was performed according to the intention-to-treat principle; a main analysis of all available data was supplemented by a sensitivity analysis of the primary outcome that included all participants and took into account any missing data with the use of multiple imputation.[12] A Poisson regression model with robust standard errors was used to estimate the relative rates and corresponding 95% two-sided confidence intervals, with adjustment for the minimization variables. This method has been shown to be appropriate and to be less prone to convergence issues than other similar methods.[13]

For the primary outcome, a P value was generated with the use of a two-sided chi-square test. The statistical analysis plan did not include a provision for correction for multiplicity when the analyses of the secondary outcomes were performed. Therefore, the results are reported as point estimates and 95% confidence intervals,

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without P values. For continuous outcomes, a linear regression model was used to estimate mean differences, with the same adjustment that was used in the analysis of the primary outcome. The widths of the confidence intervals were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

We analyzed the treatment effect on the primary outcome in prespecified subgroups defined according to maternal age (<35 years vs. ≥35 years), BMI (<30 vs. ≥30), fetal heart activity (present vs. absent), estimated gestation at presentation (<6 weeks vs. 6 to <9 weeks vs. ≥9 weeks), amount of vaginal bleeding (PBAC score of ≤2 vs. score of ≥3),[11] number of previous miscarriages (0 vs. 1 or 2 vs. ≥3), number of gestational sacs (1 vs. ≥2), race (white, black, south Asian, or other), history of polycystic ovaries (yes vs. no), and previous cervical excision (yes vs. no). The effects of these subgroups were examined by adding the variables for the interaction of subgroup with trial group to the regression model; a chi-square test was used to determine whether the effects of progesterone and placebo differed in the various subgroups.

Interim analyses of principal safety and effectiveness outcomes were performed on behalf of the data and safety monitoring committee by the trial statistician (who remained unaware of the treatment assignments) on two occasions. Because these analyses were performed with the use of the Peto principle,[14] no adjustment was made in the final P values to determine significance.

RESULTS

TRIAL PARTICIPANTS

From May 19, 2015, through July 27, 2017, a total of 12,862 women were identified as being eligible for the PRISM trial; of these women, 4153 were randomly assigned to receive either progesterone (2079 women) or placebo (2074 women) (Fig. 1). The percentage of women with available data for the primary outcome was 97% (4038 of 4153 women). Demographic and baseline characteristics were similar in the two trial groups (Table 1, and Table S1 in the Supplementary Appendix). Information on the route of administration was available for 88% (3662 of 4153) of the women: 99% (3611 of 3662 women) administered the suppositories vaginally and 1% (51 of 3662 women) administered them rectally.

OUTCOMES

The incidence of live births after at least 34 weeks of gestation was 75% (1513 of 2025 women) in the progesterone group and 72% (1459 of 2013 women) in the placebo group (relative rate, 1.03; 95% CI, 1.00 to 1.07; P=0.08). The sensitivity analysis, in which multiple imputation was used for missing data, did not change the findings (relative rate, 1.03; 95% CI, 1.00 to 1.07; P=0.08).

The incidence of ongoing pregnancy at 12 weeks was 83% (1672 of 2025 women) in the progesterone group and 80% (1602 of 2013 women) in the placebo group (relative rate, 1.04; 95% CI, 1.01 to 1.07). The incidence of miscarriage was 20% (410 of 2025 women) in the progesterone group and 22% (451 of 2013 women) in the placebo group (relative rate, 0.91; 95% CI, 0.81 to 1.01). The results of all the other secondary outcomes are presented in Table 2, and in Table S2 in the Supplementary Appendix.

A significant subgroup effect was identified for only 1 of the 10 prespecified subgroups — the subgroup of participants defined according to the number of previous miscarriages. The incidence of live births in the subgroup of women who had no previous miscarriages was 74% in the progesterone group and 75% in the placebo group (relative rate, 0.99; 95% CI, 0.95 to 1.04); the incidence among women who had one or two previous miscarriages was 76% and 72%, respectively (relative rate 1.05; 95% CI, 1.00 to 1.12); and the incidence among women who had three or more previous miscarriages was 72% and 57%, respectively (relative rate, 1.28; 95% CI, 1.08 to 1.51) (P=0.007 for the interaction between trial group and the number of miscarriages) (Fig. 2). The results of two post hoc subgroup analyses in which we categorized the number of previous miscarriages differently from the subgroup analysis described here are provided in Figure S1 in the Supplementary Appendix.

There was no significant between-group difference in the percentage of participants who had either a maternal or neonatal serious adverse event (5% [105 of 2025 participants] in the progesterone group and 5% [98 of 2013 participants] in the placebo group), including specifically the percentage of babies who had neonatal congenital abnormalities (3.4% in each group),

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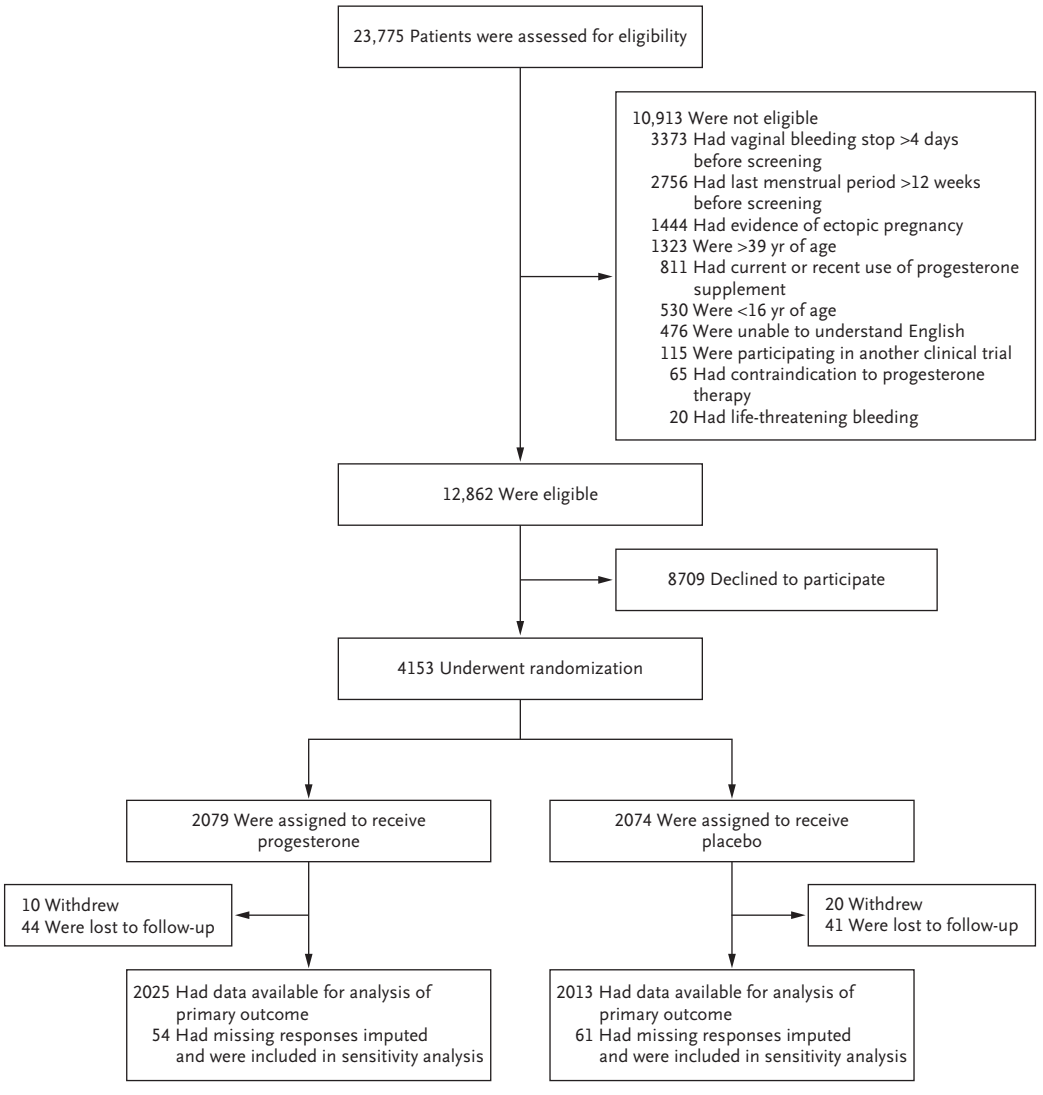


Figure 1. Enrollment, Randomization, and Follow-up.

nor was there any significant between-group difference in the number of maternal or neonatal serious adverse events. A summary of serious adverse events is provided in Table S3 in the Supplementary Appendix.

DISCUSSION

Our large multicenter, randomized, double-blind, placebo-controlled trial showed that among women with bleeding in early pregnancy, progesterone therapy administered during the first trimester of pregnancy did not result in a significantly higher incidence of live births after at least 34 weeks of gestation than placebo. There was also no significant difference between the groups in the incidence of miscarriage or stillbirth. Although there appeared to be slightly more ongoing pregnancies at 12 weeks in the progesterone group than in the placebo group, an inference of benefit cannot be drawn because the confidence interval for the relative rate was not adjusted for multiplicity of testing.

The large sample size in our trial allowed investigation of the primary outcome in prespecified subgroups. Among the 10 subgroup analyses,

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Table 1. Demographic and Baseline Characteristics of the Participants.*

Characteristic	Progesterone (N = 2079)	Placebo (N = 2074)
Demographic characteristics		
Maternal age†		
Mean — yr	30.6±5.1	30.5±5.1
Distribution — no. (%)		
<35 yr	1604 (77)	1601 (77)
≥35 yr	475 (23)	473 (23)
Body-mass index†		
Mean	26.4±6.2	26.5±6.3
Distribution — no. (%)		
<30	1589 (76)	1589 (77)
≥30	490 (24)	485 (23)
Race — no. (%)‡		
White	1714 (82)	1742 (84)
Black	84 (4)	79 (4)
South Asian	114 (5)	102 (5)
Other	167 (8)	151 (7)
Pregnancy history		
Nulliparous — no. (%)	474 (23)	514 (25)
Previous preterm births at ≥24 wk to <34 wk — no. (%)	83 (4)	90 (4)
Previous miscarriages at <24 wk of gestation — no. (%)		
0	1145 (55)	1157 (56)
1 or 2	792 (38)	758 (37)
≥3	142 (7)	159 (8)
No. of previous miscarriages — median (IQR)	0 (0–1)	0 (0–1)
Amount of bleeding as assessed by PBAC score†§ — no. (%)		
≤2	1913 (92)	1907 (92)
≥3	166 (8)	167 (8)
Fetal heart activity at presentation — no. (%)†¶	1710 (82)	1701 (82)

* Plus–minus values are means ±SD. There were no significant differences between the two groups in the characteristics listed. Further details regarding baseline characteristics are provided in Table S1 in the Supplementary Appendix. Percentages may not sum to 100 because of rounding. IQR denotes interquartile range.
† This variable was a minimization variable.
‡ Race was reported by the participant.
§ Pictorial blood-loss assessment chart (PBAC) scores range from 1 to 4, with higher scores indicating greater vaginal blood loss.[11]
¶ If more than one fetus was present, this variable was characterized as any fetus that had heart activity at presentation.

1 showed differential effects of progesterone: the effect of progesterone in women with bleeding in early pregnancy differed according to the number of previous miscarriages, with a suggestion of benefit among women who had had three or more previous miscarriages. Previous reports have indicated a steep and proportionate increase in the loss of chromosomally normal pregnancies (i.e., euploid miscarriages) with increasing number of previous miscarriages.[15] Given that the potential benefit of progesterone therapy would be expected to be specific to euploid pregnancies, an increasing level of benefit in women with increasing number of previous

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Table 2. Primary Outcome and Secondary Outcomes.*

Outcome	Progesterone (N=2025)	Placebo (N=2013)	Relative Rate or Mean Difference (95% CI)†
Primary outcome — no. (%)			
Live birth at ≥34 wk	1513 (75)	1459 (72)	1.03 (1.00 to 1.07)‡
Secondary maternal outcomes — no. (%)§			
Ongoing pregnancy at 12 wk	1672 (83)	1602 (80)	1.04 (1.01 to 1.07)
Miscarriage, defined as loss of pregnancy at <24 wk¶	410 (20)	451 (22)	0.91 (0.81 to 1.01)
Live birth at <34 wk	68 (3)	64 (3)	1.06 (0.76 to 1.49)
Ectopic pregnancy	0	2 (<1)	—
Stillbirth, defined as intrauterine death at ≥24 wk	5 (<1)	6 (<1)	0.82 (0.25 to 2.66)
Termination of pregnancy‖	34 (2)	36 (2)	0.94 (0.59 to 1.50)
Secondary neonatal outcomes among women with live births at ≥24 wk§			
Gestational age at delivery**			
Wk of gestation	38 wk 4 days±2 wk 4 days	38 wk 4 days±2 wk 3 days	0.11 days (–0 wk 1 day to 0 wk 2 days)†
No. of women	1581	1521	
Birth weight††			
Mean weight — g	3242±656	3261±659	–21 (–67 to 25)†
No. of infants	1604	1539	
Death at 28 days of neonatal life — no./total no. (%)‡‡	8/1605 (<1)	2/1533 (<1)	3.84 (0.80 to 18.40)†

* Plus–minus values are means ±SD. Additional data on outcomes are provided in Table S2 in the Supplementary Appendix.
† Relative rates are shown for the primary outcome, all secondary maternal outcomes, and the secondary neonatal outcome of death at 28 days of neonatal life. The mean difference is shown for the secondary neonatal outcomes of gestational age at delivery and birth weight. For binary outcomes, a relative rate of less than 1 favors the progesterone group, except for live birth after at least 34 weeks of gestation and ongoing pregnancy at 12 weeks, for which a relative rate greater than 1 would favor progesterone. For continuous outcomes, a mean difference of less than 0 favors the progesterone group. The widths of the confidence intervals were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.
‡ P=0.08.
§ Five women in the progesterone group and three women in the placebo group had both a live birth after at least 34 weeks of gestation and a miscarriage; one woman in the placebo group had both a termination of pregnancy and a miscarriage; and one woman in the placebo group had both a live birth before 34 weeks and a stillbirth.
¶ The median gestational age was 8 weeks (interquartile range, 7 to 10) in both trial groups.
‖ The reasons for termination of pregnancy in the progesterone group were social for 13 women and medical for 21 women. The reasons for termination of pregnancy in the placebo group were social for 12 women and medical for 24 women. The median gestational age was 14 weeks (interquartile range, 12 to 19) in the progesterone group and 15 weeks (interquartile range, 11 to 18) in the placebo group.
** The gestational age at delivery was unknown for the infants of two women in the placebo group.
†† The birth weight was unknown for the infants of 6 women in the progesterone group and 6 women in the placebo group.
‡‡ The neonatal vital status at 28 days of life was unknown for 17 women (5 in the progesterone group and 12 in the placebo group).

miscarriages is consistent with our understanding of the biologic factors associated with risk of miscarriage. A history of miscarriage is one of only two stratification or prognostic risk factors (the other being maternal age) cited in the 2017 guideline of the European Society of Human Reproduction and Embryology on recurrent pregnancy loss as being useful for identifying high-risk patients.[16] However, we did not identify this subgroup as one of special interest a priori in our statistical analysis plan,[17] and multiple comparisons were performed (without adjustment for multiplicity); thus, this observation requires validation.

Some limitations of our trial should be considered. First, we studied a vaginal preparation of progesterone, at a dose of 400 mg twice daily, and it is possible that the results observed with this regimen are not generalizable to women receiving other doses and preparations by other

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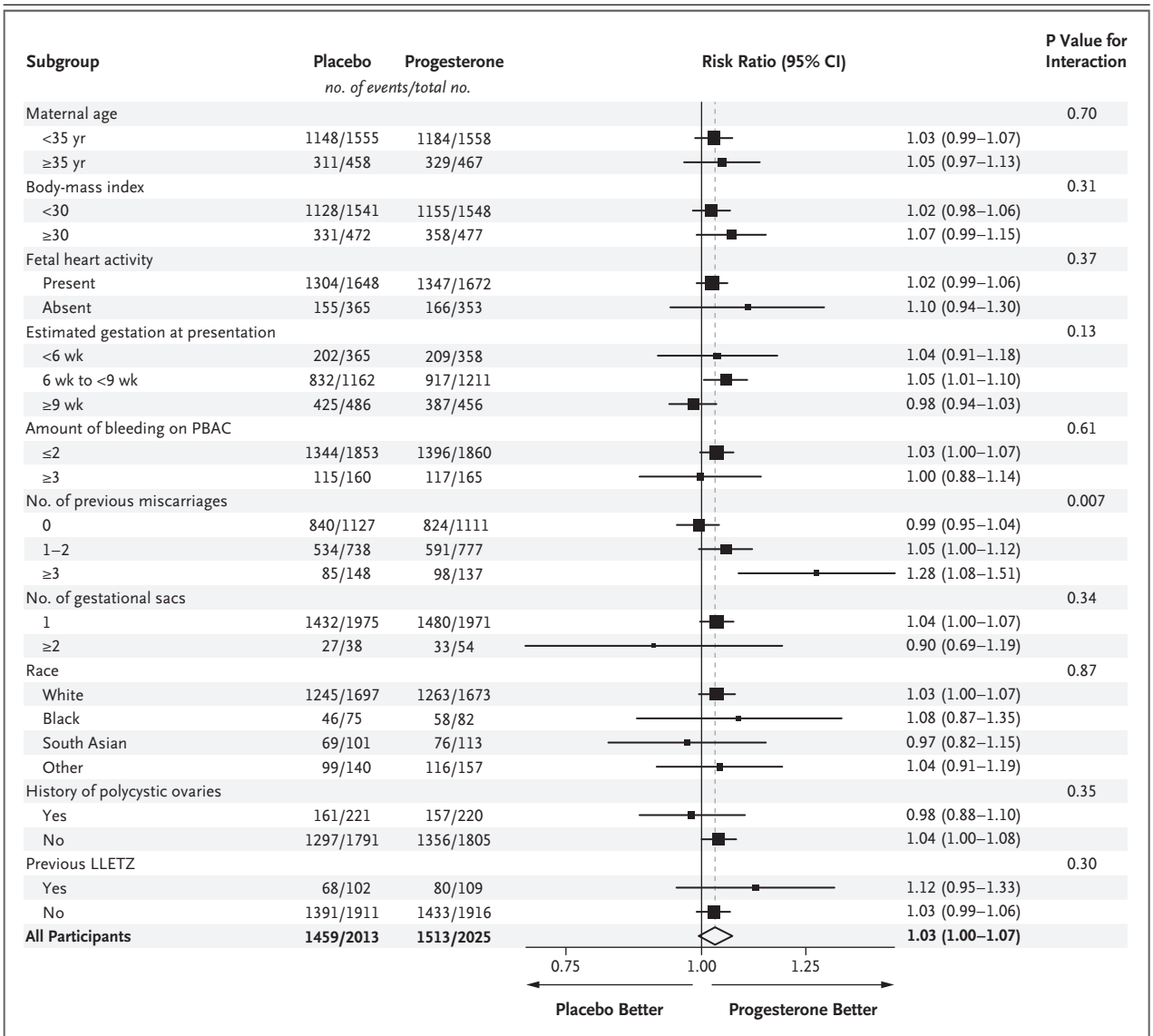


Figure 2. Subgroup Analysis.

Shown is the analysis of live births after at least 34 weeks of gestation (the primary outcome) in prespecified subgroups. The widths of the confidence intervals were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects. The size of each black square is proportional to the total number of women in the subgroup. The body-mass index is the weight in kilograms divided by the square of the height in meters. The score on the pictorial blood-loss assessment chart (PBAC) indicates the amount of vaginal bleeding; scores range from 1 to 4, with higher scores indicating greater vaginal blood loss.[11] Race was reported by the participant. LLETZ denotes large loop excision of the transformation zone of the cervix (also known as the loop electrosurgical excision procedure [LEEP]).

routes. Micronized vaginal progesterone has an identical molecular structure to natural progesterone, whereas other formulations of progestational agents have a different molecular structure and therefore potentially different mechanisms of action and pharmacologic features. Immunomodulatory effects of progesterone at the trophoblastic–decidual interface have been proposed as a mechanism whereby progesterone might prevent miscarriage.[18] The vaginal route delivers a greater proportion of drug to the relevant site (i.e., the uterus) with the use of the "first uterine pass" effect.[19,20] Furthermore, trials that have evaluated vaginal progesterone in the prevention

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of preterm birth have shown its effectiveness when administered by this route.[21,22]

Second, we started progesterone treatment only in women who had an intrauterine sac; therefore, our trial cannot provide evidence on the effects of earlier use of progesterone, before a pregnancy sac is visible on an ultrasound examination. Third, the participants discontinued progesterone at 16 weeks of gestation; however, we consider it to be unlikely that therapy beyond this time would have affected the outcomes related to miscarriage. Finally, although we found no increase in the risk of congenital abnormalities among babies of women treated with progesterone, the trial was not powered for such rare outcomes.

In conclusion, treatment with progesterone did not result in significant improvement in the incidence of live births among women with vaginal bleeding during the first 12 weeks of pregnancy.

This article presents independent research commissioned by the National Institute for Health Research (NIHR). A monograph reporting the data collected in this trial is planned for publication in the NIHR Journals Library. Further information is available at www.journalslibrary.nihr.ac.uk/hta/. The views and opinions expressed by the authors in this publication are those of the authors and do not necessarily reflect those of the National Health Service, the NIHR, the Medical Research Council, the NIHR Central Commissioning Facility, the NIHR Evaluation, Trials and Studies Coordinating Centre, the NIHR Health Technology Assessment program, or the Department of Health.

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APPENDIX

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REFERENCES

1. Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. BMJ 1997;315:32-4.
2. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-2008 — the eighth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011;118:Suppl 1:1-203.
3. Murphy FA, Lipp A, Powles DL. Follow-up for improving psychological well being for women after a miscarriage. Cochrane Database Syst Rev 2012;3:CD008679.
4. Farren J, Jalmbrant M, Ameye L, et al. Post-traumatic stress, anxiety and depression following miscarriage or ectopic pregnancy: a prospective cohort study. BMJ Open 2016;6(11):e011864.
5. Malassiné A, Frendo JL, Evain-Brion D. A comparison of placental development and endocrine functions between the human and mouse model. Hum Reprod Update 2003;9:531-9.
6. Wahabi HA, Fayed AA, Esmaeil SA, Bahkali KH. Progestogen for treating threatened miscarriage. Cochrane Database Syst Rev 2018;8:CD005943.
7. Coomarasamy A, Williams H, Truchanowicz E, et al. A randomized trial of progesterone in women with recurrent miscarriages. N Engl J Med 2015;373:2141-8.
8. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. Cochrane Database Syst Rev 2018;10:CD003511.
9. American College of Obstetricians and Gynecologists. ACOG practice bulletin — clinical management guidelines for obstetricians–gynecologists: early pregnancy loss. May 2015 (https://www.acog.org/-/media/Practice-Bulletins/Committee-on-Practice-Bulletins----Gynecology/Public/pb150.pdf).
10. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril 2012;98:1103-11.
11. Bottomley C, Van Belle V, Pexsters A, et al. A model and scoring system to predict outcome of intrauterine pregnancies of uncertain viability. Ultrasound Obstet Gynecol 2011;37:588-95.
12. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ 2011;342:d40.
13. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702-6.
14. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;34:585-612.
15. Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. Fertil Steril 2000;73:300-4.
16. ESHRE Early Pregnancy Guideline Development Group. Recurrent pregnancy loss: guideline of the European Society of Human Reproduction and Embryology. November 2017 (https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Recurrent-pregnancy-loss).
17. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine — reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-94.
18. Robinson DP, Klein SL. Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. Horm Behav 2012;62:263-71.
19. Bulletti C, de Ziegler D, Flamigni C, et al. Targeted drug delivery in gynaecology: the first uterine pass effect. Hum Reprod 1997;12:1073-9.
20. Cicinelli E, Cignarelli M, Sabatelli S, et al. Plasma concentrations of progesterone are higher in the uterine artery than in the radial artery after vaginal administration of micronized progesterone in an oil-based solution to postmenopausal women. Fertil Steril 1998;69:471-3.
21. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462-9.
22. Romero R, Conde-Agudelo A, Da Fonseca E, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. Am J Obstet Gynecol 2018;218:161-80.

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Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial

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Short Running Title: Mifepristone Antagonization

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Précis

Mifepristone ingestion without subsequent misoprostol administration in first-trimester gestations can result in hemorrhage and poses safety concerns.

Abstract

Objective: To estimate the efficacy and safety of mifepristone antagonization with high-dose oral progesterone.

Methods: We planned to enroll 40 women in a double-blind, placebo-controlled, randomized trial. We enrolled women 44-63 days gestation with ultrasound-confirmed gestational cardiac activity planning surgical abortion. Participants ingested mifepristone 200 mg and initiated oral progesterone 400 mg or placebo 24 hours later twice daily for 3 days, then once daily until their planned surgical abortion 14-16 days after enrollment. Follow-up visits were scheduled 3±1, 7±1 and 15±1 days after mifepristone intake with ultrasonography and blood testing for human chorionic gonadotropin and progesterone. Participants exited from the study when they had their surgical abortion or earlier for gestational cardiac activity absence, gestational sac expulsion or medically indicated suction aspiration. We assessed the primary outcome of continued gestational cardiac activity at approximately two weeks (15±1 days), side effects after drug ingestion, and safety outcomes including hemorrhage and emergent treatment.

Results: We enrolled participants from February to July 2019 and stopped enrollment after 12 patients for safety concerns. Mean gestational age was 52.5 days. Two (one per group) voluntarily discontinued 3 days after mifepristone ingestion for subjective complaints (nausea and vomiting, bleeding). Among the remaining 10 women (5 per group), gestational cardiac activity continued for two weeks in 4 in the progesterone group and 2 in the placebo group. One woman in the placebo group had no gestational cardiac activity 3 days after mifepristone use. Severe hemorrhage requiring ambulance transport to hospital occurred in 3 patients; 1 received progesterone (complete expulsion, no aspiration) and 2 received placebo (aspiration for both, one

required transfusion). We halted enrollment after the third hemorrhage. No other significant side effects were reported.

Conclusion: We could not estimate the efficacy of progesterone for mifepristone antagonization due to safety concerns when mifepristone is administered without subsequent prostaglandin analogue treatment. Women in early pregnancy who use only mifepristone may be at high risk of significant hemorrhage.

Clinical Trial Registration: ClinicalTrials.gov, NCT03774745.

Introduction

In the United States, approximately 862,000 abortions occur per year of which almost 40% occur using medical abortion (1). The treatment approved by the Food and Drug Administration (FDA) for medical abortion is a combination of mifepristone and misoprostol through 70 days gestation (2). Mifepristone acts as a competitive progesterone receptor antagonist and promotes decidual necrosis to weaken implantation, enhances uterine sensitivity to prostaglandins, and softens the cervix (3). Accordingly, mifepristone has some activity to induce abortion when used alone. However, overall efficacy is generally 80% or less and these studies typically included women less than 49 days gestation (4). Medical abortion efficacy is improved significantly with the addition of a prostaglandin analogue (4). Mifepristone followed in 24-48 hours by misoprostol is 96-97% effective through 70 days gestation; however, as gestation advances from 49 to 70 days, complete abortion rate decreases and continuing pregnancy rate increases (2). Approximately 0.3% of women at 49 days or less experience a continuing pregnancy compared to 3.1% of women at 64 to 70 days (2). A recent United Kingdom study of women who initiated medical abortion at 64 to 70 days found that 9/89 (10%) women with continuing pregnancies detected at follow-up opted to continue the pregnancy (5).

Case series have reported that some women may change their minds about terminating their pregnancies after ingesting mifepristone and prior to misoprostol treatment (6-8). Although an exact proportion is unknown, the best estimate is that <0.005% of women who use mifepristone choose to continue their pregnancies (9). Because mifepristone binds strongly to the progesterone receptor and has a long half-life (4), some scientists believe that this action is potentially irreversible. However, others have questioned this theory and believe that providing

high doses of progesterone may antagonize the effects of mifepristone when administered for abortion (6).

No clinical trials have been performed to adequately study antagonizing mifepristone with progesterone treatment. Case series reported to date have significant limitations, including using investigational treatment (high-dose progesterone) following mifepristone ingestion without consenting women for this experiment, incomplete reporting of outcomes, use of varying progesterone doses, routes and durations, and lack of control groups to understand true efficacy (6-8). The largest case series (547 women evaluated) reported a 48% continuing pregnancy rate using various progesterone regimens, with the highest rates (64-68%) using various intramuscular or oral treatments (8). To address these issues, we conducted a double-blind placebo-controlled randomized trial to evaluate continuing pregnancy rates, safety, and side effects of high-dose oral progesterone in women who used mifepristone during early pregnancy.

Methods

We conducted this randomized, double-blind, placebo-controlled trial at the University of California, Davis Medical Center. We approached women who had completed counseling and consent for a surgical abortion and were 63 days gestation or less about study participation. Inclusion criteria were 18 years or older, English-speaking, singleton pregnancy, and willingness to delay the abortion by approximately two weeks. Exclusion criteria were medical contraindications to medical abortion per the mifepristone FDA label (2), an allergy to mifepristone or progesterone, or a peanut allergy (on-label contraindication to oral progesterone).

The UC Davis Institutional Review Board approved this study and all participants gave written study consent prior to beginning any study procedures.

The screening visit included obtaining study consent, recording demographic information, soliciting baseline pregnancy symptoms (subjectively rated as none, mild, moderate or severe), and inquiring if they had used mifepristone or progesterone previously. Patients for whom transvaginal ultrasonography demonstrated gestational cardiac activity and a gestational age 44-63 days gestation based on Goldstein and Wolfson's criteria (10) could enroll that day. Women less than 44 days gestation at screening returned for enrollment, at which time transvaginal ultrasonography was repeated to confirm gestational cardiac activity and gestational age.

Enrolled participants had blood drawn for human chorionic gonadotropin (hCG) and progesterone levels, then swallowed mifepristone 200 mg in front of an investigator. Study treatment (progesterone or placebo) was prepared by the UC Davis Investigational Drug Service (IDS) by placing 38 capsules of progesterone 200 mg or similar-appearing placebo capsules in opaque pill containers. The IDS could not over-encapsulate the drugs due to product size. The IDS performed the randomization allocation using a computer-generated random sequence in blocks of four, sequentially numbered the containers, and maintained the randomization log to ensure drug allocation concealment until study completion. Participants were instructed to start study treatment 24 hours after mifepristone ingestion by taking two capsules twice daily for three days then two capsules once daily until the study exit visit. We chose this dosing regimen because it was the most effective option previously described in a case series of mifepristone antagonization (8). Participants received a diary to document any side effects and capsule intake.

Participants also received the standard medical abortion bleeding and side effect instructions distributed to medical abortion patients at the University of California, Davis.

Research staff contacted participants 24 hours after mifepristone administration to confirm the start of study treatment. Follow-up visits were scheduled 3±1, 7±1 and 15±1 days after mifepristone intake. Each visit included diary review, assessment of symptoms/drug side effects, ultrasonography to establish presence or absence of gestational cardiac activity, and blood testing for hCG and progesterone. Additionally, a research coordinator independently counted unused study drug to maintain investigator blinding. The subject's planned surgical abortion was scheduled concurrent with her last study visit. Participants exited from the study when they had their surgical abortion, or earlier for gestational cardiac activity absence, gestational sac expulsion, or medically-indicated suction aspiration. At the final visit, participants were asked if they knew what treatment they received or looked up the capsules online for identification.

The primary outcome was continuing pregnancy with presence of gestational cardiac activity after approximately two weeks (15±1 days). Secondary outcomes included expulsion rates over two weeks, change in hCG and progesterone during treatment, study drug side effects, and safety outcomes (e.g., hemorrhage, emergency department visit, emergent suction aspiration). Safety evaluations (adverse events review) were performed by the principal investigator after each subject completed the study and at research review meetings every two weeks by the primary study team. The principal investigator was responsible for continued safety oversight and decisions to stop the study for safety reasons.

We estimated a 68% continuing pregnancy rate with oral progesterone treatment based on a report using the same dosing after mifepristone administration in early pregnancy, stating that

68% of women had a pregnancy that continued to 20 weeks or more (8). We also estimated that only 25% of women receiving placebo would have a continuing pregnancy (10). Using 80% power and α=0.05, 20 participants per group were required.

We performed an intention-to-treat analysis, using Fisher's Exact Test or Chi-square test as indicated, t-test for continuous variables and Mann Whitney U for comparing median values.

Results

We enrolled 12 women from February to July 2019 (Figure 1). Patient characteristics are presented in Table 1. Two women exited the study voluntarily related to side effects; both had a suction aspiration 3 days after mifepristone administration. The first, in the placebo group, was 48 days at enrollment and had a prior medical abortion. She had increased anxiety about bleeding that started 2 days after mifepristone use and requested a suction aspiration. The second, in the progesterone group, had three prior pregnancies and mild nausea and vomiting at baseline. She had developed increasing nausea and vomiting after enrolling, resulting in dehydration that required intravenous fluids as an outpatient. She only took two of her four treatment doses before requesting a suction aspiration.

Overall, 4/6 women in the progesterone group and 2/6 women in the placebo group had a continuing pregnancy at two weeks. Excluding the two women who did not finish treatment, these rates are 4/5 and 2/5 respectively. A detailed listing of individual subject characteristics and outcomes is included in Appendix 1, available online at http://links.lww.com/xxx.

Four pregnancies did not continue, including one subject at 48 days in the placebo group who had no gestational cardiac activity 3 days after mifepristone use and had an uneventful suction aspiration. Three other women had severe bleeding requiring ambulance transport to an

emergency department. The first subject received progesterone treatment after enrollment at 56 days gestation. She reported no bleeding at the first follow-up visit 2 days post mifepristone. Shortly after her visit, she started having brisk bleeding and called an ambulance. Transvaginal ultrasound in the emergency department found no gestational sac and a heterogenous endometrial lining of approximately 1.5 cm. Heavy bleeding lasted about 3 hours overall and no intervention was needed. The second subject received placebo and enrolled at 60 days gestation. She noted new mild bleeding at a follow-up visit two days after mifepristone use. The following day, she called an ambulance due to onset of heavy vaginal bleeding. In the emergency department, a study physician found significant heterogenous material in the uterine cavity on ultrasound exam with continued brisk bleeding, so a suction aspiration was performed. Pathology demonstrated normal chorionic villi. The third subject also received placebo and enrolled at 60 days gestation. She noted new mild spotting at a follow-up visit two days after mifepristone use. The following days, she called an ambulance after experiencing hemorrhage. In the emergency department, a study physician evaluated the subject who had significant brisk bleeding, hypotension and tachycardia. Transvaginal sonography showed the gestational sac still in the uterine cavity, so an emergent suction aspiration was performed. This subject's hemoglobin decreased in the emergency department from 9.2 to 7.5 gm/dL and she received a one-unit transfusion of packed red blood cells. At safety contacts two and four weeks later, the subject reported no issues. We stopped enrollment for safety reasons after the third subject required emergent evaluation and a transfusion.

Baseline and follow-up serum hCG and progesterone levels are presented in Figures 2 and 3, respectively. Median baseline hCG and progesterone levels for the progesterone group were 76,776 mIU/mL (range 21,062-126,647 mIU/mL) and 12.4 ng/mL (range 10.5-24.0

ng/mL), respectively. Median baseline hCG and progesterone levels for the placebo group were 153,908 mIU/mL; range 25,450-246,638 mIU/mL) and 16.3 ng/mL (range 11.2-18.9 ng/mL), respectively. In the progesterone group, progesterone levels increased 240-1010% within a few days of starting treatment among women with continuing gestational cardiac activity at two weeks whereas the one subject with hemorrhage demonstrated an increase of only 45% despite being adherent with study drug instructions.

Table 2 describes side effects related to pregnancy or treatment. One subject in the progesterone group noted the onset of severe nausea and vomiting shortly after mifepristone intake that preceded progesterone treatment; otherwise, no appreciable differences in development of new severe side effects were identified between treatment groups. All women experienced some spotting (n=8) or bleeding (n=9) during treatment except for the subject with the highest baseline progesterone (24.1 ng/mL).

Only two participants believed they received progesterone, of whom one did (continuing pregnancy at two weeks) and one did not (hemorrhage requiring emergent aspiration). The remaining ten women were evenly split between placebo and unsure. None of the women looked on the internet to identify the study capsules they received.

Discussion

Although the study sample size was powered to demonstrate a difference in continuing pregnancy rates between progesterone and placebo treatment after mifepristone ingestion, we could not evaluate this outcome due to stopping enrollment for safety reasons. However, we can make a few global and important conclusions from this very small, randomized trial. First, women who receive high-dose oral progesterone treatment do not experience side effects that are

noticeably different than placebo. Although women using progesterone did report worsening of some pregnancy symptoms, like vomiting and tiredness, these issues were rarely severe.

Second, and most importantly, are the lessons about treatment safety. Providing treatment in any medical situation requires a full understanding of the potential benefits and risks. Previous case series reports do not describe outcomes for the one-third or more women without continuing pregnancies after progesterone treatment (8). Three of 12 women enrolled experienced very heavy bleeding resulting in ambulance transport to an emergency department visit, a rate higher than reported with medical abortion in which 0.6% of women may have emergency department visits (12). Women who use mifepristone for a medical abortion should be advised that not using misoprostol could result in severe hemorrhage, even with progesterone treatment. We stopped the study because of these complications and, thus, could not quantify the full extent of this risk. Because of the potential dangers for women who opt not to use misoprostol after mifepristone ingestion, any mifepristone antagonization treatment must be considered experimental.

The study has multiple limitations, primarily the inability to safely reach the enrollment goal to fully assess the primary outcome. Additionally, blinding for progesterone capsules is difficult and imperfect; however, we believe we maintained blinding because the women enrolled had never used progesterone and none looked up the treatment to identify the drug. Of note, the variability in progesterone level among women in the progesterone group may be explained by differential oral absorption of progesterone (13). Although one may postulate another route of progesterone administration might affect the outcome, the case reports in the literature suggest similar continuing pregnancy rates after oral and intramuscular treatment (8).

Our study established outcomes at two weeks as a surrogate for ongoing pregnancy; as such, it does not capture those who may still experience pregnancy loss more than 2 weeks after

mifepristone exposure (14). Accordingly, the outcomes described may not reflect the ultimate rate of pregnancies that continue past 20 weeks gestation. Progesterone levels declined to levels near baseline from these high peaks with continued treatment for two weeks. These findings raise two opposing questions: first, if progesterone can prevent medical abortion following mifepristone, is treatment necessary for more than two weeks? The case report from which the oral progesterone regimen for this study was based used the treatment through the "end of the first trimester" (8). Second, do those treated with placebo just expel the pregnancy earlier than those that receive progesterone but no overall long-term difference in continuing pregnancy exists?

The context of this study is the question of whether a woman who has taken mifepristone 200 mg for a medical abortion and decides not to proceed with misoprostol treatment will be less likely to expel the pregnancy if she receives high-dose progesterone as compared to no treatment. Although mifepristone can cause abortion when used by itself in early pregnancy, the exact rate is not clear because studies were small and limited primarily to pregnancies of 49 days or less. Medical abortion today is used through 70 days gestation. Additionally, a background rate of pregnancy loss is present regardless of mifepristone treatment. In women with gestational cardiac activity demonstrated by ultrasonography at 6-10 weeks, 13.4% will spontaneously have an early pregnancy loss (15).

This study, although small, provides important insight into the safety of mifepristone antagonization with progesterone during early pregnancy. We should not dismiss mifepristone antagonization as impossible; fully understanding outcomes will serve as the best means to accurately inform our patients, the medical community, and legislators. Existing literature before this study is comprised of case reports and series which are not evidence of efficacy and do not

address safety (6-8). This level of evidence is inadequate to support or refute the benefits and risks of any treatment. Unfortunately, legislators often fail to understand differences in level of evidence and some states now require physicians who provide medical abortion to counsel women that the actions of mifepristone can be reversed if they change their mind. In 2015, Arkansas implemented mandatory abortion reversal counseling followed by Arizona (later repealed in 2016), South Dakota, Utah, Idaho and, most recently, North Dakota. Several other states have introduced and passed legislation, although some were vetoed by the Governor. Abortion is no different than any other medical treatment when considering clinical practice guidelines; laws should not mandate counseling or provision of any treatment when we don't fully understand treatment efficacy (including best route of administration, dose and duration) and safety.

The dilemma that has been created around mifepristone antagonization only exists because of the void in high-quality research addressing the issue. For now, such a treatment is experimental and should only be offered in Institutional Review Board approved human clinical trials to ensure proper oversight.

References

1. Jones RK, Witwer E, Jerman J. Abortion incidence and service availability in the United States, 2017, New York: Guttmacher Institute, 2019. Available at https://www.guttmacher.org/report/abortion-incidence-service-availability-us-2017 (Accessed October 8, 2019).
2. Mifeprex® label. Danco Laboratories, LLC. March, 2016. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf (Accessed October 8, 2019).
3. Spitz IM, Bardin CW. Mifepristone (RU 486)--a modulator of progestin and glucocorticoid action. N Engl J Med 1993;329:404-12.
4. Mahajan DK, London SN. Mifepristone (RU486): a review. Fertil Steril 1997;68:967-76.
5. Hsia JK, Lohr PA, Taylor J, Creinin MD. Medical abortion with mifepristone and vaginal misoprostol between 64 and 70 days' gestation. Contraception. 2019;100:178-81.
6. Delgado G, Davenport ML. Progesterone use to reverse the effects of mifepristone. Ann Pharmacother 2012;46:e36.
7. Garratt D, Turner JV. Progesterone for preventing pregnancy termination after initiation of medical abortion with mifepristone. Eur J Contracept Reprod Health Care 2017;22:472-5.
8. Delgado G, Condly SJ, Davenport M, Tinnakornsrisuphap T, Mack J, Khauv V, Zhou PS. A case series detailing the successful reversal of the effects of mifepristone using progesterone. Issues Law Med 2018;33:3-13.
9. Grossman D, White K, Harris L, et al. Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: a systematic review. Contraception 2015;92:206-11.

10. Goldstein SR, Wolfson R. Endovaginal ultrasonographic measurement of early embryonic size as a means of assessing gestational age. J Ultrasound Med 1994;13:27-31.

11. Maria B, Chaneac M, Stampf F, Ulmann A. Early pregnancy interruption using an antiprogesterone steroid: mifepristone (RU 486). J Gynecol Obstet Biol Reprod (Paris) 1988;17:1089–94.

12. Upadhyay UD, Desai S, Zlidar V, et al. Incidence of emergency department visits and complications after abortion. Obstet Gynecol 2015;125:175-83.

13. Sitruk-Ware R, Bricaire C, De Lignieres B, Yaneva H, Mauvais-Jarvis P. Oral micronized progesterone. Bioavailability pharmacokinetics, pharmacological and therapeutic implications--a review. Contraception 1987;36:373-402.

14. Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, et al. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. BJOG 2013;120:568-74.

15. Papaioannou GI, Syngelaki A, Maiz N, Ross JA, Nicolaides KH. Ultrasonographic prediction of early miscarriage. Hum Reprod 2011;26:1685-92.

Legend

Figure 1.

Title:

Participant flow in women who received mifepristone 200 mg followed by progesterone for up to two weeks

Footer:

GCA: gestational cardiac activity

Figure 2.

Title:

Serum hCG levels in women who received mifepristone 200 mg followed by progesterone for up to two weeks

Footer:

hCG: human chorionic gonadotropin

* Participants experiencing hemorrhage

† Participant experienced loss of gestational cardiac activity

‡ Value >270,000 (upper limit of hCG test)

¥ Discontinued related to side effects

Figure 3.

Title:

Progesterone levels in women who received mifepristone 200 mg followed by progesterone (Figure A) or placebo (Figure B) for up to two weeks

Header Figure 2A: Progesterone users

Header Figure 2B: Placebo users

Footer:

* Participants experiencing hemorrhage

† Participant experienced loss of gestational cardiac activity

‡ Discontinued related to side effects.

Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *Yes.*

What data in particular will be shared? *Data included with the submission in Appendix 1, available online at http://links.lww.com/xxx*

What other documents will be available? *No.*

When will data be available (start and end dates)? *With publication.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *In Appendix 1, http://links.lww.com/xxx.*

357

358 Table 1. Characteristics at enrollment for women receiving mifepristone and randomized to
359 progesterone or placebo treatment

Characteristic	Total N=12	Progesterone n=6	Placebo n=6
Age (years)	27.3 (20.9-39.6)	29.8 (24.6-39.6)	24.1 (20.9-33.8)
Gestational age (days)	52.5 (47-61)	49.5 (47-56)	55 (48-61)
Body Mass Index (kg/m^2)	24.6 (19.0-52.3)	24.8 (19.0-36.4)	24.6 (22.7-52.3)
Obese (≥30.0)	4 (33%)	2 (33%)	2 (33%)
Race			
White	3 (25%)	0	3 (50%)
Black or African American	5 (42%)	4 (67%)	1 (17%)
Asian	4 (33%)	2 (33%)	2 (33%)
Ethnicity			
Hispanic or Latina	2 (17%)	1 (17%)	1 (17%)
Marital Status			
Never married	7 (58%)	3 (50%)	4 (67%)
Married	2 (17%)	1 (17%)	1 (17%)
Divorced/Separated	3 (25%)	2 (33%)	1 (17%)
Education Level			
High School Graduate	2 (17%)	0	2 (33%)
Some college	9 (75%)	5 (83%)	4 (67%)
College Graduate	1 (8%)	1 (17%)	0
Gravidity	4 (1-12)	4.5 (1-10)	3.5 (1-12)
>3 prior pregnancies	7 (58%)	4 (67%)	3 (33%)
Parity	1 (0-6)	1.5 (0-6)	0.5 (0-3)
Nulliparous	4 (33%)	1 (17%)	3 (33%)

360

Prior Abortion	9 (75%)	4 (67%)	5 (83%)
>3 prior abortions	4 (33%)	2 (33%)	2 (33%)
Past Mifepristone Use	4 (733%)	1 (17%)	3 (33%)
Prior Progesterone Use	0	0	0

361 Data are presented as n (%) or median (range)

Table 2. Side effects* noted during follow-up of women in early pregnancy receiving mifepristone and randomized to progesterone or placebo treatment for up to two weeks

	Reported at Baseline		Increased from Baseline†		Increased to severe during follow-up†	
	Progesterone n=6	**Placebo** n=6	**Progesterone** n=6	**Placebo** n=6	**Progesterone** n=6	**Placebo** n=6
Nausea	4 (67%)	5 (83%)	2 (33%)	2 (33%)	2 (33%)	1 (17%)
Vomiting	2 (33%)	3 (50%)	4 (67%)	0	2 (33%)	0
Mastalgia	4 (67%)	5 (83%)	1 (17%)	0	0	0
Tiredness	5 (83%)	4 (67%)	3 (50%)	0	0	1 (17%)
Mood changes	4 (67%)	5 (83%)	0	0	1 (17%)	0
Reflux	2 (33%)	2 (33%)	1 (17%)	0	0	0
Dizziness	2 (33%)	1 (17%)	0	0	0	0
Bleeding	0	0	4 (67%)	4 (67%)	1 (17%)	3 (50%)
Spotting	1 (17%)	1 (17%)	3 (50%)	4 (67%)	0	0
Cramping	3 (50%)	2 (33%)	4 (67%)	5 (83%)	0	0

* subjectively assessed by participant as none, mild, moderate or severe

† at any time during follow-up

Data are presented as n (%)

Appendix. Individual subject characteristics at enrollment and outcomes for women receiving mifepristone 200 mg and randomized to progesterone or placebo treatment

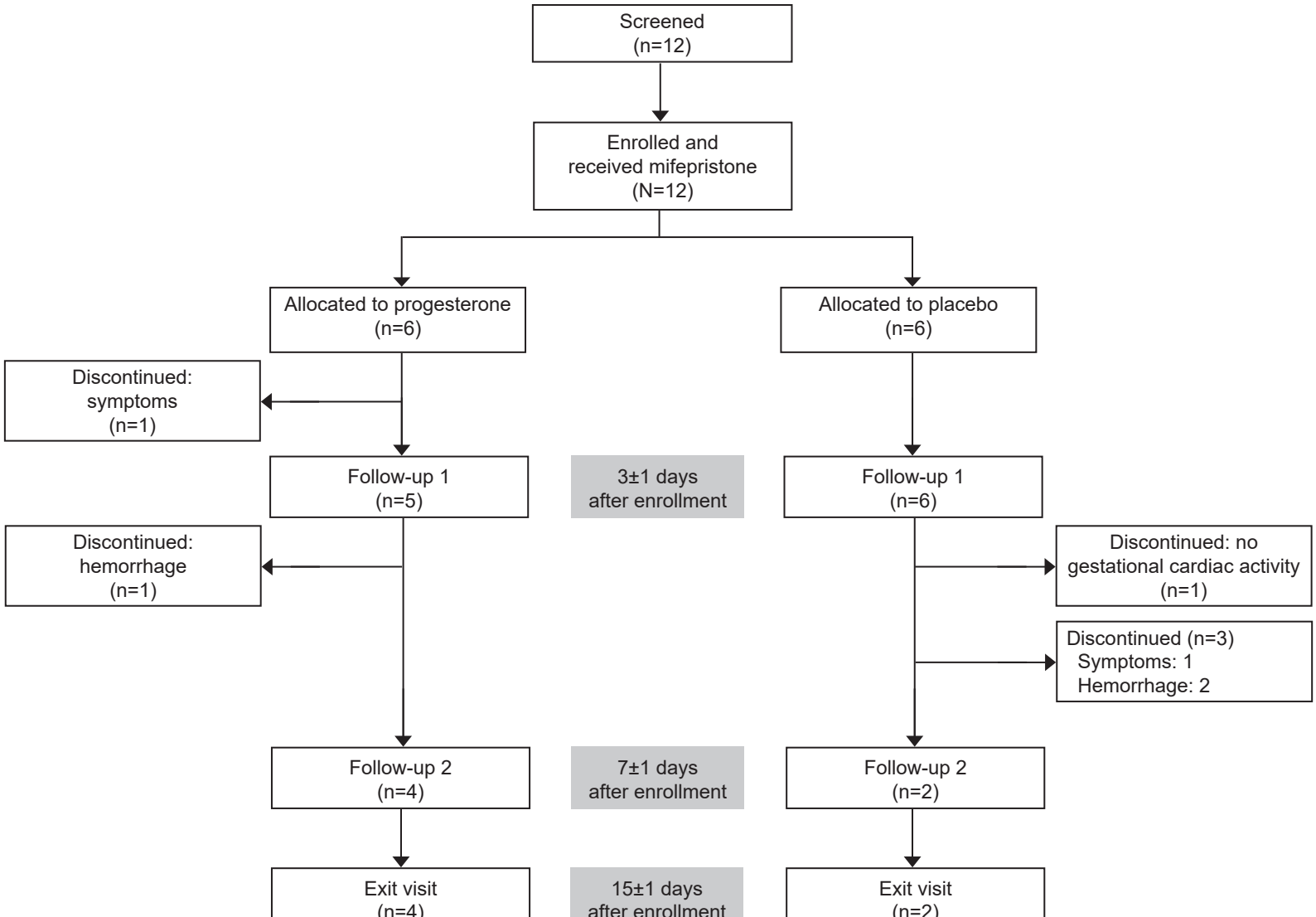
Subject Number	Study group*	Age (years)	Gestational Age (days)	Race	Ethnicity	Education	Marital Status	Smoking	Alcohol	Marijuana Use	Drug Use	Total Pregnancies	Vaginal Delivery	Cesarean Delivery	Miscarriages	Abortions	Weight (kg)	BMI (kg/m^2)
1	Progesterone	24.6	53	Asian	Not Hispanic	Some college	Never married	Never	Never	Never	Never	1	0	0	0	0	84.2	32.9
2	Progesterone	30.9	50	Black	Not Hispanic	Some college	Separated	Never	Current	Current	Never	8	3	0	0	4	68.9	23.8
3	Placebo	20.9	50	Asian	Not Hispanic	Some college	Never married	Never	Never	Never	Never	1	0	0	0	0	61.8	24.1
4	Placebo	22.6	48	White	Hispanic	Some college	Married	Current	Current	Current	Current	2	0	0	0	1	152.0	52.3
5	Progesterone	39.6	49	Black	Not Hispanic	Some college	Never married	Current	Never	Never	Never	5	2	0	0	2	51.8	19.0
6	Placebo	24.8	61	Asian	Not Hispanic	Some college	Never married	Never	Current	Current	Never	3	0	0	1	1	66.7	24.4
7	Placebo	23.5	48	White	Not Hispanic	High School graduate	Never married	Former	Never	Current	Never	7	0	1	0	5	71.8	22.7
8	Progesterone	27.7	56	Black	Not Hispanic	Some college	Never married	Never	Current	Never	Never	10	1	0	1	7	100.8	36.4
9	Progesterone	31.9	47	Asian	Not Hispanic	College graduate	Married	Never	Never	Never	Never	4	0	2	1	0	66.0	25.8
10	Placebo	27.0	60	Black	Not Hispanic	High School graduate	Never married	Never	Current	Current	Never	4	2	0	0	1	63.5	24.8
11	Placebo	33.8	60	White	Not Hispanic	Some college	Separated	Current	Former	Former	Former	12	6	0	0	5	105.5	34.3
12	Progesterone	28.6	48	Black	Hispanic	Some college	Divorced	Never	Current	Current	Never	3	1	0	0	1	53.8	19.7

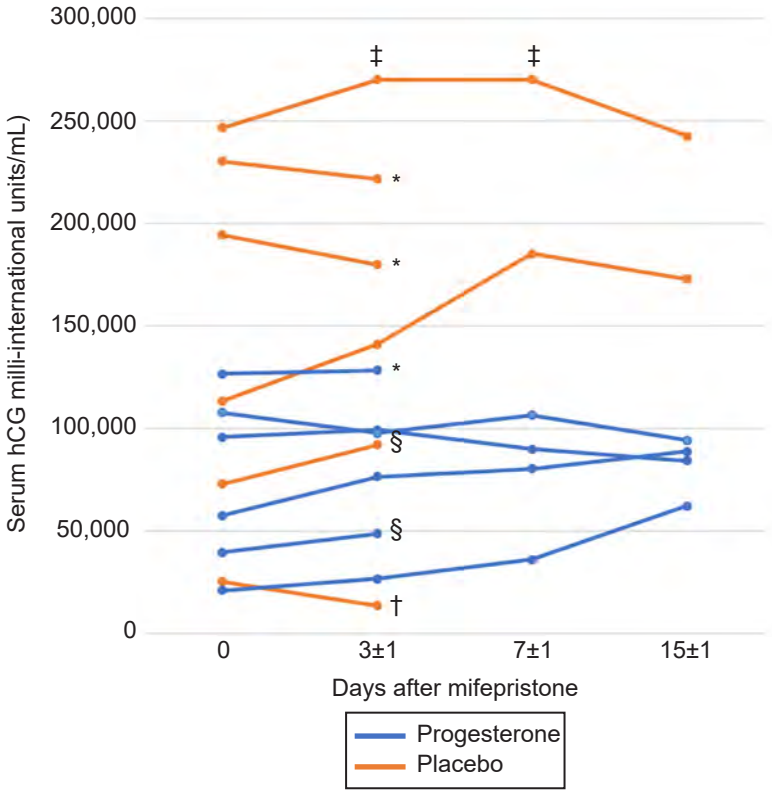
Subject Number	hCG (mIU/mL)	Progesterone (ng/mL)	Exit Study Day†	FINAL OUTCOME	Hospital visit	Reason for Hospital visit
1	95,870	12.1	17	Continuing GCA at exit visit	No	N/A
2	57,681	11.5	16	Continuing GCA at exit visit	No	N/A
3	113,431	18.9	16	Continuing GCA at exit visit	No	N/A
4	25,450	13.7	4	No GCA at follow-up visit	No	N/A
5	107,780	24.1	16	Continuing GCA at exit visit	No	N/A
6	246,638	18.9	16	Continuing GCA at exit visit	No	N/A
7	73,018	11.2	4	D&C requested (bleeding, anxiety)	No	N/A
8	126,647	12.6	3	Expelled pregnancy, no D&C	Yes (ER), Day 3	Hemorrhage, hemoglobin 10.4 gm/dL
9	39,660	10.5	4	D&C requested (nausea, vomiting)	Yes (L&D), Day 3	Dehydration, nausea, vomiting
10	230,220	16.3	5	Expelled pregnancy, incomplete, emergent D&C	Yes (ER), Day 5	Hemorrhage, hemoglobin 9.6 gm/dL
11	194,384	16.7	6	Expelled pregnancy, incomplete, emergent D&C, transfusion	Yes (ER), Day 6	Hemorrhage, hemoglobin change 9.2 to 7.5 gm/dL
12	21,062	13.9	15	Continuing GCA at exit visit	No	N/A

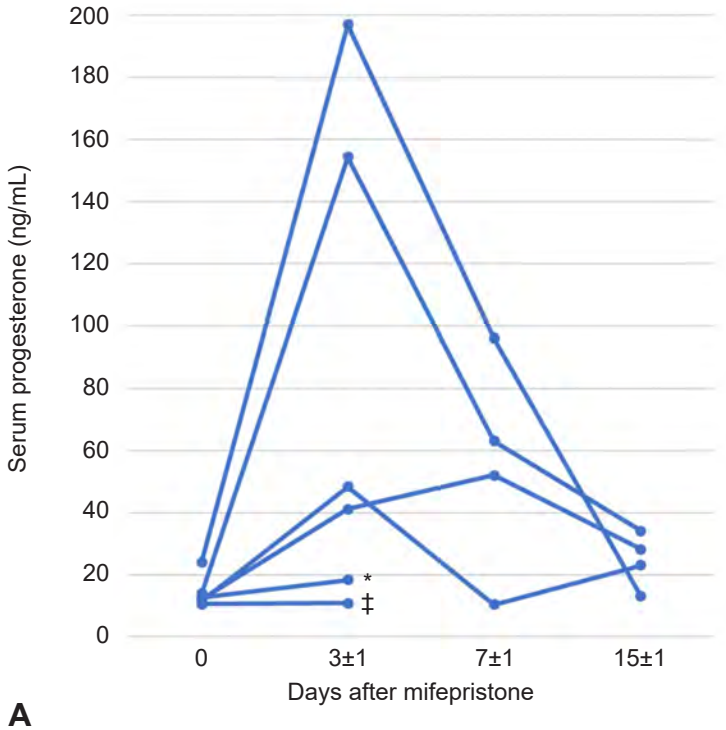
BMI: body mass index; GCA: gestational cardiac activity; ER: emergency room; L&D: labor and delivery; N/A: not applicable

* Initiated on study day 2 (24 hours after mifepristone ingestion)

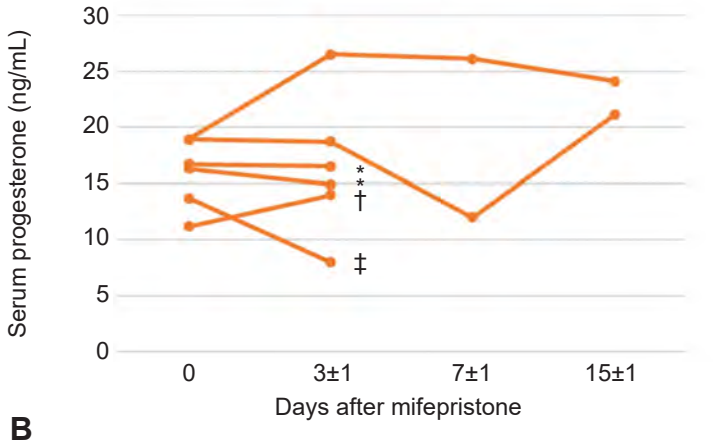
† Day 1: day of mifepristone administration


Screened
(n=12)
Enrolled and
received mifepristone
(N=12)
Allocated to progesterone
(n=6)
Allocated to placebo
(n=6)
Discontinued:
symptoms
(n=1)
Follow-up 1
(n=5)
3±1 days
after enrollment
Follow-up 1
(n=6)
Discontinued:
hemorrhage
(n=1)
Discontinued: no
gestational cardiac activity
(n=1)
Discontinued (n=3)
Symptoms: 1
Hemorrhage: 2
Follow-up 2
(n=4)
7±1 days
after enrollment
Follow-up 2
(n=2)
Exit visit
(n=4)
15±1 days
after enrollment
Exit visit
(n=2)


300,000
250,000
200,000
150,000
100,000
50,000
0
Serum hCG milli-international units/mL)
‡
‡
*
*
*
§
§
†
0
3±1
7±1
15±1
Days after mifepristone
Progesterone
Placebo


200
180
160
140
120
100
80
60
40
20
0
Serum progesterone (ng/mL)
*
‡
0
3±1
7±1
15±1
Days after mifepristone

A


30
25
20
15
10
5
0
Serum progesterone (ng/mL)
*
†
‡
0
3±1
7±1
15±1
Days after mifepristone

B

Attachment 11

A Case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone

George Delgado, M.D.,* Steven J. Condly, Ph.D.,** Mary Davenport, M.D., M.S.,*** Thidarat Tinnakornsrisuphap Ph.D.,**** Jonathan Mack, Ph.D., NP, RN***** Veronica Khauv, B.S., and Paul S. Zhou

ABSTRACT:

Background: Some women who take mifepristone, a progesterone receptor antagonist, in order to terminate their pregnancies, change their minds and desire to stop the medical abortion process. There are only two articles in the medical literature documenting the reversal of the effects of mifepristone.

Objective: We present and analyze a series of women who attempted to reverse the effects of mifepristone by taking supplemental progesterone to determine if the reversal of the effects mifepristone with progesterone is possible and safe. Additionally, we compare different progesterone regimens to determine relative efficacies.

Methods: This is a retrospective analysis of clinical data of 754 patients who decided to attempt to reverse the medical abortion process after taking mifepristone but before taking the second drug in the protocol, misoprostol. We followed the patients, who were given progesterone in an effort to reverse

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the effects of mifepristone, and conducted statistical analyses to determine the efficacies of different protocols compared to a control mifepristone embryo survival rate, derived from the literature.
***Results*: Intramuscular progesterone and high dose oral progesterone were the most effective with reversal rates of 64% ($P < 0.001$) and 68% ($P < 0.001$), respectively. There was no apparent increased risk of birth defects.**
***Conclusions*: The reversal of the effects of mifepristone using progesterone is safe and effective.**

Introduction

Medical induced abortion utilizing mifepristone has been available in the United States since 2000. In 2014, 31% of non-hospital induced abortions were medical induced abortions.[1] Some women decide to attempt to reverse the medical abortion process after taking mifepristone but before taking misoprostol, and inquire about the possibility of reversing the effects of mifepristone.[2]

The new FDA protocol, approved for medical abortion in 2016, involves the administration of mifepristone 200 mg orally as a single dose, which leads to embryonic or fetal demise, followed 24-48 hours later by misoprostol 800 mcg buccally as a single dose, which stimulates myometrial contractions. The protocol is approved up to 70 days after the first day of the last menstrual period.[3] Misoprostol is part of the protocol because mifepristone alone has an incomplete abortion rate of 20-40%, as determined by the end point of complete expulsion.[4]

Pharmacology

Mifepristone is a competitive antagonist of progesterone at the progesterone receptor (PR). It binds to the PR twice as avidly as progesterone.[5] Mifepristone is an orally active compound with a nearly 70% absorption rate, but its bioavailability is reduced to approximately 40% because of the first-pass effect.[6]

Demethylation and hydroxylation are catalyzed by CYP3A4; three metabolites retain biologic activity. The half-life of mifepristone is approximately 18-25 hours. Mifepristone and its metabolites can be measured up to 72 hours after an ingested dose.[5] The half-life of progesterone is longer, approximately 25-55 hours.[6,7]

Effects of Mifepristone

By blocking progesterone receptors, mifepristone leads to the separation of the decidua basalis from the trophoblast. This separation diminishes the oxygen and nutrients that can be delivered to the embryo or fetus by the maternal circulation and is the primary embryocidal and feticidal effect of mifepristone.[4,8,9]

In addition to this primary effect, mifepristone causes softening and dilatation of the cervix.[4] It also leads to myometrial contractions, increased myometrial sensitivity to prostaglandins[4,10] and the disinhibition of prostaglandin synthesis by the myometrium.[11]

Progesterone has been shown to have an autoregulatory effect on progesterone synthesis by the corpus luteum. Blocking progesterone receptors with mifepristone decreases progesterone secretion by the corpus luteum.[12]

Logic of Using Progesterone to Reverse Mifepristone Effects

Mifepristone is a competitive inhibitor of the progesterone receptor. It is well known that receptor agonism and antagonism are parts of a dynamic process that can be influenced by changing concentrations of the agonist or antagonist. Therefore, it makes biologic sense that increasing the progesterone levels in a pregnant woman by giving supplemental progesterone would favor the agonist progesterone effects and blunt the abortifacient effects of mifepristone.

An Animal Model

A Japanese rat study provides basic-science evidence of the ability of progesterone to negate the effects of mifepristone. In this experiment, one group of pregnant rats was given mifepristone while a second was given mifepristone and progesterone. In the group that only received mifepristone, only 33% of the pups survived. In the group that received mifepristone and progesterone, 100% of the pups survived. Furthermore, the first group had characteristic changes in the myometrium and ovaries; the group that received the combination had no such changes.[13]

Early Mifepristone Studies Reporting Continuing Pregnancy

When mifepristone was first studied as an abortifacient, misoprostol was not part of the protocol. During the 1980's, researchers determined that even though mifepristone was effective as an abortifacient, they believed it was necessary to add a prostaglandin analog to achieve a satisfactory complete uterine evacuation rate.[4] We must emphasize that the definition of incomplete abortion is incomplete emptying of the uterus.[14] Embryo or fetus survival is not implied.

The earliest studies also revealed that some embryos survived mifepristone. Baulieu, the principal developer of the drug, stated that at 4-7 weeks the percentages of efficacy of the regimen were approximately 70% for complete abortions, 20% for incomplete abortions and 10% for ongoing pregnancies (i.e., presumed embryo survival). For gestations 8-10 weeks, the comparable rates were 50% for complete abortions, 35% for incomplete abortions and 15% for embryo survival.[15]

In 2015, Grossman et al. published a review of the first case series of progesterone reversal of mifepristone, as well as 13 studies from the 1980's, addressing continuing pregnancies after mifepristone. The authors concluded that there was insufficient evidence to show that progesterone therapy improved survival over expectant management, based on the reported high ongoing pregnancy rates in some of these older studies.[16] However, closer scrutiny of the studies cited for high ongoing pregnancy rates reveals inadequate criteria for the diagnosis of continuing pregnancies. Many early researchers focused on an efficacy end point of complete uterine evacuation, and did not distinguish missed or incomplete abortions from continuing pregnancies (embryo or fetus

survival).[17] Only eight studies cited by Grossman had criteria sufficient to determine embryo survival and showed continuing pregnancy rates of 8-25%.[17]

A recent review found that 18 of the 30 articles investigating mifepristone monotherapy had adequate criteria to determine embryo survival.[17] After eliminating duplicate publications, 12 studies were identified which utilized follow-up ultrasound to distinguish between incomplete or missed abortion and embryo survival at the end of the study period. The mean percentage of embryos surviving mifepristone among all studies was 12.6%.[17] A single dose of 600 mg in five studies of early gestations 42-49 days in 493 subjects showed survivals of 9.4-17.1%.[17,18,19,20,21] Three studies of 58 women with gestations <49 days, using the current predominant 200-300 mg doses, noted embryo survival rates of 10-23.3%.[19,22,23,24] Four studies of 83 women included gestations up to 70 days, daily doses of 100-200 mg, and total doses 400-800 mg.; in three of these four studies, embryo survival was <25%.[25,26,27,28,29,30,31]

Methods

This is a retrospective analysis of clinical data of a group of pregnant women who took progesterone in an effort to reverse the effects of mifepristone. The study was reviewed and approved by an institutional review board. The lead author contributed clinical data from a variety of clinical settings across the United States and several other countries for comparison.

Subjects were pregnant women who had taken mifepristone, but had not yet taken misoprostol, and were interested in reversing its effects. Subjects called an informational hotline linked to an informational website and staffed by nurses and a physician assistant. After receiving information about the reversal process, those who decided to proceed with reversal were referred to physicians and mid-level practitioners in their respective geographic areas for treatment. The women gave written informed consent for treatment to their respective treating medical professionals that included permission to track their data. Data were collected from the women themselves and from their treating healtcare professionals.

Data were collected for different variables including gestational age at the time of mifepristone ingestion, mode of delivery of progesterone given, amounts of progesterone received, birth defects and preterm delivery. Progesterone was given in a variety of regimens by the 325 different medical professionals who treated these women. The modes of delivery of progesterone were intramuscular injection of progesterone in oil, oral administration of micronized progesterone, vaginal use of oral micronized progesterone capsules, compounded micronized progesterone vaginal suppositories, progesterone vaginal gel and progesterone vaginal suppositories.

We selected a 25% embryo or fetus survival rate, if mifepristone alone is administered, as a control because it is at the upper range of mifepristone survival rates and close to the 23% survival rate of the one early study that used a single 200 mg dose, the dose currently favored for medical abortions.[17] This study is designed to ascertain which progesterone treatments clinicians have offered to women seeking mifepristone

reversal that demonstrate efficacy beyond the 25% embryo survival rate, and compares the relative efficacies of different treatment protocols to the historic control.

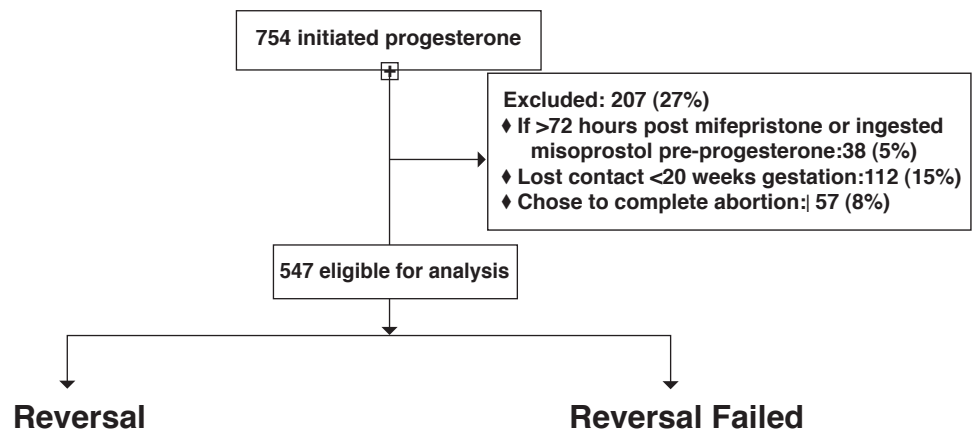
Results

From June 24, 2012 to June 21, 2016, 1,668 calls were received by the hotline from women who had taken mifepristone and were interested in reversal. Seven hundred fifty-four (45%) actually initiated progesterone therapy.

Subjects were included in the study if they were 72 hours or less post-mifepristone and had not taken misoprostol; 38 (5%) did not meet these criteria. Of the women who started progesterone therapy and met inclusion criteria, 116 (15.4%) were lost to follow-up at some point. Of those,112 (14.9%) were lost to follow-up prior to 20 weeks gestation and were excluded from the analysis. Four (0.5%) women remained pregnant with viable fetuses but were lost to follow-up after twenty weeks gestation and were included in the analysis as reversals.

Fifty-seven (7.6%) of the women, after starting progesterone therapy, changed their minds again and either took misoprostol to complete the medical abortion or procured surgical induced abortion. Of those 57, 39 (5.2%) chose to complete abortion medically with misoprostol, seven (0.9%) procured surgical abortions and 11 (1.5%) completed

Figure 1



abortion by unspecified means. These were not included in the analysis as they chose to no longer attempt reversal. See Figure 1.

Women who delivered babies after progesterone therapy or who were lost to follow-up after 20-weeks gestation were considered to have reversed their medical abortions, since any pregnancy loss after 20 weeks would be unlikely to be attributable to the early mifepristone exposure. The data analysis was accomplished using the Statistical Hypothesis Test on a population proportion.

After exclusions, there were 547 patients with analyzable outcomes who underwent progesterone therapy. There were 257 births (47%). Another four were pregnant with viable fetuses but were lost to follow-up after 20 weeks gestation (0.7%). The overall rate of reversal of mifepristone was 48%.

Two subgroups had the highest reversal rates. Those who received progesterone intramuscularly (IM) initially or exclusively had a 64% reversal rate. One subject in this group had an undocumented number of injections. The high-dose oral subgroup received oral progesterone, 400 mg twice a day for three days, followed by 400 mg once a day until the end of the first trimester and had a reversal rate of 68%, similar to the IM group. These survival rates compare favorably with published embryo and fetal survival rate of 25%, if no treatment is attempted,[17] the rate used as a control. See Table 1.

The gestational age at the time of ingestion was directly related to reversal success. See Table 2. This is not surprising since mifepristone embryocidal and feticidal rates fall with advancing gestational age.[33]

There was no correlation between maternal age and rate of reversal. In the subset of records noting time intervals, the time between mifepristone ingestion and the first progesterone dose was not statistically significant in relation to the success rate for reversals attempted within 72 hours of mifepristone injection.

Birth Defects

There were seven reported birth defects in the women who had reversals and follow-up after their deliveries for a rate of 7/257 (2.7%). See Table 3. This is equal to the birth defect rate in the general population of approximately 3%[34] and suggests that there is no increased risk of birth defects in babies born after mifepristone reversal.

Preterm Delivery

There were seven deliveries at <37weeks for a preterm delivery rate of 2.7%. The United States average is 10%.[35]

Multiple Gestations

There were nine sets of twins (4.3% of the pregnancies). There were no higher order multiples.

Discussion

Progesterone Safety

Progesterone is a naturally occurring hormone produced by the corpus luteum and by the placenta, and is essential for maintenance of the maternal fetal interface of pregnancy. It has been used safely in pregnancy for over 50 years.[36] The American Society of Reproductive Medicine states that no long-term risks have been identified when progesterone is used in pregnancy.[37] The FDA has given progesterone a category B rating in pregnancy, in contrast to synthetic progestins.[38]

Table 1: Reversals Compared to Reported Control of 25% Survival if No Treatment Undertaken

Progesterone Group	Number	Reversals	Reversal Failures	Percent Reversals	P Value	95% Confidence Intervals
All Groups	547	261	286	48%	<0.001	0.44-0.52
High Dose Oral	31	21	10	68%	<0.001	0.51-0.84
Intramuscular, All groups	125	80	45	64%	<0.001	0.56-0.72
IM, 1 Injection	50	24	26	48%	<0.001	0.34-0.62
IM, 2-5 Injec.	36	21	15	58%	<0.001	0.42-0.74
IM, 6-8 Injec.	9	9	0	100%	<0.001	0.67-1
IM, 9-10 Injec.	10	9	1	90%	<0.001	0.77-1.0
IM, 11 or More Injec.	19	17	2	89%	<0.001	0.76-1.0
Oral, All Groups	119	64	55	54%	<0.001	0.45-0.63
Oral Caps Vaginally, All Doses	156	61	95	39%	<0.001	0.31-0.47
Vaginal Suppository	34	11	23	32%	0.161	0.17-0.48

A recent retrospective study of a Danish infertility cohort suggested a possible increased risk of acute lymphocytic leukemia and sympathetic neural tumors in children born to mothers who had taken progesterone during pregnancy and before pregnancy. The increased risk was greatest in women who had taken progesterone for three or more cycles.[39] However, the infertility population examined in the Danish study, exposed to

Table 2: Gestational Age Compared to Reversal Rate

Gestational Age	Total	Reversal	Reversal Failure	Reversal %	*P* value	95% Confidence Intervals
5 weeks	76	19	57	25%	0.5	0.15-0.35
6 weeks	113	52	61	46%	<0.001	0.37-0.55
7 weeks	102	50	52	49%	<0.001	0.39-0.59
8 weeks	88	54	34	61%	<0.001	0.51-0.72
9 weeks	30	23	7	77%	<0.001	0.62-0.92

Table 3: Birth Defects

Birth Defect	Instances
Port Wine Stain	1
Bilateral Absent Toe	1
Unilateral Two Absent Fingers	1
Choroid Plexus Cyst	1
Cystic Kidney	1
Unilateral Failed Hearing Test	1
Heart Murmur	1

many cycles of progesterone and other medications, differs significantly from our population of fertile women who had a single exposure to progesterone.

Mifepristone Teratogenicity

While previous human studies are not large in number, the available evidence suggests that mifepristone is not teratogenic.[4,40,41] The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin March 2014 states that there is no evidence that mifepristone is associated with teratogenicity.[42] Our data set, the largest of babies exposed to mifepristone in utero, also indicates that the birth defect risk in women who have reversed mifepristone abortions is no higher than the risk in the general population.

Study Limitations

This study is limited in that it is not a randomized placebo-controlled trial. However, a placebo-controlled trial in the population of women who regret their abortion and

want to save the pregnancy would be unethical. Furthermore, although the number of women lost to follow-up was small, it could have affected the results. In addition, some data collection was incomplete.

One potential confounding variable is the use of ultrasound to select for living embryos prior to the first progesterone dose. It is possible that those embryos who were alive at the time of sonogram may have survived without progesterone therapy. However, our study also included some women who started progesterone therapy prior to sonographic documentation that the embryo was alive. Undoubtably, this group included women who already had an embryonic demise prior to initiation of progesterone therapy. Inclusion of these women would falsely lower the success rate of progesterone therapy. The numbers of women who received or did not receive ultrasound exams prior to initiating therapy were not available to our researchers. If ultrasound is readily available, sound practice would dictate that embryonic or fetal viability should be confirmed, or at least suggested, before treatment is started in order to avoid giving women progesterone unnecessarily and to exclude ectopic pregnancy before starting progesterone therapy.

Conclusions

The use of progesterone to reverse the effects of the competitive progesterone receptor blocker, mifepristone, appears to be both safe and effective. Progesterone therapy makes biologic sense, has been previously published as effective in an animal model and is supported by this case series which demonstrates a statistically significant difference in survival between treatment groups and the historic control. Mifepristone is embryocidal and feticidal but not teratogenic; progesterone is not associated with birth defects.

Based on these new data, two reasonable protocols can be suggested for women who seek to reverse the effects of mifepristone:

1. Progesterone micronized 200 mg capsule two by mouth as soon as possible and continued at a dose of 200 mg capsule two by mouth twice a day for three days, followed by 200 mg capsule two by mouth at bedtime until the end of the first trimester; and

2. Progesterone 200 mg intramuscular as soon as possible and continued at a dose of 200 mg intramuscular once a day on days two and three, then every other day for a total of seven injections. Some clinicians may choose to continue intramuscular treatment longer since this recommendation is based on relatively small numbers.

Recommendations for Future Research

We propose that further research employing randomized controlled trials comparing progesterone doses and routes of administration are needed to confirm which mode of delivery, dose and duration of progesterone therapy is most efficacious and carries the least burden for the patient.

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References

[1] Jones RK and Jerman J. Abortion incidence and service availability in the United States, 2014. *Perspectives on Sexual and Reproductive Health*, 2017, 49(1), DOI: 10.1363/psrh.12015.

[2] Delgado G, Davenport M. Progesterone Use to Reverse the Effects of Mifepristone. *Ann Pharmacother* 2012;46. Published Online, 27 Nov 2012, *theannals.com*, DOI: 10.1345/aph.1R252.

[3] Medication Guide, Mifeprix. www.fda.gov/downloads/drugs/drugsafety/ucm088643.pdf (accessed November 19, 2016).

[4] Creinin, M, Gemzell Danielsson, K. Chapter 9, Medical abortion in early pregnancy, *in Management of Unintended and Abnormal Pregnancy*: *Comprehensive Abortion Care*. Published Online: 22 May 2009 DOI: 10.1002/9781444313031.ch9.

[5] Heikinheimo O, Kekkonen R, Lahteenmaki P. The pharmacokinetics of mifepristone in humans reveal insights into differential mechanisms of antiprogestins action. *Contraception* 2003;68:421-6.

[6] Sarkar NN. Mifepristone: bioavailability, pharmacokinetics and use-effectiveness. *Eur J Obstet Gynaecol Reprod Bio*; 2002;101:113-20.

[7] Drug Bank Progesterone. http://www.drugbank.ca/drugs/DB00396 (accessed 2011 Oct 8).

[8] Johannisson E, Oberholzer M, Swahn ML, Bygdeman M. Vascular changes in the human endometrium following the administration of the progesterone antagonist RU 486. *Contraception* 1989; 39: 103–107.

[9] Schindler AM, Zanon P, Obradovic D, Wyss R, Graff P, Hermann WL. Early ultrastructural changes in RU-486-exposed decidua. *Gynecol Obstet Invest* 1985; 20: 62–67.

[10] Swahn ML, Bygdeman M. The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin. *Br J Obstet Gynaecol* 1988; 95: 126–134.

[11] Herrmann WL, Schindler AM, Wyss R, Bishof P. Effects of the antiprogesterone RU 486 in early pregnancy and during the menstrual cycle. In: Beaulieu EE, Siegel S, eds. *The Antiprogestin Steroid RU 486 and Human Fertility Control*. Plenum, New York, 1985: 259–262.

[12] Ottander U, et al. A Putative Stimulatory Role of Progesterone Acting via Progesterone Receptors in the Steroidogenic Cells of the Human Corpus Luteum. *Biology of Reproduction* March 1, 2000 vol. 62 no. 3 655-663.

[13] Yamabe, S; Katayana, K; Mochuzuki, M *Folio endocrine*. 65, 497-511, 1989. The Effects of RU486 and Progesterone on Luteal Function During Pregnancy.

[14] http://medical-dictionary.thefreedictionary.com/incomplete+abortion (accessed November 20, 2016).

[15] Beaulieu EE. RU-486: An antiprogestin steroid with contragestive effect in women. In Baulieu EE, Siegel S (eds): *The Antiprogestin Steroid RU 486 and Human Fertility Control*. New York, Plenum, 1985. pp. 2-6.

[16] Grossman D et al. Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: A systematic review, *Contraception* (2015) September 2015 Volume 92, Issue 3, pp. 206–211, DOI: 10.1016/j.contraception.2015.06.001).

[17] Davenport M, Delgado G, Khauv V. Embryo survival after mifepristone: review of the literature. *Issues in Law and Medicine* 2017, 32 (1): 3-18.

[18] Ylikorkala O, Alfthan H, Kääriäinen M, Rapeli T, Lähteenmäki P. Outpatient therapeutic abortion with mifepristone. *Obstet Gynecol* 1989;74:653-7.

[19] Maria B, Chaneac M, Stampf F, Ulmann A. [Early pregnancy interruption using anantiprogesterone steroid: Mifepristone (RU 486)]. *J Gynecol Obstet Biol Reprod* (Paris) 1988;17:1089-94.

[20] Carol W, Klinger G. [Experiences with the antigestagen mifepristone (RU 486) in the interruption of early pregnancy]. *Zentralbl Gynakol* 1989;111:1325-8.

[21] Somell C, Olund A. Induction of abortion in early pregnancy with mifepristone. *Gynecol Obstet Invest* 1990;29:13-5.

[22] Kovacs L, Sas M, Resch BA, Ugocsai G, Swahn ML, Bygdeman M, Rowe PJ. Termination of very early pregnancy by RU 486–an antiprogestational compound. *Contraception* 1984;29:399-410.

[23] Kovacs L, Termination of Very Early Pregnancy with Different Doses of RU-486: A Phase I Controlled Clinical Trial. *In* Beaulieu EE, Siegel S (eds): *The Antiprogestin Steroid RU 486 and Human Fertility Control*. pp. 179-198. New York, Plenum, 1985.

[24] Swahn ML. S. Cekan, G. Wang, V. Lundstom, and M. Bygdeman. *In* Beaulieu EE, Siegel S (eds): *The Antiprogestin Steroid RU 486 and Human Fertility Control*. pp. 249-258. New York, Plenum, 1985.

[25] Herrmann WL, Schindler AM, Wyss R, et al: Effects of the antiprogesterone RU 486 in early pregnancy and during the menstrual cycle. *In* Beaulieu EE, Siegel S (eds): *The Antiprogestin Steroid RU 486 and Human Fertility Control*. pp. 179-198. New York, Plenum, 1985.

[26] Herrmann W, Wyss R, Riondel A, Philibert D, Teutsch G, Sakiz E, Baulieu EE. [The effects of an antiprogesterone steroid in women: interruption of the menstrual cycle and of early pregnancy]. *Comptes Rendus Seances Acad Sci III*. 1982 May 17;294(18):933-8. French.

[27] Vervest HAM, Haspels AA, Preliminary results with antiprogesterone RU-486. (mifepristone) for interruption of early pregnancy. *FertilSteril*. 1985;44: 627-32.

[28] Haspels AA Interruption of early pregnancy by the antiprogestational compound RU 486 In Beaulieu EE, Siegel S (eds): *The Antiprogestin Steroid RU 486 and Human Fertility Control*. pp. 199-210, New York, Plenum, 1985.

[29] Haspels AA. Interruption of early pregnancy by an anti-progestational compound, RU 486. *Eur J Obstet Gynecol Reprod Biol*. 1985 Sep;20(3):169.

[30] Cameron IT, Michie AF, Baird DT. Therapeutic abortion in early pregnancy with antiprogestogen RU486 alone or in combination with prostaglandin analogue (gemeprost). *Contraception* 1986;34:459-68.

[31] Cameron IT, Baird DT. Early pregnancy termination: a comparison between vacuum aspiration and medical abortion using prostaglandin (16,16 dimethyl-trans-delta 2-PGE1 methyl ester) or the antiprogestogen RU 486. *Br J Obstet Gynaecol*. 1988 Mar; 95(3):271-6.

[32] Elia D. Clinical study of RU 486 in early pregnancy *In* Beaulieu EE, Siegel S (eds): *The Antiprogestin Steroid RU 486 and Human Fertility Control*. pp. 211-220. New York, Plenum, 1985.

[33] Spitz IM, Bardin W, Benton L, Robbins A, et al. Early pregnancy termination with mifepristone and misoprostol. *N Engl J Med* 1998;338:1241-7. DOI: 0.1056/NEJM199804303381801.

[34] CDC MMWR January 11, 2008 / 57(01);1-5.

[35] Preterm Birth. http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm (accessed December 7, 2016).

[36] Dante G, Vaccaro V, Facchinetti. Use of progestogens in early pregnancy. Facts, Views and Vision. *ObGyn*. 2013 5(1): 66-71.

[37] Progesterone. https://www.asrm.org/detail.aspx?id=1881(accessed December 3, 2016).

[38] Progesterone package insert. https://www.drugs.com/pro/progesterone-capsule.html. (accessed December, 3, 2016).

[39] Hargreave M, et al. Maternal use of fertility drugs and risk of cancer in children–a nationwide population-based cohort study in Denmark. *Int. J. Cancer*: 136, 1931–1939 (2015).

[40] Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, Amar E, Descotes J, Vial T. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. *BJOG*. 2013 Apr;120(5):568-74. DOI: 10.1111/1471-0528.12147. Epub 2013 Jan.

[41] Regine Sitruk-Ware a, Angela Davey , Edouard Sakiz. Fetal malformation and failed medical termination of pregnancy. *The Lancet*, Volume 352, Issue 9124, Page 323, 25 July 1998.

[42] Medical Management of First Trimester Abortion. *ACOG Practice Bulletin* 143 March 2014, reaffirmed 2016.

Attachment 12

Cochrane Library

Cochrane Database of Systematic Reviews

Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth (Review)

Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA

Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA.
Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth.
Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD004947.
DOI: 10.1002/14651858.CD004947.pub3.

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[Intervention Review]

Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth

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ABSTRACT

Background

Preterm birth is a major complication of pregnancy associated with perinatal mortality and morbidity. Progesterone for the prevention of preterm labour has been advocated.

Objectives

To assess the benefits and harms of progesterone for the prevention of preterm birth for women considered to be at increased risk of preterm birth and their infants.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (14 January 2013) and reviewed the reference list of all articles.

Selection criteria

Randomised controlled trials, in which progesterone was given for preventing preterm birth.

Data collection and analysis

Two review authors independently evaluated trials for methodological quality and extracted data.

Main results

Thirty-six randomised controlled trials (8523 women and 12,515 infants) were included.

Progesterone versus placebo for women with a past history of spontaneous preterm birth
Progesterone was associated with a statistically significant reduction in the risk of perinatal mortality (six studies; 1453 women; risk ratio (RR) 0.50, 95% confidence interval (CI) 0.33 to 0.75), preterm birth less than 34 weeks (five studies; 602 women; average RR 0.31, 95% CI 0.14 to 0.69), infant birthweight less than 2500 g (four studies; 692 infants; RR 0.58, 95% CI 0.42 to 0.79), use of assisted ventilation

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(three studies; 633 women; RR 0.40, 95% CI 0.18 to 0.90), necrotising enterocolitis (three studies; 1170 women; RR 0.30, 95% CI 0.10 to 0.89), neonatal death (six studies; 1453 women; RR 0.45, 95% CI 0.27 to 0.76), admission to neonatal intensive care unit (three studies; 389 women; RR 0.24, 95% CI 0.14 to 0.40), preterm birth less than 37 weeks (10 studies; 1750 women; average RR 0.55, 95% CI 0.42 to 0.74) and a statistically significant increase in pregnancy prolongation in weeks (one study; 148 women; mean difference (MD) 4.47, 95% CI 2.15 to 6.79). No differential effects in terms of route of administration, time of commencing therapy and dose of progesterone were observed for the majority of outcomes examined.

Progesterone versus placebo for women with a short cervix identified on ultrasound
Progesterone was associated with a statistically significant reduction in the risk of preterm birth less than 34 weeks (two studies; 438 women; RR 0.64, 95% CI 0.45 to 0.90), preterm birth at less than 28 weeks' gestation (two studies; 1115 women; RR 0.59, 95% CI 0.37 to 0.93) and increased risk of urticaria in women when compared with placebo (one study; 654 women; RR 5.03, 95% CI 1.11 to 22.78). It was not possible to assess the effect of route of progesterone administration, gestational age at commencing therapy, or total cumulative dose of medication.

Progesterone versus placebo for women with a multiple pregnancy
Progesterone was associated with no statistically significant differences for the reported outcomes.

Progesterone versus no treatment/placebo for women following presentation with threatened preterm labour
Progesterone, was associated with a statistically significant reduction in the risk of infant birthweight less than 2500 g (one study; 70 infants; RR 0.52, 95% CI 0.28 to 0.98).

Progesterone versus placebo for women with 'other' risk factors for preterm birth
Progesterone, was associated with a statistically significant reduction in the risk of infant birthweight less than 2500 g (three studies; 482 infants; RR 0.48, 95% CI 0.25 to 0.91).

Authors' conclusions

The use of progesterone is associated with benefits in infant health following administration in women considered to be at increased risk of preterm birth due either to a prior preterm birth or where a short cervix has been identified on ultrasound examination. However, there is limited information available relating to longer-term infant and childhood outcomes, the assessment of which remains a priority.

Further trials are required to assess the optimal timing, mode of administration and dose of administration of progesterone therapy when given to women considered to be at increased risk of early birth.

PLAIN LANGUAGE SUMMARY

Prenatal administration of progesterone to prevent preterm birth in women considered to be at risk of having their baby early

Babies who are born before 37 weeks, and particularly those born before 34 weeks, are at greater risk of having problems at birth and complications in infancy. Infants who are born preterm are at greater risk of dying in their first year of life, and of those infants who survive, there is an increased risk of repeated admission to hospital and adverse outcomes including cerebral palsy and long-term disability. Progesterone is a hormone that reduces contractions of the uterus and has an important role in maintaining pregnancy and is suggested for the prevention of preterm labour. Maternal side-effects from progesterone therapy include headache, breast tenderness, nausea, cough and local irritation if administered intramuscularly. At present, there is little information available regarding the optimal dose of progesterone, mode of administration, gestation to commence therapy, or duration of therapy.

The review of 36 randomised controlled trials, involving a total of 8523 women considered to be at increased risk of preterm birth, and 12,515 infants, found that where progesterone was given (by injection into the muscle in some studies and as a pessary into the vagina in others), it had beneficial effects, including reducing the risk of the baby dying after birth, suffering complications such as requiring assisted ventilation, necrotising enterocolitis or requiring admission to neonatal intensive care, prolonging the pregnancy, and reducing the chance of neonatal intensive care admission.

Information related to longer-term infant and childhood outcomes was limited. Overall, the trials included in this review were considered to be of good to fair quality. Further trials are required to assess the optimal timing, mode of administration and dose of administration of progesterone therapy.

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BACKGROUND

Description of the condition

Preterm birth before 37 weeks' gestation is a common problem in obstetric care, with estimates ranging from 5% in several European countries to 18% in some African countries (Blencowe 2012). In Australia, approximately 8% of all infants were born preterm in 2000, with 2.7% of these births occurring prior to 34 weeks' gestation (AIHW 2003). Figures are similar for the United States, with a preterm birth rate of 12.0% (Blencowe 2012). While less than 2% of these infants were born prior to 32 weeks' gestation (Martin 2003), they are at increased risk of complications in infancy, and contribute in excess of 50% of the overall perinatal mortality (AIHW 2003). Infants who are born preterm are at greater risk of dying in their first year of life (Martin 2003), and of those infants who survive, there is an increased risk of repeated admission to hospital (Elder 1999) and adverse outcomes including cerebral palsy and long-term disability (Hack 1999; Stanley 1992), creating a significant burden upon the community (Kramer 2000).

The 'cause' of preterm labour is multifactorial in origin, and it is important to consider the role of any identifiable risk factors in a woman's pregnancy.

The most significant and consistently identified risk factor for preterm birth, is a woman's history of previous preterm birth (Adams 2000; Bakketeig 1979; Berkowitz 1993; Bloom 2001; Goldenberg 1998; Kaminski 1973; Kistka 2007; Papiernik 1974; Petrini 2005; Robinson 2001). Estimates suggest the rate of recurrent preterm birth in this group of women to be 22.5% (Petrini 2005), a 2.5 times increased risk ratio when compared with women with no previous spontaneous preterm birth (Mercer 1999). For women with a history of a single preterm birth, the recurrence risk in a subsequent pregnancy is approximately 15%, increasing to 32% where there have been two previous preterm births (Carr-Hill 1985). Information derived from population-based cohort data suggests that for women who give birth between 20 and 31 weeks' gestation in one pregnancy, 29.3% will give birth prior to 37 weeks in a subsequent pregnancy (Adams 2000). For approximately 10% of these women, the preterm birth will occur at a similar gestational age (Adams 2000; Kistka 2007). In up to 50% of cases of preterm birth, the cause is spontaneous onset of labour or preterm premature rupture of membranes (PPROM) (Hewitt 1988; Mattison 2001; McLaughlin 2002).

Other characteristics in a woman's current pregnancy may place her at increased risk of preterm birth, including women with a short cervix identified by ultrasound assessment, the presence of fetal fibronectin in the vaginal secretions, and presentation with symptoms or signs of threatened preterm labour.

The identification of a short cervix (considered to be less than 2.5cm) on ultrasound examination has been associated with an increased likelihood of preterm birth before 34 weeks' gestation (Smith 2007). Identification of fetal fibronectin present in cervico-vaginal secretions has also been proposed as a means of identifying women at risk of preterm birth. Overall, the value of fetal fibronectin in women presenting with symptoms of threatened preterm labour, is a negative test, where women are unlikely to proceed to preterm birth before 34 weeks' gestation or within seven days of testing (Smith 2007).

Multiple pregnancy is a strong risk factor for preterm birth though the mechanisms may be different to those operating in women with a singleton pregnancy. Up to 50% of women with a twin pregnancy will give birth prior to 37 weeks' gestation (AIHW 2003). The preterm birth risk of early birth before 37 weeks for women with a singleton pregnancy is 6.3% compared with 97% for women with a triplet pregnancy (AIHW 2003).

Description of the intervention

Progesterone may be administered in various forms and by various routes. These different formulations and modes of administration will have different absorption patterns and potentially have differing bio effects. Whilst no teratogenic effects have been described with most progesterones, there is little in the way of long-term safety data. Maternal side-effects from progesterone therapy include headache, breast tenderness, nausea, cough and local irritation if administered intramuscularly. At present, there is little information available regarding the optimal dose of progesterone, mode of administration, gestation to commence therapy, or duration of therapy (Greene 2003; Iams 2003).

How the intervention might work

Progesterone has a role in maintaining pregnancy (Haluska 1997; Pepe 1995; Pieber 2001) and is thought to act by suppressing smooth muscle activity in the uterus (Astle 2003; Grazzini 1998). In many animal species, there is a reduction in the amount of circulating progesterone before the onset of labour. While these changes have not been shown to occur in women (Astle 2003; Block 1984; Lopez-Bernal 2003; Pieber 2001; Smit 1984), it has been suggested that there is a 'functional' withdrawal of progesterone related to changes in the expression of progesterone receptors in the uterus (Astle 2003; Condon 2003; Haluska 2002; Pieber 2001). There have been recent reports in the literature advocating the use of progesterone to reduce the risk of preterm birth (da Fonseca 2003; Meis 2003), rekindling interest that dates back to the 1960s (Le Vine 1964).

This review was modified in 2006, from the original protocol published in *The Cochrane Library* in Issue 4, 2004, in order to clarify the scope of the review. The title and objectives changed, and the description of participants expanded to include the reason the women were considered to be at increased risk of preterm birth. The primary outcome measure of preterm birth less than 32 weeks' gestation has been changed to preterm birth less than 34 weeks' gestation to be consistent with World Health Organization definitions of preterm birth. Secondary outcome measures reflecting childhood developmental assessment have been added, reflecting the need for ongoing evaluation of children participating in randomised trials.

Why it is important to do this review

Preterm birth and its consequences for women and their babies is a significant health problem in pregnancy and childbirth. While the suppression or prevention of preterm labour should lead to improved survival through a lower incidence of premature delivery, there are theoretical reasons why a fetus may not survive without disability. It is possible that an intrauterine mechanism that would trigger preterm labour could also cause neurological injury to the fetus and that progesterone may prevent labour but not fetal injury. The purpose of this review is to assess the benefits and harms of progesterone administration for the prevention of preterm birth for

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both women and their infants, when considering the risk factors present for preterm birth.

OBJECTIVES

To assess the benefits and harms of progesterone administration for the prevention of preterm birth in women and their infants.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials, in which progesterone was administered for the prevention of preterm birth, subdivided by the reason women were considered to be at risk for preterm birth.

Trials were excluded if:

- they utilised quasi-randomised methodology; cross-over design;
- progesterone was administered for the acute treatment of actual or threatened preterm labour (that is, where progesterone was administered as an acute tocolytic medication); or
- progesterone was administered in the first trimester only for preventing miscarriage.

Types of participants

Pregnant women considered to be at increased risk of preterm birth. These reasons include:

- past history of spontaneous preterm birth (including preterm prelabour rupture of membranes);
- multiple pregnancy;
- ultrasound identified short cervical length;
- fetal fibronectin testing;
- following acute presentation with symptoms or signs of threatened preterm labour (where a tocolytic medication may have been administered);
- other reason considered to be at increased risk of preterm birth.

Types of interventions

Administration of progesterone by any route for the prevention of preterm birth.

Types of outcome measures

Primary outcomes

1. Perinatal mortality
2. Preterm birth (less than 34 weeks' gestation)
3. Major neurodevelopmental handicap at childhood follow-up

Secondary outcomes

Maternal

1. Threatened preterm labour (as defined by trial authors)
2. Prelabour spontaneous rupture of membranes
3. Adverse drug reaction
4. Pregnancy prolongation (interval between randomisation and birth)
5. Mode of birth
6. Number of antenatal hospital admissions
7. Satisfaction with the therapy
8. Use of tocolysis
9. Antenatal corticosteroids (not a prespecified outcome)
10. Maternal quality of life (not a prespecified outcome)

Infant

1. Birth before 37 completed weeks
2. Birth before 28 completed weeks
3. Birthweight less than the third centile for gestational age
4. Birthweight less than 2500 g
5. Apgar score of less than seven at five minutes
6. Respiratory distress syndrome
7. Use of mechanical ventilation
8. Duration of mechanical ventilation
9. Intraventricular haemorrhage - grades III or IV
10. Periventricular leucomalacia
11. Retinopathy of prematurity
12. Retinopathy of prematurity - grades III or IV
13. Chronic lung disease
14. Necrotising enterocolitis
15. Neonatal sepsis
16. Fetal death
17. Neonatal death
18. Admission to neonatal intensive care unit
19. Neonatal length of hospital stay
20. Teratogenic effects (including virilisation in female infants)
21. Patent ductus arteriosis (not a prespecified outcome)

Child

1. Major sensorineural disability (defined as any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than -2 standard deviations below mean))
2. Developmental delay (however defined by the authors)
3. Intellectual impairment
4. Motor impairment
5. Visual impairment
6. Blindness
7. Deafness
8. Hearing impairment
9. Cerebral palsy
10. Child behaviour
11. Child temperament
12. Learning difficulties
13. Growth assessments at childhood follow-up (weight, head circumference, length, skin fold thickness)

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Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (14 January 2013).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

For details of searching carried out for the initial version of the review, please see Appendix 1.

Searching other resources

We also manually cross-referenced key publications.

We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, see Appendix 2.

For this update we used the following methods when assessing the reports identified by the updated search.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted third author. We entered data into Review Manager software (RevMan 2012) and checked for accuracy. When information regarding any of the above was unclear, we contacted authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Disagreement was resolved by discussion or by involving the third author.

(1) Sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We planned to assess blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We planned to assess blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

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(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups; or less than 20% losses to follow-up);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting bias

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other sources of bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

We assessed whether studies that included multiple pregnancies accounted appropriately for non-independence of babies from the same pregnancy in the analysis. There are several ways this can be done, and these studies should present something like an odds ratio adjusted for non-independence. If adjustment was not done, we assessed the potential for bias i.e. if multiples only made up a small proportion of the total then there is probably not much potential for bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods, if required.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials for inclusion in this review, but we may include trials of this type in future updates. If we do, we plan to include cluster-randomised trials in the analyses along with individually-randomised trials. Their sample sizes will be adjusted using the methods described in the *Cochrane Handbook* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we planned to synthesise the relevant information. We consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We also planned to acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials were not included.

Other unit of analysis issues

The analysis in this review involves multiple pregnancies, therefore, wherever possible, analyses should be adjusted for clustering to take into account the non-independence of babies from the same pregnancy (Gates 2004). Treating babies from multiple pregnancies as if they are independent, when they are more likely to have similar outcomes than babies from different pregnancies, will overestimate the sample size and give confidence intervals that are too narrow. Each woman can be considered a cluster in multiple pregnancy, with the number of individuals in the cluster being equal to the number of fetuses in her pregnancy. Analysis using cluster trial methods allows calculation of relative risk and adjustment of confidence intervals. Usually this will mean that the confidence intervals get wider. Although this may make little

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difference to the conclusion of a trial, it avoids misleading results in those trials where the difference may be substantial.

We planned to adjust for clustering in the analyses, wherever possible, and to use the inverse variance method for adjusted analyses, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, due to insufficient information in the included trials, we were not able to adjust our analyses. In future updates, if possible, we will adjust for clustering in the analyses.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the T^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If 10 or more studies contributed data to meta-analysis for any particular outcome, we investigated reporting biases (such as publication bias) using funnel plots. We assessed possible asymmetry visually. If asymmetry was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it. In this version of the review insufficient data were available to allow us to carry out this planned analysis.

Data synthesis

We carried out statistical analysis using the RevMan software (RevMan 2012). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials examined the same intervention, and where we judged the trials' populations and methods to be sufficiently similar. If we suspected clinical heterogeneity sufficient to expect the underlying treatment effects to differ between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary provided that we considered an average treatment effect across trials was clinically meaningful. The random-effects summary was treated as the average of the range of possible treatment effects and the clinical implications of treatment effects differing between trials is discussed. If the average treatment effect was not clinically meaningful we did not combine trials.

Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Results were analysed according to the reason women were considered to be at risk of preterm birth, including:

- past history of spontaneous preterm birth (including preterm prelabour rupture of membranes);
- multiple pregnancy;
- ultrasound identified short cervical length;
- fetal fibronectin testing;
- presentation with symptoms or signs of threatened preterm labour;
- other reason for risk of preterm birth.

For analyses where there are high levels of heterogeneity we have provided an estimate of the 95% range of underlying intervention effects (prediction interval).

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, we used random-effects analysis to produce it.

We planned, where possible, to carry out the following subgroup analyses:

1. time of treatment commencing (before 20 weeks' gestation versus after 20 weeks' gestation);
2. route of administration (intramuscular, intravaginal, oral, intravenous);
3. different dosage regimens (divided arbitrarily into a cumulative dose of less than 500 mg per week and a dose of greater than or equal to 500 mg per week).

All outcomes were considered in subgroup analyses.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2012).

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates (greater than 20%), or both, with poor-quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result.

RESULTS

Description of studies

Results of the search

In the 2006 update, our search strategy identified 22 studies for consideration. Eleven studies met the inclusion criteria stated (Borna 2008; da Fonseca 2003; Facchinetti 2007; Fonseca 2007; Hartikainen 1980; Hauth 1983; Johnson 1975; Meis 2003; O'Brien 2007; Papiernik 1970; Rouse 2007) involving a total of 2714 women and 3452 infants. The study by Northern (Northen 2007) reports the follow-up of children involved in the Meis study (Meis 2003).

Sixty-four reports from an updated search in January 2013 have been assessed for this update. Of these 64 reports, an additional 25 studies (33 reports) to the original 11 studies, were included

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(Aboulghar 2012; Akbari 2009; Briery 2011; Caritis 2009; Cetingoz 2011; Combs 2010; Combs 2011; Combs 2011a; Elsheikhah 2010; Glover 2011; Grobman 2012; Hassan 2011; Ibrahim 2010; Lim 2011; Majhi 2009; Moghtadaei 2008; Ndoni 2010; Norman 2009; Rai 2009; Rode 2011; Rozenberg 2012; Saghafi 2011a; Senat 2012; Serra 2013; Sharami 2010); seven studies (seven reports) were excluded (Abbott 2012; Arikan 2011; Berghella 2010; Chandiramani 2012; Ionescu 2012; Keeler 2009; Rust 2006); two studies (two reports) are ongoing studies (Coomarasamy 2012; van Os 2011); one is an additional report of an ongoing study (Crowther 2007); one additional report was added to each of the following included studies (Combs 2010; Combs 2011; Facchinetti 2007; Lim 2011; Nassar 2007). Two additional reports were identified for the Norman 2009; O'Brien 2007; Rode 2011 and Rouse 2007 included studies. Three additional reports were identified for the Meis 2003 included study.

A total of 36 studies are included in this update.

Included studies

Refer to table Characteristics of included studies for further details.

Use of progesterone in women with a history of prior spontaneous preterm birth

Description of studies

Eleven studies were included involving a total of 1936 women with a past history of spontaneous preterm birth (Akbari 2009; Cetingoz 2011; da Fonseca 2003; Glover 2011; Johnson 1975; Ibrahim 2010; Majhi 2009; Meis 2003; O'Brien 2007; Rai 2009; Saghafi 2011a). Four studies compared weekly intramuscular injection with placebo (Ibrahim 2010; Johnson 1975; Meis 2003) or routine care (Saghafi 2011a); five studies compared daily vaginal progesterone, three with placebo (Cetingoz 2011; da Fonseca 2003; O'Brien 2007) and two with routine care (Akbari 2009; Majhi 2009); and two studies compared daily oral progesterone with placebo (Glover 2011; Rai 2009). Dose of progesterone administered varied from 90 mg daily (O'Brien 2007), to 100 mg daily (Akbari 2009; Cetingoz 2011; da Fonseca 2003; Majhi 2009), to 200 mg daily (Rai 2009), to 400 mg daily (Glover 2011), to 200 mg weekly (Rai 2009), to 250 mg weekly (Johnson 1975; Meis 2003; Saghafi 2011a). Supplementation commenced prior to 20 weeks' gestation in four trials (Glover 2011; Johnson 1975; Meis 2003; O'Brien 2007), and continued up to a gestational age varying from 24 weeks (Johnson 1975; Majhi 2009; Rai 2009), to 28 weeks (da Fonseca 2003), to 34 weeks (Akbari 2009; Cetingoz 2011), to 36 weeks (Ibrahim 2010; Meis 2003), and to 37 weeks (O'Brien 2007; Saghafi 2011a) gestation.

The primary outcomes reported by the trials related to the occurrence of preterm birth prior to 28 weeks' gestation (Rai 2009), 32 weeks' gestation (O'Brien 2007), 34 weeks' gestation (Akbari 2009; Majhi 2009), and 37 weeks' gestation (Akbari 2009; Cetingoz 2011; da Fonseca 2003; Ibrahim 2010; Johnson 1975; Majhi 2009; Meis 2003; Saghafi 2011a). Eight trials involved single centres (Akbari 2009; da Fonseca 2003; Glover 2011; Ibrahim 2010; Johnson 1975; Majhi 2009; Rai 2009; Saghafi 2011a), and two were multicentre trials (Meis 2003; O'Brien 2007), conducted principally from the United States of America (Glover 2011; Johnson 1975; Meis 2003; O'Brien 2007), India (Majhi 2009; Rai 2009), Iran (Akbari 2009; Saghafi 2011a), Egypt (Ibrahim 2010), Istanbul (Cetingoz 2011), and Brazil (da Fonseca 2003). The report by Northen 2007 reports childhood follow-up of 348 participants in the Meis randomised trial (Meis 2003).

One study (Cetingoz 2011) included a mix of women with a history of prior preterm birth (n = 71) and women with a multiple pregnancy (n = 67) and the results for this study have been analysed separately for the two risk groups.

Use of progesterone in women with a short cervix identified on transvaginal ultrasound examination

Description of studies

Four studies were included involving 1560 women who were identified with a short cervix (various definitions: less than 15 mm (Fonseca 2007); less than 30 mm (Grobman 2012); between 10 and 20mm (Hassan 2011); and less than 25 mm (Rozenberg 2012)) at the time of transvaginal ultrasound examination. One study compared weekly intramuscular injection with placebo (Grobman 2012); one study compared twice weekly intramuscular injection with no treatment (Rozenberg 2012) and two studies compared daily intravaginal progesterone with placebo (Fonseca 2007; Hassan 2011). Dose of progesterone administered varied from 90 mg daily in the morning (Hassan 2011), to 200 mg nightly (Fonseca 2007), to 250 mg weekly (Grobman 2012), to 500 mg twice weekly (Rozenberg 2012). Supplementation commenced from 16 to 22 weeks' gestation in one study (Grobman 2012), from 19 to 23 weeks in another study (Hassan 2011), from 24 to 31 weeks in another study (Rozenberg 2012), and from 24 to 33 completed weeks of gestation in another study (Fonseca 2007).

The primary outcomes reported by the trials related to the occurrence of preterm birth prior to 33 weeks' gestation (Hassan 2011), 34 weeks' gestation (Fonseca 2007), 35 weeks' gestation (Grobman 2012), or 37 weeks' gestation (Grobman 2012) and time from randomisation to delivery in one study (Rozenberg 2012). All trials were multicentre conducted in centres worldwide, including the United Kingdom, USA, France, Greece, Chile and Brazil.

One study (Fonseca 2007) included a mix of singleton and twin pregnancies (226 singleton and 24 twin pregnancies), but due to the small proportion of twin pregnancies in this study, we have analysed all of this data within the short cervix subgroup.

Use of progesterone in women with a multiple pregnancy

Description of studies

Fourteen studies were included involving 3792 women; 11 trials with a twin pregnancy (Aboulghar 2012; Cetingoz 2011; Combs 2011; Elsheikhah 2010; Fonseca 2007; Hartikainen 1980; Norman 2009; Rode 2011; Rouse 2007; Senat 2012; Serra 2013), two trials with a triplet pregnancy (Caritis 2009; Combs 2010) or one trial with any multiple pregnancy, e.g. twins, triplets or quadruplets (Lim 2011). Six studies compared 250 mg weekly intramuscular progesterone injections with placebo (Caritis 2009; Combs 2010; Combs 2011; Hartikainen 1980; Lim 2011; Rouse 2007); one study compared 1000 mg weekly intramuscular progesterone injections with no treatment (Senat 2012); three studies compared intravaginal progesterone with placebo (Aboulghar 2012; Cetingoz 2011; Elsheikhah 2010), one at a daily dose of 100 mg (Cetingoz 2011), one at a daily dose of 200 mg (Elsheikhah 2010) and one at a daily dose of 400 mg Aboulghar 2012); one study compared 90 mg daily intravaginal gel with placebo (Norman 2009); and one study compared 100 mg daily oral progesterone with placebo (Rode 2011). One trial (Serra 2013) consisted of three groups and compared 200 mg daily intravaginal progesterone with 400 mg daily intravaginal progesterone with placebo. Supplementation

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commenced from 16 to 20 weeks' gestation in three studies (Caritis 2009; Lim 2011; Rouse 2007), from 16 to 22 weeks in one study (Combs 2010), from 16 to 24 weeks in one study (Combs 2011), from 18 to 24 weeks in one study (Aboulghar 2012; Rode 2011), from 24 to 34 weeks in two studies (Cetingoz 2011; Elsheikhah 2010), from 24 weeks' gestation in one study (Norman 2009), and from 28 completed weeks' of gestation in one study (Hartikainen 1980).

The primary outcomes reported by the trials related to the occurrence of preterm birth prior to 34 weeks' gestation (Aboulghar 2012; Cetingoz 2011; Rode 2011; Senat 2012) or 37 weeks' gestation (Aboulghar 2012; Cetingoz 2011; Serra 2013), delivery or fetal loss before 34 weeks' gestation (Norman 2009), delivery or fetal loss before 35 weeks' gestation (Caritis 2009), mean cervical length and mean gestational age at delivery (Elsheikhah 2010), perinatal death (Hartikainen 1980) or composite neonatal morbidity (Combs 2010; Combs 2011; Lim 2011; Senat 2012). Five trials were multicentre conducted in centres worldwide, including the United Kingdom, USA, the Netherlands, Denmark, Austria and France (Caritis 2009; Combs 2010; Combs 2011; Lim 2011; Norman 2009; Rode 2011; Rouse 2007) and four were single-centre trials conducted in Istanbul, Egypt and Finland (Aboulghar 2012; Cetingoz 2011; Elsheikhah 2010; Hartikainen 1980).

Two studies included a mix of women with multiple and singleton pregnancies (Aboulghar 2012; Cetingoz 2011). One study (Aboulghar 2012) included a mix of women with singleton pregnancies (n = 215) and women with a multiple pregnancy (n = 91) all conceived by IVF/ICSI (in vitro fertilisation/intracytoplasmic sperm injection) and the results for this study have been analysed separately for the two risk groups: women at risk of preterm birth for 'other' reasons; and women with a multiple pregnancy. One study (Cetingoz 2011) included a mix of women with a history of prior preterm birth (n = 71) and women with a multiple pregnancy (n = 67) and the results for this study have been analysed separately for the two risk groups.

Use of progesterone in women following symptoms or signs of threatened preterm labour

Description of studies

Six small studies were included involving a total of 505 women presenting with symptoms or signs of threatened preterm labour (Borna 2008; Briery 2011; Combs 2011a; Facchinetti 2007; Ndoni 2010; Sharami 2010). Two studies compared 250 mg weekly progesterone injections with placebo (Briery 2011; Combs 2011a), one study compared vaginal progesterone pessaries on a daily basis (400 mg) with no treatment (Borna 2008), one study compared 341 mg intramuscular progesterone injection every four days with no treatment (Facchinetti 2007), one study had three arms and compared intramuscular progesterone with oral progesterone with placebo (Ndoni 2010) and one study compared vaginal pessaries on a daily basis (200 mg) with placebo pessaries (Sharami 2010). Women presented with symptoms and signs between 24 and 34 weeks' gestation (Borna 2008), between 25 and 33 weeks' gestation (Facchinetti 2007), between 20 and 30 weeks' gestation (Briery 2011), between 23 and 31.9 weeks' gestation (Combs 2011a), between 15 and 22 weeks' gestation (Ndoni 2010) and between 28 and 36 weeks' gestation (Sharami 2010). The primary outcomes reported included the interval from randomisation to birth in one study (Borna 2008), transvaginal ultrasound assessment of cervical length in one study (Facchinetti 2007), gestational age at birth in one study (Briery 2011), prolongation of pregnancy and composite neonatal morbidity in one study (Combs 2011a) and time until delivery and birth before 34 or 37 completed weeks in one study (Sharami 2010). In one study, reported only in abstract form, data relating to outcomes was not reported (Ndoni 2010). One study was a multicentre study conducted in the USA (Combs 2011a) and the remaining five studies were single-centre studies conducted in Iran, the USA, Italy, and Albania (Borna 2008; Briery 2011; Facchinetti 2007; Ndoni 2010; Sharami 2010).

Use of progesterone in women at risk of preterm birth for 'other' reasons

Description of studies

Papiernik 1970 recruited 99 women from Paris, France, in a single centred trial, with a 'high preterm risk score'. Women were allocated to receive intramuscular progesterone three times per week or placebo, from 28 to 32 weeks' gestation.

Hauth 1983 involved 168 women from the United States of America who were considered to be at risk of preterm birth due to active military service. Women received 1000 mg of progesterone weekly or placebo, from 16 to 20 weeks' gestation, up until 36 weeks' gestation. The primary outcome for the study related to the incidence of preterm birth at less than 37 weeks' gestation.

Moghtadaei 2008 involved 260 women from Iran, in a single centre trial, who were considered to be at risk of preterm birth due to advanced maternal age (greater than 35 years). Women received weekly injections of 17P (250 mg) starting at 16 to 20 weeks' gestation until 34 weeks or matching placebo. The main outcomes for the study included delivery before 37, 35 or 32 weeks' gestation, hypertension, diabetes, intrauterine growth restriction or side effects at the injection site. Data from this study could not be included in a meta-analysis because the number of women randomised to each group was not reported in the brief abstract report of the study.

Aboulghar 2012 recruited 313 women from Egypt who were considered to be at high risk of preterm birth because all the pregnancies were conceived by IVF or ICSI. Women received vaginal progesterone 200 mg twice daily from randomisation until delivery or 37 weeks' gestation or matching placebo. The primary outcomes included preterm birth of singleton and twin pregnancies before 37 completed weeks and before 34 completed weeks. This study contains a mix of singleton pregnancies (n = 215) and twin pregnancies (n = 91) and presented some outcome data separately, as well as for the whole group. The results for this study have been analysed separately for the two risk groups: multiple pregnancies and women at risk for 'other' reasons.

Excluded studies

In total, 16 studies were excluded (Abbott 2012; Arikan 2011; Berghella 2010; Breart 1979; Brenner 1962; Chandiramani 2012; Corrado 2002; Hobel 1986; Ionescu 2012; Keeler 2009; Le Vine 1964; Rust 2006; Suvonnakote 1986; Turner 1966; Walch 2005; Yemini 1985). Three studies were excluded as they used a quasi-randomised method of treatment allocation (Le Vine 1964; Suvonnakote 1986; Yemini 1985). One study (Hobel 1986) compared an oral progestogen with placebo, but presented outcomes only as percentages. Five studies were excluded as progesterone was administered in the first trimester to prevent miscarriage (Breart

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1979; Brenner 1962; Corrado 2002; Turner 1966; Walch 2005), and are covered by the Cochrane review relating to the use of progesterone for prevention of miscarriage (Haas 2008). One study was excluded because progesterone was administered as an acute tocolytic medication (Arikan 2011). A further six studies were excluded because they compared progesterone with cerclage (Abbott 2012; Chandiramani 2012; Ionescu 2012; Keeler 2009; Rust 2006) or compared cerclage with no cerclage (Berghella 2010), and are covered by other Cochrane reviews (Alfirevic 2012; Rafael 2011).

Refer to table Characteristics of excluded studies for further details.

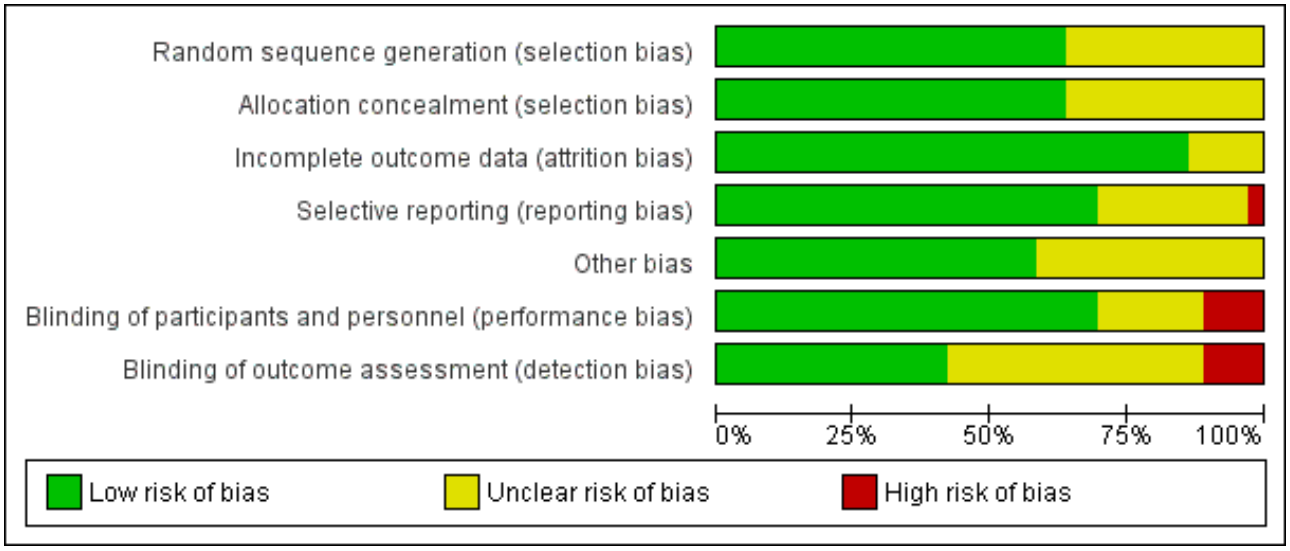
Studies awaiting assessment

There are 11 ongoing studies awaiting assessment (Coomarasamy 2012; Creasy 2008; Crowther 2007; Martinez 2007; Nassar 2007; Norman 2012; Perlitz 2007; Starkey 2008; Swaby 2007; van Os 2011; Wood 2007).

Risk of bias in included studies

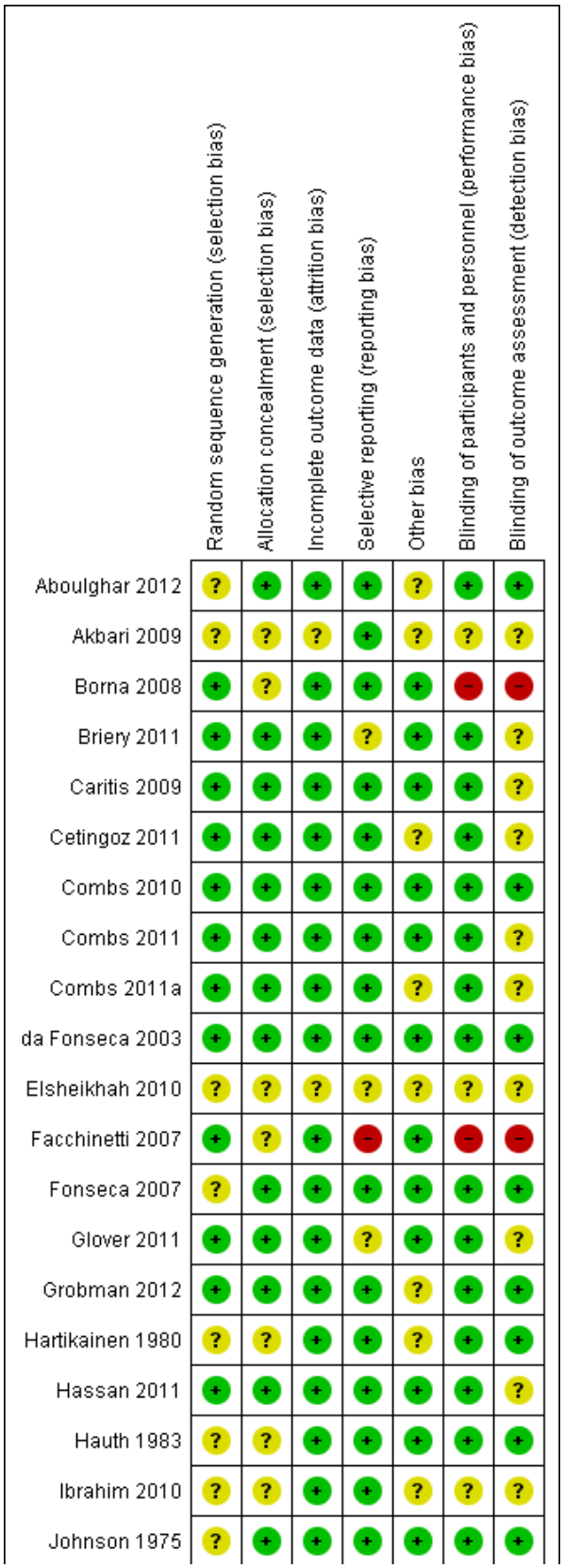
The overall quality of the included trials varied from good to fair. Refer to table Characteristics of included studies for further details and to Figure 1; Figure 2, for a summary of 'Risk of bias' assessments.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



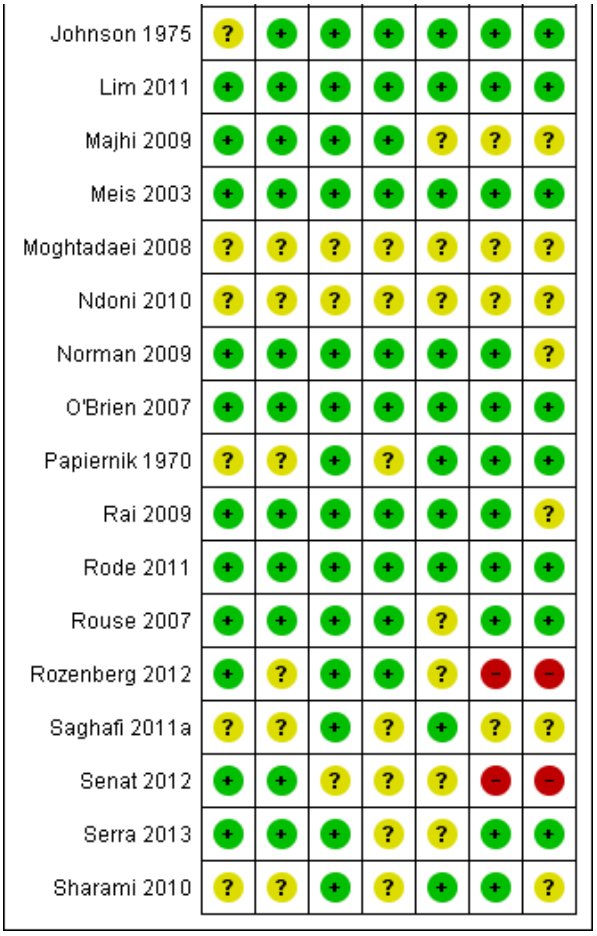
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Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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Figure 2. (Continued)



Allocation

While all trials were stated to be randomised and placebo controlled, the method of randomisation was only described in 23 trials (Borna 2008; Briery 2011; Caritis 2009; Cetingoz 2011; Combs 2010; Combs 2011; Combs 2011a; da Fonseca 2003; Facchinetti 2007; Glover 2011; Grobman 2012; Hassan 2011; Lim 2011; Majhi 2009; Meis 2003; Norman 2009; O'Brien 2007; Rai 2009; Rode 2011; Rouse 2007; Rozenberg 2012; Senat 2012; Serra 2013). Allocation concealment was assessed as low risk of bias in 23 trials (Aboulghar 2012; Briery 2011; Caritis 2009; Cetingoz 2011; Combs 2010; Combs 2011; Combs 2011a; da Fonseca 2003; Fonseca 2007; Glover 2011; Grobman 2012; Hassan 2011; Johnson 1975; Lim 2011; Majhi 2009; Meis 2003; Norman 2009; O'Brien 2007; Rai 2009; Rode 2011; Rouse 2007; Senat 2012; Serra 2013); and unclear in 13 trials (Akbari 2009; Borna 2008; Elsheikhah 2010; Facchinetti 2007; Hartikainen 1980; Hauth 1983; Ibrahim 2010; Moghtadaei 2008; Ndoni 2010; Papiernik 1970; Rozenberg 2012; Saghafi 2011a; Sharami 2010).

Blinding

Twenty-five of the 32 included trials were placebo controlled, with blinding of caregivers and participants (Aboulghar 2012; Briery 2011; Caritis 2009; Cetingoz 2011; Combs 2010; Combs 2011; Combs 2011a; da Fonseca 2003; Fonseca 2007; Glover 2011; Grobman 2012; Hartikainen 1980; Hassan 2011; Hauth 1983; Johnson 1975; Lim 2011; Meis 2003; Norman 2009; O'Brien 2007; Papiernik 1970; Rai 2009; Rode 2011; Rouse 2007; Serra 2013; Sharami 2010).

Blinding of outcome assessment was evident in 15 of the trials (Aboulghar 2012; Combs 2010; da Fonseca 2003; Fonseca 2007; Grobman 2012; Hartikainen 1980; Hauth 1983; Johnson 1975; Lim 2011; Meis 2003; O'Brien 2007; Papiernik 1970; Rode 2011; Rouse 2007; Serra 2013).

Four trials were assessed as high risk of bias for both blinding of caregivers and participants and outcome assessment as no blinding was attempted (Borna 2008; Facchinetti 2007; Rozenberg 2012; Senat 2012).

Incomplete outcome data

Thirty-one studies were assessed as being at low risk of bias for attrition bias. Thirteen studies reported no losses to follow-up (Borna 2008; Caritis 2009; Combs 2010; Combs 2011a; Facchinetti 2007; Fonseca 2007; Hartikainen 1980; Hauth 1983; Ibrahim 2010; Majhi 2009; Meis 2003; Papiernik 1970; Saghafi 2011a) and 18 studies reported less than 20% loss to follow-up (Aboulghar 2012; Briery 2011; Cetingoz 2011; Combs 2011; da Fonseca 2003; Glover 2011; Grobman 2012; Hassan 2011; Johnson 1975; Lim 2011; Norman 2009; O'Brien 2007; Rai 2009; Rode 2011; Rouse 2007; Rozenberg 2012; Serra 2013; Sharami 2010). In five studies reported only in abstract form, it was unclear whether attrition bias was present (Elsheikhah 2010; Grobman 2012; Moghtadaei 2008; Ndoni 2010; Senat 2012) and in one study details were insufficient to make a judgement (Akbari 2009).

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Selective reporting

Twenty-five studies were assessed as being at low risk of bias for selective reporting (Aboulghar 2012; Akbari 2009; Borna 2008; Caritis 2009; Cetingoz 2011; Combs 2010; Combs 2011; Combs 2011a; da Fonseca 2003; Fonseca 2007; Grobman 2012; Hartikainen 1980; Hassan 2011; Hauth 1983; Ibrahim 2010; Johnson 1975; Lim 2011; Majhi 2009; Meis 2003; Norman 2009; O'Brien 2007; Rai 2009; Rode 2011; Rouse 2007; Rozenberg 2012) as all expected outcomes were reported. One study was assessed as being at high risk of bias, because one of the outcomes was incompletely reported on (Facchinetti 2007) and in one study it was difficult to assess selective reporting based on a translation of the original report (Papiernik 1970). In all the other study reports, it was not possible to determine whether or not selection bias was present (Briery 2011; Elsheikhah 2010; Glover 2011; Moghtadaei 2008; Ndoni 2010; Rozenberg 2012; Saghafi 2011a; Senat 2012; Serra 2013; Sharami 2010).

Other potential sources of bias

Twenty-one studies were assessed as being at low risk of bias for other potential sources of bias based on baseline characteristics being similar between groups and no other bias apparent (Borna 2008; Briery 2011; Caritis 2009; Combs 2010; Combs 2011; da Fonseca 2003; Facchinetti 2007; Fonseca 2007; Glover 2011; Hassan 2011; Hauth 1983; Johnson 1975; Lim 2011; Meis 2003; Norman 2009; O'Brien 2007; Papiernik 1970; Rai 2009; Rode 2011; Saghafi 2011a; Sharami 2010). In the remaining studies, it was not possible to determine whether or not other sources of bias were present (Aboulghar 2012; Akbari 2009; Cetingoz 2011; Combs 2011a; Elsheikhah 2010; Grobman 2012; Hartikainen 1980; Ibrahim 2010; Majhi 2009; Moghtadaei 2008; Ndoni 2010; Rouse 2007; Rozenberg 2012; Senat 2012; Serra 2013).

Assessment of studies that included multiple pregnancies

We assessed whether studies that included multiple pregnancies accounted appropriately for non-independence of babies from the same pregnancy in the analysis. There were 14 studies that included a multiple pregnancy (Aboulghar 2012; Caritis 2009; Cetingoz 2011; Combs 2010; Combs 2011; Elsheikhah 2010; Fonseca 2007; Hartikainen 1980; Lim 2011; Norman 2009; Rode 2011; Rouse 2007; Senat 2012; Serra 2013) and in seven studies adjustment appears to have been made in the analysis (Caritis 2009; Combs 2010; Combs 2011; Fonseca 2007; Lim 2011; Norman 2009; Rode 2011). In the remaining seven studies (Aboulghar 2012; Cetingoz 2011; Elsheikhah 2010; Hartikainen 1980; Rouse 2007; Senat 2012; Serra 2013), it is not clear that any adjustment was made.

There were insufficient data presented in the trial reports to allow us to carry out necessary adjustment for cluster design effect ourselves and, although in several trials results had already been adjusted, we were not able to present these data in our data and analyses tables because they were not reported in a consistent way.

Effects of interventions

Thirty-six randomised controlled trials (8523 women and 12,515 infants) in total were included in this review.

Data were only available in a suitable format from 30 randomised controlled trials involving a total of 7561 women and 10,114 infants. Data from these 30 trials contributed data that were included in meta-analyses. As the aetiology of preterm birth is multifactorial, results are presented according to the reason considered to be at risk for preterm birth (past history of spontaneous preterm birth (including preterm premature rupture of membranes), ultrasound identified short cervical length, multiple pregnancy, prior presentation with threatened preterm labour, and other reason for risk of preterm birth).

Progesterone versus placebo/no treatment for women with a past history of spontaneous preterm birth

Eleven randomised controlled trials involving a total of 1899 women and infants were included in the meta-analysis.

Primary outcomes

For women administered progesterone during pregnancy, there was a statistically significant reduction in perinatal mortality overall (six studies; 1453 women; risk ratio (RR) 0.50, 95% confidence interval (CI) 0.33 to 0.75), Analysis 1.1. For the primary outcome preterm birth less than 34 weeks' gestation, there was also a statistically significant difference between progesterone when compared with placebo (five studies; 602 women; average RR 0.31, 95% CI 0.14 to 0.69), Analysis 1.2. Substantial heterogeneity was evident for Analysis 1.2 (heterogeneity: $Tau^2 = 0.45$, $Chi^2 = 9.15$, $df = 4$ ($P = 0.06$), $I^2 = 56\%$) and so a random-effects model was used. Major neurodevelopmental handicap in childhood was not reported.

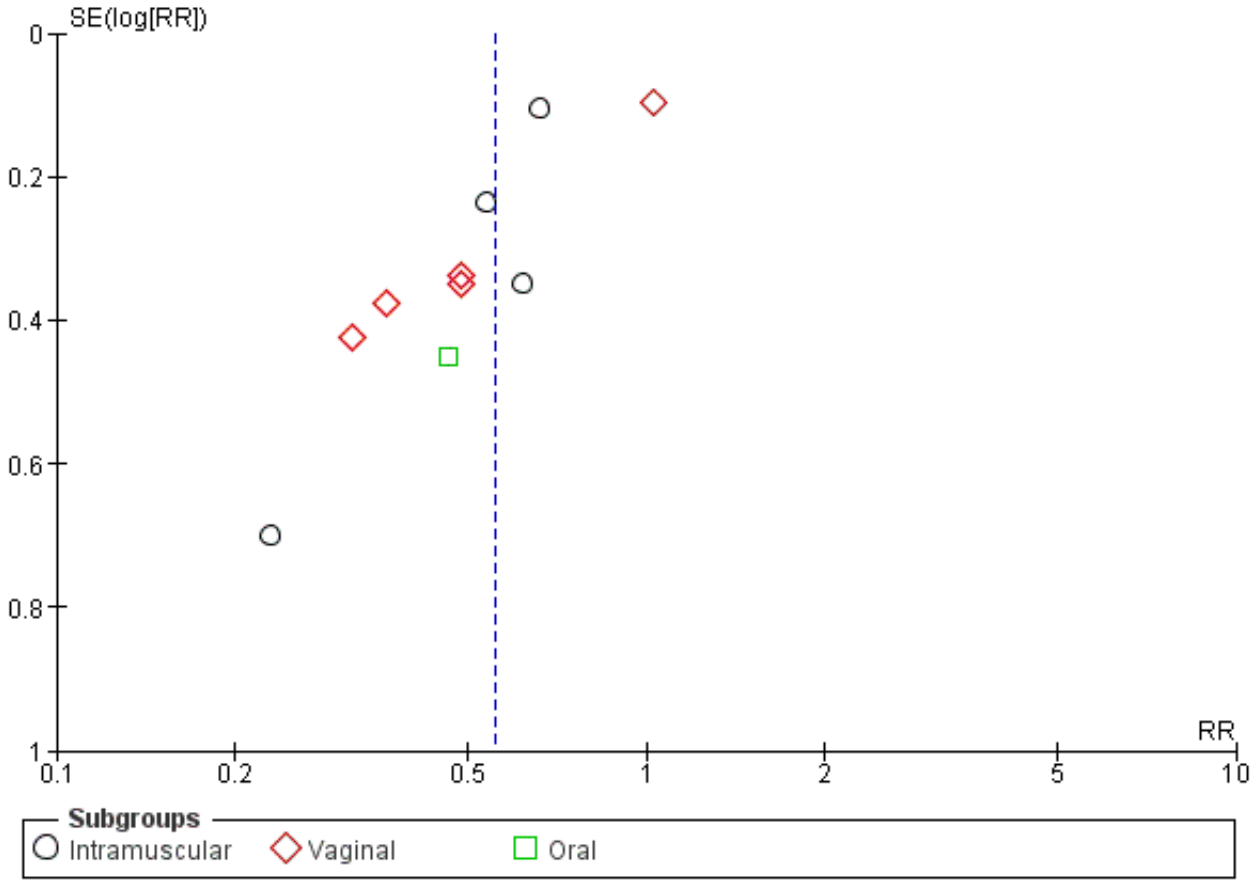
Secondary infant outcomes

For women administered progesterone during pregnancy, when compared with placebo, the results showed:

- preterm birth less than 37 weeks' gestation (10 studies; 1750 women; average RR 0.55, 95% CI 0.42 to 0.74); considerable heterogeneity was identified, and a random-effects model was used (heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 29.60$, $df = 9$ ($P = 0.0005$); $I^2 = 70\%$), Analysis 1.3. This was also evident for the intramuscular subgroup (four studies; 652 women; average RR 0.62, 95% CI 0.52 to 0.75), Analysis 1.3.1. However, for the oral subgroup, no statistically significant differences were observed, Analysis 1.3.3. A funnel plot for this analysis (Figure 3), including the 10 studies was very asymmetrical. This suggests that there may be some important biases or small-study effects in the set of studies in this analysis and so these results should be viewed with caution.

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Figure 3. Funnel plot of comparison: 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth, outcome: 1.3 Preterm birth less than 37 weeks.



There was also a statistically significant reduction in the risk of:

- infant birthweight less than 2500 g (four studies; 692 infants; RR 0.58, 95% CI 0.42 to 0.79), Analysis 1.9;
- use of assisted ventilation (three studies; 633 women; RR 0.40, 95% CI 0.18 to 0.90), Analysis 1.11;
- necrotising enterocolitis (three studies; 1170 infants; RR 0.30, 95% CI 0.10 to 0.89), Analysis 1.16;
- neonatal death (six studies; 1453 women; RR 0.45, 95% CI 0.27 to 0.76), Analysis 1.20;
- admission to neonatal intensive care unit (three studies; 389 women; RR 0.24, 95% CI 0.14 to 0.40), Analysis 1.33.

For infant outcomes Apgar score less than seven at five minutes Analysis 1.32, respiratory distress syndrome Analysis 1.10, intrauterine fetal death Analysis 1.19, intraventricular haemorrhage (all grades) Analysis 1.12, intraventricular haemorrhage (grade III or IV) Analysis 1.13, periventricular leucomalacia Analysis 1.14, retinopathy of prematurity Analysis 1.15, neonatal sepsis Analysis 1.17, patent ductus arteriosus Analysis 1.18, intrauterine fetal death Analysis 1.19, or neonatal length of hospital stay Analysis 1.34, there were no statistically significant differences identified.

Secondary maternal outcomes

For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant increase in:

- pregnancy prolongation in weeks (one study; 148 women; mean difference (MD) 4.47, 95% CI 2.15 to 6.79), Analysis 1.31.

There were no statistically significant differences for the outcomes threatened preterm labour Analysis 1.4, spontaneous vaginal birth Analysis 1.5, adverse drug reaction Analysis 1.30, caesarean birth Analysis 1.6, use of antenatal corticosteroids Analysis 1.7, or the use of antenatal tocolysis Analysis 1.8.

Secondary childhood outcomes

There were no statistically significant differences identified for the outcomes developmental delay Analysis 1.21, intellectual impairment Analysis 1.22, motor impairment Analysis 1.23, visual impairment Analysis 1.24, hearing impairment Analysis 1.25, cerebral palsy Analysis 1.26, learning difficulties Analysis 1.27, height less than fifth centile Analysis 1.28 , weight less than the fifth centile Analysis 1.29, infant weight at six, 12 and 24 months' follow-up Analysis 1.34; Analysis 1.35; Analysis 1.36, infant length (cm) at six, 12 and 24 months' follow-up Analysis 1.38; Analysis 1.39;

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Analysis 1.40, and infant head circumference (cm) at six, 12 and 24 months' follow-up Analysis 1.41; Analysis 1.42; Analysis 1.43.

Effect of route of administration, time of commencing therapy, and dose of progesterone

We investigated statistical heterogeneity (I^2 > 30%) by performing subgroup analyses where possible for all outcomes and found no differential effect on the majority of outcomes examined when considering route of administration of progesterone (intramuscular versus vaginal versus oral). However, for respiratory distress syndrome, the subgroup analysis indicated a differential effect between the different routes of administration (test for subgroup differences: P = 0.001, I^2 = 84.8%, Analysis 1.10), although only one trial was included in each subgroup of intramuscular versus vaginal versus oral, Analysis 1.10.

We performed subgroup analysis to investigate the differential effect of time of commencement of supplementation (prior to 20 weeks' gestation versus after 20 weeks' gestation) where outcome data allowed, and found no subgroup differences (test for subgroup differences: P = 0.28, I^2 = 15.9%, Analysis 2.1).

We also performed subgroup analysis by total weekly cumulative dose of progesterone (less than 500 mg versus greater than 500 mg) and found no differential effect for the majority of outcomes examined: Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.6; Analysis 3.7; Analysis 3.9; Analysis 3.10; Analysis 3.11; Analysis 3.12. However, for intraventricular haemorrhage (all grades), the subgroup analysis indicated a differential effect between the different doses of progesterone (test for subgroup differences: P = 0.04, I^2 = 76.2%, Analysis 1.38), although only one trial was included in each subgroup of intramuscular versus vaginal versus oral, Analysis 1.10.

Progesterone versus placebo for women with a short cervix identified on ultrasound

Four randomised controlled trials involving a total of 1556 women and infants were included in the meta-analysis.

Primary outcomes

For women administered progesterone during pregnancy, for the primary outcome perinatal death, there were no statistically significant differences identified when compared with placebo, Analysis 4.1. Women administered progesterone were significantly less likely to have a preterm birth at less than 34 weeks' gestation (two studies; 438 women; RR 0.64, 95% CI 0.45 to 0.90), Analysis 4.2. Major neurodevelopmental handicap in childhood was not reported.

Secondary infant outcomes

For women administered progesterone during pregnancy, for the outcome preterm birth at less than 37 weeks' gestation, there were no statistically significant differences identified when compared with placebo, Analysis 4.12. However, women administered progesterone were significantly less likely to have a preterm birth at less than 28 weeks' gestation (two studies; 1115 women; RR 0.59, 95% CI 0.37 to 0.93), Analysis 4.13.

For infant outcomes infant birthweight less than 2500 g Analysis 4.14, respiratory distress syndrome Analysis 4.15, Apgar score less than seven at five minutes Analysis 4.16, need for assisted ventilation Analysis 4.17, intraventricular haemorrhage (all grades) Analysis 4.18, intraventricular haemorrhage (grades III or IV) Analysis 4.19, periventricular leucomalacia Analysis 4.20, retinopathy of prematurity Analysis 4.21, necrotising enterocolitis Analysis 4.22, neonatal sepsis Analysis 4.23, intrauterine fetal death Analysis 4.24, neonatal death Analysis 4.25 or admission to neonatal intensive care unit Analysis 4.26, there were no statistically significant differences identified.

Secondary maternal outcomes

Women administered progesterone were significantly more likely to experience the adverse drug reaction urticaria (one study; 654 women; RR 5.03, 95% CI 1.11 to 22.78), Analysis 4.7. For all other maternal outcomes, threatened preterm labour Analysis 4.3, prelabour spontaneous rupture of membranes Analysis 4.4, adverse drug reactions (any, injection site, nausea) Analysis 4.5; Analysis 4.6; Analysis 4.8, pregnancy prolongation Analysis 4.9, caesarean section Analysis 4.10, or antenatal tocolysis Analysis 4.11, there were no statistically significant differences identified.

Secondary childhood outcomes

None of the secondary childhood outcomes were reported.

Effect of route of administration, time of commencing therapy, and dose of progesterone

We investigated statistical heterogeneity (I^2 > 30%) by performing subgroup analyses where possible for all outcomes and found no differential effect on the outcomes examined when considering route of administration of progesterone (intramuscular versus vaginal), Analysis 4.20; Analysis 4.21; Analysis 4.23. It was not possible to assess the effect of gestational age at commencing therapy.

We also performed subgroup analysis by total weekly cumulative dose of progesterone (less than 500 mg versus greater than 500 mg) and found no differential effect for the two outcomes examined: Analysis 5.1; Analysis 5.2.

Progesterone versus placebo for women with a multiple pregnancy

Ten randomised controlled trials involving a total of 3395 women and 6178 infants were included in the meta-analysis.

One trial (Serra 2013) consisted of three groups: progesterone 200 mg versus progesterone 400 mg versus placebo. This trial has been analysed as separate pair-wise comparisons, with separate analyses for progesterone 200 mg versus placebo (Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.5; Analysis 6.9; Analysis 6.10; Analysis 6.11; Analysis 6.12; Analysis 6.13; Analysis 6.14; Analysis 6.21; Analysis 6.24; Analysis 6.25; Analysis 6.26) and progesterone 400 mg versus placebo (Analysis 6.27; Analysis 6.28; Analysis 6.29; Analysis 6.30; Analysis 6.31; Analysis 6.32; Analysis 6.33; Analysis 6.34; Analysis 6.35; Analysis 6.36; Analysis 6.37; Analysis 6.38; Analysis 6.39; Analysis 6.40; Analysis 6.41; Analysis 6.42; ; Analysis 7.1; Analysis 7.2; Analysis 7.3).

Primary outcomes

For women administered progesterone during pregnancy, for the primary outcomes perinatal death Analysis 6.1, Analysis 6.27, and preterm birth less than 34 weeks' gestation Analysis 6.2; Analysis 6.28, there were no statistically significant differences identified

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when compared with placebo. Major neurodevelopmental handicap in childhood was not reported.

Secondary infant outcomes

For women administered progesterone during pregnancy, when compared with placebo, there were no statistically significant differences identified in the risk of birth before 37 Analysis 6.11; Analysis 6.33 or 28 weeks Analysis 6.12; Analysis 6.34, infant birthweight less than 2500 g Analysis 6.13; Analysis 6.35, Apgar score less than seven at five minutes Analysis 6.14; Analysis 6.36, respiratory distress syndrome Analysis 6.15, need for ventilation Analysis 6.16; Analysis 6.37, intraventricular haemorrhage Analysis 6.17; Analysis 6.18, periventricular leucomalacia Analysis 6.19, retinopathy of prematurity Analysis 6.20, chronic lung disease Analysis 6.21, necrotising enterocolitis Analysis 6.22, neonatal sepsis Analysis 6.23, fetal death Analysis 6.24; Analysis 6.38, neonatal death Analysis 6.25; Analysis 6.39, or admission to neonatal intensive care unit (NICU) Analysis 6.26; Analysis 6.40. Due to extreme heterogeneity, we did not combine data from trials for the outcomes neonatal length of hospital stay or patent ductus arteriosus.

Secondary maternal outcomes

For women administered progesterone during pregnancy, when compared with placebo, there were no statistically significant differences identified in any of the following maternal outcomes: prelabour spontaneous rupture of membranes Analysis 6.3, adverse drug reaction Analysis 6.4, caesarean section Analysis 6.5, spontaneous birth Analysis 6.6, assisted birth Analysis 6.7, satisfaction with the therapy Analysis 6.8, antenatal tocolysis Analysis 6.9, or antenatal corticosteroids Analysis 6.10.

Secondary childhood outcomes

None of the secondary childhood outcomes were reported.

Sensitivity analyses to account for multiple pregnancies

For multiple pregnancies we had planned to analyse neonatal data as 'clusters' to account for dependency between twins and triplets. We anticipated that the degree of dependence between twins would vary at the outcome level i.e. in the case of preterm birth the dependency (ICC) is likely to be high, whereas in some outcomes, such as perinatal death or morbidity, the ICC may be much lower. However, there were insufficient data presented in the trial reports to allow us to carry out necessary adjustment for cluster design effect ourselves and, although in several trials results had already been adjusted, we were not able to present these data in our data and analyses tables because they were not reported in a consistent way.

For the primary outcome perinatal death, we therefore carried out a sensitivity analysis assuming two extremes. In the first we assumed complete dependence between infants in multiple pregnancies, i.e. we assumed outcomes were the same for all infants within that pregnancy; in this case the effective sample size for twin pregnancies would be the total number of women rather than infants, and for infant outcomes all event rates and sample sizes were therefore divided by two. In the second sensitivity analyses we assumed very limited dependence (1%) and in this case event rates and sample sizes were divided by 1.01. Results from sensitivity analyses were very similar to those from the unadjusted analyses although the effect estimates changed slightly due to rounding up of event rates and sample sizes, and the 95% CIs were generally slightly wider. Adjusted analyses showed that for women administered progesterone during pregnancy, for the primary outcome perinatal death, there were no statistically significant differences identified when compared with placebo. (Data not shown, available from the authors on request).

Effect of route of administration, time of commencing therapy, and dose of progesterone

We investigated statistical heterogeneity (I^2 > 30%) by performing subgroup analyses and found no differential effect on the majority of outcomes examined when considering route of administration of progesterone (intramuscular versus vaginal). However, for spontaneous birth, infant birthweight less than 2500 g and admission to NICU, the subgroup analyses indicated a differential effect between the different routes of administration (test for subgroup differences: P = 0.0008, I^2 = 91.1%, Analysis 6.6; P = 0.02, I^2 = 80.8% Analysis 6.13; P = 0.009, I^2 = 85.5%, Analysis 6.26) although it must be noted that in Analysis 6.6; Analysis 6.26, some of the subgroups contained only one trial.

We performed subgroup analysis to investigate the differential effect of time of commencement of supplementation (prior to 20 weeks' gestation versus after 20 weeks' gestation) where outcome data allowed, and found no subgroup differences for the outcomes examined, Analysis 7.1; Analysis 7.2; Analysis 7.3.

We also performed subgroup analysis by total weekly cumulative dose of progesterone (less than 500 per week mg versus greater than 500 mg per week) and found no differential effect for the majority of outcomes examined, Analysis 8.1; Analysis 8.2; Analysis 8.3; Analysis 8.4; Analysis 8.5; Analysis 8.6; Analysis 8.7. However, for infant birthweight less than 2500 g and admission to NICU, the subgroup analyses indicated a differential effect between the cumulative doses of progesterone (test for subgroup difference: P = 0.02, I^2 = 80.8%, Analysis 8.5; P = 0.009, I^2 = 85.5%, Analysis 8.8).

Progesterone versus placebo/no treatment for women following presentation with threatened preterm labour

Five randomised controlled trials involving a total of 384 women and infants were included in the meta-analysis.

Primary outcomes

For women administered progesterone during pregnancy, for the primary outcomes perinatal death Analysis 9.1, and preterm birth less than 34 weeks' gestation Analysis 9.2, there were no statistically significant differences identified when compared with placebo. Major neurodevelopmental handicap in childhood was not reported.

Secondary infant outcomes

For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant reduction in the risk of:

- infant birthweight less than 2500 g (one study; 70 infants; RR 0.52, 95% CI 0.28 to 0.98), Analysis 9.11.

There were no statistically significant differences for any of the other outcomes analysed: preterm birth less than 37 weeks' gestation Analysis 9.10, respiratory distress syndrome Analysis

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9.12, intraventricular haemorrhage grade III or IV Analysis 9.13, periventricular leucomalacia Analysis 9.14, needed for mechanical ventilation Analysis 9.15, necrotising enterocolitis Analysis 9.16, neonatal sepsis Analysis 9.17, fetal death Analysis 9.18, neonatal death Analysis 9.19, or neonatal length of hospital stay Analysis 9.20.

Secondary maternal outcomes

For women administered progesterone during pregnancy, when compared with placebo, there were no statistically significant differences for any of the outcomes analysed: pregnancy prolongation Analysis 9.3; Analysis 9.4; Analysis 9.5; Analysis 9.6, spontaneous vaginal birth Analysis 9.7, caesarean section Analysis 9.8, or use of tocolysis Analysis 9.9.

Secondary childhood outcomes

There were no secondary childhood outcomes reported.

Effect of route of administration, time of commencing therapy, and dose of progesterone

We investigated statistical heterogeneity (I^2 > 30%) by performing subgroup analyses where possible for all outcomes and found no differential effect on some of the outcomes examined when considering route of administration of progesterone (intramuscular versus vaginal), Analysis 9.2; Analysis 9.9; Analysis 9.12; Analysis 9.17; Analysis 9.19. However, for pregnancy prolongation and preterm birth less than 37 weeks' gestation, the subgroup analyses indicated a differential effect between the different routes of administration (test for subgroup differences: P = 0.001, I^2 = 90.5%, Analysis 9.3; P = 0.04, I^2 = 75.6%, Analysis 9.10), although it must be noted that in both analyses the subgroups contained only one trial.

It was not possible to assess the effect of gestational age at commencing therapy.

We also performed subgroup analysis by total weekly cumulative dose of progesterone (less than 500 mg versus greater than 500 mg) and found no differential effect for three outcomes examined: Analysis 10.3; Analysis 10.4; Analysis 10.5. However, for the two outcomes, pregnancy prolongation and preterm birth less than 37 weeks' gestation, the subgroup analyses indicated a differential effect between the different drug doses (test for subgroup differences: P = 0.001, I^2 = 90.5%, Analysis 10.1; P = 0.04, I^2 = 75.6% , Analysis 10.2).

Progesterone versus placebo for women with 'other' risk factors for preterm birth

Three randomised controlled trials involving a total of 482 women and infants were included in the meta-analysis. Data from a fourth study (Moghtadaei 2008), could not be included in the meta-analysis because the number of women randomised to each group was not reported in the brief abstract report of the study.

Primary outcomes

For women administered progesterone during pregnancy, for the primary outcomes perinatal death Analysis 11.1 and preterm birth less than 34 weeks' gestation Analysis 11.2, there were no statistically significant differences identified when compared with placebo. The outcome major neurodevelopmental handicap in childhood were not reported.

Secondary infant outcomes

For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant reduction in the risk of:

- infant birthweight less than 2500 g (three studies; 482 infants; RR 0.48, 95% CI 0.25 to 0.91) Analysis 11.4.

In addition, for women administered progesterone who were considered to be at risk of preterm birth for 'other' reasons, when compared with placebo, there were no statistically significant differences for the outcomes preterm birth less than 37 weeks' gestation Analysis 11.3., perinatal death Analysis 11.1, intrauterine fetal death Analysis 11.5 or neonatal death Analysis 11.6.

Secondary childhood outcomes

There were no secondary childhood outcomes reported.

Effect of route of administration, time of commencing therapy, and dose of progesterone

We investigated statistical heterogeneity (I^2 > 30%) by performing subgroup analysis for perinatal death Analysis 12.1, preterm birth less than 37 weeks Analysis 12.2, and infant birthweight less than 2500 g, Analysis 12.3, and no differential effect was observed related for gestational age at commencing therapy, (test for subgroup differences: P = 0.10, I^2 = 63.9%, Analysis 12.2; P = 0.19, I^2 = 42.2%, Analysis 12.3).

DISCUSSION

The randomised trials identified assessed the use of progesterone in women considered to be at increased risk of preterm birth by virtue of history of spontaneous preterm birth, ultrasonographic evaluation of cervical length, presentation in threatened preterm labour, multiple pregnancy, or other reasons (including 'high preterm risk score' and active military duty).

Summary of main results

Progesterone for women with a past history of spontaneous preterm birth

For women with a past history of spontaneous preterm birth, there was a statistically significant reduction in the risk of the primary outcomes, perinatal death and in the risk of preterm birth less than 34 weeks' gestation. The reduction in risk of perinatal death is confined to the subgroup of women receiving intramuscular progesterone. There was significant heterogeneity identified for the outcomes preterm birth before 34 and 37 weeks' gestation, with evidence of funnel plot asymmetry, raising questions about potential bias and therefore caution in interpretation. For the secondary infant and maternal outcomes, the use of progesterone was associated with a reduction in the risk of infant birthweight less than 2500 g, use of assisted ventilation, necrotising enterocolitis, neonatal death, admission to neonatal intensive care unit, preterm birth less than 37 weeks' gestation and a significant increase in prolongation in pregnancy prolongation. There were no significant differences identified for other secondary infant and maternal health outcomes with the use of progesterone. Information related to childhood health and well being is limited, with only two trials reporting two-year follow-up results to date (Northen 2007; O'Brien 2007), in which there were no documented differences in growth or

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developmental outcomes between those infants exposed in utero to progesterone and those to placebo. There was no differential effect on outcomes in terms of time of commencing therapy and dose of progesterone from the available evidence.

Further information is required about the optimal route of administration of progesterone, with the largest study to date using vaginal progesterone gel suggesting no benefit in this group of women (O'Brien 2007).

Progesterone for women with a short cervix identified on ultrasound

In the trials to date assessing the role of progesterone in women with a short cervix identified on ultrasound (Fonseca 2007; Grobman 2012; Hassan 2011; Rozenberg 2012), there were no statistically significant differences identified for the primary outcome perinatal death. Women administered progesterone were significantly less likely to have preterm birth less than 34 weeks' gestation. For the secondary infant outcomes, the use of progesterone was associated with a reduction in risk of preterm birth at less than 28 weeks' gestation. There was also a significant increase in the risk urticaria in women receiving progesterone. Further information is required about the risk of other infant health outcomes, and maternal health outcomes in this group of women. Reporting of childhood outcomes is lacking, with no trials reporting this information to date. The relative efficacy of progesterone compared with cerclage for women with a short cervix remains uncertain, as does the use of progesterone as an adjunct therapy following cerclage placement (Conde-Agudelo 2013).

Progesterone for women with a multiple pregnancy

The role of progesterone in women with a multiple pregnancy is less clear, with no identified differences in the primary outcomes perinatal death, and preterm birth less than 34 weeks' gestation. There were also no differences identified for the other secondary infant and maternal health outcomes. Information relating to long-term childhood health outcomes is unavailable to date. There are several ongoing randomised trials assessing the role of intramuscular (Nassar 2007) and vaginal (Wood 2007) progesterone in women with a multiple pregnancy which will contribute information about the role of progesterone in this group of women.

For multiple pregnancies, we had planned to analyse neonatal data as 'clusters' to account for dependency between twins and triplets. We anticipated that the degree of dependence between twins would vary at the outcome level i.e. in the case of preterm birth the dependency (ICC) is likely to be high, whereas in some outcomes such as perinatal death or morbidity, the ICC may be much lower. However, there were insufficient data presented in the trial reports to allow us to carry out necessary adjustment for cluster design effect ourselves and, although in several trials results had already been adjusted, we were not able to present these data in our data and analyses tables because they were not reported in a consistent way. In future updates, we will contact trial authors for additional information to allow us to carry out necessary adjustments in the analysis of the neonatal data.

Progesterone for women following presentation with threatened preterm labour

The role of progesterone for women following presentation with threatened preterm labour remains uncertain. The identified randomised trials indicate a reduction in only the risk of infant birthweight less than 2500 g. However, the outcomes have been reported in only five small trials (332 women), with only four contributing data to meta-analysis (211 women) and are underpowered to detect differences in both maternal and infant health outcomes. There is an ongoing randomised trial assessing the role of vaginal progesterone in women presenting with symptoms or signs of threatened preterm labour which will contribute information about the role of progesterone in this group of women (Martinez 2007).

Progesterone versus placebo for women with 'other' risk factors for preterm birth

The role of progesterone in women considered to be at risk of preterm birth for 'other reasons' is uncertain, with the three randomised trials that contributed data to the meta-analysis to date indicating no benefit in terms of perinatal death or preterm birth less than 37 weeks' gestation. However, the combined sample size of these trials is significantly underpowered to detect all but large differences in these outcomes.

There is evidence that progesterone for women with a history of previous preterm birth is associated with a reduction in preterm birth before 34 and 37 weeks gestation. As indicated earlier, there was considerable heterogeneity identified, in addition to evidence of funnel plot asymmetry, raising concern about potential bias. The observed reduction in perinatal mortality appears confined to the use of intramuscular progesterone.

However, information relating to longer-term infant and childhood outcomes is currently insufficient, with only two randomised trials reporting to date. Ongoing follow-up of children exposed to progesterone in utero remains a priority. Maternal outcomes following antenatal progesterone therapy were poorly reported in the available literature, including treatment side-effects, preferences of mode of administration and satisfaction of care. Further information is required on these important issues (Greene 2003; Iams 2003). In addition, there remains uncertainty as to the optimal dose of progesterone to be administered, the optimal route of administration, and the optimal gestational age at which to commence therapy. The American College of Obstetricians and Gynecologists have issued a committee opinion relating to the use of progesterone for the prevention of preterm birth, indicating the need for further information about the optimal mode of administration (ACOG 2003), including studies directly comparing the relative efficacy of vaginal and intramuscular preparations.

Overall completeness and applicability of evidence

The majority of studies to date have reported short-term maternal and infant outcomes, with only two studies reporting longer-term childhood outcomes (Northen 2007; O'Brien 2007).

As outlined above, there are a number of ongoing studies which will contribute to the evidence relating to the use of progesterone for women considered at risk of preterm birth. The trials by Crowther (Crowther 2007), Norman (Norman 2012), and Perlitz (Perlitz 2007) will contribute data from women with a prior preterm birth; van Os (van Os 2011) will contribute data from women with a short cervix identified by ultrasound; Nassar (Nassar 2007), and Wood (Wood 2007) will contribute data from women with a multiple pregnancy; and Martinez (Martinez 2007) will contribute data from women who present with symptoms or signs of threatened preterm labour.

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Quality of the evidence

Overall, the trials included in this review were considered to be of good to fair quality. Of the 36 included trials, adequate randomisation methods were described in 23 (Borna 2008; Briery 2011; Caritis 2009; Cetingoz 2011; Combs 2010; Combs 2011; Combs 2011a; da Fonseca 2003; Facchinetti 2007; Glover 2011; Grobman 2012; Hassan 2011; Lim 2011; Majhi 2009; Meis 2003; Norman 2009; O'Brien 2007; Rai 2009; Rode 2011; Rouse 2007; Rozenberg 2012; Senat 2012; Serra 2013), allocation concealment was assessed to be at low risk of bias in 23 (Aboulghar 2012; Briery 2011; Caritis 2009; Cetingoz 2011; Combs 2010; Combs 2011; Combs 2011a; da Fonseca 2003; Fonseca 2007; Glover 2011; Grobman 2012; Hassan 2011; Johnson 1975; Lim 2011; Majhi 2009; Meis 2003; Norman 2009; O'Brien 2007; Rai 2009; Rode 2011; Rouse 2007; Senat 2012; Serra 2013), and blinding was achieved with the use of a placebo agent in 25 (Aboulghar 2012; Briery 2011; Caritis 2009; Cetingoz 2011; Combs 2010; Combs 2011; Combs 2011a; da Fonseca 2003; Fonseca 2007; Glover 2011; Grobman 2012; Hartikainen 1980; Hassan 2011; Hauth 1983; Johnson 1975; Lim 2011; Meis 2003; Norman 2009; O'Brien 2007; Papiernik 1970; Rai 2009; Rode 2011; Rouse 2007; Serra 2013; Sharami 2010).Twenty-one of the 36 included studies were assessed as being at low risk of bias for other potential sources of bias (Borna 2008; Briery 2011; Caritis 2009; Combs 2010; Combs 2011; da Fonseca 2003; Facchinetti 2007; Fonseca 2007; Glover 2011; Hassan 2011; Hauth 1983; Johnson 1975; Lim 2011; Meis 2003; Norman 2009; O'Brien 2007; Papiernik 1970; Rai 2009; Rode 2011; Saghafi 2011a; Sharami 2010).

We assessed whether studies that included multiple pregnancies accounted appropriately for non-independence of babies from the same pregnancy in the analysis. There were 14 studies that included a multiple pregnancy (Aboulghar 2012; Caritis 2009; Cetingoz 2011; Combs 2010; Combs 2011; Elsheikhah 2010; Fonseca 2007; Hartikainen 1980; Lim 2011; Norman 2009; Rode 2011; Rouse 2007; Senat 2012; Serra 2013) and in seven studies adjustment appears to have been made in the analysis (Caritis 2009; Combs 2010; Combs 2011; Fonseca 2007; Lim 2011; Norman 2009; Rode 2011). In the remaining seven studies (Aboulghar 2012; Cetingoz 2011; Elsheikhah 2010; Hartikainen 1980; Rouse 2007; Senat 2012; Serra 2013), it is not clear that any adjustment was made. There was not enough information in the trial reports for us to carry out the necessary adjustments ourselves in the analysis of neonatal outcomes. This information will be sought for future updates.

Potential biases in the review process

The possibility of introducing bias was present at every stage of the reviewing process. We attempted to minimise bias in a number of ways: two review authors assessed eligibility for inclusion, carried out data extraction and assessed risk of bias. Each worked independently. Nevertheless, the process of assessing risk of bias is not an exact science and includes many personal judgements.

Agreements and disagreements with other studies or reviews

Despite the differences in methodology and included studies, our findings of a reduction in preterm birth before 34 weeks' and 28 weeks' gestation for women with a short cervix identified on ultrasound examination, and a reduction in infant respiratory distress syndrome are consistent with those reported in an individual patient data meta-analysis by Romero and colleagues (Romero 2012). Similarly, the findings of a proposed individual patient data meta-analysis for women with a multiple pregnancy are awaited to evaluate if there are specific subgroups of women with a multiple pregnancy who may receive benefit from progesterone therapy (Schuit 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Summary of the available information

Progesterone for women with a past history of spontaneous preterm birth

The use of progesterone in this group of women is associated with a reduction in the risk of perinatal death, preterm birth before 34 weeks' and 37 weeks' gestation, infant birthweight less than 2500 g, use of assisted ventilation, necrotising enterocolitis, neonatal death, admission to neonatal intensive care unit, and prolongation of pregnancy. There is limited information about longer-term childhood health. In addition, further information is required as to the optimal route of administration of progesterone, the optimal dose to be administered, and the best time to commence therapy.

Progesterone for women with a short cervix identified on ultrasound

The use of progesterone in this group of women is associated with a reduction in the risk of preterm birth less than 34 and 28 weeks' gestation, and a significant increase in the risk urticaria in women receiving progesterone. Further information is required about other maternal, infant and childhood health outcomes. Of particular note, there are no comparative data reported on longer-term childhood health from trials conducted to date. In addition, further information is required as to the optimal route of administration of progesterone, the optimal dose to be administered, and the best time to commence therapy.

Progesterone for women with a multiple pregnancy

The use of progesterone in this group of women is not associated with any statistically significant differences in perinatal death, preterm birth and other maternal, infant, and childhood health outcomes.

Progesterone for women following presentation with threatened preterm labour

The use of progesterone in this group of women was associated with a statistically significant reduction in the risk of infant birthweight less than 2500 g. However, for all other outcomes, the role of progesterone for women presenting following symptoms or signs of threatened preterm labour is uncertain.

Progesterone for women with 'other' risk factors for preterm birth

The use of progesterone in this group of women was associated with a statistically significant reduction in the risk of infant birthweight less than 2500 g. However, for all other outcomes, the role of progesterone in women considered to be at risk of preterm birth for 'other reasons' is uncertain.

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Implications for research

Further well-designed randomised controlled trials are required to assess the optimal timing, mode of administration and dose of administration of progesterone when given to women considered to be at increased risk of early birth, by virtue of previous history of spontaneous preterm birth, short cervix identified by transvaginal ultrasound, following arrest of symptoms or signs of threatened preterm labour, or on the basis of 'other' risk factors. Assessment of longer-term infant and childhood outcomes remains a priority.

There are several randomised trials that are currently addressing the use of progesterone for preterm birth which will contribute data in the future - *see* Characteristics of ongoing studies for details.

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REFERENCES

References to studies included in this review

Aboulghar 2012 *{published data only}*

Aboulghar MM, Aboulghar MA, Amin YM, Al-Inany HG, Mansour RT, Serour GI. The use of vaginal natural progesterone for prevention of preterm birth in IVF/ICSI pregnancies. *Reproductive BioMedicine Online* 2012;**25**(2):133-8.

Akbari 2009 *{published data only}*

Akbari S, Birjandi M, Mohtasham N. Evaluation of the effect of progesterone on prevention of preterm delivery and its complications. *Scientific Journal of Kurdistan University of Medical Sciences* 2009;**14**(3):11-9.

Borna 2008 *{published data only}*

* Borna S, Sahabi N. Progesterone for maintenance tocolytic therapy after threatened preterm labour: a randomised controlled trial. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2008;**48**(1):58-63.

Borna S, Shakoie S, Borna H. Progesterone for maintenance tocolytic therapy after threatened preterm labor. Randomized controlled trial. Journal of Maternal-Fetal and Neonatal Medicine 2008; Vol. 21, issue Suppl 1:151-2.

Briery 2011 *{published data only}*

Briery C, Veillon E, Klauser CK, Martin R, Chauhan S, Magann EF, et al. Women with prolonged premature rupture of the membrane do not benefit from weekly progesterone: a randomized clinical trial. *American Journal of Obstetrics and Gynecology* 2009;**201**(6 Suppl 1):S189.

Briery CM, Veillon EW, Klauser CK, Martin RW, Chauhan SP, Magann EF, et al. Progesterone does not prevent preterm births in women with twins. *Southern Medical Journal* 2009;**102**(9):900-4.

* Briery CM, Veillon EW, Klauser CK, Martin RW, Magann EF, Chauhan SP, et al. Women with preterm premature rupture of the membranes do not benefit from weekly progesterone. *American Journal of Obstetrics and Gynecology* 2011;**204**(1):54.e1-5.

Caritis 2009 *{published data only}*

Caritis SN, Rouse DJ, Peaceman AM, Sciscione A, Momirova V, Spong CY, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. *Obstetrics & Gynecology* 2009;**113**(2 Pt 1):285-92.

Cetingoz 2011 *{published data only}*

Cetingoz E, Cam C, Sakalli M, Karateke A, Celik C, Sancak A. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. *Archives of Gynecology and Obstetrics* 2011;**283**(3):423-9.

Combs 2010 *{published data only}*

* Combs CA, Garite T, Maurel K, Das A, Porto M, for the OCRN. Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial. *American Journal of Obstetrics and Gynecology* 2010;**203**(3):248.e1-9.

Combs CA, Garite T, Porto M, Maurel K, for the OCRN. 17-hydroxyprogesterone for triplet pregnancy does not reduce prematurity or neonatal morbidity, may increase midtrimester loss. *American Journal of Obstetrics and Gynecology* 2009;**201**(6 Suppl 1):S168.

Heitmann E, Lu G, Combs CA, Garite TJ, Maurel K. The impact of maternal weight upon the effectiveness of 17-hydroxyprogesterone in preventing preterm birth among twin gestations. *American Journal of Obstetrics and Gynecology* 2012;**206**(Suppl 1):S98.

Maurel K, Combs A. 17OHP for reduction of neonatal morbidity due to preterm birth (PTB) in twin and triplet pregnancies. http://controlledtrials.com (accessed 2007).

Combs 2011 *{published data only}*

* Combs CA, Garite T, Maurel K, Das A, Porto M, for theOCRN. 17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial. *American Journal of Obstetrics and Gynecology* 2011;**204**:221.e1-8.

Combs CA, Garite TJ, Maurel K, Cebrik D. 17-hydroxyprogesterone caproate for women with history of preterm birth in a prior pregnancy and twins in the current pregnancy. *American Journal of Obstetrics and Gynecology* 2012;**206**(Suppl 1):S213.

Combs CA, Maurel K, Garite T, for theOCRN. 17-hydroxyprogesterone for twin pregnancy: no reduction in prematurity or neonatal morbidity. *American Journal of Obstetrics and Gynecology* 2011;**204**(1 Suppl 1):S7.

Maurel K, Combs A. 17OHP for reduction of neonatal morbidity due to preterm birth (PTB) in twin and triplet pregnancies. http://controlledtrials.com (accessed 2007).

Combs 2011a *{published data only}*

Combs CA, Garite TJ, Maurel K, Mallory K, Edwards RK, Lu G, et al. 17-Hydroxyprogesterone caproate to prolong pregnancy after preterm rupture of the membranes: early termination of a double-blind, randomized clinical trial. *BMC Research Notes* 2011;**4**(1):568.

da Fonseca 2003 *{published data only}*

* da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. *American Journal of Obstetrics & Gynecology* 2003;**188**(2):419-24.

da Fonseca EB, Bittar RE, Carvalho MHB, Martinelli S, Zugaib M. Uterine contraction monitoring in pregnant women using vaginal natural progesterone. *Journal of Perinatal Medicine* 2001;**29 Suppl 1**(Pt 2):525.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Elsheikhah 2010 *{published data only}*

Elsheikhah AZ, Dahab S, Negm S, Ebrashy A. Effect of prophylactic progesterone on incidence of preterm labour in spontaneous twin pregnancy, randomized controlled study. *Ultrasound in Obstetrics and Gynecology* 2010;**36**(Suppl 1):108.

Facchinetti 2007 *{published data only}*

Facchinetti F, Dante G, Venturini P, Paganelli S, Volpe A. 17alpha-hydroxy-progesterone effects on cervical proinflammatory agents in women at risk for preterm delivery. *American Journal of Perinatology* 2008;**25**(8):503-6.

* Facchinetti F, Paganelli S, Comitinit G, Dante G, Volpe A. Cervical length changes during preterm cervical ripening: effects of 17-alpha-hydroxyprogesterone caproate. *American Journal of Obstetrics and Gynecology* 2007;**196**:453e1-453e4.

Facchinetti F, Paganelli S, Venturini P, Dante G. 17 alpha hydroxy-progesterone caproate (17P) treatment reduced cervical shortening inhibiting cervical interleukin-1 secretion. *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1):S5.

Fonseca 2007 *{published data only}*

Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. *New England Journal of Medicine* 2007;**357**:462-9.

Glover 2011 *{published data only}*

Glover M, Croom CS, Sonek JD, Kovac C, McKenna D. A randomized placebo controlled trial of oral micronized progesterone to prevent recurrent preterm birth. *American Journal of Obstetrics and Gynecology* 2009;**201**(6 Suppl 1):S172.

* Glover MM, McKenna DS, Downing CM, Smith DB, Croom CS, Sonek JD. A randomized trial of micronized progesterone for the prevention of recurrent preterm birth. *American Journal of Perinatology* 2011;**28**(5):377-81.

Grobman 2012 *{published data only}*

Grobman W. RCT of progesterone to prevent preterm birth in nulliparous women with a short cervix. http://controlledtrials.com (accessed 2007).

Grobman W. Randomized controlled trial of progesterone treatment for preterm birth prevention in nulliparous women with cervical length less than 30 mm. *American Journal of Obstetrics and Gynecology* 2012;**206**(Suppl 1):S367.

* Grobman WA, Thom EA, Spong CY, Iams JD, Saade GR, Mercer BM, et al. 17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm. *American Journal of Obstetrics and Gynecology* 2012;**207**(5):390.e1-8.

Hartikainen 1980 *{published data only}*

* Hartikainen-Sorri AL, Kauppila A, Tuimala R. Inefficacy of 17 alpha-hydroxyprogesterone caproate in the prevention of prematurity in twin pregnancy. *Obstetrics & Gynecology* 1980;**56**(6):692-5.

Hartikainen-Sorri AL, Kauppila A, Tuimala R. Management of twin pregnancy with 17 alpha- hydroxyprogesterone caproate [abstract]. 9th World Congress of Gynecology and Obstetrics 1979 October 26-31; Tokyo, Japan. 1979:298-9.

Hassan 2011 *{published data only}*

Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound in Obstetrics & Gynecology* 2011;**38**(1):18-31.

Hauth 1983 *{published data only}*

Hauth JC, Gilstrap LC, Brekken AL, Hauth JM. The effect of 17 alpha-hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. *American Journal of Obstetrics and Gynecology* 1983;**146**(2):187-90.

Ibrahim 2010 *{published data only}*

Ibrahim M, Mohamed Ramy AR, Younis MA-F. Progesterone supplementation for prevention of preterm labor: a randomized controlled trial. *Middle East Fertility Society Journal* 2010;**15**(1):39-41.

Johnson 1975 *{published data only}*

* Johnson JWC, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17 alpha-hydroxyprogesterone caproate in the prevention of premature labor. *New England Journal of Medicine* 1975;**293**(14):675-80.

Klebanoff M, for the NICHD MFMU Network. Impact of 17alpha hydroxyprogesterone caproate administration on salivary progesterone and estriol [abstract]. *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1):S140.

Lim 2011 *{published data only}*

Bruinse HW. 17 alpha hydroxyprogesterone in multiple pregnancies to prevent handicapped infants (The AMPHIA Study). http://www.controlledtrials.com (accessed 2007).

Lim AC. The effect of 17-alpha hydroxyprogesterone caproate on cervical length in multiple pregnancies. *Reproductive Sciences* 2010;**17**(3 Suppl 1):282A.

Lim AC, Bloemenkamp KW, Boer K, Duvekot JJ, Erwich JJ, Hasaart TH, et al. Progesterone for the prevention of preterm birth in women with multiple pregnancies: the AMPHIA trial. BMC Pregnancy & Childbirth 2007; Vol. 7:7.

* Lim AC, Schuit E, Bloemenkamp K, Bernardus RE, Duvekot JJ, Erwich JJ, et al. 17alpha-hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: A randomized controlled trial. *Obstetrics and Gynecology* 2011;**118**(3):513-20.

Lim AC, for the ASG. Is second trimester cervical length a predictor for an effect of 17-alpha hydroxyprogesterone caproate on neonatal morbidity in multiple pregnancies? Results from the AMPHIA trial (ISRCTN40512715). *Reproductive Sciences* 2010;**17**(3 Suppl 1):282A.

Willekes C, Lim A, Vijgen S, Mol B, Papatsonis D, Hasaart T, et al. Mid-pregnancy cervical length as a predictor of preterm birth

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in multiple pregnancies. *American Journal of Obstetrics and Gynecology* 2011;**204**(1 Suppl 1):S54.

Majhi 2009 *{published data only}*

Majhi P, Bagga R, Kalra J, Sharma M. Intravaginal use of natural micronised progesterone to prevent pre-term birth: a randomised trial in India. *Journal of Obstetrics and Gynaecology* 2009;**29**(6):493-8.

Meis 2003 *{published data only}*

Gyamfi C, Horton AL, Momirova V, Rouse DJ, Caritis SN, Peaceman AM, et al. The effect of 17-alpha hydroxyprogesterone caproate on the risk of gestational diabetes in singleton or twin pregnancies. *American Journal of Obstetrics and Gynecology* 2009;**201**(4):392.e1-5.

Klebanoff MA, Meis PJ, Dombrowski MP, Zhao Y, Moawad AH, Northen A, et al. Salivary progesterone and estriol among pregnant women treated with 17-alpha-hydroxyprogesterone caproate or placebo. *American Journal of Obstetrics and Gynecology* 2008;**199**(5):506.e1-7.

Koontz G. Does gestational age at randomization affect the efficacy of alpha hydroxyprogesterone caproate (17-OHCP) in preventing recurrent preterm delivery? [abstract]. *American Journal of Obstetrics and Gynecology* 2005;**193**(6 Suppl 1):S55.

Manuck TA, Lai Y, Meis PJ, Dombrowski MP, Sibai B, Spong CY, et al. Progesterone receptor polymorphisms and clinical response to 17-alpha-hydroxyprogesterone caproate. *American Journal of Obstetrics & Gynecology* 2011;**205**(2):135.e1-9.

Meis P, NICHD MFMU Network. More than one previous preterm delivery and the risk of preterm birth in women treated with 17 alpha-hydroxyprogesterone (17P) [abstract]. *American Journal of Obstetrics and Gynecology* 2003;**189**(6):S168.

Meis PJ, Klebanoff M, Dombrowski MP, Sibai BM, Leindecker S, Moawad AH, et al. Does progesterone treatment influence risk factors for recurrent preterm delivery?. *Obstetrics & Gynecology* 2005;**106**(3):557-61.

* Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *New England Journal of Medicine* 2003;**348**(24):2379-85.

Meis PJ, NICHD MFMU Network. 17 alphahydroxyprogesterone caproate prevents recurrent preterm birth [abstract]. *American Journal of Obstetrics and Gynecology* 2002;**187**(6 Pt 2):S54.

Northen A. 4-year follow-up of children exposed to 17alpha hydroxyprogesterone caproate (17P) in utero. *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1):S6.

Northen AT, Norman GS, Anderson K, Moseley, L, Divito M, Cotroneo M, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. *Obstetrics & Gynecology* 2007;**110**(4):864-72.

Sibai B. Plasma CRH levels at 16-20 weeks do not predict preterm delivery in women at high-risk for preterm delivery [abstract]. *American Journal of Obstetrics and Gynecology* 2004;**191**(6 Suppl 1):S114.

Sibai B, Meis PJ, Klebanoff M, Dombrowski MP, Weiner SJ, Moawad AH, et al. Plasma CRH measurement at 16 to 20 weeks' gestation does not predict preterm delivery in women at high-risk for preterm delivery. *American Journal of Obstetrics and Gynecology* 2005;**193**(3 Pt 2):1181-6.

Spong CY. Progesterone for prevention of recurrent preterm birth: impact of gestational age at prior delivery [abstract]. *American Journal of Obstetrics and Gynecology* 2004;**191**(6 Suppl 1):S11.

Spong CY, Meis PJ, Thom EA, Sibai B, Dombrowski MP, Moawad AH, et al. Progesterone for prevention of recurrent preterm birth: impact of gestational age at previous delivery. *American Journal of Obstetrics and Gynecology* 2005;**193**(3 Pt 2):1127-31.

Moghtadaei 2008 *{published data only}*

Moghtadaei P, Sardari F, Latifi M. Progesterone for prevention of preterm birth and improvement in pregnancy outcomes among primiparae of advanced maternal age. Archives of Disease in Childhood. Fetal and Neonatal Edition 2008; Vol. 93, issue Suppl 1:Fa71.

Moghtadei P, Sardari F, Latifi M. Progesterone for prevention of preterm birth and improvement pregnancy outcomes among primiparae of advanced maternal age. Journal of Maternal-Fetal and Neonatal Medicine 2008; Vol. 21, issue Suppl 1:122.

Ndoni 2010 *{published data only}*

Ndoni E, Bimbashi A, Dokle A, Kallfa E. Treatment with different types of progesterone in prevention of preterm delivery. *Journal of Maternal-Fetal and Neonatal Medicine* 2010;**23**(S1):305.

Norman 2009 *{published data only}*

Eddama O, Petrou S, Regier D, Norrie J, MacLennan G, MacKenzie F, et al. Study of progesterone for the prevention of preterm birth in twins (STOPPIT): findings from a trial-based cost-effectiveness analysis. *International Journal of Technology Assessment in Health Care* 2010;**26**(2):141-8.

Norman J. Double blind randomised placebo controlled trial of progesterone for the prevention of preterm birth. http://controlledtrials.com (accessed 2007).

* Norman JE, Mackenzie F, Owen P, Mactier H, Hanretty K, Cooper S, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. *Lancet* 2009;**373**(9680):2034-40.

Norman JE, Yuan M, Anderson L, Howie F, Harold G, Young A, et al. Effect of prolonged in vivo administration of progesterone in pregnancy on myometrial gene expression, peripheral blood leukocyte activation, and circulating steroid hormone levels. *Reproductive Sciences* 2011;**18**(5):435-46.

O'Brien 2007 *{published data only}*

DeFranco EA, O'Brien JM, Adair CD, Lewis DF, Hall DR, Fusey S, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a

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randomized, double-blind, placebo-controlled trial. Ultrasound in Obstetrics and Gynecology 2007; Vol. 30, issue 5:697-705.

Defranco E, O'Brien J, Adair J, Lewis DF, Hall D, Phillips J, et al. Is there a racial disparity of progesterone to prevent preterm birth. American Journal of Obstetrics and Gynecology 2007; Vol. 197, issue 6 Suppl 1:S200, Abstract no: 702.

O'Brien J, Defranco E, Adair D, Lewis DF, Hall D, Bsharat M, et al. Progesterone reduces the rate of cervical shortening in women at risk for preterm birth: secondary analysis from a randomized, double-blind, placebo-controlled trial. American Journal of Obstetrics and Gynecology 2007; Vol. 197, issue 6 Suppl 1:S7, Abstract no: 15.

O'Brien J, Defranco E, Hall D, Creasy G. Natural progesterone administration and the risk of medical complications of pregnancy: secondary analysis from a multinational, randomized, double blind, placebo-controlled trial. American Journal of Obstetrics and Gynecology 2008; Vol. 199, issue 6 Suppl 1:S139.

O'Brien J, Defranco E, Hall D, Phillips J, Creasy G. Do other elements of the obstetrical history provide a possible indication for progesterone supplementation? Secondary analysis from the progesterone vaginal gel trial. American Journal of Obstetrics and Gynecology 2008; Vol. 199, issue 6 Suppl 1:S42.

* O'Brien JM, Adair CD, Lewis DF, Hall DR, Defranco EA, Fusey S, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized double blind placebo controlled trial. *Ultrasound in Obstetrics and Gynecology* 2007;**30**(5):687-96.

O'Brien JM, Defranco EA, Adair CD, Lewis DF, Hall DR, How H, et al. Effect of progesterone on cervical shortening in women at risk for preterm birth: secondary analysis from a multinational, randomized, double-blind, placebo-controlled trial. *Ultrasound in Obstetrics & Gynecology* 2010;**34**(6):653-9.

O'Brien JM, Steichen JJ, Phillips JA, Creasy GW. Two year infant outcomes for children exposed to supplemental intravaginal progesterone gel in utero: secondary analysis of a multicenter, randomized, double-blind, placebo-controlled trial. *American Journal of Obstetrics and Gynecology* 2012;**206**(Suppl 1):S223.

Papiernik 1970 *{published data only}*

Papiernik-Berkhauer E. Double blind study of an agent to prevent preterm delivery among women at increased risk [Etude en double aveugle d'un medicament prevenant la survenue prematuree de l'accouchement chez les femmes a risque eleve d'accouchement premature]. Edition Schering Serie IV 1970; Vol. 3:65-8.

Rai 2009 *{published data only}*

Rai P, Rajaram S, Goel N, Ayalur Gopalakrishnan R, Agarwal R, Mehta S. Oral micronized progesterone for prevention of preterm birth. *International Journal of Gynecology & Obstetrics* 2009;**104**(1):40-3.

Rode 2011 *{published data only}*

Klein K, Rode L, Nicolaides K, Krampl-Bettelheim E, Larsen H, Holmskov A, et al. Vaginal progesterone and the risk of preterm delivery in high-risk twin gestations - secondary analysis of a placebo-controlled randomized trial. *Ultrasound in Obstetrics & Gynecology* 2011;**38**(S1):11.

* Klein K, Rode L, Nicolaides KH, Krampl-Bettelheim E, Tabor A, PREDICT Group. Vaginal micronized progesterone and risk of preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis. *Ultrasound in Obstetrics & Gynecology* 2011;**38**(3):281-7.

Rode L. The PREDICT study. http://controlledtrials.com (accessed 2007).

Rode L, Klein K, Nicolaides K, Krampl-Bettelheim E, Vogel I, Larsen H, et al. Prevention of preterm delivery in twin gestations (PREDICT): a multicentre randomised placebo-controlled trial on the effect of vaginal micronised progesterone. *Ultrasound in Obstetrics & Gynecology* 2011;**38**(Suppl 1):1.

Rode L, Klein K, Nicolaides KH, Krampl-Bettelheim E, Tabor A, PREDICT G. Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. *Ultrasound in Obstetrics & Gynecology* 2011;**38**(3):272-80.

Rouse 2007 *{published data only}*

Caritis S, Rouse D. A randomized controlled trial of 17-hydroxyprogesterone caproate (17-OHPC) for the prevention of preterm birth in twins. *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1):S2.

Caritis SN, Simhan H. Relationship of 17-alpha hydroxyprogesterone caproate (17-OHPC) concentrations and gestational age at delivery in twins. 55th Annual Meeting of the Society of Gynecologic Investigation; 2008 March 26-29; San Diego, USA 2008:Abstract no: 139.

Caritis SN, Simhan HN, Zhao Y, Rouse DJ, Peaceman AM, Sciscione A, et al. Relationship between 17-hydroxyprogesterone caproate concentrations and gestational age at delivery in twin gestation. *American Journal of Obstetrics and Gynecology* 2012;**207**(5):396.e1-8.

Caritis SN, Venkat R. Impact of body mass index (BMI) on plasma concentrations of 17-alpha hydroxyprogesterone caproate (17-OHPC). 55th Annual Meeting of the Society of Gynecologic Investigation; 2008 March 26-29; San Diego, USA 2008:Abstract no: 138.

Durnwald C. The impact of cervical length on risk of preterm birth in twin gestations. American Journal of Obstetrics and Gynecology 2008; Vol. 199, issue 6 Suppl 1:S10.

Durnwald CP, Momirova V, Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, et al. Second trimester cervical length and risk of preterm birth in women with twin gestations treated with 17-hydroxyprogesterone caproate. *Journal of Maternal-Fetal and Neonatal Medicine* 2010;**23**(12):1360-4.

Gyamfi C, Horton AL, Momirova V, Rouse DJ, Caritis SN, Peaceman AM, et al. The effect of 17-alpha hydroxyprogesterone caproate on the risk of gestational diabetes in singleton or twin

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

pregnancies. *American Journal of Obstetrics and Gynecology* 2009;**201**(4):392.e1-5.

Horton A, Gyamfi C. 17-alpha hydroxyprogesterone caproate does not increase the risk of gestational diabetes in singleton and twin pregnancies. American Journal of Obstetrics and Gynecology 2008; Vol. 199, issue 6 Suppl 1:S197.

Manuck T, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The relationship between polymorphisms in the human progesterone receptor and clinical response to 17 alpha-hydroxyprogesterone caproate for the prevention of recurrent spontaneous preterm birth. American Journal of Obstetrics and Gynecology 2008; Vol. 199, issue 6 Suppl 1:S18.

Refuerzo JS, Momirova V, Peaceman AM, Sciscione A, Rouse DJ, Caritis SN, et al. Neonatal outcomes in twin pregnancies delivered moderately preterm, late preterm, and term. *American Journal of Perinatology* 2010;**27**(7):537-42.

* Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, et al. A trial of 17 Alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *New England Journal of Medicine* 2007;**357**:454-61.

Simhan HN, Caritis SN. The effect of 17-alpha hydroxyprogesterone caproate (17-OHPC) on maternal plasma CRP levels in twin pregnancies. 55th Annual Meeting of the Society of Gynecologic Investigation; 2008 March 26-29; San Diego, USA 2008:Abstract no: 140.

Rozenberg 2012 *{published data only}*

Rozenberg P. Efficacy of 17 alpha-hydroxyprogesterone caproate for the prevention of preterm delivery. http://controlledtrials.com (accessed 2007).

* Rozenberg P, Chauveaud A, Deruelle P, Capelle M, Winer N, Desbriere R, et al. Prevention of preterm delivery after successful tocolysis in preterm labor by 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. *American Journal of Obstetrics & Gynecology* 2012;**206**(3):206.e1-9.

Rozenberg P, Deruelle P, Chauveaud A, Capelle M, Winer N, Porcher R, et al. Prevention of preterm delivery after successful tocolysis in preterm labour by 17 alpha-hydroxyprogesterone caproate: a randomised controlled trial. *American Journal of Obstetrics and Gynecology* 2012;**206**(Suppl 1):S2-S3.

Saghafi 2011a *{published data only}*

Saghafi N, Khadem N, Mohajeri T, Shakeri MT. Efficacy of 17alpha-hydroxyprogesterone caproate in prevention of preterm delivery. *Journal of Obstetrics and Gynaecology Research* 2011;**37**(10):1342-5.

* Saghafi N, Khadem N, Mohajeri T, Shakeri MT, Amini M. Efficacy of 17alpha-hydroxyprogesterone caproate in preterm delivery prevention. *Iranian Journal of Obstetrics, Gynecology and Infertility* 2011;**14**(2):28-33.

Senat 2012 *{published data only}*

Senat MV, Winer N, Porcher R, Rozenberg P. Prevention of preterm delivery in asymptomatic women with twin pregnancy by 17 alpha-Hydroxyprogesterone caproate: A randomised controlled trial. *Journal of Maternal-Fetal and Neonatal Medicine* 2012;**25**(S2):14.

Serra 2013 *{published data only}*

Serra V. Natural progesterone and preterm birth in twins. http://controlledtrials.com (accessed 2007).

Serra V, Perales A, Meseguer J, Parrilla J, Lara C, Bellver J, et al. Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. *BJOG: an international journal of obstetrics and gynaecology* 2013;**120**(1):50-7.

Sharami 2010 *{published data only}*

Sharami SH, Zahiri Z, Shakiba M, Milani F. Maintenance therapy by vaginal progesterone after threatened idiopathic preterm labor: a randomized placebo-controlled double-blind trial. *International Journal of Fertility and Sterility* 2010;**4**(2):45-50.

References to studies excluded from this review

Abbott 2012 *{published data only}*

Abbott D. Relationship between cervical-vaginal fluid elafin concentrations and subsequent cervical shortening in women at high risk of spontaneous preterm birth. *Reproductive Sciences* 2012;**19**(3Suppl):73A.

Arikan 2011 *{published data only}*

Arikan I, Barut A, Harma M, Harma IM. Effect of progesterone as a tocolytic and in maintenance therapy during preterm labor. *Gynecologic and Obstetric Investigation* 2011;**72**(4):269-73.

Berghella 2010 *{published data only}*

Berghella V, Figueroa D, Szychowski JM, Owen J, Hankins GD, Iams JD, et al. 17-alpha-hydroxyprogesterone caproate for the prevention of preterm birth in women with prior preterm birth and a short cervical length. *American Journal of Obstetrics and Gynecology* 2010;**202**(4):351.e1-6.

Breart 1979 *{published data only}*

Breart G, Lanfranchi M, Chavigny C, Rumeau-Rouquette C, Sureau C. A comparative study of the efficiency of hydroxyprogesterone caproate and of chlormadinone acetate in the prevention of premature labor. *International Journal of Gynecology & Obstetrics* 1979;**16**(5):381-4.

Brenner 1962 *{published data only}*

Brenner WE, Hendricks CH. Effect of medroxyprogesterone acetate upon the duration and characteristics of human gestation and labor. *American Journal of Obstetrics and Gynecology* 1962;**83**:1094-8.

Chandiramani 2012 *{published data only}*

Chandiramani M. Serum progesterone concentrations in women with a previous preterm birth treated with vaginal progesterone supplementation. *Reproductive Sciences* 2012;**19**(3Suppl):189A.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Corrado 2002 *{published data only}*

Corrado F, Dugo C, Cannata M, Di Bartolo M, Scilipoti A, Stella N. A randomised trial of progesterone prophylaxis after midtrimester amniocentesis. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2002;**100**(2):196-8.

Hobel 1986 *{published data only}*

* Hobel CJ, Bemis RL. West Area Los Angeles prematurity prevention demonstration project. In: Papiernik E, Breart G, Spira N editor(s). Prevention of Preterm Birth. Paris: INSERM, 1986:205-22.

Hobel CJ, Bragonier R, Ross M, Bear M, Bemis R, Mori B. West Los Angeles premature prevention program: significant impact. *Journal of Perinatal Medicine* 1987;**15**:112.

Hobel CJ, Ross MG, Bemis RL, Bragonier JR, Bear M, Mori B. West Los Angeles preterm birth prevention project (LAPPP): program impact. *American Journal of Obstetrics and Gynecology* 1992;**166**:363.

Hobel CJ, Ross MG, Bemis RL, Bragonier JR, Nessim S, Sandhu M, et al. The West Los Angeles preterm birth prevention project: I. program impact on high-risk women. *American Journal of Obstetrics and Gynecology* 1994;**170**:54-62.

Ionescu 2012 *{published data only}*

Ionescu AC, Gheorghiu D, Pacu I, Davitoiu B, Dimitriu M, Haradja H. Randomized trial of cerclage and progesterone to prevent spontaneous preterm brith in high-risk women with a short cervix. *Journal of Perinatal Medicine* 2012;**39 Suppl**:Abstract no. 008.

Keeler 2009 *{published data only}*

Keeler SM, Kiefer D, Rochon M, Quinones JN, Novetsky AP, Rust O. A randomized trial of cerclage vs. 17 alpha-hydroxyprogesterone caproate for treatment of short cervix. *Journal of Perinatal Medicine* 2009;**37**(5):473-9.

Le Vine 1964 *{published data only}*

Le Vine L. Habitual abortion. A controlled clinical study of progestational therapy. *Western Journal of Surgical Obstetrics and Gynecology* 1964;**72**:30-6.

Rust 2006 *{published data only}*

Rust O, Larkin R, Roberts W, Quinones J, Rochon M, Reed J, et al. A randomized trial of cerclage versus 17 hydroxyprogesterone for the treatment of short cervix. *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1):S112.

Suvonnakote 1986 *{published data only}*

Suvonnakote T. Prevention of preterm labour with progesterone. *Journal of the Medical Association of Thailand* 1986;**69**(10):538-42.

Turner 1966 *{published data only}*

Turner SJ, Mizock GB, Feldman GL. Prolonged gynecologic and endocrine manifestations subsequent to administration of medroxyprogesterone acetate during pregnancy. *American Journal of Obstetrics and Gynecology* 1966;**95**(2):222-7.

Walch 2005 *{published data only}*

Walch K, Hefler L, Nagele F. Oral dydrogesterone treatment during the first trimester of pregnancy: the prevention of miscarriage study. A double blind, prospectively randomised placebo controlled parallel group trial. *Journal of Maternal-Fetal and Neonatal Medicine* 2005;**18**(4):265-9.

Yemini 1985 *{published data only}*

Yemini M, Borenstein R, Dreazen E, Apelman Z, Mogilner B, Kessler I, et al. Prevention of premature labor by 17 alpha-hydroxyprogesterone caproate. *American Journal of Obstetrics and Gynecology* 1985;**151**(5):574-7.

References to ongoing studies

Coomarasamy 2012 *{published data only}*

Coomarasamy A. First trimester progesterone therapy in women with a history of unexplained recurrent miscarriages: a randomised double-blind placebo-controlled multi-centre trial (The PROMISE [PROgesterone in recurrent MIScarriagE] Trial). http://www.controlled-trials.com/ISRCTN92644181/ISRCTN92644181 (accessed 11.01.2012).

Creasy 2008 *{published data only}*

Creasy GW. The effect of vaginal progesterone administration in the prevention of preterm birth in women with a short cervix. ClinicalTrials.gov (http://clinicaltrials.gov/) (accessed 2008).

Crowther 2007 *{published data only}*

Armson BA, Dodd J, for the POPPI Collaborative Trial Group. POPPI: prevention of problems of preterm birth with progesterone in women at increased risk: a multicentre randomised controlled trial [abstract]. *Journal of Paediatrics and Child Health* 2007;**43**:A29.

Ashwood P. Progesterone after previous preterm birth for the prevention of neonatal respiratory distress syndrome. WOMBAT Collaboration (www.wombatcollaboration.net/trials) (accessed 4 October 2006).

Crowther CA, Dodd JM, McPhee AJ, Flenady V. Australasian Collaborative Trial of Vaginal Progesterone Therapy (The PROGRESS Trial). http://controlledtrials.com (accessed 2007).

* Dodd JM, Crowther CA, McPhee AJ, Flenady V, Robinson JS. Progesterone after previous preterm birth for prevention of neonatal respiratory distress syndrome (PROGRESS): a randomised controlled trial. *BMC Pregnancy and Childbirth* 2009;**9**:6.

Martinez 2007 *{published data only}*

Matrinez de Tajada B. Vaginal progesterone to prevent preterm delivery in women with preterm labor. http://controlledtrials.com (accessed 2007).

Nassar 2007 *{published data only}*

Nassar A. Prevention of preterm delivery in twin pregnancies by 17 alpha hydroxyprogesterone caproate. http://controlledtrials.com (accessed 2007).

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

* Nassar A, Awwad J, Succar J, Saassouh W, Khalife T, Hayek S, et al. Incidence of GDM in twin pregnancies of women receiving prophylactic 17-A OH progesterone caproate. *Journal of Maternal-Fetal and Neonatal Medicine* 2010;**23**(S1):307-8.

Norman 2012 *{published data only}*

Norman JE, Shennan A, Bennett P, Thornton S, Robson S, Marlow N, et al. Trial protocol OPPTIMUM- Does progesterone prophylaxis for the prevention of preterm labour improve outcome?. *BMC pregnancy and childbirth* 2012;**12**(1):79. [PUBMED: 22866909]

Perlitz 2007 *{published data only}*

Perlitz Y. Prevention of recurrent preterm delivery by a natural progesterone agent. http://controlledtrials.com (accessed 2007).

Starkey 2008 *{published data only}*

Starkey M. Comparing IM vs. vaginal progesterone for pre-term birth. ClinicalTrials.gov (http://clinicaltrials.gov/) (accessed 20 April 2008).

Swaby 2007 *{published data only}*

Swaby C. Pilot randomized controlled trial of vaginal progesterone to prevent preterm birth in multiple pregnancy. JOGC: Journal of Obstetrics and Gynaecology Canada 2007; Vol. 29, issue 6 Suppl 1:S47.

van Os 2011 *{published data only}*

van Os MA, van der Ven JA, Kleinrouweler CE, Pajkrt E, de Miranda E, van Wassenaer A, et al. Preventing preterm birth with progesterone: Costs and effects of screening low risk women with a singleton pregnancy for short cervical length, the Triple P study. *BMC Pregnancy and Childbirth* 2011;**11**:77.

Wood 2007 *{published data only}*

Wood S. Vaginal progesterone versus placebo in multiple pregnancy. http://controlledtrials.com (accessed 2007).

Additional references

ACOG 2003

American College of Obstetrics and Gynecology. Committee opinion: use of progesterone to reduce preterm birth. *Obstetrics & Gynecology* 2003;**102**:1115-6.

Adams 2000

Adams MM, Elam-Evans LD, Wilson HG, Gilbertz DA. Rates and factors associated with recurrence of preterm delivery. *JAMA* 2000;**283**(12):1591-6.

AIHW 2003

Australian Institute of Health and Welfare. Australia's Mothers and Babies 2000. National Perinatal Statistics Unit, 2003.

Alfirevic 2012

Alfirevic Z, Stampalija T, Roberts D, Jorgensen AL. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD008991.pub2]

Astle 2003

Astle S, Slater DM, Thornton S. The involvement of progesterone in the onset of human labour. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2003;**108**(2):177-81.

Bakketeig 1979

Bakketeig LS, Hoffman HJ, Harley EE. The tendency to repeat gestational age and birth weight in successive births. *American Journal of Obstetrics and Gynecology* 1979;**135**(8):1086-103.

Berkowitz 1993

Berkowitz G, Papiernik E. Epidemiology of preterm birth. *Epidemiologic Reviews* 1993;**88**:233-8.

Blencowe 2012

Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012;**379**(9832):2162-72. [PUBMED: 22682464]

Block 1984

Block BS, Liggins GC, Creasy RK. Preterm delivery is not predicted by serial plasma estradiol or progesterone concentration measurements. *American Journal of Obstetrics and Gynecology* 1984;**150**(6):716-22.

Bloom 2001

Bloom SL, Yost NP, McIntire DD, Leveno KJ. Recurrence of preterm birth in singleton and twin pregnancies. *Obstetrics & Gynecology* 2001;**98**:379-85.

Carr-Hill 1985

Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. *BJOG:an international journal of obstetrics and gynaecology* 1985;**92**(9):921-8.

Conde-Agudelo 2013

Conde-Agudelo A, Romero R, Nicolaides K, Chaiworapongsa T, O'Brien JM, Cetingoz E, et al. Vaginal progesterone vs. cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis. *American Journal of Obstetrics and Gynecology* 2013;**208**(1):42.e1-42.e18.

Condon 2003

Condon JC, Jeyasuria P, Faust JM, Wilson JW, Mendelson CR. A decline in the levels of progesterone receptor coactivators in the pregnant uterus at term may antagonize progesterone receptor function and contribute to the initiation of parturition. *Proceedings of the National Academy of Sciences of the United States of America* 2003;**100**(16):9518-23.

Elder 1999

Elder DE, Haga R, Evans SF, Benninger HR, French NP. Hospital admissions in the first year of life in very preterm infants. *Journal of Paediatrics and Child Health* 1999;**35**(2):145-50.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gates 2004

Gates S, Brocklehurst P. How should randomised trial including multiple pregnancies be analysed?. *BJOG: an international journal of obstetrics and gynaecology* 2004;**111**:213-9.

Goldenberg 1998

Goldenberg RL, Rouse DJ. Prevention of premature birth. *New England Journal of Medicine* 1998;**339**:313-20.

Grazzini 1998

Grazzini E, Guillon G, Mouillac B, Zingg HH. Inhibition of oxytocin receptor function by direct binding of progesterone. *Nature* 1998;**392**(6675):509-12.

Greene 2003

Greene MF. Progesterone and preterm delivery - deja vu all over again. *New England Medical Journal* 2003;**348**:2453-5.

Haas 2008

Haas DM, Ramsey PS. Progestogen for preventing miscarriage. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD003511.pub2]

Hack 1999

Hack M. Consideration of the use of health status, functional outcome, and quality-of-life to monitor neonatal intensive care practice. *Pediatrics* 1999;**103**(1 Suppl E):319-28.

Haluska 1997

Haluska GJ, Cook MJ, Novy MJ. Inhibition and augmentation of progesterone production during pregnancy: effects on parturition in rhesus monkeys. *American Journal of Obstetrics and Gynecology* 1997;**176**(3):682-91.

Haluska 2002

Haluska GJ, Wells TR, Hirst JJ, Brenner RM, Sadowsky DW, Novy MJ. Progesterone receptor localisation and isoforms in myometrium, decidua, and fetal membranes from rhesus macaques: evidence for functional progesterone withdrawal at parturition. *Journal of the Society for Gynecological Investigation* 2002;**9**(3):125-36.

Hewitt 1988

Hewitt BC, Newnham JP. A review of the obstetric and medical complications leading to the delivery of very low birth weight infants. *Medical Journal of Australia* 1988;**149**:234-7.

Higgins 2002

Higgins J, Thompson S. Quantifying heterogeneity in meta-analysis. *Statistics in Medicine* 2002;**21**:1559-74.

Higgins 2008

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Higgins 2011

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Iams 2003

Iams JD. Supplemental progesterone to prevent preterm birth. *American Journal Obstetrics and Gynecology* 2003;**188**(2):303.

Kaminski 1973

Kaminski M, Goujard J, Rumeau-Rouquette C. Prediction of low birthweight and prematurity by a multiple regression analysis with maternal characteristics known since the beginning of the pregnancy. *International Journal of Epidemiology* 1973;**2**:195-204.

Kistka 2007

Kistka ZA, Palomar L, Lee KA. Racial disparity in the frequency of recurrence of preterm birth. *American Journal of Obstetrics and Gynecology* 2007;**196**:131.e1-131.e6.

Kramer 2000

Kramer M, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. *JAMA* 2000;**284**:843-9.

Lopez-Bernal 2003

Lopez-Bernal A. Mechanism of labour - biochemical aspects. *BJOG: an international journal of obstetrics and gynaecology* 2003;**110**(Suppl 20):39-45.

Martin 2003

Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Munson ML. Births: final data for 2002. *National Vital Statistics Report* 2003;**52**(10):1-113.

Mattison 2001

Mattison DR, Damus K, Fiore E, Petrini J, Alter C. Preterm delivery: a public health perspective. *Paediatric and Perinatal Epidemiology* 2001;**15**(Suppl. 2):7-16.

McLaughlin 2002

McLaughlin KJ, Crowther CA, Vigneswaran P, Hancock E, Willson K. Who remains undelivered more than seven days after a single course of prenatal corticosteroids and gives birth at less than 34 weeks?. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2002;**42**(4):353-7.

Mercer 1999

Mercer BM, Goldenberg RL, Moawad AH. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcomes. *American Journal of Obstetrics and Gynecology* 1999;**181**(5 Pt 1):1216-21.

Northen 2007

Northen AT, Norman GS, Anderson K, Moseley, L, Divito M, Cotroneo M, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. *Obstetrics & Gynecology* 2007;**110**(4):864-72.

Papiernik 1974

Papiernik E, Kaminski M. Multifactorial study of the risk of prematurity at 32 weeks of gestation: a study of the frequency

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

of 30 predictive characteristics. *Journal of Perinatal Medicine* 1974;**2**:30-6.

Pepe 1995

Pepe GJ, Albrecht ED. Actions of placental and fetal adrenal steroid hormones in primate pregnancy. *Endocrine Review* 1995;**16**(5):608-48.

Petrini 2005

Petrini J, Callaghan W, Klebanoff M. Estimated effect of 17 alpha hydroxyprogesterone caproate on preterm birth in the United States. *Obstetrics & Gynecology* 2005;**105**:267-72.

Pieber 2001

Peiber D, Allport VC, Hills F, Johnson M, Bennett PR. Interactions between progesterone receptor isoforms in myometrial cells in human labour. *Molecular Human Reproduction* 2001;**7**(9):875-9.

Rafael 2011

Rafael TJ, Berghella V, Alfirevic Z. Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy. *Cochrane Database of Systematic Reviews* 2011, Issue 6. [DOI: 10.1002/14651858.CD009166]

RevMan 2008 [Computer program]

The Cochrane Collaboration. Review Manager (RevMan). Version 5.0. Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration, 2008.

RevMan 2012 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Robinson 2001

Robinson JN, Regan JA, Norwitz ER. The epidemiology of preterm labour. *Seminars in Perinatology* 2001;**25**:204-14.

Romero 2012

Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. *American Journal of Obstetrics and Gynecology* 2012;**206**(2):124: 1-19.

Schuit 2012

Schuit E, Stock S, Groenwold RH, Maurel K, Combs CA, Garite T, et al. Progestogens to prevent preterm birth in twin pregnancies: an individual participant data meta-analysis of randomized trials. *BMC Pregnancy Childbirth* 2012;**15**(12):13.

Smit 1984

Smit DA, Essed GG, deHaan J. Predictive value of uterine contractility and the serum levels of progesterone and oestrogens with regard to preterm labour. *Gynecologic and Obstetric Investigation* 1984;**18**(5):252-63.

Smith 2007

Smith V, Devane D, Begley CM, Clarke M, Higgins S. A systematic review and quality assessment of systematic reviews of fetal fibronectin and transvaginal length for predicting preterm birth. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2007;**133**(2):134-42.

Stanley 1992

Stanley F. Survival and cerebral palsy in low birthweight infants: implications for perinatal care. *Paediatric and Perinatal Epidemiology* 1992;**6**(2):298-310.

References to other published versions of this review

Cincotta 2004

Cincotta R, Gardener G, Duncombe G, Flenady V, Dodd J. Antenatal administration of progesterone for preventing spontaneous preterm birth. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004947]

Dodd 2006

Dodd JM, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD004947.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aboulghar 2012

Methods	Single-centre prospective placebo-controlled randomised clinical trial. IVF Center, Cairo, Egypt.
Participants	313 women at high risk of preterm birth with pregnancies conceived by IVF or ICSI. Inclusion criteria: Healthy pregnant women who conceived after IVF/ICSI between 18-24 weeks of gestation, with a first pregnancy, singleton or dichorionic twins, normal uterine and cervical anatomy, and normal fetal anatomy.

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Aboulghar 2012 *(Continued)*

	Exclusion criteria: Previous pregnancy, serious fetal anomalies for which termination may be considered such as major heart anomaly or major CNS anomaly. All women received progesterone injections as luteal phase support which they continued if pregnant until the day of the first ultrasound
Interventions	Vaginal progesterone 200 mg twice daily from randomisation until delivery or 37 weeks' gestation. Total number randomised: n = 161 women (161 analysed, 210 babies). Placebo vaginal suppositories from randomisation until 37 weeks' gestation. Total number randomised: n = 152 women (145 women analysed, 187 babies).
Outcomes	Primary outcomes were: preterm birth of singleton and twin pregnancies before 37 completed weeks and before 34 completed weeks. Secondary outcomes: neonatal morbidity and mortality (live-born children who died < 28 days after delivery) and take-home baby rate (live-birth rate per patient). Birthweight > 2500 g; 1500-2500 g; < 1500 g; NICU admissions.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States, "Dark, sealed envelopes containing the intervention taken from a table of numbers" – not clear how the table of number generated – does not state "random number table".
Allocation concealment (selection bias)	Low risk	Refers to "dark, sealed, sequentially numbered envelopes" and the envelopes were picked by a nurse not involved in the study. The envelopes had been created by a third party not involved in the allocation process.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study flow diagram clearly displays participant flow in the study. 410 women recruited, 313 randomised; none lost to follow-up in progesterone group and 6 lost to follow-up in placebo group and 1 excluded because of termination of pregnancy after diagnosis of trisomy 21. States "Intention–to-treat principle was followed during data analysis."
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Unclear risk	None apparent, although baseline characteristics table not presented.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States "single blinding" and that "the patient was informed about the allocated arm" so presumably the clinician/personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.

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Akbari 2009

Methods	Randomised. Single centre, Lorestan.
Participants	150 women randomised: 75 to each group. Inclusion criteria: 1. Single child pregnancy with the exact age of conception based on LMP was determined and was verified by sonogram before reaching 20 weeks. If the LMP was not available the exact age of pregnancy was based on 2 sonograms that were verified on at least 2 separate weeks; 2. Women with a history of 1 or 2 previous early childbirths before reaching 37 weeks of pregnancy or women with a history of prophylactic cervical cerclage or uterine anomalies (unicornuate uterus, bicornuate uterus, septate uterus, arcuate uterus, uterus didelphys); and 3. Older than 18 years, younger than 35 years. Exclusion criteria: 1. Rupture of membranes PROM; 2. Large known fetal anomalies; 3 Cervix dilatation larger than 4 cm; 4. Contraindications for tocolysis including fetal distress, chorioamnionitis, preeclampsia, and haemodynamic instability; 5. Allergies to progesterone (dizziness, mygan, visual disturbances, depression, and increased blood sugar during previous consumption of this drug were considered allergic reactions to the hormone.); 6. Not following up with patients; 7. Multiple pregnancies; 8.The existence of an illness in the mother that necessitated medication, such as high blood pressure, cancer, tension, thromboembolic disease, Kennedy's disease, illnesses that are treated for asthma with oral beta-adrenergic; 9. Age younger than 18 or older than 35; 10. Existence of IUGR fetuses; 11. Unwarranted vaginal bleeding.
Interventions	Experimental intervention: 100 mg of prophylactic vaginal progesterone daily between 24th and 34th week of gestation - Cyclogest. Control/Comparison intervention: the other group received no treatment and were monitored.
Outcomes	Mean gestational age at time of delivery. Preterm delivery before 37th week gestation. Preterm delivery before 34th week gestation. Respiratory distress syndrome. Low birthweight. Birthweight. Need for oxygen. Infant Apgar score. Need for mechanical ventilator. Hospitalisation in NICU.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear "150 women that had passed the entrance criterion to the study were divided randomly into two groups of 75."
Allocation concealment (selection bias)	Unclear risk	Not reported.

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Akbari 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 individuals from the control group and 4 from the group receiving progesterone were excluded from the study – reasons for exclusion not clear – but in table of results – 6 people appear to be missing from denominator for the progesterone group (report 69) and not 4 as described? Results presented for 69 women in progesterone group and 72 in control.
Selective reporting (reporting bias)	Low risk	All expected outcomes appear to have been reported.
Other bias	Unclear risk	Unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Borna 2008

Methods	Method of randomisation: random number table. Allocation concealment: unclear. Blinded outcome assessment: no. Completeness of follow-up: outcome data available for 70 women.
Participants	70 women presenting between 24 and 34 weeks' gestation with symptoms and signs of threatened preterm labour, where acute symptoms were arrested following use of tocolytic medication.
Interventions	Daily intravaginal pessary (400 mg) versus no treatment.
Outcomes	Interval from randomisation to birth.
Notes	Trial conducted in Tehran, Iran.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data available.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported in the abstract appear to have been reported upon (latency period until delivery; respiratory distress syndrome; low birthweight; birthweight; recurrent preterm birth; admission to intensive care unit; neonatal sepsis).

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Borna 2008 *(Continued)*

Other bias	Low risk	Baseline characteristics were similar (see table 1, page 61).
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of care givers and women.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment.

Briery 2011

Methods	Placebo-controlled double-blind randomised clinical trial. Single site, USA.
Participants	69 women randomised: 33 to 17-OH group and 36 to placebo. Inclusion criteria: women who presented with singleton, vertex gestations to university's obstetric emergency area with a diagnosis of PPROM at 20-30 weeks' gestation, typically dated by ultrasound, were eligible. Exclusion criteria: severe fetal or placental disease that might bias neonatal outcomes such as intrauterine growth restriction (< 5th percentile), suspected placental abruption, and confirmed placenta previa. Also excluded were patients already taking 17P, and some with signs and symptoms of chorioamnionitis, non-reassuring fetal assessments or severe medical/obstetric diseases such as sickle cell disease with the crisis, insulin-dependent diabetes, and severe pre-eclampsia.
Interventions	Experimental intervention: weekly injections of 17P (250 mg) until 34 weeks or delivery, whichever came first. Control/Comparison intervention: weekly injections of placebo until 34 weeks or delivery, whichever came first.
Outcomes	Gestational age at birth; route of delivery; indications for delivery; birthweight; 5-minute Apgar score; total NICU days; significant neonatal morbidity (sepsis, seizures); respiratory distress syndrome; patent ductus arteriosis; intraventricular haemorrhage; necrotising enterocolitis; bronchopulmonary dysplasia; death during neonatal period.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Central allocation – pharmacy-controlled.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients lost – 1 person from 17P group who was previously enrolled in another study and 1 in placebo group refused the injection.

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Briery 2011 *(Continued)*

		"All 69 were analyzed (intention to treat)."
Selective reporting (reporting bias)	Unclear risk	All expected outcomes, apart from intraventricular haemorrhage, are reported in tables – although number of seizures were recorded.
Other bias	Low risk	No significant differences in demographic statistics between groups.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, their families, research personnel, and physicians/nurses were not aware of the study group assignment". Also described as "double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Caritis 2009

Methods	Randomised, double-blinded, placebo-controlled trial. 14 centres, USA.
Participants	134 women randomised: 71 to 17 alph-hydroxyprogesterone caproate; 63 to placebo Inclusion criteria: pregnant women with triplets were eligible if their gestational age was at least 16 weeks and no more than 20 weeks. Exclusion criteria: serious fetal anomalies, 2 or more fetuses in 1 amniotic sac, suspected twin-to-twin transfusion syndrome, marked ultrasonographic growth discordance, planned non study progesterone therapy after 16 weeks, in-place or planned cerclage, major uterine anomaly, unfractionated heparin therapy at any dose, and major chronic medical diseases.
Interventions	Experimental intervention: weekly injections of 17-OHPC* (250 mg in 1 mL castor oil) starting at 16-20 weeks and ending at delivery or 35 weeks' gestation. *17 Alpha-Hydroxyprogesterone Caproate Control/Comparison intervention: weekly injections of placebo (1mL castor oil) starting at 16-20 weeks and ending at delivery or 35 weeks' gestation.
Outcomes	Primary outcomes: composite of delivery or fetal loss before 35 completed weeks of gestation (245 days) – fetal loss included: miscarriage, termination, or stillbirth occurring any time after randomisation. Secondary outcomes: selected individual maternal and neonatal outcomes and a composite of serious neonatal outcomes. Composite serious adverse neonatal outcomes included: neonatal death, respiratory distress syndrome, culture-proven sepsis, necrotising enterocolitis stage II or III, bronchopulmonary dysplasia, intraventricular haemorrhage grade III or IV, or periventricular leucomalacia or severe retinopathy of prematurity stage III or higher.
Notes	

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Caritis 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The simple urn method of randomization with stratification according to clinical center, was used to create a randomization sequence for each center."
Allocation concealment (selection bias)	Low risk	The injections were prepared by a research pharmacy and boxes of 17-OHPC and placebo were packaged for each centre according to randomisation sequences – so appears to be central allocation – pharmacy-controlled.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Outcome data were available for 100% of the assigned women, and for all of the 402 fetuses." No exclusions apparent. ITT stated in statistical methods.
Selective reporting (reporting bias)	Low risk	All expected outcomes appear to have been reported.
Other bias	Low risk	The baseline characteristics of the 2 study groups were similar (Table 1). This study included women with multiple pregnancies (triplet) and there appears to be adjustment for neonatal binary outcomes - used log binomial regression to calculate relative risk.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The participating women, their caregivers, and the research personnel were not aware of the study group assignment". Also described as "double-blinded".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Cetingoz 2011

Methods	Randomised placebo-controlled double-blind study. Department of Obstetrics and Gynecology, Istanbul.
Participants	160 women randomised: 84 allocated to intervention and 76 allocated to placebo. Inclusion criteria: high-risk pregnant women: twin pregnancies; pregnancies with at least 1 spontaneous preterm birth; uterine malformation. Exclusion criteria: not stated.
Interventions	Experimental intervention: micronized progesterone (100 mg) administered daily by vaginal suppository between 24 and 34 weeks of gestation.

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Cetingoz 2011 *(Continued)*

	Control/Comparison intervention: placebo (100 mg) administered daily by vaginal suppository between 24 and 34 weeks of gestation.
Outcomes	Delivery < 37 weeks. Delivery < 34 weeks. Preterm labour admission. NICU admission. Neonatal death.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random-number list - “Patients were allocated according to randomised number table".
Allocation concealment (selection bias)	Low risk	Random-number list generated centrally by research hospital pharmacy.
Incomplete outcome data (attrition bias) All outcomes	Low risk	170 high-risk women were eligible – 10 women were excluded before randomisation due to abortion (n = 2), delivery between 20 and 24 weeks (n = 7) and application of cervical cerclage (n = 1). 160 women were randomised – 10 lost during follow-up, 6 from the placebo group and 4 from intervention group. 150 women analysed (intervention group - n = 80 - prior preterm birth = 37; uterine malformation = 4; twin gestation = 39) and (placebo group - n = 70 - prior preterm birth = 34; uterine malformation = 8; twin gestation = 28). Analysis was performed according to ITT principle.
Selective reporting (reporting bias)	Low risk	Yes – all expected outcomes reported
Other bias	Unclear risk	Groups were similar in regard to age, pregravid BMI, parity, abortion, and ratio of high-risk groups according to baseline characteristics table. There were no statistically significant differences in demographics. This study included singleton and twin pregnancies - Odd ratio presented, but does not state whether any adjustments made in the analysis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“The participating women, their care-givers, and the research personnel were unaware of the woman’s study-group assignments.”
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

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Combs 2010

Methods	Double-blind, randomised clinical trial. Multicentre, Obstetrix Collaborative Research Network, USA.
Participants	81 women randomised: 56 allocated to 17P and 25 to placebo. Inclusion criteria: mothers carrying trichorionic-triamniotic triplets – confirmed at 15-23 week detailed second-trimester ultrasound examination – showing normal amniotic fluid volume and no major fetal anomalies. Exclusion criteria: women with symptomatic uterine contractions, rupture of fetal membranes, any contraindication to interventions intended to prolong the pregnancy, a pre-existing medical condition that might be worsened by progesterone, or a pre-existing medical condition carrying a high risk of preterm delivery. Women less than 18 years of age, had an allergy to 17P or the oil vehicle, had taken any progesterone-derivative medication after 15 weeks of gestation, or had undergone placement of cervical cerclage for treatment of cervical change in the current pregnancy.
Interventions	Experimental intervention: 17 alpha-hydroxyprogesterone caproate (17P) (250 mg in 1 mL castor oil) – weekly injections starting at 16-22 weeks and continued until 34 weeks or delivery. Weekly repeat injections were carried out at the site or at home with partner administering after training. Injection diary for partner injections and measurement of unused medication returned by patient used to assess compliance with home administration. Control/Comparison intervention: identical appearing placebo (in 1 mL castor oil).
Outcomes	Primary outcomes: composite neonatal morbidity defined as 1 or more of: perinatal death (stillbirth, neonatal death, miscarriage); respiratory distress syndrome; use of oxygen therapy at 28 days of life; neonatal sepsis proven by blood culture; pneumonia; intraventricular haemorrhage (grade III or IV); periventricular leucomalacia; necrotising enterocolitis requiring surgery; retinopathy of prematurity; newborn asphyxia. Secondary outcomes: individual neonatal morbidities listed above; gestational age at delivery; birthweight; maternal side effects. Other outcomes reported: Mean weeks of gestation. Delivery before 28, 32 or 35 week. Reason for delivery before 32 weeks (spontaneous; indicated). Reason for delivery, all deliveries (spontaneous; indicated). Caesarean delivery. Tocolysis used. Antenatal corticosteroids. Maternal complications: Pre-eclampsia or gestational hypertension. Gestational diabetes. Chorioamnionitis. Sepsis.

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Combs 2010 *(Continued)*

	Postpartum endometritis. Neonatal outcomes: Birthweight, g. Head circumference, cm. Total hospital stay, days. NICU. Intermediate care.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated scheme.
Allocation concealment (selection bias)	Low risk	Random-number generated centrally by pharmacy. "Progesterone or identical-appearing placebo was compounded by pharmacy and shipped in advance to each study site in coded prenumbered kits. To randomise the research nurse contacted the central pharmacy by telephone or fax to obtain the code number for the kit assigned to that patient."
Incomplete outcome data (attrition bias) All outcomes	Low risk	248 women identified with triplets, 147 eligible for trial inclusion, of these 89 gave consent (61%) and were given trial injection. Of these, 81 (91%) returned for randomisation. No loss – 81 women randomised and outcome data available for all 81 mothers and 243 offspring. "Analysis was by the "intention-to-treat" principle. Accordingly, outcomes for each patient were tabulated according to the assigned group (17P vs placebo) regardless of her compliance."
Selective reporting (reporting bias)	Low risk	Yes – all expected outcomes reported.
Other bias	Low risk	Baseline characteristics of the participants were similar. There were no significant difference between the groups in the percentage with cervix length less than 2.5 cm 17% in the 17P group versus 35% in the placebo group or with positive fibronectin, 11% versus 9%. Mean compliance was 98.5% in the 17P group and 96.1% in the placebo group. There was no significant difference between groups in the percentage of injections given by clinic staff (27% versus 30%), by patients themselves (13% versus 15%), or by their designated representatives (61% versus 56%). Included multiple pregnancies (triplet) - adjustment made in analysis - used repeated measures model, where each infant was considered as a repeated measure.
Blinding of participants and personnel (performance bias)	Low risk	"Subjects, physicians, and study personnel remained blinded as to group assignment until after completion of the trial."

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Combs 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Data were abstracted by study personnel who remained blinded to each subject's group assignment."

Combs 2011

Methods	Double-blind, randomised clinical trial. Multicentre – 18 sites, Obstetrix Collaborative Research Network, USA.
Participants	240 women randomised: 160 allocated to 17Pc and 80 to placebo. Inclusion criteria: women were eligible if they had a dichorionic-diamniotic twin pregnancy at 15-23 weeks' gestation and if they had completed a detailed ultrasound examination – showing no major fetal anomalies. Exclusion criteria: women were excluded if they were < 18 years old; had taken any progestins > 15 weeks of gestation; or had symptomatic uterine contractions, rupture of the fetal membranes, any contraindication to prolonging the pregnancy, any pre-existing condition that might be worsened by progesterone, or a pre-existing medical condition carrying a high risk of preterm delivery.
Interventions	Experimental intervention: 17 alpha-hydroxyprogesterone caproate (17P) (250 mg in 1 mL castor oil) – weekly injections starting at 16-24 weeks and continued until 34 weeks or delivery. Weekly repeat injections were carried out at the site or at home with partner administering after training. Injection diary for partner injections and measurement of unused medication returned by patient used to assess compliance with home administration. Control/Comparison intervention: identical appearing placebo (in 1 mL castor oil).
Outcomes	Primary outcomes: composite neonatal morbidity defined as 1 or more of: perinatal death (stillbirth, neonatal death, miscarriage); respiratory distress syndrome; use of oxygen therapy at 28 days of life; neonatal sepsis proven by blood culture; pneumonia; intraventricular haemorrhage (grade III or IV); periventricular leucomalacia; necrotising enterocolitis requiring surgery; retinopathy of prematurity; newborn asphyxia. Secondary outcomes: individual neonatal morbidities listed above; gestational age at delivery; birthweight; maternal side effects. Other outcomes reported: Mean weeks of gestation. Delivery before 28, 32 or 34 or 37 weeks. Reason for delivery before 37 weeks (spontaneous; indicated). Caesarean delivery. Tocolysis used. Antenatal corticosteroids. Maternal complications: Pre-eclampsia or gestational hypertension.

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Combs 2011 *(Continued)*

	Gestational diabetes.
	Chorioamnionitis.
	Sepsis.
	Postpartum endometritis.
	Neonatal outcomes:
	Birthweight, g.
	Birthweight < 2500 g.
	Birthweight < 1500 g.
	Birthweight < 1000 g.
	Small-for-gestational age.
	All births.
	Births < 2500 g.
	Head circumference, cm.
	Total hospital stay, days.
	NICU.
	Intermediate care.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated scheme.
Allocation concealment (selection bias)	Low risk	Random-number generated centrally by pharmacy. "Progesterone or identical-appearing placebo was compounded by pharmacy and shipped in advance to each study site in coded prenumbered kits. To randomise the research nurse contacted the central pharmacy by telephone or fax to obtain the code number for the kit assigned to that patient."
Incomplete outcome data (attrition bias) All outcomes	Low risk	1450 women identified with twin pregnancy, 254 eligible and consented and were given trial injection. Of these, 240 returned for randomisation. No loss in progesterone group – 160 women allocated, 160 mothers delivered and 320 perinates with known outcome. 80 women allocated to placebo – 2 lost to follow-up – 78 women delivered and 156 perinates with known outcome. "Outcomes for each patient were tabulated according to assigned group regardless of her compliance."
Selective reporting (reporting bias)	Low risk	Yes – all expected outcomes reported.
Other bias	Low risk	Baseline characteristics of the subjects were similar.

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Combs 2011 *(Continued)*

		Mean compliance was 96.4% in the 17P group and 98.7% in the placebo group. Included multiple pregnancies (twin) - adjustment made in analysis - used repeated measures model, where each infant was considered as the repeated measure.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subjects, physicians, and study personnel remained blinded as to group assignment until after completion of the trial."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Combs 2011a

Methods	Double-blind, placebo-controlled randomised clinical trial. Multicentre – 18 sites, Obstetrix Collaborative Research Network, USA.
Participants	12 women randomised: 4 allocated to 17P and 8 to placebo. The trial was terminated early because of 2 separate issues related to the supply of 17P. Inclusion criteria:**w**omen were eligible if they were at least 18 years old, had a singleton pregnancy at 23.0 to 31.9 weeks of gestation and PROM. Exclusion criteria: women were excluded with contraindications to expectant management; with known fetal abnormalities; with history of allergy to 17P or castor oil; with medical conditions that might adversely interact with 17P; with medical conditions treated with systemic steroid medications; or with a cervical cerclage present at the time of PROM.
Interventions	Experimental intervention: 17 alpha-hydroxyprogesterone caproate (17P) (250 mg in 1 mL castor oil) – weekly intramuscular injections Control/Comparison intervention: identical appearing placebo (in 1 mL castor oil).
Outcomes	Primary outcomes: prolongation of pregnancy until favourable gestational age. Composite neonatal morbidity defined as 1 or more of: stillbirth, neonatal death, infant death before hospital discharge; respiratory distress syndrome; intracranial haemorrhage grade III or IV; necrotising enterocolitis stage 2 or 3; culture proven sepsis within 72 hours of birth; periventricular leucomalacia. Secondary outcomes: pregnancy prolongation (interval from randomisation to delivery). Individual neonatal morbidities listed above; gestational age at delivery; birthweight; maternal side effects. Other outcomes reported: Delivery at 34 weeks or more. Delivery at 32-33.9 weeks with documented fetal lung maturity. Mean gestational age at delivery.

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Combs 2011a *(Continued)*

Delivery before 32 or 34 weeks.

Pulmonary maturity testing.

Latency – randomisation to delivery.

Less than 1 week.

1.0 to 1.9 weeks.

2.0 2.0 weeks or more.

Reason for delivery before 34 weeks (spontaneous; chorioamnionitis; fetal indications).

Maternal complications:

Pre-eclampsia or gestational hypertension.

Gestational diabetes.

Chorioamnionitis.

Sepsis.

Caesarean delivery.

Tocolysis in first 48 hours.

Antenatal corticosteroids.

Neonatal outcomes:

Birthweight, g.

Total hospital stay, days.

NICU stay, days.

Newborns with congenital anomaly.

Adverse events not tabulated elsewhere.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence was used by the trial statistician to generate a randomisation code.
Allocation concealment (selection bias)	Low risk	Random-number generated by a statistician and held centrally at each site's inpatient pharmacy.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up – but only 12 patients were randomised – 8 to placebo and 4 to 17P Appears to have been ITT.
Selective reporting (reporting bias)	Low risk	Yes – all expected outcomes reported .
Other bias	Unclear risk	The trial was stopped early due to 2 separate issues related to the supply of 17P. Only 12 patients were randomised and because of the early termination,

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Combs 2011a *(Continued)*

		the trial was grossly under-powered to make conclusions as to the efficacy or safety of 17P in women with PROM. Too few patients to assess baseline imbalance.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“Participants and research personnel were blinded to group assignment throughout.”
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

da Fonseca 2003

Methods	Method of randomisation: random number table. Allocation concealment: sequential sealed envelopes; allocation to either drug A or B; allocation of groups revealed after last woman birthed. Blinded outcome assessment: yes. Completeness of follow-up: outcome data available for 142 women (15 women excluded after randomisation).
Participants	157 women considered to be at 'high risk' for preterm birth due to history of previous preterm birth, cervical suture, uterine malformation.
Interventions	Nightly intravaginal pessary of either 100 mg progesterone or placebo from 24 weeks until 28 weeks' gestation, or birth if earlier.
Outcomes	Preterm birth before 37 weeks' gestation; preterm birth before 34 weeks' gestation.
Notes	Trial conducted in Sao Paulo, Brazil.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Adequate; sequential sealed opaque envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	15 women (less than 1%) post-randomisation exclusions.
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes (incidence of preterm delivery; frequency of uterine contractions).
Other bias	Low risk	"The two groups were found similar in regard to age, risk factors for preterm delivery, and obstetric history."

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da Fonseca 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Caregivers and participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded.

Elsheikhah 2010

Methods	Described as “randomized controlled study” in abstract title. Single centre, Cairo, Egypt.
Participants	100 women: 50 allocated to progesterone group and 50 to placebo. Inclusion criteria: women with twin pregnancy. Exclusion criteria: patients with anomalies were excluded.
Interventions	Experimental intervention: vaginal progesterone 200 mg daily for 10 weeks from the 24th to the 34th week of gestation. Control/Comparison intervention: placebo for the same duration.
Outcomes	Mean cervical length. Mean gestational age at delivery. Fetal complications (not specified). NICU admissions.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Data limited – only reported as an abstract.
Allocation concealment (selection bias)	Unclear risk	Data limited – only reported as an abstract.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data limited – only reported as an abstract.
Selective reporting (reporting bias)	Unclear risk	Data limited – only reported as an abstract.
Other bias	Unclear risk	Data limited – only reported as an abstract. Multiple pregnancies - no adjustment apparent from abstract report.

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Elsheikhah 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Data limited – only reported as an abstract.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Data limited – only reported as an abstract.

Facchinetti 2007

Methods	Method of randomisation: random number table. Allocation concealment: randomisation list managed by senior midwife; allocation to either progesterone or placebo. Blinding of outcome assessment: no. Completeness of follow-up: outcome data available for 60 women.
Participants	60 women presenting between 25 and 33 + 6 weeks' gestation with symptoms and signs of threatened preterm labour, where acute symptoms were arrested following use of tocolytic medication (atosiban).
Interventions	341 mg intramuscular 17OHP administered every 4 days to 36 weeks' gestation.
Outcomes	Cervical length as assessed by transvaginal ultrasound. Secondary outcomes included preterm birth < 37 weeks, and infant birthweight.
Notes	Trial conducted in Modena, Italy.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Unclear risk	Unclear; list managed by "senior midwife" with allocation to either progesterone or placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for all women.
Selective reporting (reporting bias)	High risk	Cervical length was measured by transvaginal ultrasound scanning at discharge and at day 7 and 21. Results for cervical length at discharge were not fully reported. All other outcomes appear to have been reported upon (cervical length at 7 and 21 days; preterm delivery < 37 weeks and < 35 weeks; birthweight).
Other bias	Low risk	No differences were found between the 2 groups for baseline characteristics (see table, page 3).
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding - not possible "The study was not double blind because it was not sponsored; therefore, the preparation of true placebo (same vial, same oil without active compound) was not possible."

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Facchinetti 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessor.

Fonseca 2007

Methods	Method of randomisation: not stated. Allocation concealment: central randomisation process; identically appearing treatment packs. Blinded outcome assessment: yes. Completeness of follow-up: outcome data available for all 250 women randomised.
Participants	250 women undergoing transvaginal ultrasound assessment of cervical length, where the cervical length was measured to be 15 mm or less. Women with both singleton and multiple pregnancies were eligible to participate (226 singleton and 24 with twin pregnancies).
Interventions	Nightly intravaginal pessary of either 200 mg micronised progesterone or placebo from 24 weeks until 33 + 6 weeks' gestation, or birth if earlier.
Outcomes	Primary outcome: spontaneous preterm birth less than 34 weeks' gestation. Secondary outcomes: infant birthweight, fetal death, neonatal death, major adverse outcomes (intraventricular haemorrhage, respiratory distress syndrome, retinopathy of prematurity, necrotising enterocolitis), need for neonatal special care (NICU, ventilation, phototherapy, treatment for proven or suspected sepsis, blood transfusion).
Notes	Trial conducted in 5 maternity hospitals in London (UK), Santiago (Chile), Sao Paulo (Brazil), and Greece. This data analysed in subgroup of women with short cervix - multiples only made up a small proportion of total group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation generation not stated.
Allocation concealment (selection bias)	Low risk	Adequate; central randomisation; identical appearing treatment packs.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.
Selective reporting (reporting bias)	Low risk	All expected outcomes are reported (spontaneous delivery before 34 completed weeks; birthweight; fetal or neonatal death; major adverse outcomes before discharge; need for neonatal special care).
Other bias	Low risk	"There were no significant differences in baseline characteristics between the placebo and progesterone groups" (see Table 1, page 465). Singleton and twin pregnancies - adjustment made for infant outcomes, " the analyses of infant outcomes used robust standard errors and were clustered on a maternal identifier to account for the non-independence of twin pairs."

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Fonseca 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants, caregivers, outcome assessors.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants, caregivers, outcome assessors.

Glover 2011

Methods	Pilot, single-centre, randomised, double-blind, placebo-controlled trial. Single centre, Miami Valley Hospital, Ohio, USA.
Participants	Inclusion criteria: women < 20 weeks' gestation and had at least 1 prior spontaneous preterm birth of a live-born singleton infant between $20^{0}/_{7}$ weeks and $36^{6}/_{7}$ weeks' gestation. Exclusion criteria: multiple gestations, the presence of major fetal anomalies, progesterone use in current pregnancy, the presence of a cervical cerclage and the presence of a placenta previa.
Interventions	36 women randomised: 20 allocated to progesterone group and 16 allocated to placebo group. Experimental intervention: 400 mg (2 200-mg capsules) of oral micronized progesterone MP. Administration of the tables was initiated between $16^{0}/_{7}$ and $19\ ^{6}/_{7}$weeks and was continued until the completion of the 33rd week of gestation. Control/Comparison intervention: control group took 2 identical placebo capsules for the same time period.
Outcomes	Rate of recurrent spontaneous preterm birth. Serum progesterone levels. Neonatal morbidity and mortality: birthweight (g) mean (SD); male gender; 5-minute Apgar (mean); ventilator use; neonatal length of stay (mean), days.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done by the hospital's research pharmacy using a standard randomization table methodology for two groups."

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Glover 2011 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central allocation – pharmacy controlled: "After subjects were randomized to their respective group, the research pharmacy dispensed a 1-month supply of either progesterone or placebo tablets in identical prescription bottles, which were labelled identically as "progesterone study medication."
Incomplete outcome data (attrition bias) All outcomes	Low risk	45 patients were eligible for randomisation – 9 women didn't complete the initial evaluation or failed to present to the pharmacy for randomisation and were excluded. Appears that 36 were randomised, but only 33 analysed. 3 more participants were excluded – 1 from the MP group as became apparent that she had not had previous spontaneous preterm birth as she had been induced for severe eclampsia; 1 from the placebo group had a spontaneous abortion at 14 weeks; and another from placebo group did not complete her prenatal care at this centre and delivered elsewhere. 3 appear to have been excluded after randomisation, see above. Analysis appears to be ITT: 2 women ended their participation in the study – but both delivered at this institution and were included in their respective group for all analyses.
Selective reporting (reporting bias)	Unclear risk	In methods reports that neonatal mortality will be reported – but was not reported.
Other bias	Low risk	Similar baseline characteristics – no statistically significant differences between groups.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study subjects' physicians were aware of the study participation but were blinded to the group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Grobman 2012

Methods	Multicentre, randomised controlled trial. Multicentre, Maternal-Fetal Units Network, USA.
Participants	657 women recruited between April 2007 and May 2011 in various centres in the USA 657 women randomised: 327 to OHPc group and 330 to placebo. Inclusion criteria: nulliparous women with a singleton gestation between 16 and 22 3/7 weeks with cervical length less than 30 mm.

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Grobman 2012 *(Continued)*

	Exclusion criteria: Women that had selective fetal reduction for multiple pregnancy, had evidence of additional fetal pole/embryo at 12 weeks or more, vaginal bleeding, prolapsed membranes, major fetal anomaly, current or planned cerclage, maternal medical condition associated with preterm delivery (e.g. hypertension) prior cervical surgery, or planned preterm delivery.
Interventions	Experimental intervention: 250 mg IM weekly 17 alpha hydroxyprogesterone caproate (17-OHPc) given by nurse until delivery or up to 36 weeks and 6 days gestation. Control/Comparison intervention: An identical appearing placebo.Weekly IM injections of placebo (castor oil) given by study nurse until delivery or up to 36 weeks and 6 days gestation.
Outcomes	Maternal outcomes: Preterm birth before 37 weeks Birth before 35 weeks Preterm rupture of membranes Delivery < 28 weeks Tocolytic therapy Caesarean delivery Side effects (any; injection site; urticaria; nausea) Perinatal outcomes: Fetal death Neonatal death Respiratory distress syndrome Necrotising enterocolitis grade II or III Intraventricular haemorrhage grade II or IV Periventricular leucomalacia Early-onset sepsis Retinopathy of prematurity grade III or IV Birthweight < 2500 g 5-minute Apgar < 7 NICU admission Length of NICU stay, days
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data co-ordinating centre to created the computer-generated randomisation sequence. Simple turn method of randomisation used.

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Grobman 2012 *(Continued)*

Allocation concealment (selection bias)	Low risk	Simple randomisation method stratified by centre. Study treatments were research pharmacy prepared.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised were accounted for in the analysis. Discontinuation of treatment was greater in the placebo group 33/330 vs 18/327 but there was an ITT analysis.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported upon.
Other bias	Unclear risk	Groups appeared balanced at baseline (slightly more white Hispanic in the placebo group and this group were slightly younger). The study was stopped early as the study monitoring committee decided that further recruitment after data for 591 available for interim analysis would be unlikely to show benefit (planned 1000 women , data for 657).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	It was stated that neither patients nor medical staff were aware of treatment group and the study was placebo controlled. It was stated that the IM injections appeared identical.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was stated that the trial was blinded to research staff collecting outcome data. The trial was placebo controlled.

Hartikainen 1980

Methods	Method of randomisation: stated to be "placebo controlled and double blind". Allocation concealment: not stated. Blinded outcome assessment: yes. Completeness of follow-up: outcome data available for 77 women.
Participants	77 women with a twin pregnancy.
Interventions	Weekly intramuscular injection of either 250 mg 17-hydroxyprogesterone caproate or placebo from 28 weeks' gestation until 37 weeks' gestation or birth if earlier.
Outcomes	Perinatal death.
Notes	Trial conducted in Finland.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Process of sequence generation not stated.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for all participants.

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Hartikainen 1980 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes are reported (duration of pregnancy; spontaneous delivery before 37 weeks; weights of neonates; perinatal mortality; neonatal morbidity (respiratory problems; omphalitis; pulmonary infection); maternal levels of progesterone; estradiol).
Other bias	Unclear risk	"The gestational age at the onset of medication, the gestational age at diagnosis of twin pregnancy and the patient's age were similar in both groups." (see table 1, page 693). "The factors commonly regarded as risk factors for premature delivery showed no differences between groups." (see table 2, page 693). Multiple pregnancies - abstract only available – limited data – no adjustment apparent.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Caregivers and participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors.

Hassan 2011

Methods	Multicentre randomised double-blind placebo-controlled trial. Multicentre – 44 centres in 10 countries, USA.
Participants	465 women randomised: 236 allocated to progesterone and 229 to placebo. Inclusion criteria: singleton gestation; gestational age between 19 + 0 and 23 + 6 weeks; transvaginal sonographic cervical length between 10 and 20 mm; without signs and symptoms of preterm labour. Exclusion criteria: planned cerclage; acute cervical dilation; allergic reaction to progesterone; current or recent progestogen treatment within 4 weeks; chronic medical conditions that would interfere with study participation or evaluation of the treatment; major fetal anomaly or known chromosomal abnormality; uterine anatomic malformation; vaginal bleeding; known or suspected clinical chorioamnionitis.
Interventions	Experimental intervention: daily micronised vaginal progesterone gel – women self-administered the study drug once daily in the morning. Each applicator delivered 1.125 g gel containing 90 mg progesterone. Control/Comparison intervention: an identical appearing placebo - each applicator delivered 1.125 g gel containing 90 mg placebo.
Outcomes	Primary outcome: preterm birth before 33 weeks. Secondary outcomes: neonatal morbidity - respiratory distress syndrome; bronchopulmonary dysplasia; intraventricular haemorrhage grade III or IV; periventricular leucomalacia; proven sepsis; necrotising enterocolitis; perinatal mortality (fetal death or neonatal death) – composite scores were used to assess perinatal mortality and morbidity.

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Hassan 2011 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation allocation was 1:1 and was accomplished using a centralised interactive voice response system. Randomisation was stratified according to centre and risk strata (previous preterm birth between 20 and 35 weeks or no previous preterm birth) using a permuted blocks strategy with a block size of 4.
Allocation concealment (selection bias)	Low risk	Reported that allocation concealment accomplished in 3 ways: 1. participant study kits at each site were numbered independently from the treatment assignments in the randomisation blocks; 2. IVR system specified which kit number was to be dispensed to the subject; 3. the study drug packaging , applicators and contents were identical in appearance.
Incomplete outcome data (attrition bias) All outcomes	Low risk	733 women eligible, 268 declined, 465 randomised. 1 lost to follow-up from progesterone group and 6 from placebo group. ITT analysis performed.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported upon.
Other bias	Low risk	Baseline characteristics were similar between groups.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Hauth 1983

Methods	Method of randomisation: stated to be "randomised, double blind intervention". Allocation concealment: not stated. Blinded outcome assessment: yes. Completeness of follow-up: outcome data available for all women randomised.
Participants	168 women on active military duty.
Interventions	Weekly intramuscular injection of either 1000 mg 17-hydroxyprogesterone caproate or placebo from 16 to 20 weeks until 36 weeks' gestation, or birth if earlier.
Outcomes	Preterm birth before 37 weeks' gestation; birthweight less than 2.5 kg; perinatal death.

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Hauth 1983 *(Continued)*

Notes	Trial conducted in Lackland Airforce Base, Texas, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not stated.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for all women recruited.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported (low birthweight; perinatal mortality; pregnancy-induced hypertension; premature labour).
Other bias	Low risk	The groups were similar for parity, previous abortion, race, cigarette smoking, and marital status.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Caregivers and participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors.

Ibrahim 2010

Methods	Randomised placebo-controlled trial. Ain Shams University Maternity Hospital, Cairo, Egypt.
Participants	50 women randomised: 25 allocated to progesterone group and 25 to placebo group. Inclusion criteria: singleton pregnant women in their second trimester with a history of preterm labour. Exclusion criteria: women with a history medical disease during pregnancy, multiple pregnancy, abdominal or cervical cerclage, known fetal anomalies or scarred uterus.
Interventions	Experimental intervention: 17-α-hydoxy progesterone caproate – 1 dose of 250 mg intramuscular progesterone- weekly until 36 weeks. Control/Comparison intervention: standard dose of placebo IM per week until 36 weeks.
Outcomes	Mean gestation age. Birth < 37 weeks. Birth > 37 weeks. Live neonates. Need for NICU.

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Ibrahim 2010 *(Continued)*

	Neonatal death. Birthweight < 2500 g. Birthweight > 2500 g. Apgar score < 7. Apgar score > 7.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported – says women were divided into 2 groups –but no details of method of randomisation.
Allocation concealment (selection bias)	Unclear risk	"Randomisation was done by the use of sealed envelopes which were opened by the nurse responsible for giving the injections to all participants whether Cidolut depot or placebo" – unclear whether the envelopes were opaque and sequentially numbered – so nurse may have been able to foresee assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women appear to be included in the results – 25 in each group.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported upon.
Other bias	Unclear risk	Baseline demographic characteristics not fully reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double blind – but no details described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Johnson 1975

Methods	Method of randomisation: stated to be "random double blind fashion". Allocation concealment: next of identical drug packages. Blinded outcome assessment: yes. Completeness of follow-up: outcome data available for 43 women (7 women excluded after randomisation).
Participants	50 women with a history of 2 previous spontaneous abortions or previous preterm birth before 36 weeks' gestation.
Interventions	Weekly intramuscular injection of either 250 mg 17-hydroxyprogesterone caproate or placebo from 'booking' until 24 weeks' gestation.
Outcomes	Preterm birth before 37 weeks' gestation; birthweight less than 2.5 kg; perinatal death.

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Johnson 1975 *(Continued)*

Notes	Trial conducted in Baltimore, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Generation of sequence not stated.
Allocation concealment (selection bias)	Low risk	Adequate; identical appearing treatment packs.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 women excluded post-randomisation (1%).
Selective reporting (reporting bias)	Low risk	All expected outcomes reported (premature delivery; birthweight; perinatal mortality).
Other bias	Low risk	Groups were similar for baseline characteristics, (see table 2, page 678), although placebo group included fewer smokers and less heavy smokers than progesterone group.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Caregivers and participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.

Lim 2011

Methods	Multicentre, double-bind, placebo-controlled randomised trial. Multicentre, 55 obstetric clinics in Netherland.
Participants	671 women randomised: 336 allocated to progesterone and 326 allocated to placebo. Inclusion criteria: women with a multiple pregnancy and gestational age between 15 and 19 weeks. Exclusion criteria: women with a previous spontaneous preterm birth before 34 weeks, serious congenital defects or death of 1 or more fetuses, early signs of twin-to-twin transfusion syndrome, or primary cerclage were excluded from participation.
Interventions	Experimental intervention: 1 mL 17-α-hydoxyprogesterone caproate (250 mg/mL in castor oil) – starting between 16 and 20 weeks and continuing to 36 weeks. Injections were administered at the clinic, by a general practitioner or, in case the patient or a family member had a background in medical practice, at the patient's home. Control/Comparison intervention: 1 mL placebo (castor oil) – study medication and placebo were identical in packaging, colour and consistency.
Outcomes	Primary outcomes: composite adverse neonatal outcome – severe respiratory distress syndrome; bronchopulmonary dysplasia; intraventricular haemorrhage grade II B or worse;necrotising enterocolitis; proven sepsis; death before discharge.

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Lim 2011 *(Continued)*

	Secondary outcomes: Side effects (soreness, itching, and swelling). Gestational age at delivery. Preterm birth before 28, 32 and 37 weeks. Length of admission to the NICU. Maternal morbidity. Hospitalisation of the mother due to (threatened) preterm labour. Costs.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An independent data manager rendered a computer-generated list that was stratified by chorionicity, parity, and number of multiples, using random blocks of maximum block size."
Allocation concealment (selection bias)	Low risk	Web-based randomisation – "Randomization was accessible through a website" and "Allocation code was known only to ACE Pharmaceuticals"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1865 women eligible, 1194 declined participation, 671 women entered trial. 336 randomised to progesterone group and no women lost to follow-up/326 randomised to placebo and 4 lost to follow-up. 681 children born to 336 women in progesterone group/ 680 children born to 331 women in placebo group. Neonatal outcome available for 681 in progesterone group and 674 in placebo group. States that "all analyses were based on the intention-to-treat principle."
Selective reporting (reporting bias)	Low risk	All expected outcomes reported upon.
Other bias	Low risk	Baseline characteristics similar. Multiple pregnancies (twin, triplet and 1 quadruplet) - adjustments made for all neonatal, delivery, pregnancy and side effect outcomes.
Blinding of participants and personnel (performance bias)	Low risk	"Participants, caregivers, and data collectors were all blinded to allocation."

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Lim 2011 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, caregivers, and data collectors were all blinded to allocation."

Majhi 2009

Methods	Prospective randomised trial. Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.
Participants	50 women randomised: 50 allocated to progesterone and 50 allocate to no treatment. Inclusion criteria: women at high risk for preterm birth, having a singleton pregnancy and current gestation 16-24 weeks. High risk was defined by history of at least once prior spontaneous preterm birth of a singleton infant > 20 and < 37 weeks due to spontaneous labour or preterm rupture of fetal membranes. Exclusion criteria: women with multifetal gestation, congenital malformation in the fetus, current or planned cervical cerclage or with any associated medical disorder were excluded.
Interventions	Experimental intervention: 100 mg natural micronised progesterone capsule intravaginally once daily at bedtime from 20-24 weeks' gestation until 36 weeks. Control/Comparison intervention: no placebo – just managed according to the institute protocol.
Outcomes	Primary outcomes: Preterm birth < 37 weeks. Preterm birth ≤ 34 weeks. Secondary outcomes: Maternal hospitalisation. Vaginal delivery. LSCS. Birthweight (Mean SD). NICU. Sepsis. Hyperbilirubinaemia. Necrotising enterocolitis. Cord pH (Mean SD).
Notes	
Risk of bias	

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Majhi 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random-number tables.
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes – provided centrally by Dept Biostatistics and investigators were not involved in the randomisation procedure.
Incomplete outcome data (attrition bias) All outcomes	Low risk	118 women met the inclusion criteria; 100 women consented and were included – 50 assigned to each group. There was no attrition during follow-up.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported upon.
Other bias	Unclear risk	Both groups were similar in all characteristics except BV, which was commoner in the study group. It was treated in both groups.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported – no placebo used though – so participants would have been aware of assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Meis 2003

Methods	Method of randomisation: computer-generated 2:1 random number schedule. Allocation concealment: next of identical drug packages. Blinded outcome assessment: yes. Completeness of follow-up: outcome data available for 463 women.
Participants	463 women with a history of previous spontaneous preterm birth; exclusion women with multiple pregnancy, known fetal anomaly, progesterone or heparin treatment during pregnancy, current or planned cervical cerclage, hypertension, seizure disorder.
Interventions	Weekly intramuscular injection of either 250 mg 17-hydroxyprogesterone caproate or placebo from 16 to 20 weeks until 36 weeks' gestation, or birth if earlier.
Outcomes	Preterm birth before 37 weeks' gestation; birthweight less than 2.5 kg; stillbirth; neonatal death; intraventricular haemorrhage; respiratory distress syndrome; bronchopulmonary dysplasia; sepsis; necrotising enterocolitis; retinopathy of prematurity; patent ductus arteriosus.
Notes	Trial conducted by the Maternal-Fetal Medicine Network, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence.

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Meis 2003 *(Continued)*

Allocation concealment (selection bias)	Low risk	Adequate; identical appearing treatment packs.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for all 463 women recruited.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported (preterm delivery < 37, < 35, < 32 weeks; pregnancy outcomes (e.g. caesarean delivery; chorioamnionitis; fetal and neonatal outcomes (e.g. birthweight; neonatal death; ventilatory support; necrotizing enterocolitis; proven sepsis).
Other bias	Low risk	Groups were similar for baseline characteristics, (see table 1, page 2382), although the women in the placebo group had had more previous preterm deliveries.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, caregivers and outcome assessors blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women, caregivers and outcome assessors blinded.

Moghtadaei 2008

Methods	Randomised, double-blind, placebo-controlled trial. Single site, Iran.
Participants	260 women randomised to treatment - number randomised to placebo not reported. Inclusion criteria: women in advanced maternal age – primiparous aged 35 years or more. Exclusion criteria: not reported.
Interventions	Experimental intervention: weekly injections of 17P (250 mg) starting at 16-20 weeks' gestation until 34 weeks. Control/Comparison intervention: matching placebo.
Outcomes	Delivery before 37 weeks. Delivery before 35 weeks. Delivery before 32 weeks. Hypertension. Diabetes. Intrauterine growth restriction. Side effects at injection site.
Notes	

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Moghtadaei 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only abstract available – data limited.
Allocation concealment (selection bias)	Unclear risk	Only abstract available – data limited.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only abstract available – data limited.
Selective reporting (reporting bias)	Unclear risk	Only abstract available – data limited.
Other bias	Unclear risk	Only abstract available – data limited.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only abstract available – data limited – although states “double blind”.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only abstract available – data limited.

Ndoni 2010

Methods	Prospective randomised placebo-controlled study. Single centre, Albania.
Participants	121 women randomised into 3 groups: IM injection prontogest (n = 52); oral progesterone (n = 43); placebo (n = 26). Inclusion criteria: 15-22 weeks' gestation at high risk for preterm labour, hospitalised in the pathology of pregnancy clinic. Exclusion criteria: not stated.
Interventions	Experimental intervention: Group 1: Daily intramuscular injection of 17 alpha-hydroxyprogesterone caproate (Prontogest) (n = 52). Group 2: Oral progesterone (Utrogestan) (n = 43). Control/Comparison intervention: Group 3: Identical-looking placebo (n = 26).
Outcomes	Not reported.
Notes	

Risk of bias

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Ndoni 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States “The participants were separated in three groups..”
Allocation concealment (selection bias)	Unclear risk	Data limited – only reported as an abstract.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data limited – only reported as an abstract.
Selective reporting (reporting bias)	Unclear risk	No outcome data was reported in the abstract.
Other bias	Unclear risk	Data limited – only reported as an abstract.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Data limited – only reported as an abstract.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Data limited – only reported as an abstract.

Norman 2009

Methods	Double-blind randomised placebo-controlled trial. Multicentre, 9 UK NHS hospitals – STOPPIT study (Study Of Progesterone for the Prevention of Preterm Birth In Twins), UK.
Participants	500 women randomised: 250 allocated to progesterone and 250 allocated to placebo. Inclusion criteria: women with twin pregnancy, with gestation and chorionicity established by scan before 20 weeks’ gestation and attending the antenatal clinic during the recruitment period. Exclusion criteria: pregnancy complicated by a recognised structural or chromosomal fetal abnormality at the time of recruitment, or if they had contraindications to progesterone, planned cervical suture, planned elective delivery before 34 weeks’ gestation, or planned intervention for twin-to-twin transfusion before 22 weeks’ gestation. Women with higher multiple pregnancy were also excluded.
Interventions	Experimental intervention: daily vaginal progesterone gel 90 mg starting at 24 weeks and 0 days of gestation. Each applicator of intervention contained 1.45 g of gel and delivered 1.125 g of gel containing 8% progesterone Control/Comparison intervention: placebo gel – administered in the same way as active treatment, daily from 24 weeks' gestation. Each applicator of intervention contained 1.45 g of gel and delivered 1.125 g of gel containing 8% excipients.
Outcomes	Primary: Delivery or intrauterine death before 34 weeks.

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Norman 2009 *(Continued)*

	Secondary: Gestation at delivery. Mode of delivery. Duration of each stage of labour. Safety outcomes: Admission to neonatal unit. Duration of neonatal unit stay. Mother died. Intrauterine death. Neonatal death. Involved or prolonged inpatient maternal hospital admission. Involved persistent/significant maternal disability or incapacity. Life threatening. Chorioamnionitis or intrauterine infection. Congenital anomaly or birth defect. Maternal symptoms. Maternal satisfaction.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We used a randomisation schedule with permuted blocks of randomly mixed sizes to make up treatment packs (either active or placebo) for every patient, which were held in individual hospital pharmacies until use."
Allocation concealment (selection bias)	Low risk	Central allocation from research network – local researcher telephoned the interactive voice response randomisation application at the UK Clinical Research Network registered trials unit to be given a participant number that corresponded to a specific treatment pack.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1483 assessed for eligibility, 983 excluded (did not meet eligibility; declined participation), 500 enrolled and randomised. 250 randomised to each group, 3 lost to follow-up from both treatment and control groups (6 altogether) – because of withdrawal of consent or not traceable after moving out of study area. 3 therefore excluded from each analysis. Analysis was by ITT. 494 mothers and 988 babies remained for the per-protocol analysis.
Selective reporting (reporting bias)	Low risk	All expected outcomes appear to have been reported.

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Norman 2009 *(Continued)*

Other bias	Low risk	Baseline characteristics similar. Multiple pregnancies - adjustment for some neonatal outcomes – give Odds Ratios: admission to neonatal unit; duration of neonatal unit stay.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All study personnel and participants were masked to treatment assignment for the duration of the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

O'Brien 2007

Methods	Method of randomisation: random number table. Allocation concealment: identical appearing sequentially numbered treatment packs. Blinded outcome assessment: yes. Completeness of follow-up: outcome data available for 611 of 659 women randomised (48 (7.3%) women lost to follow-up).
Participants	659 women with a history of prior spontaneous preterm birth. Exclusions: adverse reaction to progesterone; progesterone treatment within 4 weeks of randomisation; medical conditions; suspected genital tract malignancy; thromboembolic disease; fetal anomaly; multiple pregnancy; planned cervical cerclage.
Interventions	Nightly vaginal progesterone gel (90 mg) versus placebo.
Outcomes	Preterm birth less than 32 weeks; Apgar scores, infant birthweight, NICU admission. Secondary analysis of data from O'Brien 2012: infant weight, length and head circumference at 6, 12 and 24 months.
Notes	Trial conducted in 53 centres worldwide.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Adequate; identical appearing treatment packs.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for 611 of 659 women randomised (7.3% women lost to follow-up).
Selective reporting (reporting bias)	Low risk	All expected outcomes reported (preterm birth; maternal, fetal and neonatal outcomes), detailed in table 2, page 692.
Other bias	Low risk	Baseline characteristics similar between groups (see table 1, page 691).

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O'Brien 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, caregivers and outcome assessors blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women, caregivers and outcome assessors blinded.

Papiernik 1970

Methods	Method of randomisation: unclear. Allocation concealment: unclear. Blinded outcome assessment: yes. Completeness of follow-up: outcome data available for 99 women.
Participants	99 women with a "high preterm risk score".
Interventions	Every 3 days intramuscular injection of either 250 mg 17-hydroxyprogesterone caproate or placebo from 28 weeks' gestation until 32 weeks' gestation.
Outcomes	Preterm birth before 37 weeks' gestation; birthweight less than 2.5 kg; perinatal death.
Notes	Trial conducted in Paris, France.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for 99 women randomised.
Selective reporting (reporting bias)	Unclear risk	Not possible to tell from translation.
Other bias	Low risk	From the translation of the paper "Each group studied was similar in age, the number of previous pregnancies, the onset of treatment and risk of preterm birth".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Caregivers and participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded.

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Rai 2009

Methods	Randomised, double-blind, placebo-controlled trial. Single centre, Dept Obstetrics & Gynaecology, University College of Medical Science and Guru Teg Bahadur Hospital, Delhi.
Participants	150 women randomised: 75 allocated to progesterone and 75 allocated to placebo. Inclusion criteria: asymptomatic women aged between 18 and 35 years who were between 18 and 24 weeks of pregnancy, with a history of at least 1 spontaneous preterm delivery (between 20 weeks and 36 weeks plus 6 days) and with a singleton live pregnancy. Exclusion criteria: women with first trimester bleeding, PROM, multiple pregnancy, fetal anomalies or active liver disease were excluded.
Interventions	Experimental intervention: 100 mg oral micronised progesterone – twice a day from recruitment (18-24 weeks) until 36 weeks or delivery. Control/Comparison intervention: placebo - twice a day from recruitment (18-24 weeks) until 36 weeks or delivery.
Outcomes	Primary: Mean prolongation of pregnancy in weeks and days of gestation. Gestational age at delivery: < 28. 28-31 + 6. 32-33 + 6. 34-36 + 6. Secondary: Use of tocolysis. Adverse drug effects. Neonatal outcomes: Neonatal age at delivery, week. Birthweight, g. NICU stay. < 24 hours. 24 hours – 1 week. > 1 week. Apgar score at 1 minute. < 6.

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Rai 2009 *(Continued)*

	> 6. Apgar score at 10 minute. < 6. > 6. Neonatal deaths. Respiratory distress syndrome. RDS with septicaemia. RDS with hyperbilirubinaemia.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated numbers table."
Allocation concealment (selection bias)	Low risk	Central allocation suggested - random number table provided by the Department of Biostatistics.
Incomplete outcome data (attrition bias) All outcomes	Low risk	150 assessed for eligibility, all enrolled and randomised. 75 randomised to each group – and 1 lost to follow-up from each group – 74 analysed in each group. ITT not mentioned – but 74 from each group analysed.
Selective reporting (reporting bias)	Low risk	All expected outcomes appear to have been reported .
Other bias	Low risk	Baseline characteristics similar.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patients and the medical staff were blinded to the study medication allocation until after the last patient had delivered and the study was complete."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Rode 2011

Methods	Randomised, double-blind, placebo-controlled trial.

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Rode 2011 *(Continued)*

	Multicentre, 17 centres in Denmark and Austria.
Participants	677 women were randomised: 334 allocated to progesterone and 343 allocated to placebo Inclusion criteria: women with a live, diamniotic twin pregnancy and chorionicity assessed by ultrasound before 16 weeks' gestation were eligible for recruitment. Exclusion criteria: age < 18 years; known allergy to progesterone or peanuts (active treatment contained peanuts); history of hormone-associated thromboembolic disorders; rupture of membranes; treatment for or signs of twin-to-twin transfusion syndrome; intentional fetal reduction; known major structural or chromosomal fetal abnormality; known or suspected malignancy in genitals or breasts; known liver disease; women with higher-order multiple pregnancies; women who did not speak and understand Danish or German.
Interventions	Experimental intervention: vaginal micronized progesterone pessaries (200 mg) – self-administered daily by participants – starting from 20-24 weeks until 34 weeks' gestation. Control/Comparison intervention: vaginal placebo pessaries (200 mg) – self-administered daily by participants – starting from 20-24 weeks until 34 weeks' gestation.
Outcomes	Primary: Incidence of delivery before 34 + 0 weeks' gestation. Secondary: Delivery before 22, 28, 32, 37 weeks' gestation. Delivery by caesarean section (emergency and planned). Number of liveborn infants. Miscarriage. Intrauterine death. Infant death during delivery. Neonatal death. Death after 28 days. Sudden infant death. Corticosteroids for fetal lung maturation. Tocolytic therapy. Maternal adverse outcomes (gestational diabetes; increased liver enzymes; pre-eclampsia; thromboembolic event). Birthweight < 2500 g. Birthweight < 1500 g. Apgar score < 7 at 5 minutes. Congenital or chromosomal anomalies. Perinatal complication: Hypoglycaemia.

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Rode 2011 *(Continued)*

	Intraventricular haemorrhage. Jaundice. Necrotising enterocolitis. Patent ductus arteriosis. Respiratory distress syndrome. Retinopathy of prematurity. Septicemia. Admission to NICU. CPAP treatment of at least 24 hours. Respirator treatment. Neurophysiological development 6 and 18 months after estimated date of delivery (assessed via Ages and Stages Questionnaire (ASQ).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The Perinatal Epidemiology Research Unit created a randomization sequence with a 1:1 ratio."
Allocation concealment (selection bias)	Low risk	Central allocation suggested - used an interactive voice-response randomisation system: "We stratified by center and chorionicity using an interactive voice-response randomization system at the Perinatal Epidemiology Research Unit. Each local researcher telephoned the randomization system, was given a randomization number that corresponded to a specific treatment box from a given batch".
Incomplete outcome data (attrition bias) All outcomes	Low risk	1507 assessed for eligibility, 219 excluded, 1288 informed about the trial, 526 declined to participate/did not answer, 677 randomised – 343 to each group. 2 from placebo group lost to follow-up - 343 included in analysis for progesterone group and 341 in placebo group. 9 women in the progesterone group and 4 in the placebo group never started treatment because they changed their minds with respect to participation (n = 8), they miscarried or a fetus died in utero (n = 2) or they were withdrawn from the study (n = 3). Analyses based on 343 from progesterone group and 341 from placebo group. States that all analyses were performed according to the ITT principle.

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Rode 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes appear to have been reported.
Other bias	Low risk	Baseline characteristics were comparable for the groups but there were slightly more monochorionic gestations in the placebo group – but the difference was not statistically significant. Multiple pregnancies - adjustments made for infant outcomes – present Relative Risks.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All participants and study personnel were blinded to treatment assignment for the duration of the trial, and the randomization code was not broken before all data had been collected, including the infant follow-up at 18 months of age."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Appears that outcome assessment was blinded – "Only the statistician and the independent Data Monitoring and Safety Committee had access to unblinded data during the study period".

Rouse 2007

Methods	Method of randomisation: the "urn" method of randomisation. Allocation concealment: next of identical appearing treatment injections. Blinded outcome assessment: yes. Completeness of follow-up: 661 women randomised with outcome data available for 655 women.
Participants	661 women with a twin pregnancy; exclusion women with known fetal anomaly, spontaneous fetal death of a fetus after 12 weeks, presumed monoamnionic placenta, suspected twin-twin transfusion syndrome, marked ultrasonographic growth discordance, progesterone or heparin treatment during pregnancy, current or planned cervical cerclage, hypertension, insulin-dependent diabetes, and twin pregnancies that were the result of intentional fetal reduction.
Interventions	Weekly intramuscular injection of either 250 mg 17-hydroxyprogesterone caproate or placebo (castor oil) from 16 - 20 + 3 weeks until 34 completed weeks' gestation, or birth if earlier.
Outcomes	Primary outcome: composite of delivery or death prior to 35 weeks' gestation. Secondary outcomes: randomisation to delivery interval; composite adverse outcomes (retinopathy of prematurity, respiratory distress syndrome, sepsis, necrotising enterocolitis, bronchopulmonary dysplasia, grade III or IV intraventricular haemorrhage, periventricular leucomalacia), birthweight (less than 2500 g and less than 1500 g), 5-minute Apgar score < 7, patent ductus arteriosus, pneumonia, mechanical ventilation, seizures. Preterm birth before 37 weeks' gestation; birthweight less than 2.5 kg; stillbirth; neonatal death; intraventricular haemorrhage; respiratory distress syndrome; bronchopulmonary dysplasia; sepsis; necrotising enterocolitis; retinopathy of prematurity; patent ductus arteriosus.
Notes	Trial conducted by the Maternal-Fetal Medicine Network, USA.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The simple urn method of randomisation with stratification according to clinical center was used by the George Washington University Biostatistical Co-ordinating Center to create a randomization sequence for each center,..."

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Rouse 2007 *(Continued)*

Allocation concealment (selection bias)	Low risk	Adequate; identical appearing treatment packs.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for 655 of 661women (less than 1% loss to follow-up).
Selective reporting (reporting bias)	Low risk	All expected outcomes reported (delivery or fetal death before 35 weeks' gestation; other obstetric and neonatal outcomes) see table 2 and 3.
Other bias	Unclear risk	"Baseline demographic data were similar in the two study groups" (see table 1). Multiple pregnancies - no adjustment in analysis apparent.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, caregivers and outcome assessors blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women, caregivers and outcome assessors blinded.

Rozenberg 2012

Methods	Open-label randomised controlled trial. Multicentre, 13 French university hospitals.
Participants	188 women randomised. Inclusion criteria: women with singleton pregnancies admitted at 24 + 0 through 31 + 6 weeks of gestation with a cervical length < 25 mm for an episode of preterm labour that was then successfully arrested by tocolytic treatment. A course of betamethasone 12 mg, repeated after 24 hours, was given intramuscularly in all patients. Exclusion criteria: cervical dilatation > 3cm, chorioamnionitis, fetal heart rate abnormalities, placenta previa, adruptio placentae, PROM, polyhydramnios, IUGR, pregnancy-related hypertension or pre-eclampsia, maternal or fetal condition requiring immediate delivery, anticonvulsive treatment or participation in any other trial.
Interventions	Experimental intervention: 500 mg of intramuscular 17 alpha-hydroxyprogesterone caproate (17 P) started after tocolysis ended and repeated twice weekly until 36 weeks or until preterm delivery. Control/Comparison intervention: no treatment with 17P. Additional management in the 2 arms was left to the discretion of the attending physician, except that progesterone was not allowed in the control group.
Outcomes	Time from randomisation to delivery, preterm delivery before 37, 34 and 32 weeks, readmissions for preterm labour, NICU, birthweight, respiratory distress, bronchopulmonary dysplasia, necrotising enterocolitis, periventricular leucomalacia, perinatal death, severe maternal or neonatal adverse effect.
Notes	

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Rozenberg 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised, computer-generated randomisation process in a 1:1 ratio.
Allocation concealment (selection bias)	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 188 women were randomised. Outcome data available for 184 women. States “assessed according to the intention-to-treat principle”.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Unclear risk	A subsequent letter to the journal questioned the use of the study medication unless it had been tested for purity and many samples of the medication did not meet FDA specifications. The letter stated that this casts doubt on the findings of any study using 17Pc. The authors confirmed that the study medication was not of questionable quality. Study groups appeared similar at baseline although 12% of the intervention group and 24% of controls had had a previous preterm delivery.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding - trial is described as “open label”.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned. High risk of bias (randomisation to the control group may have affected subsequent treatment and outcome assessment).

Saghafi 2011a

Methods	Described as an interventional study. Obstetrics Clinic of Ghaem Hospital, Mashad University of Medical Sciences, Iran.
Participants	100 women randomised: 50 allocated to progesterone and 50 allocated to placebo. Inclusion criteria: pregnant women with a previous history of preterm delivery who had no contraindication for continuing pregnancy.

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Saghafi 2011a *(Continued)*

	Exclusion criteria: women who had entered the active phase of delivery, cases of preterm PROM, pre-eclampsia, vaginal bleeding, maternal-fetal diseases for which continuation of the pregnancy was dangerous, symptoms of distress, and fetal anomalies.
Interventions	Experimental intervention: 250 mg of intramuscular 17 alpha-hydroxyprogesterone caproate (17 P) weekly from 16 weeks' gestation up to a maximum of 37 weeks' gestation. Control/Comparison intervention: routine perinatal care.
Outcomes	Preterm delivery (< 37 weeks). Apgar score at 1 and 5 minutes (mean values given). Newborn weight (g) mean values. Vaginal delivery (n). Low birthweight neonates (%) – didn't specify what low birthweight was.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described - just says "They were randomly divided into two groups...".
Allocation concealment (selection bias)	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no loss. Outcome data available for all 100 women, 50 randomised to each group.
Selective reporting (reporting bias)	Unclear risk	Data limited – only reported as an abstract.
Other bias	Low risk	States that the 2 groups were similar for age, gravidity, abortions, previous preterm births - see table 1.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.

Senat 2012

Methods	Open-label multicentre, randomised controlled trial in France – 13 French university hospitals.
Participants	165 women randomised and 161 followed up – it was not clear how many were randomised to each group.

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Senat 2012 *(Continued)*

	Inclusion criteria: asymptomatic women with twin pregnancy and cervical length < 25 mm between 20 and 32 weeks of gestation. Exclusion criteria: not reported in the abstract.
Interventions	Experimental intervention: 500 mg intramuscular 17 alpha-hydroxyprogesterone caproate (17P) – twice weekly until 36 weeks or until preterm delivery. Control/Comparison intervention: no 17P. Additional management in the 2 arms was left to the discretion of the attending physician, except that progesterone was not allowed in the control group.
Outcomes	Median time to delivery; delivery before 32 and 34 weeks' gestation.
Notes	Not able to report any outcome data because the number randomised to each group is not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned by computer-generated randomisation process in a 1:1 ratio.
Allocation concealment (selection bias)	Low risk	States – central randomisation. "A centralised, computer generated randomised process in a 1:1 ratio."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear – limited data reported as only an abstract.
Selective reporting (reporting bias)	Unclear risk	Unclear – limited data reported as only an abstract.
Other bias	Unclear risk	Unclear – limited data reported as only an abstract.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as an "open label trial".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Described as an "open label trial".

Serra 2013

Methods	3-arm RCT in 5 centres in Spain, individual randomisation.
Participants	294 women attending 1 of 5 university hospital centres in Spain between December 2005 and January 2008. Inclusion criteria: women were recruited at 11-13 weeks' gestation. If they had previously been treated with vaginal progesterone it was stopped. Women were 18 years or more, dichorionic, diamniotic twin pregnancy.

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Serra 2013 *(Continued)*

	Exclusion criteria: singleton pregnancy, mono-chorionic twin pregnancies, triplets or higher multiple pregnancies, elective cervical cerclage before 14 weeks' gestation, history of hepatic problems, pregnancy cholestasis, abnormal liver or kidney function, allergy to peanuts or study medication, recurrent vaginal bleeding or infection, fetal anomalies, alcohol or illicit drug use and smoking more than 10 cigarettes per day.
Interventions	Intervention: 1. 200 mg vaginal progesterone self-inserted daily at bedtime. (98 women). 2. 400 mg vaginal progesterone self-inserted daily at bedtime (98 women). 3. (control) placebo vaginal pessaries self-inserted daily at bedtime (98 women). All women were provided with specially manufactured identical looking pessaries, 2 to be administered each evening. Total number randomised: n = 294.
Outcomes	Preterm birth rate < 37 weeks of gestation; early preterm birth rate < 34, 32, 28 weeks of gestation; need for tocolytic treatment; steroid treatment; rate of preterm premature rupture of membranes < 37 weeks of gestation; cervical length measurements at 20, 24, 28 weeks of gestation; perinatal mortality and morbidity; caesarean section. Local tolerance to the treatment; number of serious systemic adverse effects. Perinatal outcomes: short-term neonatal morbidity (respiratory distress syndrome; pneumonia; early onset sepsis; seizures; graded III-IV intraventricular haemorrhage; stage II-II necrotising enterocolitis; and/or patent duct arteriosus). Long-term neonatal morbidity included: broncho-pulmonary dysplasia; periventricular leucomalacia; and/or severe retinopathy of prematurity. Birthweight < 2500 g; 5 minute Apgar score; major congenital malformation; admission to NICU; mechanical ventilation; neonatal death.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Randomisation was performed by computer (SPSS Random Number Generator, using a randomisation sequence 1:1:1 ratio (blocks of nine, with no stratification).”
Allocation concealment (selection bias)	Low risk	Central allocation “An external monitoring centre provided a randomisation code number for each pregnant woman” “The medication was given at each visit by the hospital pharmacy department."
Incomplete outcome data (attrition bias) All outcomes	Low risk	It was stated that an ITT analysis was carried out. There was very little loss to follow-up. 294 randomised at 20 weeks. 290 analysed – analysed as ITT. Placebo group – n = 98, n = 10 discontinued study, n = 2 lost to follow-up, 96 analysed 200 mg progesterone group = n = 98, n = 11 discontinued study, n = 1 lost to follow-up, 97 analysed. 400 mg progesterone group = n = 98, n = 10 discontinued study, n = 1 lost to follow-up, 97 analysed.

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Serra 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Most expected outcomes reported upon. However – individual outcome results for short-term and long-term neonatal morbidity were not reported, e.g. respiratory distress syndrome, periventricular leucomalacia.
Other bias	Unclear risk	Baseline characteristics similar. Management may have differed in the 5 participating centres although this was not clear. Groups appeared similar at baseline.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and staff were blinded. Medication packs were coded and contained identical appearing pessaries.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was reported that all study personnel were blind to treatment allocation for the duration of the project.

Sharami 2010

Methods	Described as placebo-controlled double-blind RCT. Alzhara Hospital, Iran. Recruitment between 2007 and 2009.
Participants	Inclusion criteria:173 randomised. Women with singleton pregnancies, gestational age 28-36 weeks admitted with threatened preterm labour successfully treated with tocolysis with intact membranes and less than 2cm cervical dilatation. Exclusion criteria: patients with intrauterine infection, vaginal bleeding, pre-eclampsia, urinary tract infection, intrauterine growth retardation, hypertension and heart disease, dilatation ≥ 2 cm, fetal distress and fetal abnormalities.
Interventions	Intervention: n = 86 women. 200 mg vaginal progesterone daily until 36 weeks' gestation. Control/comparison intervention: n = 87 women. Placebo vaginal suppositories until 36 weeks' gestation. All patients (in both groups) received 12 mg betamethasone and antibiotic prophylaxis and advised to restrict physical activity.
Outcomes	Primary: Time until delivery (latency time) PTB before 34 and 37 weeks of gestation Secondary: Selected maternal and neonatal outcomes including nausea, headache, pre-eclampsia, PROM, chorioamnionitis, post-partum haemorrhage for maternal complications and birth weight, Apgar score, admission to the NICU, fetal death, neonatal death, RDS, sepsis, and intraventricular haemorrhage (IVH).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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Sharami 2010 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Just states, "Random block allocation method" – no other details.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	270 eligible, 97 women delivered within 48 hours, a total of 173 randomised. Placebo group – n = 87, n = 4 lost to follow-up, 83 completed follow-up – 83 included in analysis. Progesterone group = n = 86, n = 6 lost to follow-up, 80 completed follow-up – 80 included in analysis.
Selective reporting (reporting bias)	Unclear risk	Not clear. Several outcomes stated as secondary outcomes in the methods were not reported (this may have been because there were no cases but this was not stated, e.g. fetal death, intraventricular haemorrhage).
Other bias	Low risk	Baseline characteristics similar.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both patients and physician were blinded to the type of suppositories.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind. Not clear if outcome assessment was blind.

CNS: central nervous system
CPAP: continuous positive airways pressure
ITT: intention-to-treat
ICSI: intracytoplasmic sperm injection
IUGR: intrauterine growth restriction
IVF: in vitro fertilisation
LSCS: lower segment Cesarian section
LMP: last menstrual period
NICU: neonatal intensive care unit
PROM: premature rupture of membranes
PPROM: preterm premature rupture of membranes
PTB:preterm birth
RDS: respiratory distress syndrome
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbott 2012	RCT embedded in a longitudinal study, but comparison of progesterone versus cerclage, so not relevant to this review.
Arikan 2011	Acute treatment – being used as a tocolytic.
Berghella 2010	Women were randomised to cerclage versus no cerclage – not randomised to 17P use or not – stratified at randomisation to intent to use or not use 17P.
Breart 1979	Progesterone administration for prevention of miscarriage.

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Study	Reason for exclusion
Brenner 1962	Progesterone administration for prevention of miscarriage.
Chandiramani 2012	Not clear that this is an RCT and also compares progesterone with cerclage, so not relevant to this review.
Corrado 2002	Progesterone administered after amniocentesis for the prevention of miscarriage.
Hobel 1986	Compares an oral progesterone agent with placebo but the only outcome reported is the rate of preterm birth as a percentage (not able to determine n = in either progesterone or placebo group). Other results reported as experimental group versus control (this allocation is not randomised but based on risk assessment at first and second antenatal visit).
Ionescu 2012	Progesterone versus cerclage – so not relevant to this review.
Keeler 2009	Comparison with McDonald cerclage, not placebo – topic of another review.
Le Vine 1964	Quasi-randomised trial.
Rust 2006	Progesterone versus cerclage – so not relevant to this review.
Suvonnakote 1986	Quasi-randomised trial - women were 'divided' into 2 groups (trial group and control group).
Turner 1966	Progesterone administration for prevention of miscarriage.
Walch 2005	Progesterone administration for prevention of miscarriage.
Yemini 1985	Quasi-randomised trial.

RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Coomarasamy 2012

Trial name or title	Progesterone in recurrent miscarriages (PROMISE) study.
Methods	
Participants	1. Women with unexplained recurrent miscarriages (3 or more consecutive first trimester miscarriages). 2. Age 18-39 years at randomisation (likelihood of miscarriages due to chromosomal aberrations is higher in older women; such miscarriages are unlikely to be prevented by progesterone therapy). 3. Spontaneous conception (as confirmed by urinary pregnancy tests). 4. Willing and able to give informed consent.
Interventions	Intervention group: progesterone pessaries (400 mg twice daily) started soon as possible after a positive pregnancy test (and no later than 6 weeks' gestation) and continued to 12 weeks of gestation. Control group: placebo. Total duration of follow-up per participant: 42 weeks.
Outcomes	Primary outcome: live births beyond 24 weeks. Secondary outcomes:

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Coomarasamy 2012 *(Continued)*

	1. Gestation at delivery. 2. Clinical pregnancy at 6-8 weeks. 3. On-going pregnancy at 12 weeks (range 11-13 weeks). 4. Miscarriage rate. 5. Survival at 28 days of neonatal life. 6. Congenital abnormalities with specific examination for genital anomalies. 7. Adverse events.
Starting date	01/05/2009, anticipated end date 0105/2012.
Contact information	Dr Arri Coomarasamy: a.coomarasamy@bham.ac.uk
Notes	

Creasy 2008

Trial name or title	The effect of vaginal progesterone administration in the prevention of preterm birth in women with a short cervix. NCT00615550.
Methods	
Participants	Women with a singleton gestation and a short cervical length by transvaginal ultrasound defined as 10-20 mm.
Interventions	Progesterone 8% vaginal gel, 1.125 g once daily, beginning at 19 0/7 to 23 6/7 weeks' gestation through 36 6/7 weeks' gestation. Placebo vaginal gel, 1.125 g once daily, beginning at 19 0/7 to 23 6/7 weeks' gestation through 36 6/7 weeks' gestation.
Outcomes	Reduction in the frequency of preterm birth (less than or equal to 32 6/7 weeks' gestation.
Starting date	March 2008.
Contact information	Joseph R Parella: jparella@columbialabs.com
Notes	

Crowther 2007

Trial name or title	Progesterone for the prevention of neonatal respiratory distress syndrome (The PROGRESS Study). ISRCTN20269066.
Methods	
Participants	Women with a history of previous spontaneous preterm birth.
Interventions	Daily vaginal progesterone vs placebo.
Outcomes	Neonatal lung disease.
Starting date	October 2005.

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Crowther 2007 *(Continued)*

Contact information	progress@adelaide.edu.au caroline.crowther@adelaide.edu.au
Notes	

Martinez 2007

Trial name or title	Vaginal progesterone to prevent preterm delivery in women with preterm labour. NCT00536003.
Methods	
Participants	Women presenting with symptoms and signs of preterm labour, and evidence of cervical change or positive fetal fibronectin testing.
Interventions	Vaginal progesterone vs placebo.
Outcomes	Preterm birth less than 37 weeks.
Starting date	July 2006.
Contact information	Begona Martinez de Tejada: begona.mdt@bluewin.ch
Notes	

Nassar 2007

Trial name or title	Prevention of preterm delivery in twin pregnancies by 17 alpha hydroxyprogesterone caproate. NCT00141908.
Methods	
Participants	Women with a twin pregnancy.
Interventions	Weekly IM 17OHP vs placebo.
Outcomes	Preterm birth.
Starting date	March 2006.
Contact information	Anwar Nassar: an21@aub.edu.lb
Notes	

Norman 2012

Trial name or title	Trial protocol OPPTIMUM - Does progesterone prophylaxis for the prevention of preterm labour improve outcome?

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Norman 2012 *(Continued)*

	ISRCTN14568373.
Methods	Double-blind randomised placebo controlled trial.
Participants	Women with singleton pregnancy and at high risk of preterm labour.
Interventions	Prophylactice vaginal natural progesterone, 200 mg daily from 22-34 weeks' gestation vs placebo.
Outcomes	Incidence of preterm delivery (before 34 weeks); neonatal outcome (composite of death and major morbidity); childhood cognitive and neurosensory outcomes at 2 years of age.
Starting date	Recruitment began in 2009 and is scheduled to close in Spring 2013.
Contact information	Jane E Norman.
Notes	

Perlitz 2007

Trial name or title	Prevention of recurrent preterm delivery by a natural progesterone agent. NCT00329316.
Methods	
Participants	Women with preterm labour in a prior pregnancy.
Interventions	Daily vaginal progesterone gel vs placebo.
Outcomes	Not specified.
Starting date	Not yet recruiting.
Contact information	Yuri Perlitz: yperlitz@poria.health.gov.il
Notes	

Starkey 2008

Trial name or title	Comparing intramuscular versus vaginal progesterone for prevention of preterm birth. NCT00579553.
Methods	
Participants	Women with singleton pregnancies and history of prior spontaneous preterm birth.
Interventions	Weekly intramuscular injection of 17 alpha hydroxylprogesterone caproate (250 mg) or daily vaginal progesterone (100 mg).
Outcomes	Maternal, fetal and neonatal outcomes.
Starting date	October 2006.

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Starkey 2008 *(Continued)*

Contact information	Christy Zornes: christina-zornes@ouhsc.edu
Notes	

Swaby 2007

Trial name or title	Pilot randomised controlled trial of vaginal progesterone to prevent preterm birth in multiple pregnancy.
Methods	
Participants	Women with a multiple pregnancy.
Interventions	Vaginal progesterone (90 mg) or placebo gel.
Outcomes	Duration of pregnancy.
Starting date	
Contact information	C Swaby. University of Calgary, 1403-29 Street, Calgary, Canada.
Notes	

van Os 2011

Trial name or title	Preventing preterm birth with progesterone: costs and effects of screening low risk women with a singleton pregnancy for short cervical length, the Triple P study. Netherlands Trial Register (NTR): NTR207.
Methods	Cohort study with a randomised placebo-controlled trial embedded. Multicentre, Dutch Obstetric Consortium.
Participants	Inclusion criteria: women with low risk singleton pregnancies at 18-22 weeks' gestation with a short cervix <= 30 mm.
Interventions	Vaginal progesterone 200 mg-capsules of micronised progesterone - vs placebo, taken between 22 and 34 weeks.
Outcomes	Primary outcome: composite poor neonatal outcome (death or severe morbidity): severe respiratory distress syndrome; bronchopulmonary dysplasia; periventricular leucomalacia > grade 1; intracerebral haemorrhage > grade II; necrotising enterocolitis > stage 1; proven sepsis and death before discharge from the nursery. Secondary outcomes: time to delivery; preterm birth rate before 32, 34 and 37 weeks; days of admission in neonatal intensive care unit; maternal morbidity; maternal admission days for preterm labour; costs; growth, physical condition (close examination of genital tract), neurodevelopmental outcome of child at 24 month age; cost-effectiveness of screening for short cervical length.
Starting date	October 2011 - not clear from paper.

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van Os 2011 *(Continued)*

Contact information	Paper reporting study protocol - Melanie A van Os first author - correspondence email: m.vanos@vumc.nl
Notes	

Wood 2007

Trial name or title	Vaginal progesterone versus placebo in multiple pregnancy. NCT00343265.
Methods	
Participants	Women with a multiple pregnancy.
Interventions	Daily vaginal progesterone gel vs placebo.
Outcomes	Primary: gestational age.
Starting date	June 2006.
Contact information	Stephen Wood: stephen.wood@calgaryhealthregion.ca
Notes	

IM: intramuscular
vs: versus

DATA AND ANALYSES

Comparison 1. Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	6	1453	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.33, 0.75]
1.1 Intramuscular	3	553	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.23, 0.73]
1.2 Vaginal	2	752	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.29]
1.3 Oral	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.12, 1.59]
2 Preterm birth less than 34 weeks	5	602	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.14, 0.69]
2.1 Intramuscular	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Vaginal	4	454	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.10, 0.44]
2.3 Oral	1	148	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.39, 0.90]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Preterm birth less than 37 weeks	10	1750	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.42, 0.74]
3.1 Intramuscular	4	652	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.52, 0.75]
3.2 Vaginal	5	1065	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.29, 0.92]
3.3 Oral	1	33	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.19, 1.11]
4 Threatened preterm labour	2	601	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.47, 1.62]
4.1 Intramuscular	1	459	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.73, 1.87]
4.2 Vaginal	1	142	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.35, 1.11]
5 Spontaneous vaginal delivery	2	200	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.97, 1.18]
5.1 Vaginal	2	200	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.97, 1.18]
6 Caesarean section	3	1170	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.20]
6.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.68, 1.30]
6.2 Vaginal	2	711	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.79, 1.30]
7 Antenatal corticosteroids	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.73, 1.16]
7.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.30]
7.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.26]
8 Antenatal tocolysis	4	1262	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.78, 1.35]
8.1 Intramuscular	2	503	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.72]
8.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.70, 1.74]
8.3 Oral	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.42, 1.35]
9 Infant birthweight less than 2500 g	4	692	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.42, 0.79]
9.1 Intramuscular	3	551	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.49, 0.81]
9.2 Vaginal	1	141	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.07, 0.74]
10 Respiratory distress syndrome	3	1217	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.17, 1.16]
10.1 Intramuscular	1	458	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.38, 1.04]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Vaginal	1	611	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.59, 1.43]
10.3 Oral	1	148	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.03, 0.30]
11 Use of assisted ventilation	3	633	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.18, 0.90]
11.1 Intramuscular	1	459	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.35, 1.01]
11.2 Oral	1	33	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.92]
11.3 Vaginal	1	141	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.07, 0.81]
12 Intraventricular haemorrhage - all grades	3	1211	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.20, 2.46]
12.1 Intramuscular	1	459	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.08, 0.82]
12.2 Vaginal	2	752	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.46, 3.77]
13 Intraventricular haemorrhage - grade III or IV	2	1069	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.21, 11.75]
13.1 Intramuscular	1	458	Risk Ratio (M-H, Fixed, 95% CI)	2.52 [0.12, 52.09]
13.2 Vaginal	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.55]
14 Periventricular leucomalacia	1	141	Risk Ratio (M-H, Fixed, 95% CI)	3.13 [0.13, 75.52]
14.1 Vaginal	1	141	Risk Ratio (M-H, Fixed, 95% CI)	3.13 [0.13, 75.52]
15 Retinopathy of prematurity	1	458	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.15, 1.69]
15.1 Intramuscular	1	458	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.15, 1.69]
16 Necrotising enterocolitis	3	1170	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.10, 0.89]
16.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.03]
16.2 Vaginal	2	711	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.15, 1.92]
17 Neonatal sepsis	3	700	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.08, 2.23]
17.1 Intramuscular	1	459	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.35, 3.59]
17.2 Vaginal	2	241	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 1.01]
18 Patent ductus arteriosus	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.16, 1.18]
18.1 Intramuscular	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.16, 1.18]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19 Intrauterine fetal death	4	1164	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.26, 1.69]
19.1 Intramuscular	3	553	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.14, 1.69]
19.2 Vaginal	1	611	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.33, 4.51]
20 Neonatal death	6	1453	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.27, 0.76]
20.1 Intramuscular	3	553	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.17, 0.87]
20.2 Vaginal	2	752	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.24, 1.18]
20.3 Oral	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.12, 1.59]
21 Developmental delay	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.36, 2.04]
21.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.36, 2.04]
22 Intellectual impairment	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.05, 31.34]
22.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.05, 31.34]
23 Motor Impairment	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.11, 3.76]
23.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.11, 3.76]
24 Visual Impairment	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.16, 4.57]
24.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.16, 4.57]
25 Hearing Impairment	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.09, 1.24]
25.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.09, 1.24]
26 Cerebral palsy	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.48]
26.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.48]
27 Learning difficulties	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.38, 1.92]
27.1 Intramuscular	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.38, 1.92]
28 Height less than 5th centile	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.23, 2.49]
28.1 Intramuscular	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.23, 2.49]
29 Weight less than 5th centile	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.30, 2.05]
29.1 Intramuscular	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.30, 2.05]

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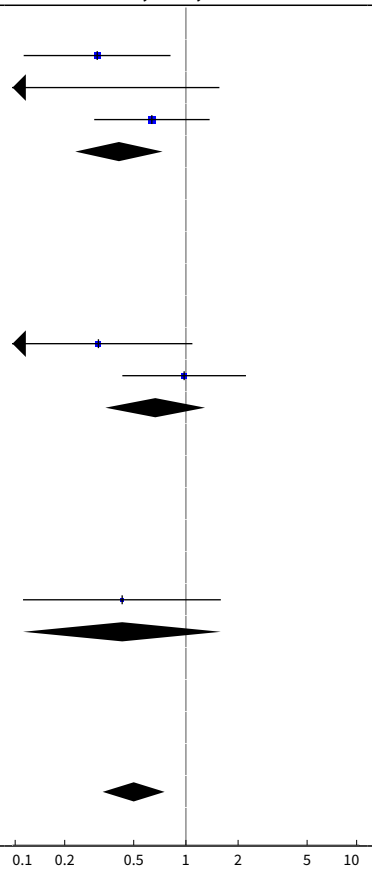
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30 Adverse drug reaction	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.24, 2.15]
30.1 Oral	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.24, 2.15]
31 Pregnancy prolongation (weeks)	1	148	Mean Difference (IV, Fixed, 95% CI)	4.47 [2.15, 6.79]
31.1 Oral	1	148	Mean Difference (IV, Fixed, 95% CI)	4.47 [2.15, 6.79]
32 Apgar score < 7	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.24, 1.25]
32.1 Intramuscular	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.24, 1.25]
33 Admission to neonatal intensive care unit	3	389	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.14, 0.40]
33.1 Oral	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.14, 0.49]
33.2 Vaginal	2	241	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.09, 0.49]
34 Neonatal length of hospital stay (days)	1	33	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-7.67, 5.67]
34.1 Oral	1	33	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-7.67, 5.67]
35 Infant weight at 6 months follow-up (g)	1	436	Mean Difference (IV, Fixed, 95% CI)	29.0 [-209.62, 267.62]
35.1 Vaginal	1	436	Mean Difference (IV, Fixed, 95% CI)	29.0 [-209.62, 267.62]
36 Infant weight at 12 months follow-up (g)	1	379	Mean Difference (IV, Fixed, 95% CI)	-88.0 [-381.48, 205.48]
36.1 Vaginal	1	379	Mean Difference (IV, Fixed, 95% CI)	-88.0 [-381.48, 205.48]
37 Infant weight at 24 months follow-up (g)	1	287	Mean Difference (IV, Fixed, 95% CI)	-40.0 [-482.41, 402.41]
37.1 Vaginal	1	287	Mean Difference (IV, Fixed, 95% CI)	-40.0 [-482.41, 402.41]
38 Infant length at 6 months follow-up (cm)	1	430	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.59, 0.79]
38.1 Vaginal	1	430	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.59, 0.79]
39 Infant length at 12 months follow-up (cm)	1	376	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.80, 0.60]
39.1 Vaginal	1	376	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.80, 0.60]
40 Infant length at 24 months follow-up (cm)	1	284	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.23, 0.83]
40.1 Vaginal	1	284	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.23, 0.83]

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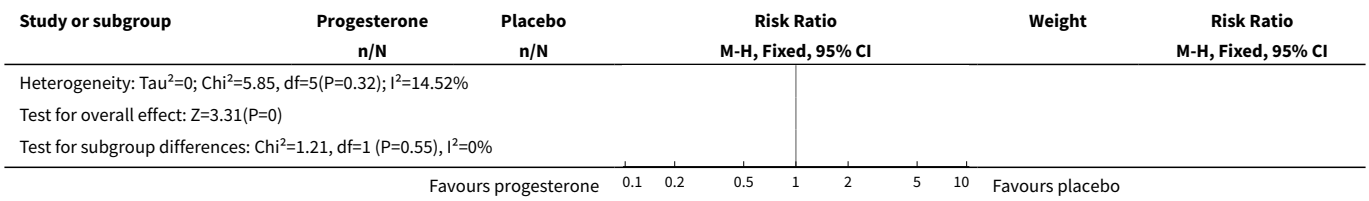
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
41 Infant head circumference at 6 months follow-up (cm)	1	426	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.23, 0.43]
41.1 Vaginal	1	426	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.23, 0.43]
42 Infant head circumference at 12 months follow-up (cm)	1	372	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.26, 0.46]
42.1 Vaginal	1	372	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.26, 0.46]
43 Infant head circumference at 24 months follow-up (cm)	1	264	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.21, 0.61]
43.1 Vaginal	1	264	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.21, 0.61]

Analysis 1.1. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 1 Perinatal mortality.

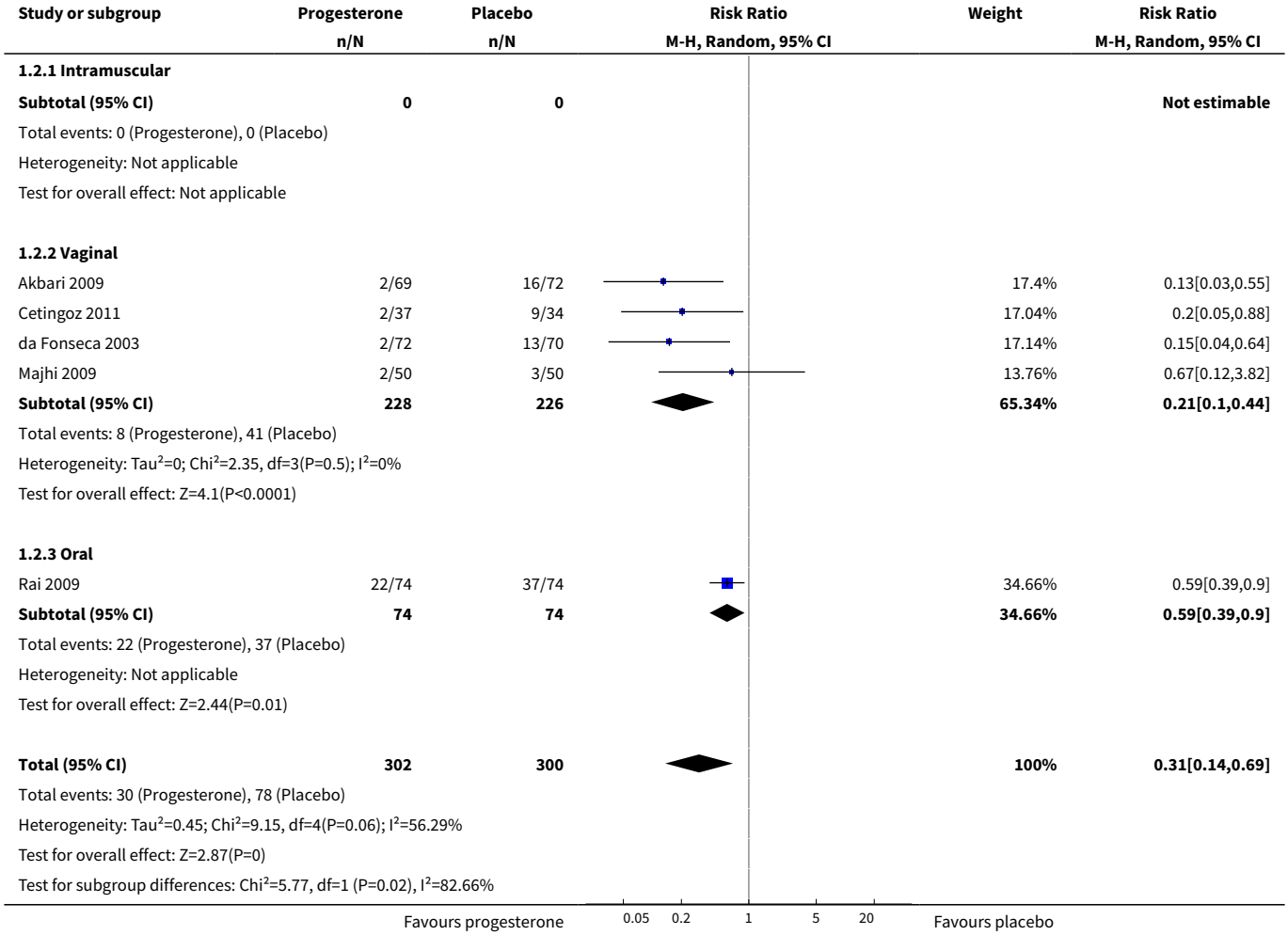
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Intramuscular					
Ibrahim 2010	4/25	13/25		21.04%	0.31[0.12,0.81]
Johnson 1975	0/18	7/26		10.03%	0.09[0.01,1.56]
Meis 2003	14/306	11/153		23.74%	0.64[0.3,1.37]
Subtotal (95% CI)	**349**	**204**		**54.82%**	**0.41[0.23,0.73]**
Total events: 18 (Progesterone), 31 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.65, df=2(P=0.27); I^2=24.41%					
Test for overall effect: Z=3.01(P=0)					
1.1.2 Vaginal					
Akbari 2009	3/69	10/72		15.84%	0.31[0.09,1.09]
O'Brien 2007	11/309	11/302		18.01%	0.98[0.43,2.22]
Subtotal (95% CI)	**378**	**374**		**33.85%**	**0.67[0.34,1.29]**
Total events: 14 (Progesterone), 21 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.25, df=1(P=0.13); I^2=55.48%					
Test for overall effect: Z=1.2(P=0.23)					
1.1.3 Oral					
Rai 2009	3/74	7/74		11.33%	0.43[0.12,1.59]
Subtotal (95% CI)	**74**	**74**		**11.33%**	**0.43[0.12,1.59]**
Total events: 3 (Progesterone), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.26(P=0.21)					
Total (95% CI)	**801**	**652**		**100%**	**0.5[0.33,0.75]**
Total events: 35 (Progesterone), 59 (Placebo)					



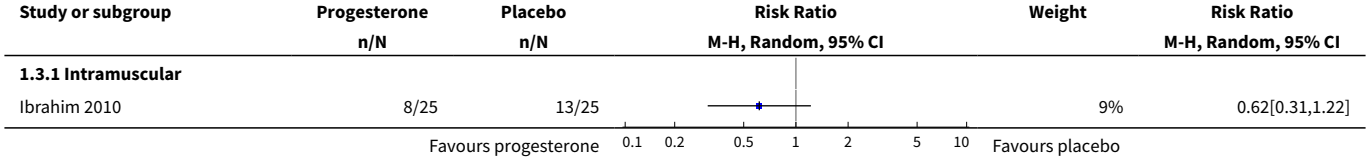
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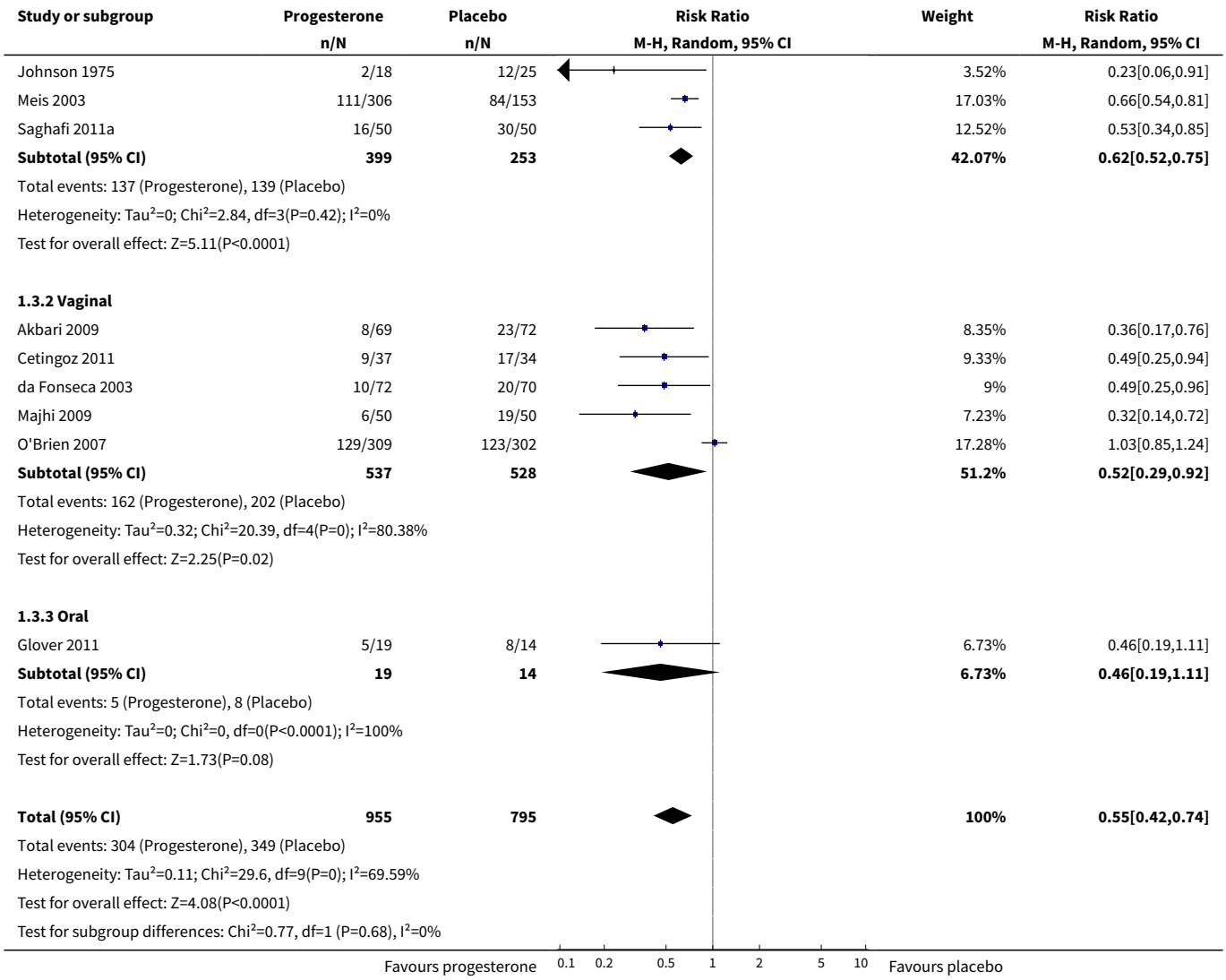
Analysis 1.2. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 2 Preterm birth less than 34 weeks.



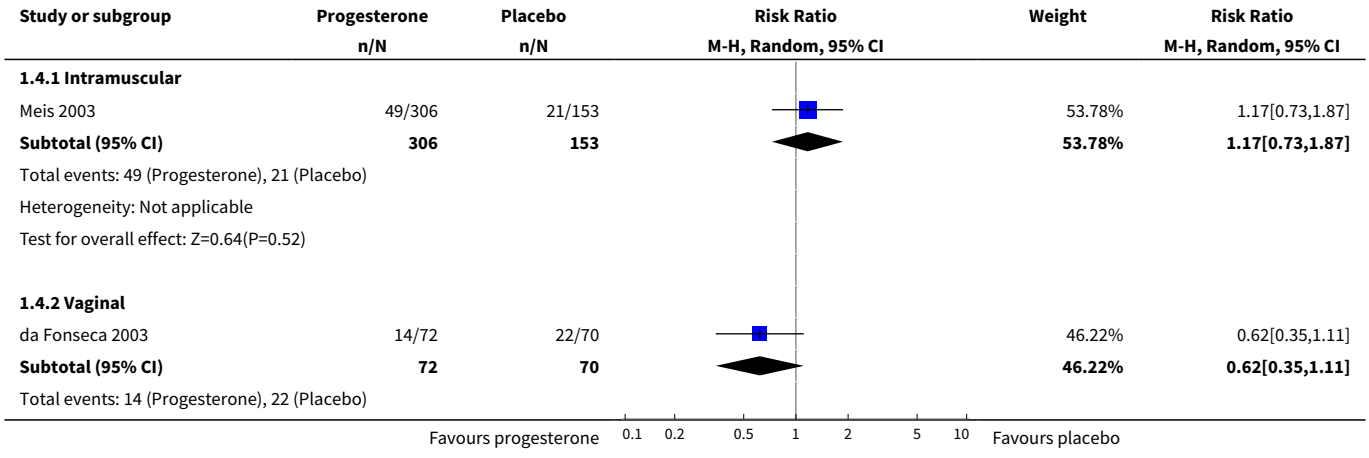
Analysis 1.3. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 3 Preterm birth less than 37 weeks.



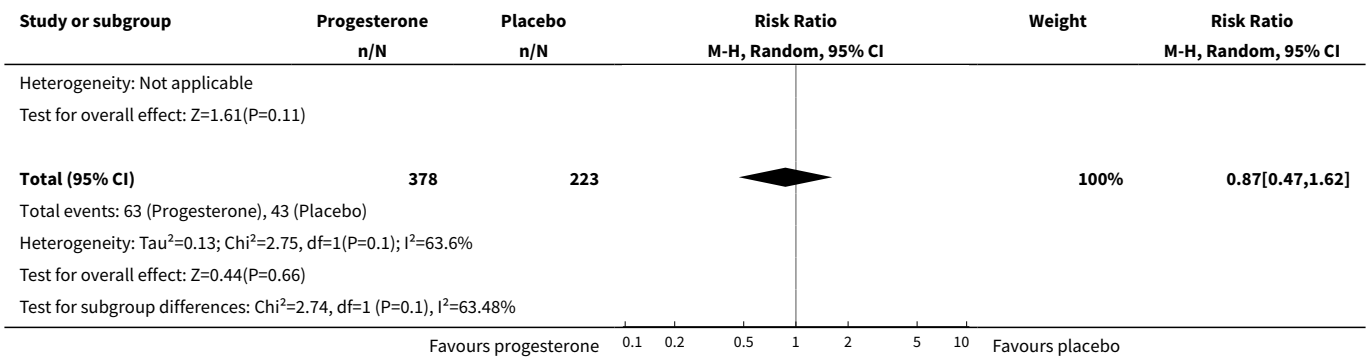
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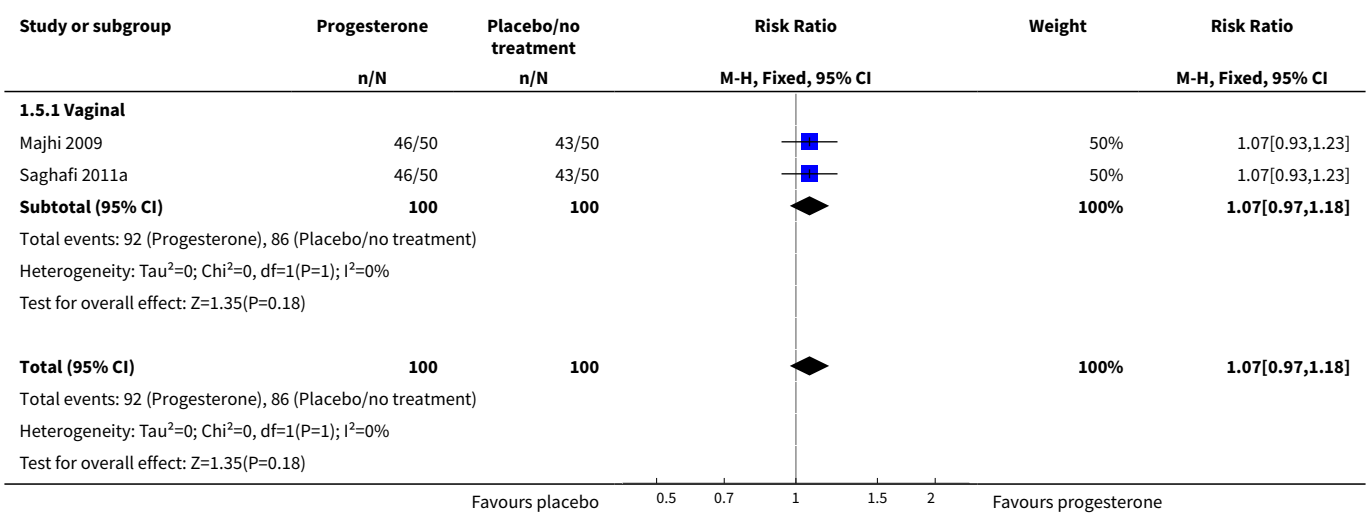
Analysis 1.4. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 4 Threatened preterm labour.



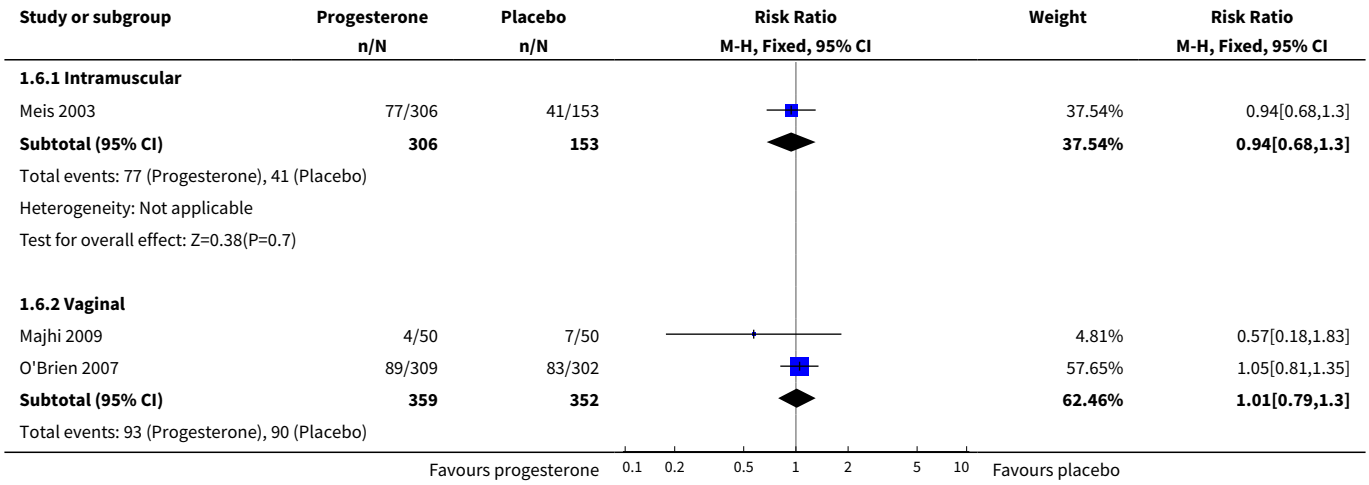
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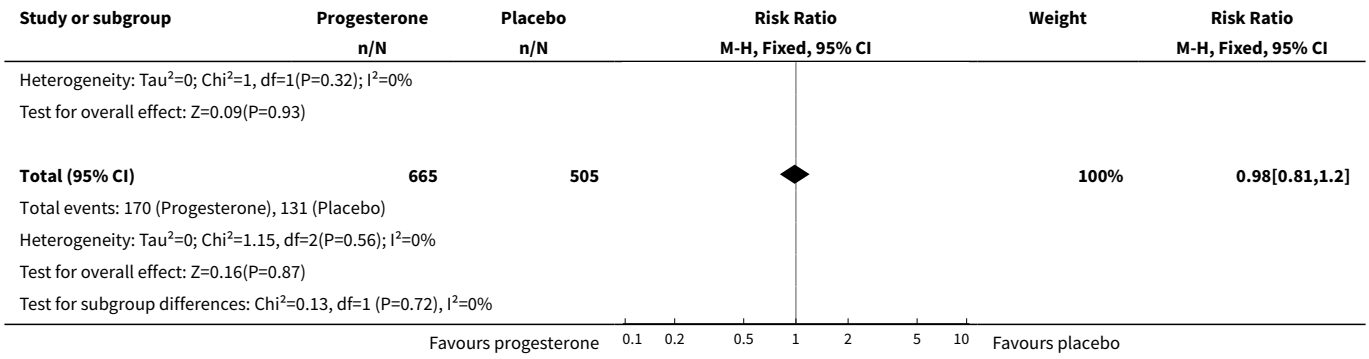
Analysis 1.5. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 5 Spontaneous vaginal delivery.



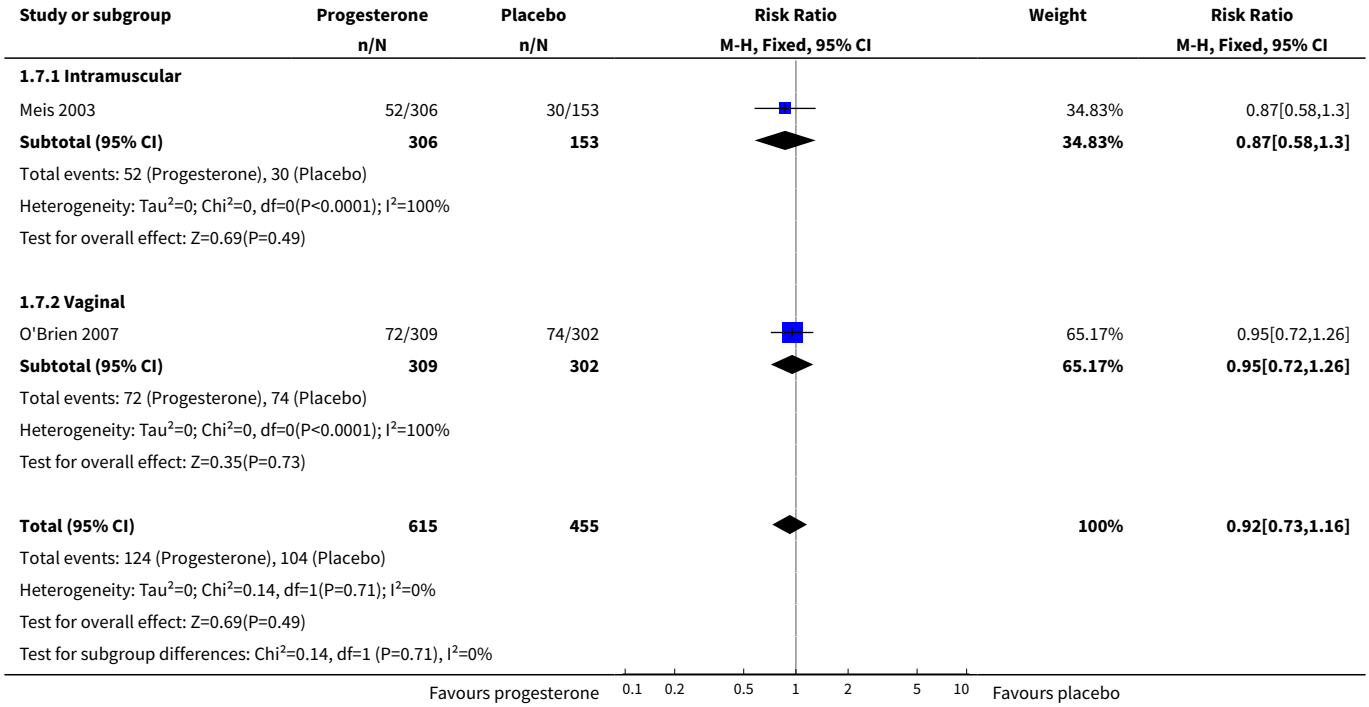
Analysis 1.6. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 6 Caesarean section.



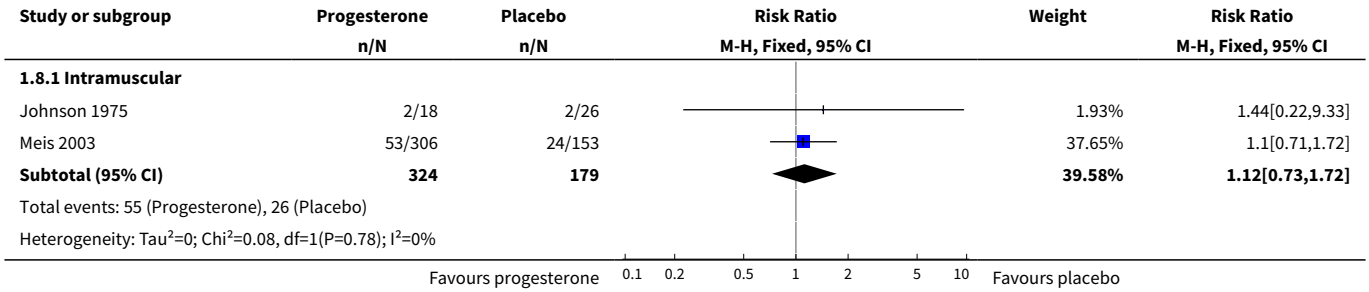
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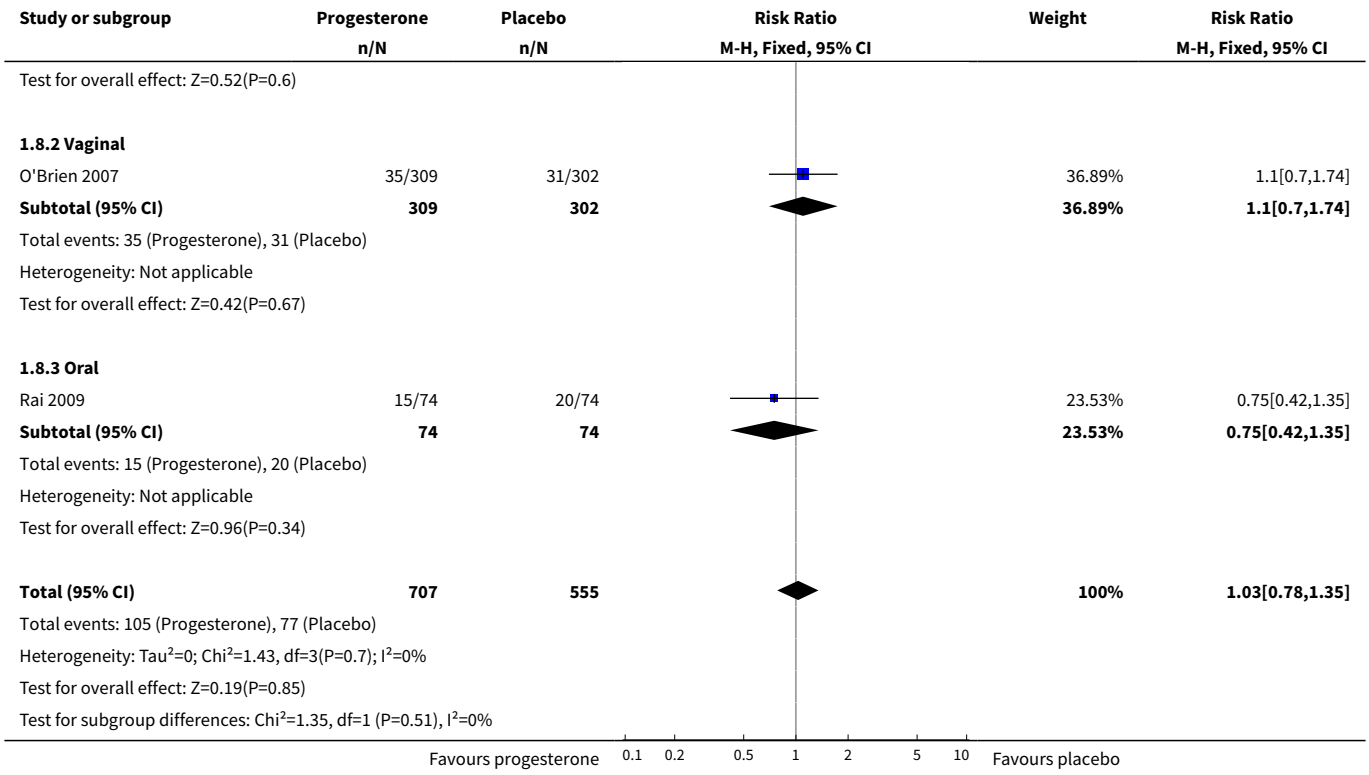
Analysis 1.7. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 7 Antenatal corticosteroids.



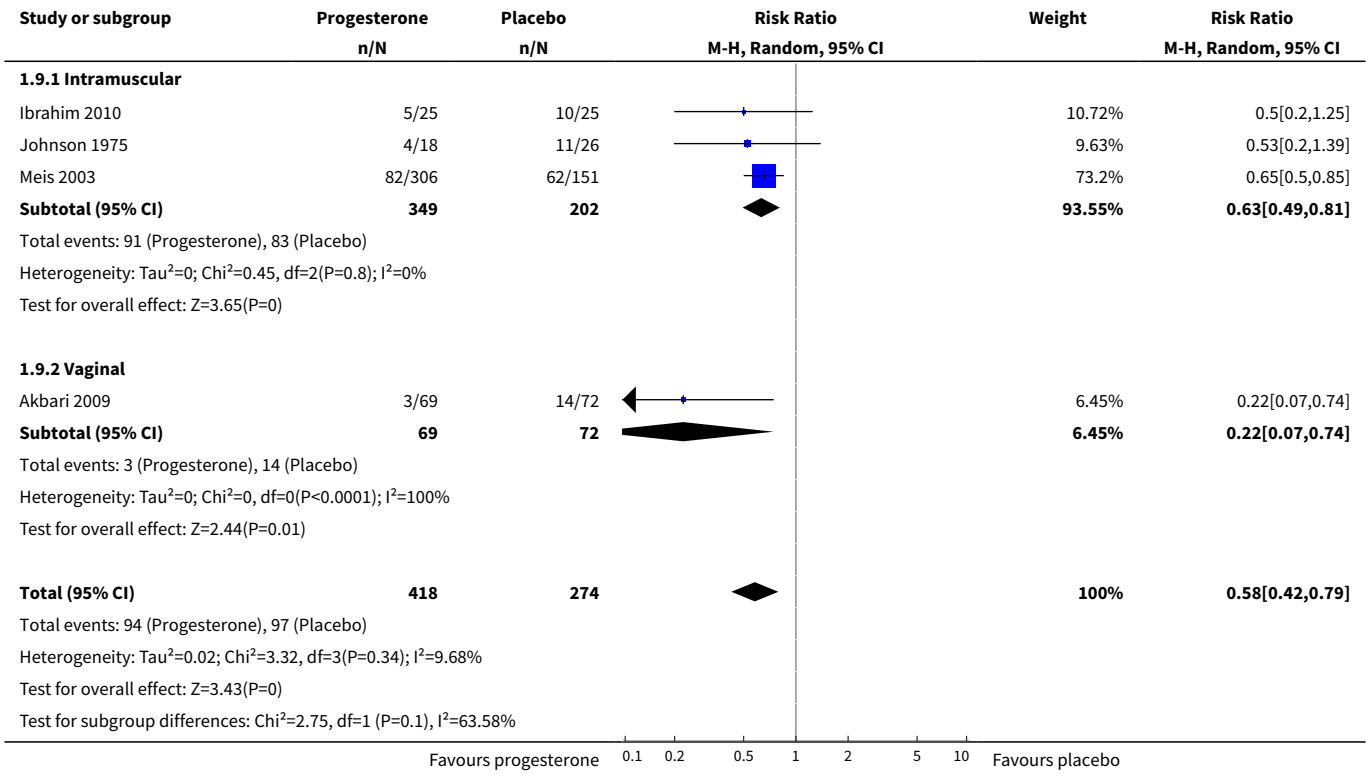
Analysis 1.8. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 8 Antenatal tocolysis.



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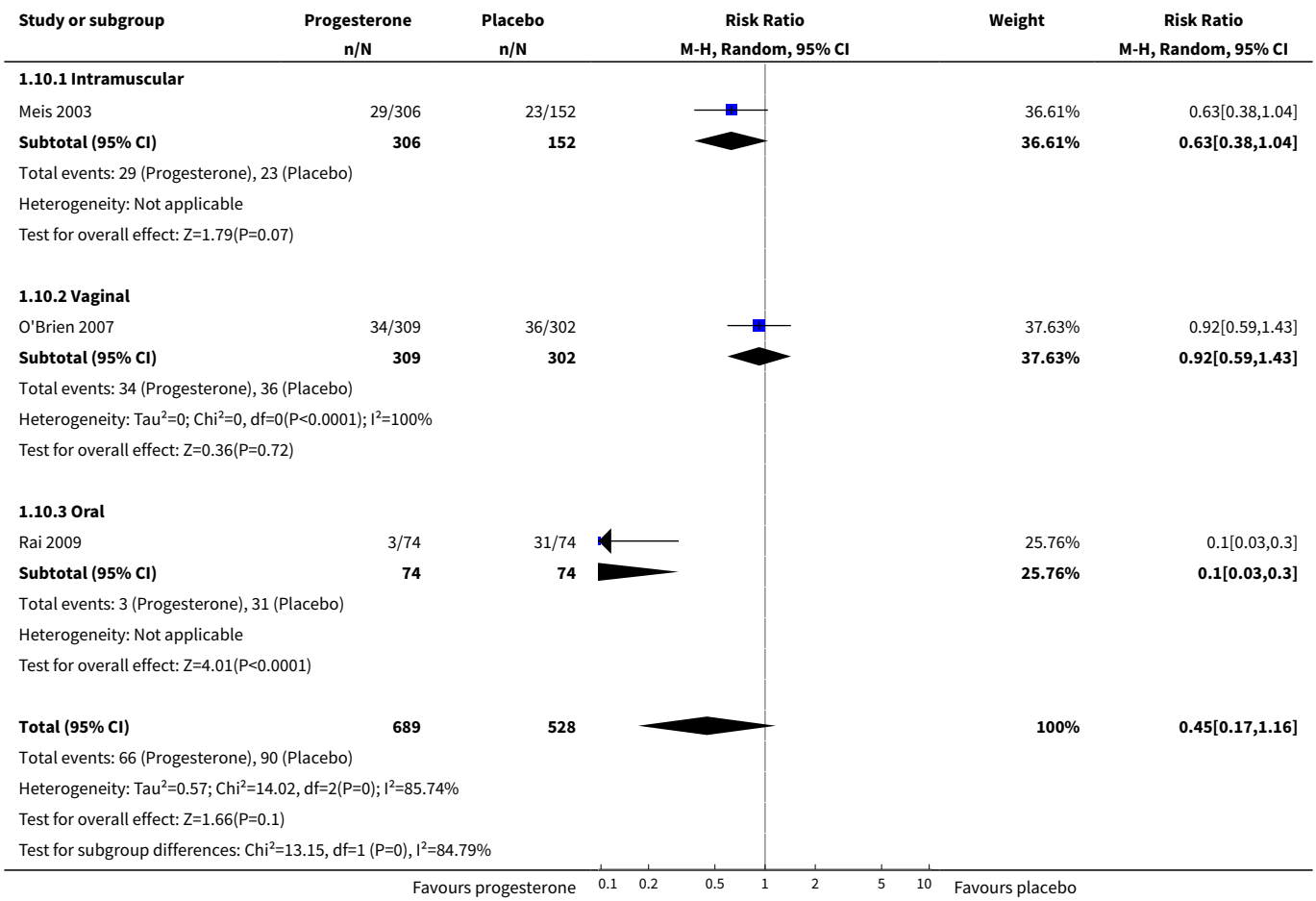


Analysis 1.9. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 9 Infant birthweight less than 2500 g.

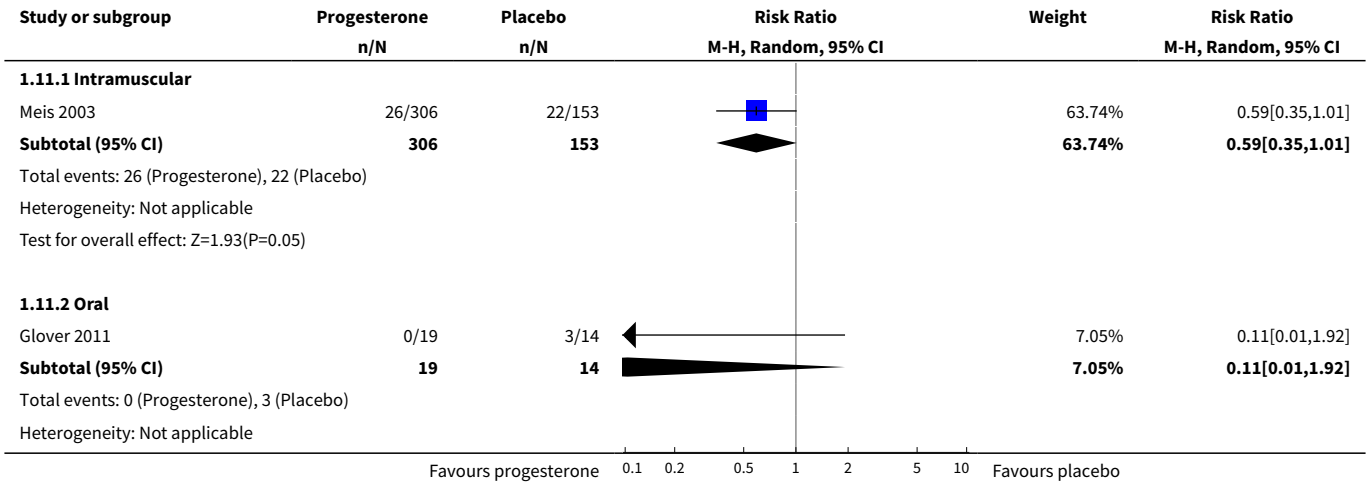


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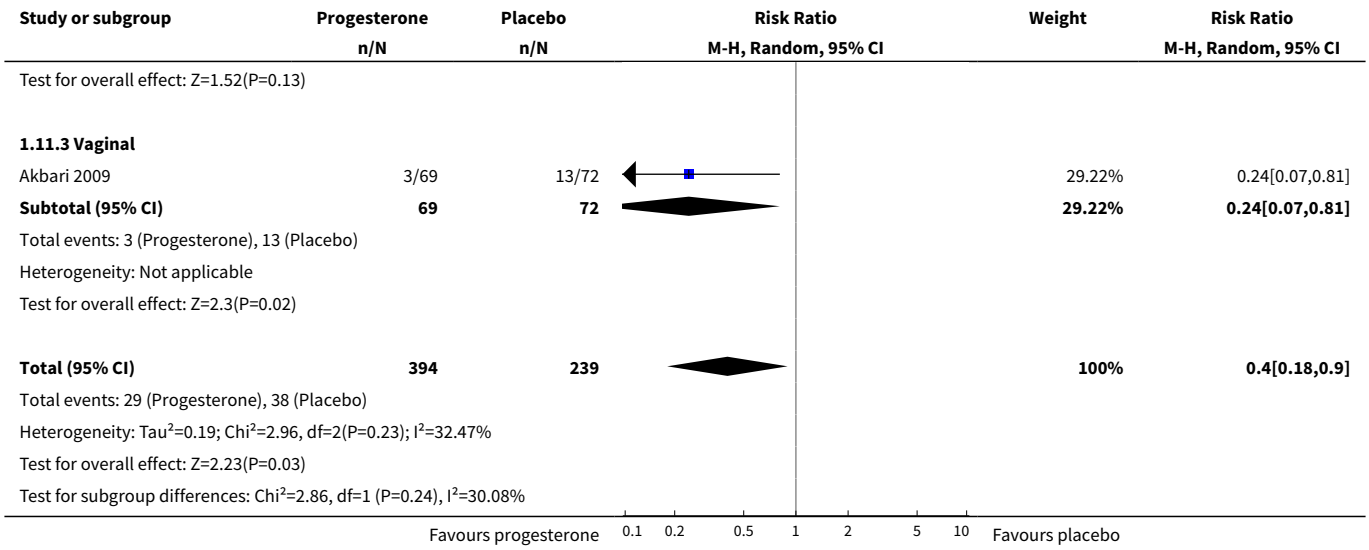
Analysis 1.10. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 10 Respiratory distress syndrome.



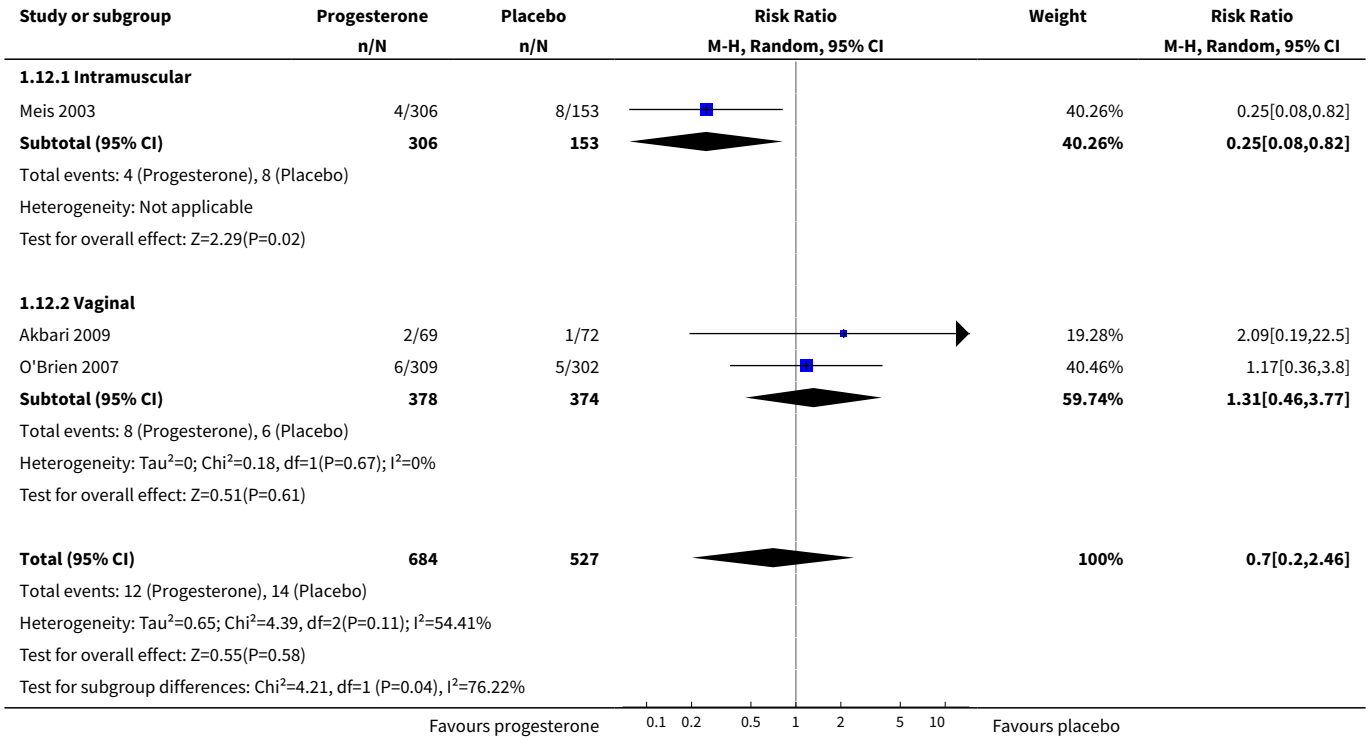
Analysis 1.11. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 11 Use of assisted ventilation.



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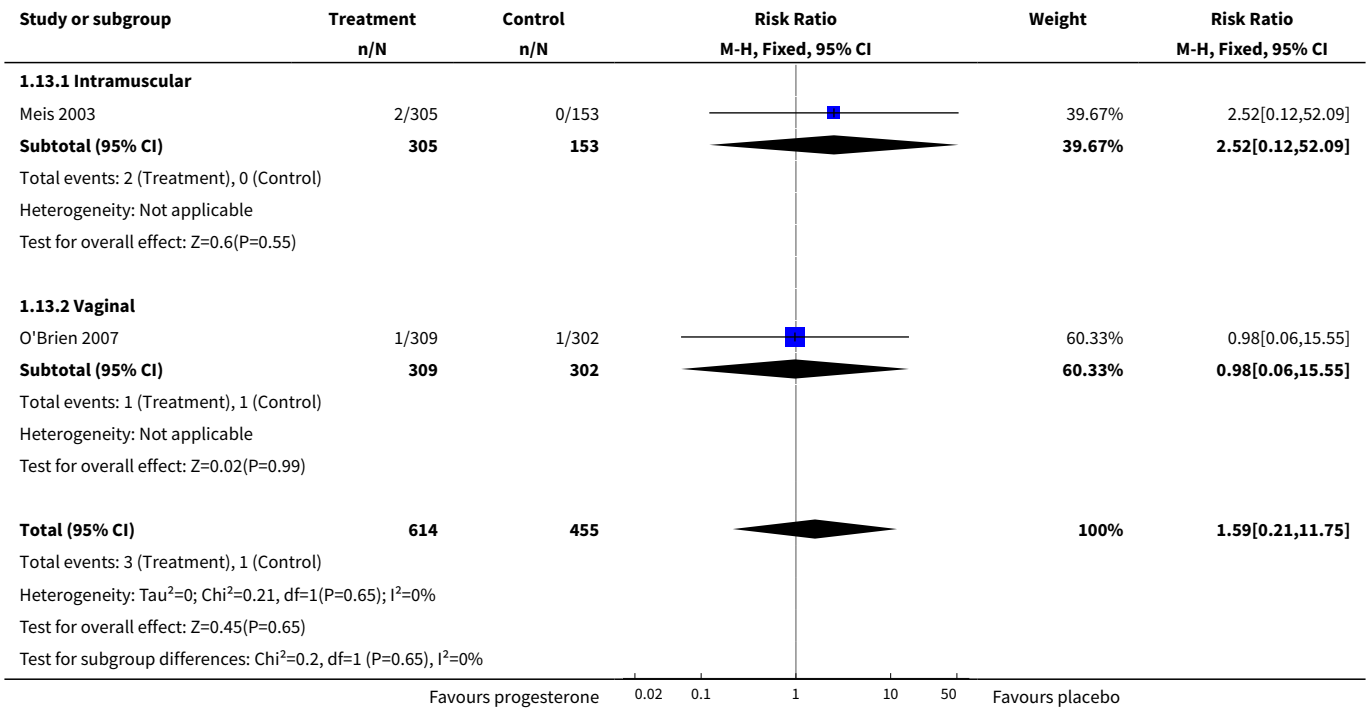


Analysis 1.12. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 12 Intraventricular haemorrhage - all grades.

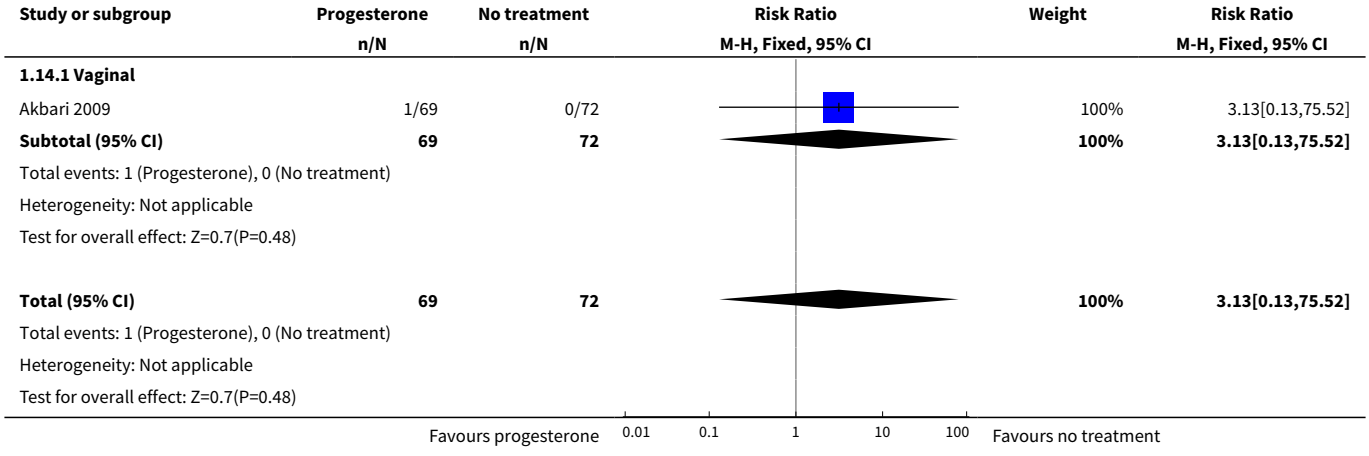


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Analysis 1.13. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 13 Intraventricular haemorrhage - grade III or IV.

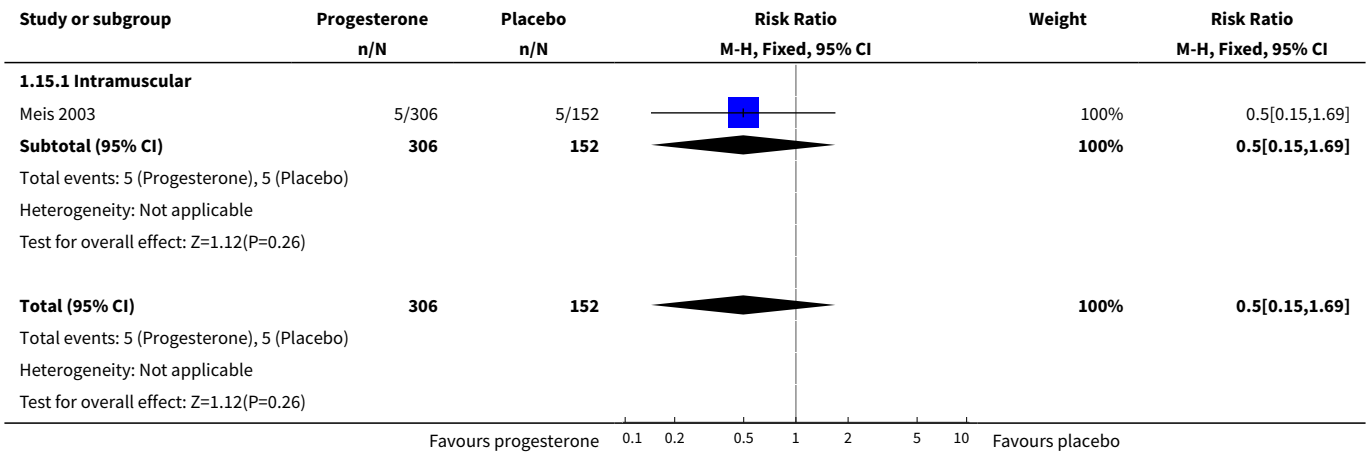


Analysis 1.14. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 14 Periventricular leucomalacia.

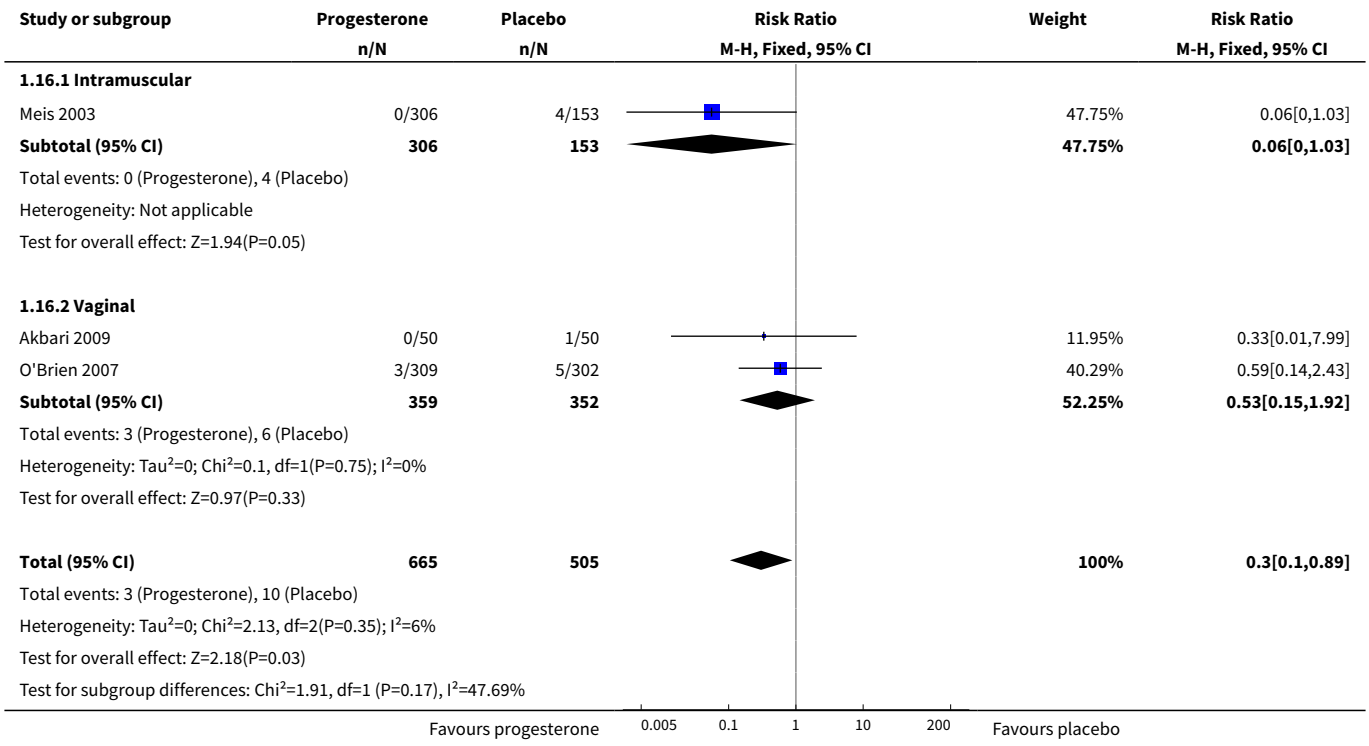


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Analysis 1.15. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 15 Retinopathy of prematurity.



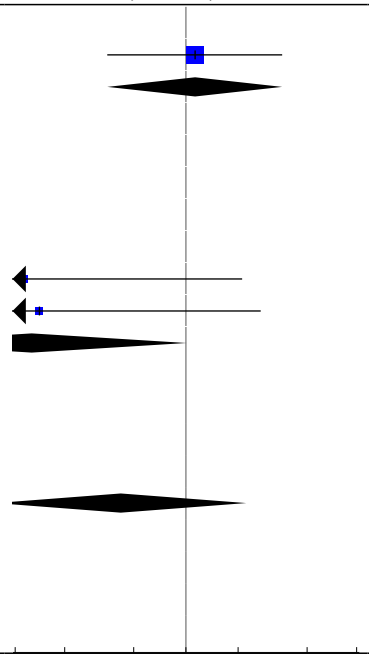
Analysis 1.16. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 16 Necrotising enterocolitis.



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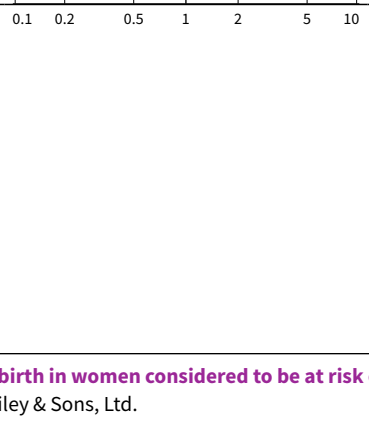
Analysis 1.17. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 17 Neonatal sepsis.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 Intramuscular					
Meis 2003	9/306	4/153		54.69%	1.13[0.35,3.59]
Subtotal (95% CI)	**306**	**153**		**54.69%**	**1.13[0.35,3.59]**
Total events: 9 (Progesterone), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.2(P=0.84)					
1.17.2 Vaginal					
Akbari 2009	0/69	4/72		22.84%	0.12[0.01,2.11]
Majhi 2009	0/50	3/50		22.47%	0.14[0.01,2.7]
Subtotal (95% CI)	**119**	**122**		**45.31%**	**0.13[0.02,1.01]**
Total events: 0 (Progesterone), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=1.95(P=0.05)					
Total (95% CI)	**425**	**275**		**100%**	**0.42[0.08,2.23]**
Total events: 9 (Progesterone), 11 (Placebo)					
Heterogeneity: Tau^2=0.97; Chi^2=3.43, df=2(P=0.18); I^2=41.74%					
Test for overall effect: Z=1.02(P=0.31)					
Test for subgroup differences: Chi^2=3.22, df=1 (P=0.07), I^2=68.96%					



Analysis 1.18. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 18 Patent ductus arteriosus.

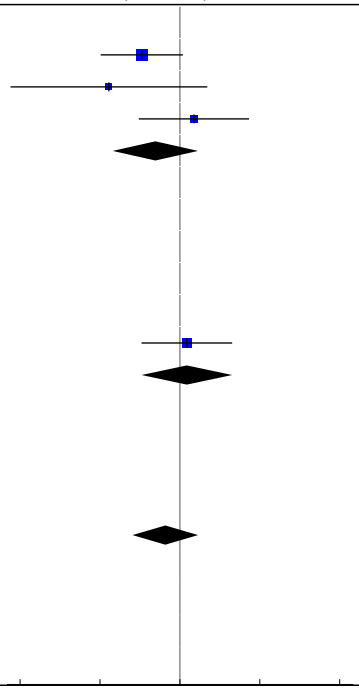
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Intramuscular					
Meis 2003	7/306	8/153		100%	0.44[0.16,1.18]
Subtotal (95% CI)	**306**	**153**		**100%**	**0.44[0.16,1.18]**
Total events: 7 (Progesterone), 8 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.63(P=0.1)					
Total (95% CI)	**306**	**153**		**100%**	**0.44[0.16,1.18]**
Total events: 7 (Progesterone), 8 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.63(P=0.1)					



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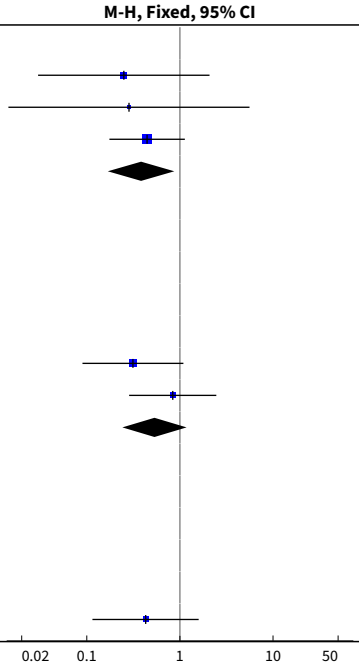
Analysis 1.19. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 19 Intrauterine fetal death.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 Intramuscular					
Ibrahim 2010	3/25	9/25		34.87%	0.33[0.1,1.09]
Johnson 1975	0/18	5/26		9.71%	0.13[0.01,2.2]
Meis 2003	6/306	2/153		24.24%	1.5[0.31,7.34]
Subtotal (95% CI)	**349**	**204**		**68.82%**	**0.49[0.14,1.69]**
Total events: 9 (Progesterone), 16 (Placebo)					
Heterogeneity: Tau^2=0.45; Chi^2=3.17, df=2(P=0.2); I^2=36.97%					
Test for overall effect: Z=1.13(P=0.26)					
1.19.2 Vaginal					
O'Brien 2007	5/309	4/302		31.18%	1.22[0.33,4.51]
Subtotal (95% CI)	**309**	**302**		**31.18%**	**1.22[0.33,4.51]**
Total events: 5 (Progesterone), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.3(P=0.76)					
Total (95% CI)	**658**	**506**		**100%**	**0.66[0.26,1.69]**
Total events: 14 (Progesterone), 20 (Placebo)					
Heterogeneity: Tau^2=0.3; Chi^2=4.46, df=3(P=0.22); I^2=32.74%					
Test for overall effect: Z=0.87(P=0.38)					
Test for subgroup differences: Chi^2=0.98, df=1 (P=0.32), I^2=0%					

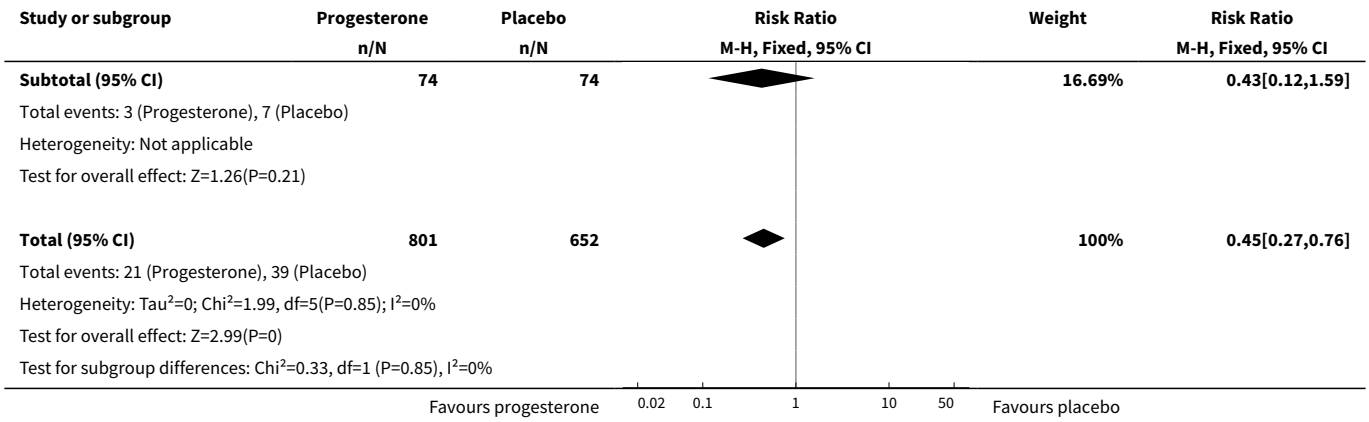


Analysis 1.20. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 20 Neonatal death.

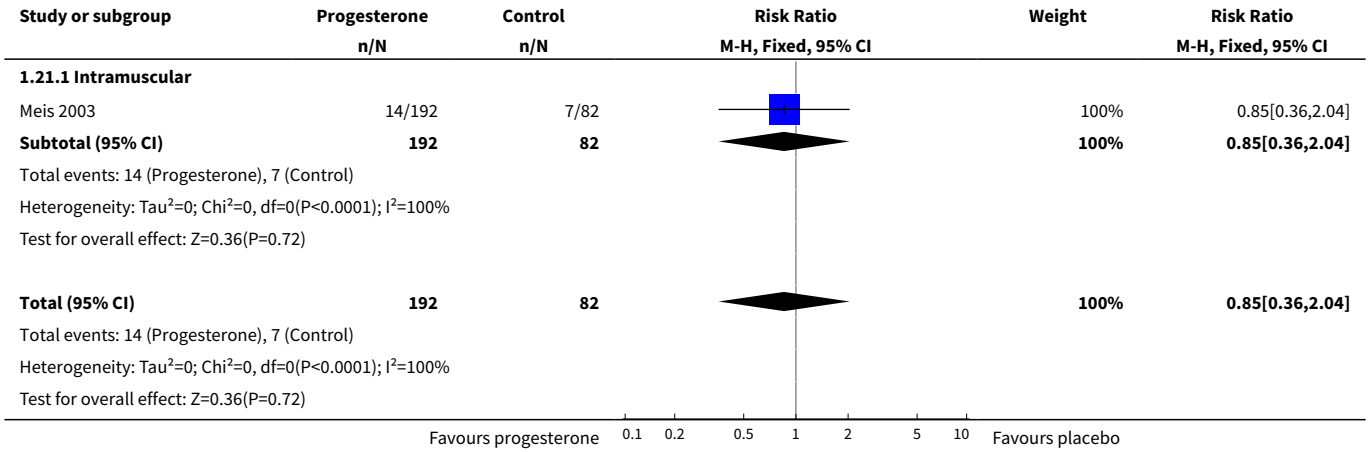
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.20.1 Intramuscular					
Ibrahim 2010	1/25	4/25		9.54%	0.25[0.03,2.08]
Johnson 1975	0/18	2/26		4.93%	0.28[0.01,5.59]
Meis 2003	8/306	9/153		28.62%	0.44[0.17,1.13]
Subtotal (95% CI)	**349**	**204**		**43.08%**	**0.38[0.17,0.87]**
Total events: 9 (Progesterone), 15 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=2(P=0.86); I^2=0%					
Test for overall effect: Z=2.29(P=0.02)					
1.20.2 Vaginal					
Akbari 2009	3/69	10/72		23.34%	0.31[0.09,1.09]
O'Brien 2007	6/309	7/302		16.88%	0.84[0.28,2.46]
Subtotal (95% CI)	**378**	**374**		**40.23%**	**0.53[0.24,1.18]**
Total events: 9 (Progesterone), 17 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.37, df=1(P=0.24); I^2=27.22%					
Test for overall effect: Z=1.55(P=0.12)					
1.20.3 Oral					
Rai 2009	3/74	7/74		16.69%	0.43[0.12,1.59]



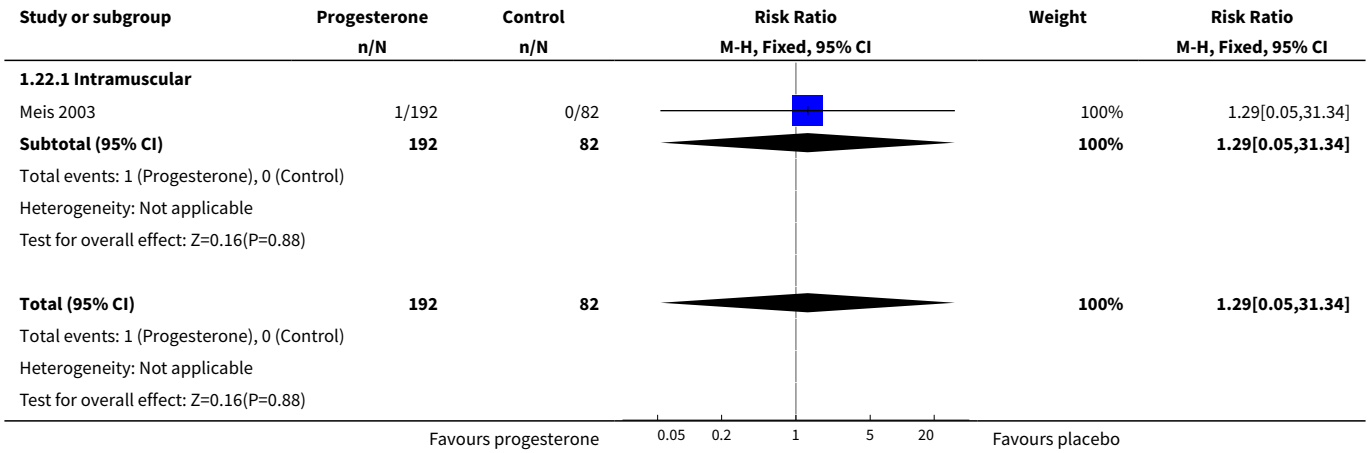
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Analysis 1.21. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 21 Developmental delay.

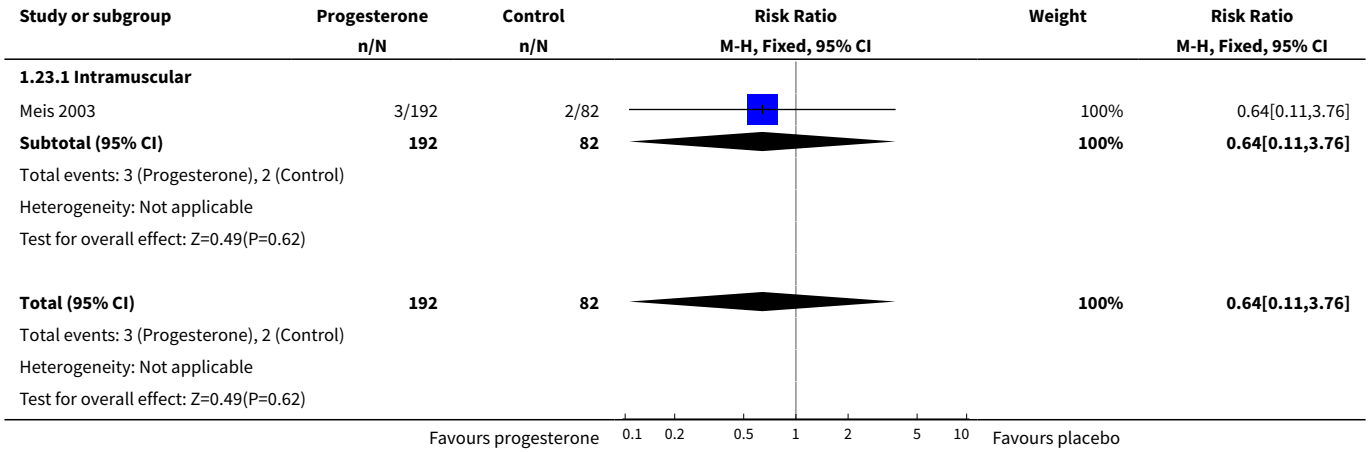


Analysis 1.22. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 22 Intellectual impairment.

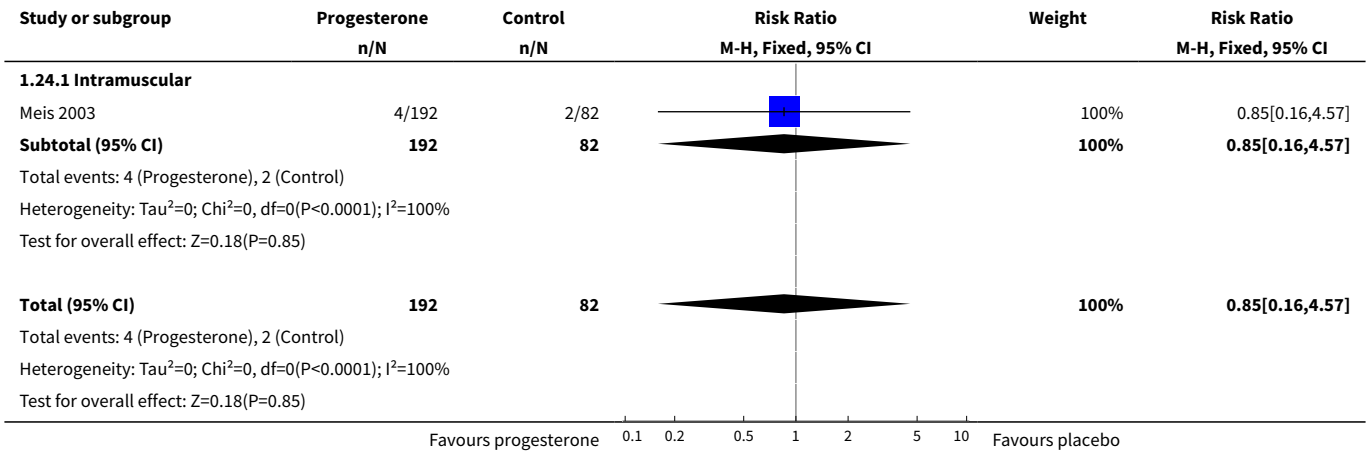


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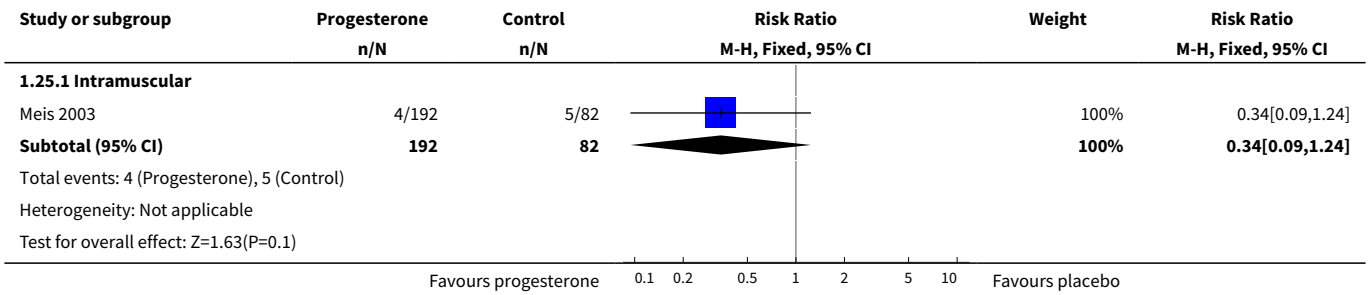
Analysis 1.23. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 23 Motor Impairment.



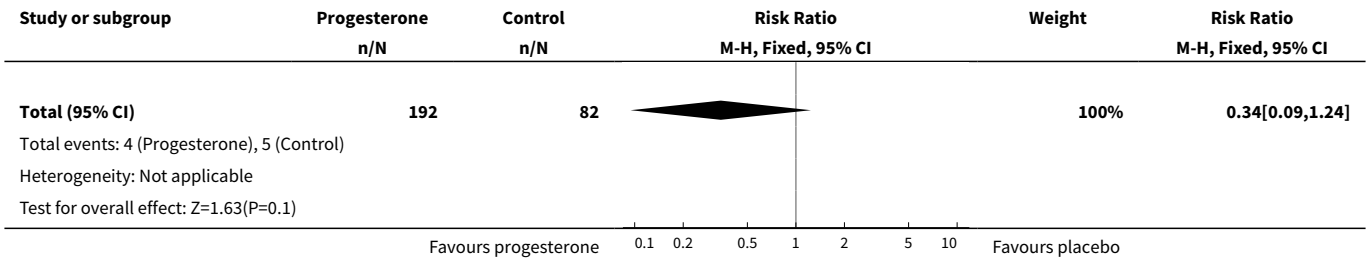
Analysis 1.24. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 24 Visual Impairment.



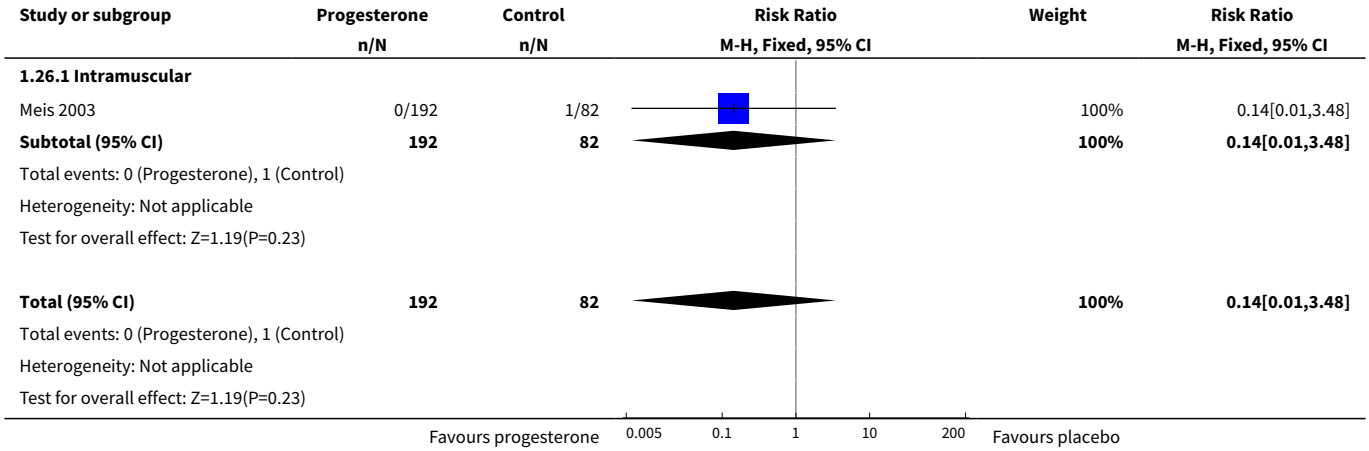
Analysis 1.25. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 25 Hearing Impairment.



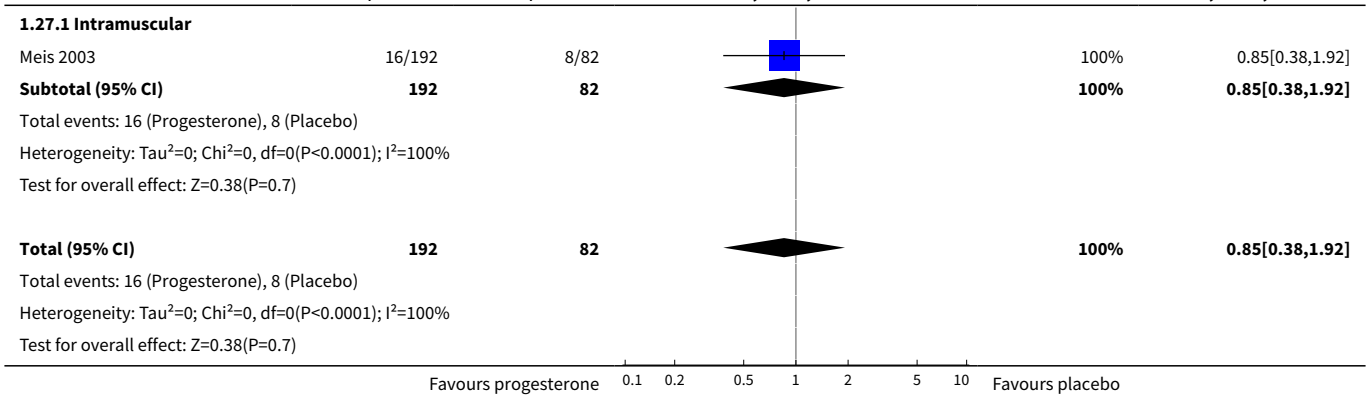
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Analysis 1.26. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 26 Cerebral palsy.

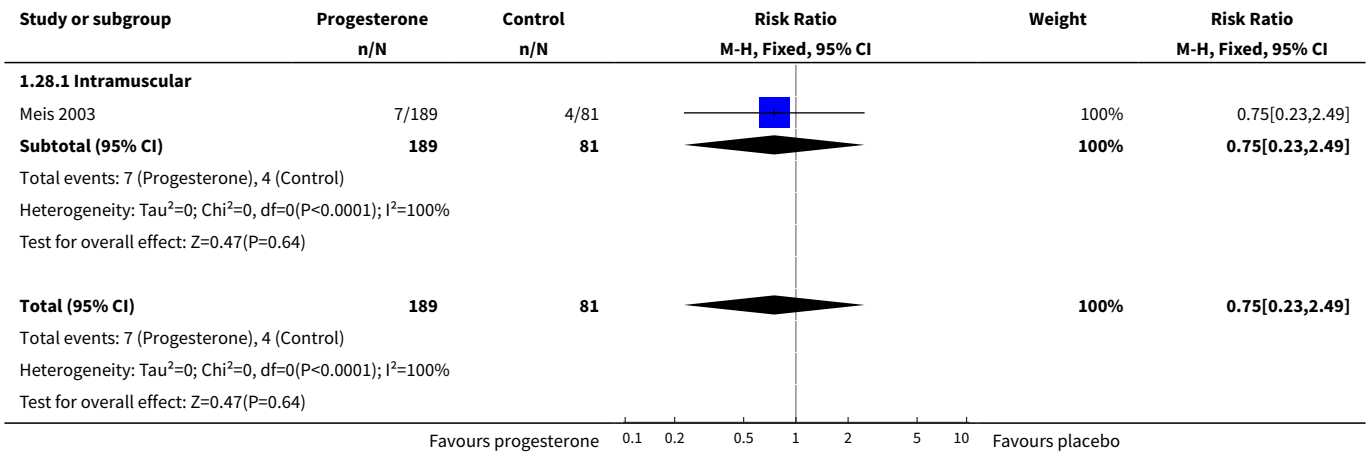


Analysis 1.27. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 27 Learning difficulties.

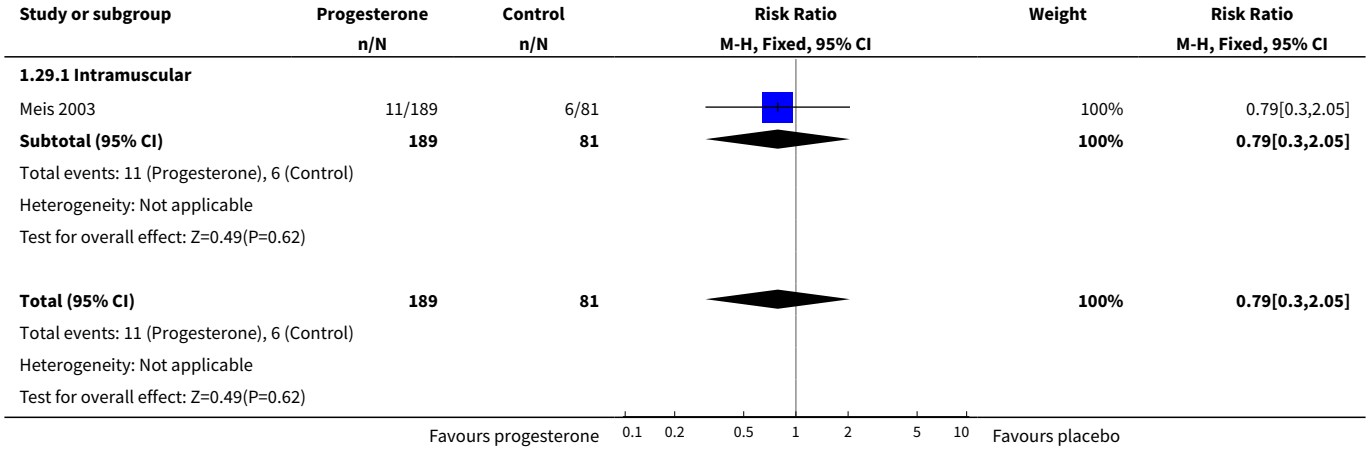


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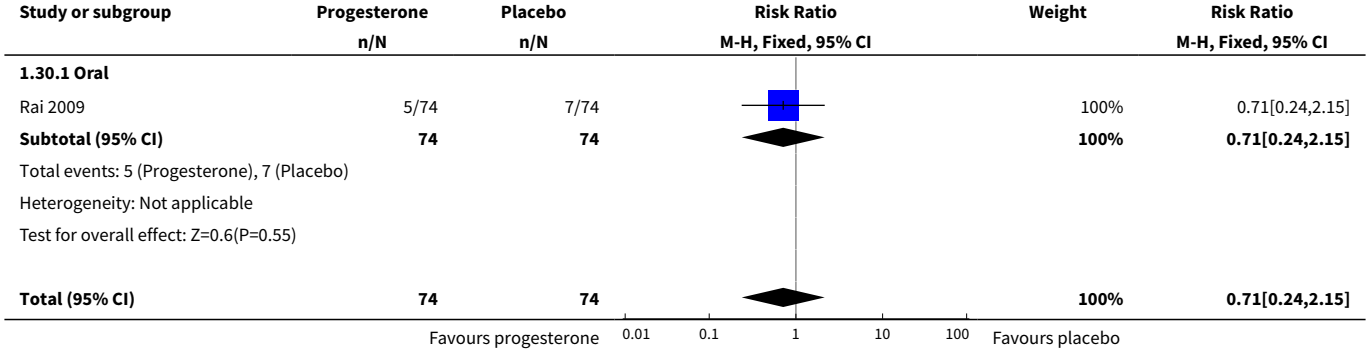
Analysis 1.28. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 28 Height less than 5th centile.



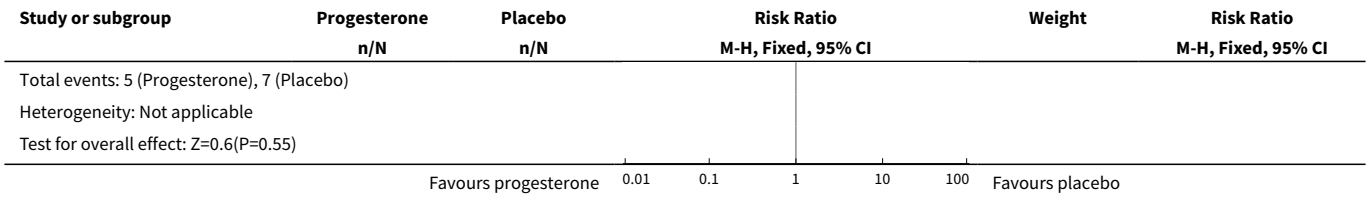
Analysis 1.29. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 29 Weight less than 5th centile.



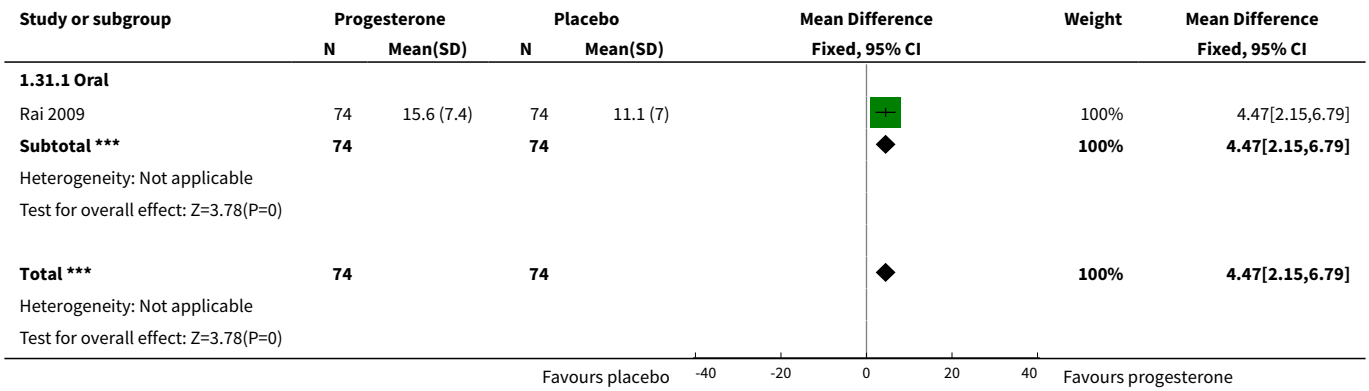
Analysis 1.30. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 30 Adverse drug reaction.



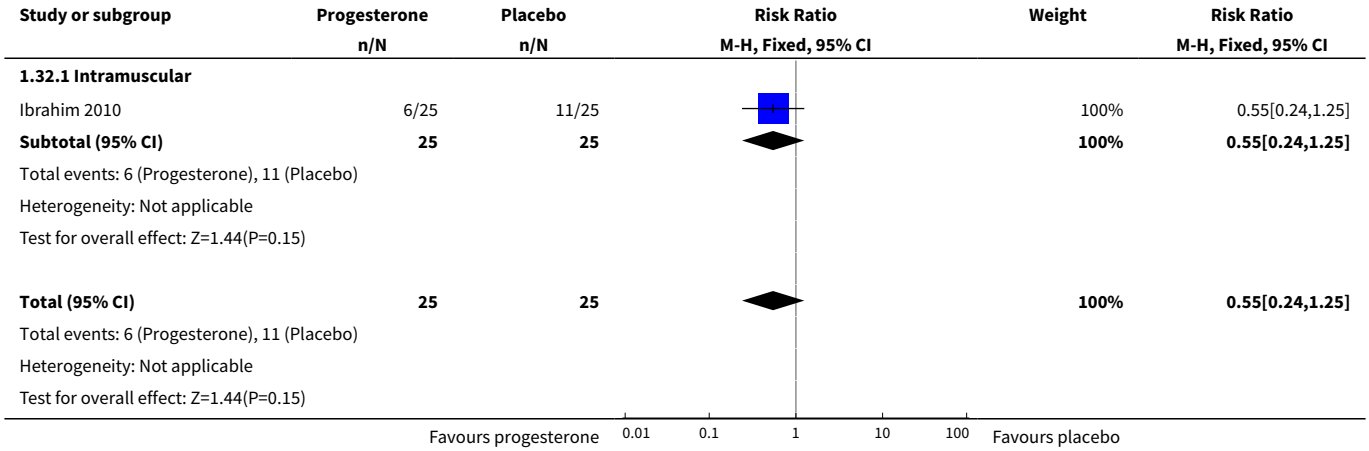
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Analysis 1.31. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 31 Pregnancy prolongation (weeks).

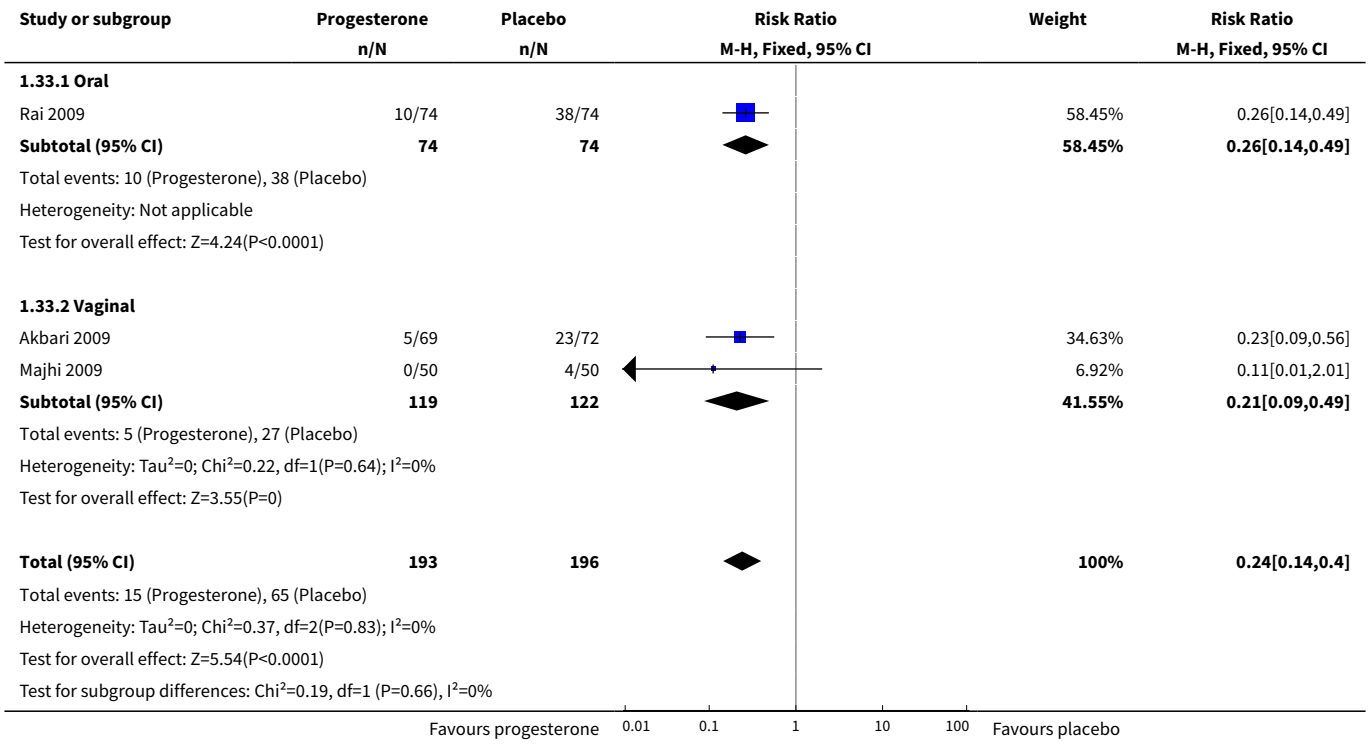


Analysis 1.32. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 32 Apgar score < 7.

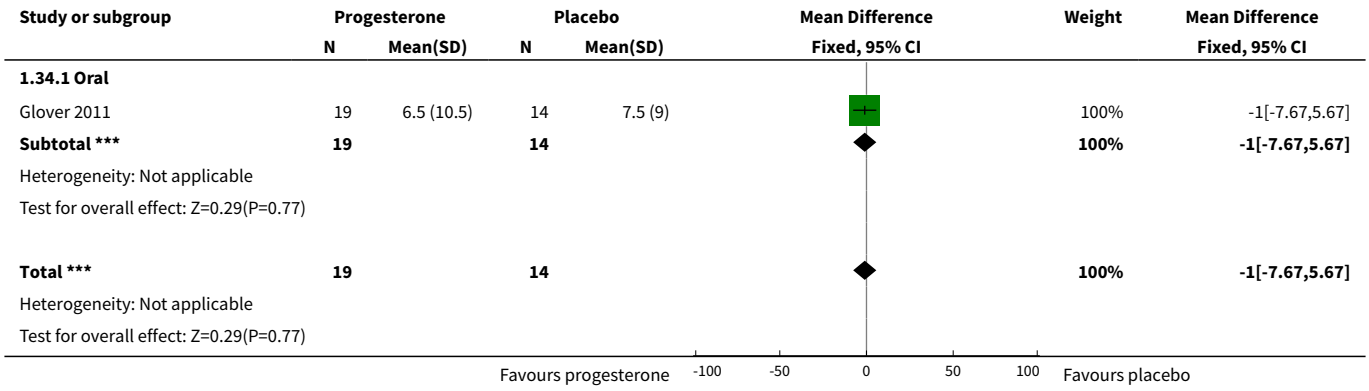


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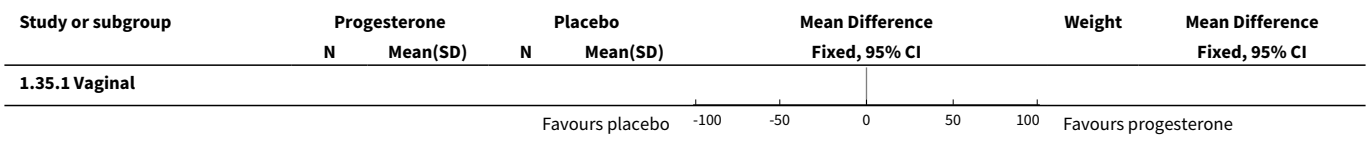
Analysis 1.33. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 33 Admission to neonatal intensive care unit.



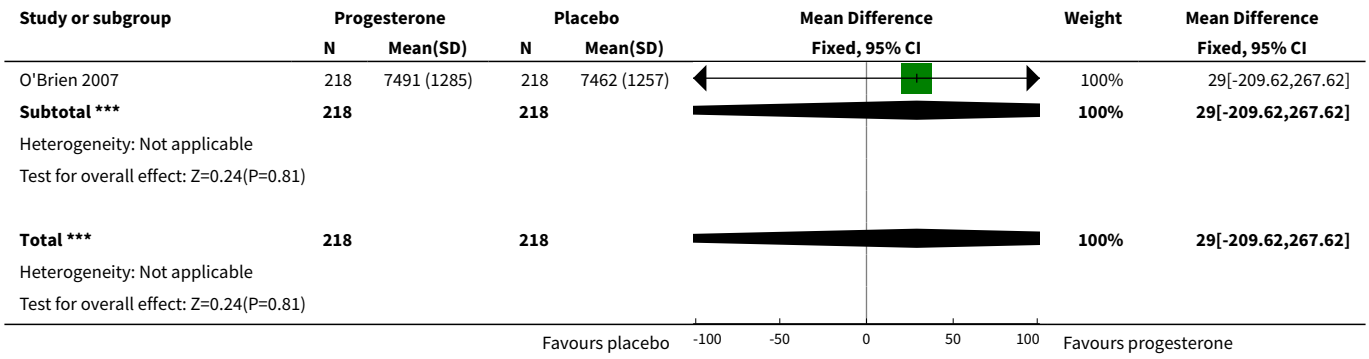
Analysis 1.34. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 34 Neonatal length of hospital stay (days).



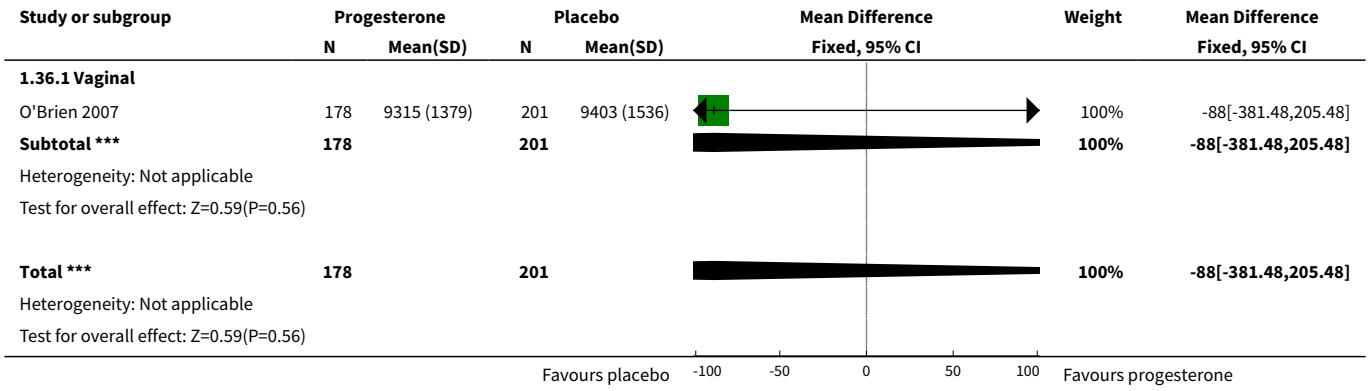
Analysis 1.35. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 35 Infant weight at 6 months follow-up (g).



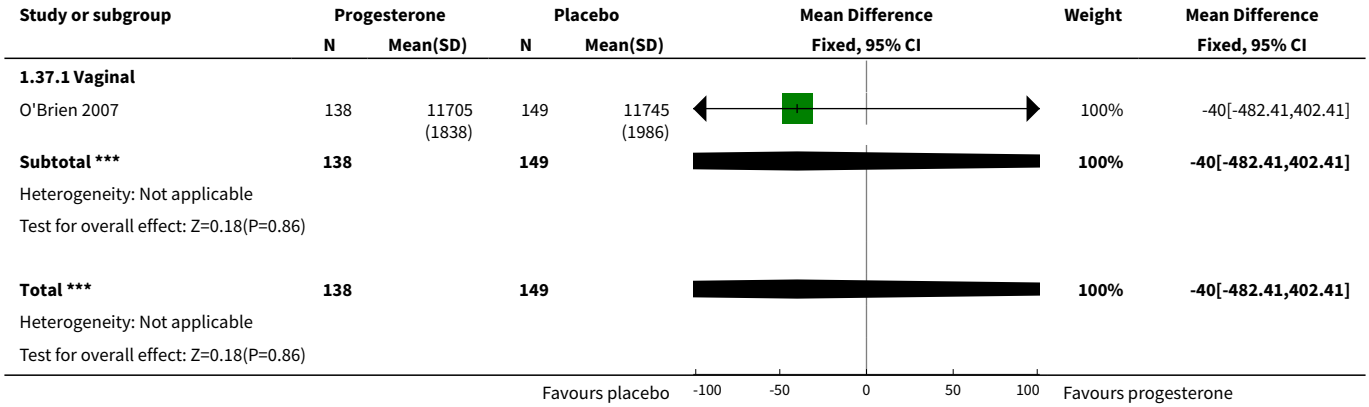
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Analysis 1.36. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 36 Infant weight at 12 months follow-up (g).



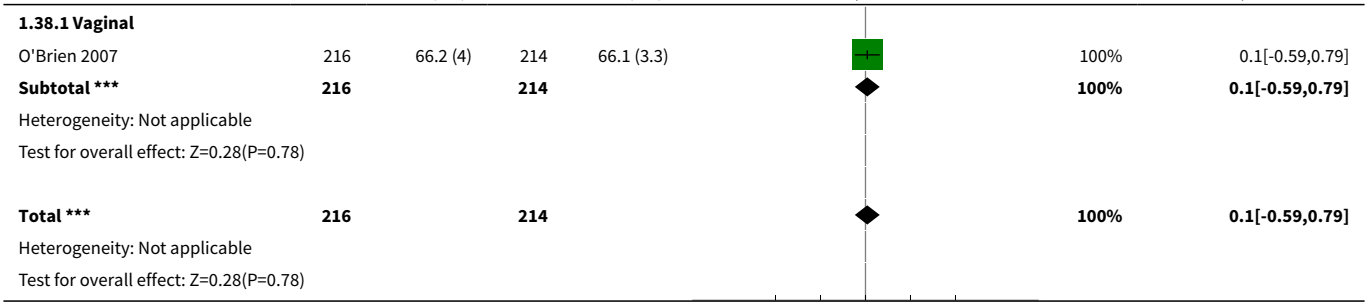
Analysis 1.37. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 37 Infant weight at 24 months follow-up (g).



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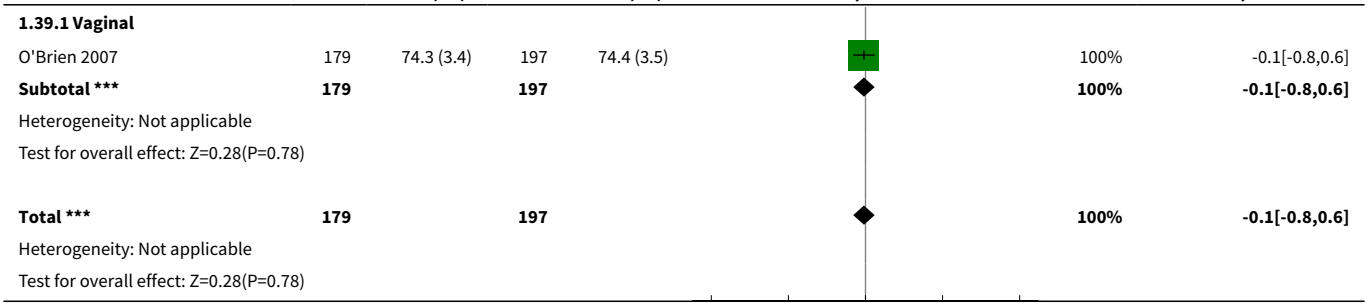
Analysis 1.38. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 38 Infant length at 6 months follow-up (cm).

Study or subgroup	Progesterone N	Progesterone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.38.1 Vaginal							
O'Brien 2007	216	66.2 (4)	214	66.1 (3.3)		100%	0.1[-0.59,0.79]
Subtotal ***	**216**		**214**			**100%**	**0.1[-0.59,0.79]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.28(P=0.78)							
Total ***	**216**		**214**			**100%**	**0.1[-0.59,0.79]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.28(P=0.78)							



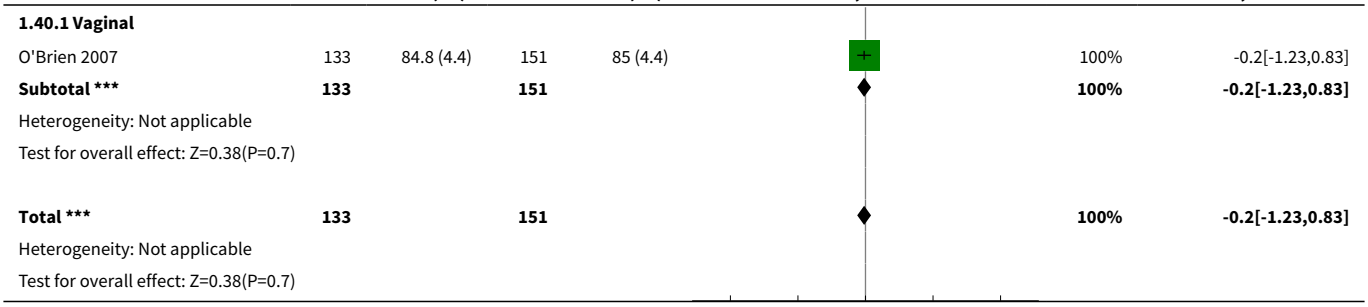
Analysis 1.39. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 39 Infant length at 12 months follow-up (cm).

Study or subgroup	Progesterone N	Progesterone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.39.1 Vaginal							
O'Brien 2007	179	74.3 (3.4)	197	74.4 (3.5)		100%	-0.1[-0.8,0.6]
Subtotal ***	**179**		**197**			**100%**	**-0.1[-0.8,0.6]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.28(P=0.78)							
Total ***	**179**		**197**			**100%**	**-0.1[-0.8,0.6]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.28(P=0.78)							



Analysis 1.40. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 40 Infant length at 24 months follow-up (cm).

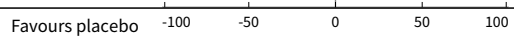
Study or subgroup	Progesterone N	Progesterone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.40.1 Vaginal							
O'Brien 2007	133	84.8 (4.4)	151	85 (4.4)		100%	-0.2[-1.23,0.83]
Subtotal ***	**133**		**151**			**100%**	**-0.2[-1.23,0.83]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.38(P=0.7)							
Total ***	**133**		**151**			**100%**	**-0.2[-1.23,0.83]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.38(P=0.7)							



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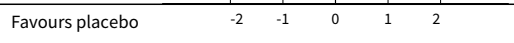
Analysis 1.41. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 41 Infant head circumference at 6 months follow-up (cm).

Study or subgroup	Progesterone N	Progesterone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.41.1 Vaginal							
O'Brien 2007	212	43.1 (1.8)	214	43 (1.7)		100%	0.1[-0.23,0.43]
Subtotal ***	**212**		**214**			**100%**	**0.1[-0.23,0.43]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.59(P=0.56)							
Total ***	**212**		**214**			**100%**	**0.1[-0.23,0.43]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.59(P=0.56)							



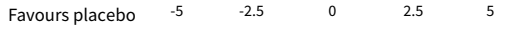
Analysis 1.42. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 42 Infant head circumference at 12 months follow-up (cm).

Study or subgroup	Progesterone N	Progesterone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.42.1 Vaginal							
O'Brien 2007	179	45.9 (1.8)	193	45.8 (1.7)		100%	0.1[-0.26,0.46]
Subtotal ***	**179**		**193**			**100%**	**0.1[-0.26,0.46]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.55(P=0.58)							
Total ***	**179**		**193**			**100%**	**0.1[-0.26,0.46]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.55(P=0.58)							



Analysis 1.43. Comparison 1 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth (singletons), Outcome 43 Infant head circumference at 24 months follow-up (cm).

Study or subgroup	Progesterone N	Progesterone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.43.1 Vaginal							
O'Brien 2007	128	48.1 (1.8)	136	47.9 (1.6)		100%	0.2[-0.21,0.61]
Subtotal ***	**128**		**136**			**100%**	**0.2[-0.21,0.61]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.95(P=0.34)							
Total ***	**128**		**136**			**100%**	**0.2[-0.21,0.61]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.95(P=0.34)							



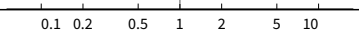
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Comparison 2. Progesterone versus placebo/no treatment: previous history spontaneous preterm birth, by timing of commencement (< 20 wk v > 20 wk, singletons)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth less than 37 weeks	6	1360	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.44, 0.89]
1.1 Therapy commences before 20 weeks	4	1147	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.46, 1.04]
1.2 Therapy commences after 20 weeks	2	213	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.30, 0.78]

Analysis 2.1. Comparison 2 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth, by timing of commencement (< 20 wk v > 20 wk, singletons), Outcome 1 Preterm birth less than 37 weeks.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Therapy commences before 20 weeks					
Glover 2011	5/19	8/14		10.36%	0.46[0.19,1.11]
Johnson 1975	2/18	12/26		5.31%	0.24[0.06,0.95]
Meis 2003	111/306	84/153		27.66%	0.66[0.54,0.81]
O'Brien 2007	129/309	123/302		28.1%	1.03[0.85,1.24]
Subtotal (95% CI)	**652**	**495**		**71.43%**	**0.69[0.46,1.04]**
Total events: 247 (Progesterone), 227 (Placebo)					
Heterogeneity: Tau^2=0.1; Chi^2=14.26, df=3(P=0); I^2=78.96%					
Test for overall effect: Z=1.76(P=0.08)					
2.1.2 Therapy commences after 20 weeks					
Cetingoz 2011	9/37	17/34		14.55%	0.49[0.25,0.94]
da Fonseca 2003	10/72	20/70		14.01%	0.49[0.25,0.96]
Subtotal (95% CI)	**109**	**104**		**28.57%**	**0.49[0.3,0.78]**
Total events: 19 (Progesterone), 37 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=2.97(P=0)					
Total (95% CI)	**761**	**599**		**100%**	**0.63[0.44,0.89]**
Total events: 266 (Progesterone), 264 (Placebo)					
Heterogeneity: Tau^2=0.1; Chi^2=18.53, df=5(P=0); I^2=73.01%					
Test for overall effect: Z=2.65(P=0.01)					
Test for subgroup differences: Chi^2=1.19, df=1 (P=0.28), I^2=15.88%					



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Comparison 3. Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons)

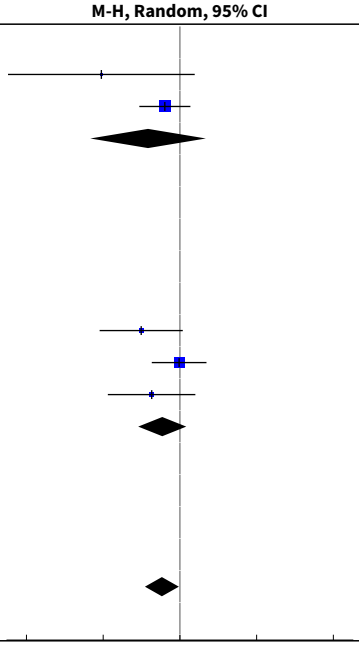
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	5	1403	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.35, 0.97]
1.1 Dose < 500 mg per week	2	503	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.07, 2.18]
1.2 Dose >= 500 mg per week	3	900	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.29, 1.21]
2 Preterm birth less than 37 weeks	9	1700	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.40, 0.74]
2.1 Dose < 500 mg per week	3	602	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.44, 0.80]
2.2 Dose >= 500 mg per week	6	1098	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.31, 0.85]
3 Threatened preterm labour	2	601	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.47, 1.62]
3.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.73, 1.87]
3.2 Dose >= 500 mg per week	1	142	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.35, 1.11]
4 Caesarean section	3	1170	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.72, 1.13]
4.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.30]
4.2 Dose >= 500 mg per week	2	711	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.70, 1.21]
5 Antenatal corticosteroids	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.73, 1.16]
5.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.30]
5.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.26]
6 Need for tocolysis	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.81, 1.52]
6.1 Dose < 500 mg per week	2	503	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.72]
6.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.70, 1.74]
7 Respiratory distress syndrome	4	1359	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.16, 0.89]
7.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.38, 1.05]
7.2 Dose >= 500 mg per week	3	900	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.07, 1.23]
8 Intraventricular haemorrhage - all grades	3	1211	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.20, 2.46]
8.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.08, 0.82]
8.2 Dose >= 500 mg per week	2	752	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.46, 3.77]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Intraventricular haemorrhage - grade III or IV	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.21, 11.73]
9.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.12, 51.92]
9.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.55]
10 Necrotising enterocolitis	3	1170	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.10, 1.25]
10.1 Dose < 500 mg per week	1	459	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.00, 1.03]
10.2 Dose >= 500 mg per week	2	711	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.15, 1.95]
11 Intrauterine fetal death	3	1114	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.32, 2.91]
11.1 Dose < 500 mg per week	2	503	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.05, 6.51]
11.2 Dose >= 500 mg per week	1	611	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.33, 4.51]
12 Neonatal death	5	1403	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.28, 0.81]
12.1 Dose < 500 mg per week	2	503	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.03]
12.2 Dose >= 500 mg per week	3	900	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.26, 0.99]

Analysis 3.1. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 1 Perinatal death.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Dose < 500 mg per week					
Johnson 1975	0/18	7/26		3.25%	0.09[0.01,1.56]
Meis 2003	14/306	11/153		35.69%	0.64[0.3,1.37]
Subtotal (95% CI)	**324**	**179**		**38.94%**	**0.38[0.07,2.18]**
Total events: 14 (Progesterone), 18 (Placebo)					
Heterogeneity: Tau^2=0.91; Chi^2=1.83, df=1(P=0.18); I^2=45.36%					
Test for overall effect: Z=1.08(P=0.28)					
3.1.2 Dose >= 500 mg per week					
Akbari 2009	3/69	10/72		15.3%	0.31[0.09,1.09]
O'Brien 2007	11/309	11/302		31.86%	0.98[0.43,2.22]
Rai 2009	3/74	7/74		13.9%	0.43[0.12,1.59]
Subtotal (95% CI)	**452**	**448**		**61.06%**	**0.59[0.29,1.21]**
Total events: 17 (Progesterone), 28 (Placebo)					
Heterogeneity: Tau^2=0.1; Chi^2=2.65, df=2(P=0.27); I^2=24.45%					
Test for overall effect: Z=1.44(P=0.15)					
Total (95% CI)	**776**	**627**		**100%**	**0.58[0.35,0.97]**
Total events: 31 (Progesterone), 46 (Placebo)					



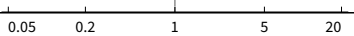
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Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.04; Chi²=4.46, df=4(P=0.35); I²=10.28%					
Test for overall effect: Z=2.08(P=0.04)					
Test for subgroup differences: Chi²=0.2, df=1 (P=0.66), I²=0%					

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Analysis 3.2. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 2 Preterm birth less than 37 weeks.

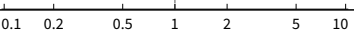
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Dose < 500 mg per week					
Johnson 1975	2/18	12/25		4.04%	0.23[0.06,0.91]
Meis 2003	111/306	84/153		18.24%	0.66[0.54,0.81]
Saghafi 2011a	16/50	30/50		13.72%	0.53[0.34,0.85]
Subtotal (95% CI)	**374**	**228**		**36%**	**0.59[0.44,0.8]**
Total events: 129 (Progesterone), 126 (Placebo)					
Heterogeneity: Tau²=0.03; Chi²=2.85, df=2(P=0.24); I²=29.82%					
Test for overall effect: Z=3.4(P=0)					
3.2.2 Dose >= 500 mg per week					
Akbari 2009	8/69	23/72		9.35%	0.36[0.17,0.76]
Cetingoz 2011	9/37	17/34		10.39%	0.49[0.25,0.94]
da Fonseca 2003	10/72	20/70		10.04%	0.49[0.25,0.96]
Glover 2011	5/19	8/14		7.6%	0.46[0.19,1.11]
Majhi 2009	6/50	19/50		8.14%	0.32[0.14,0.72]
O'Brien 2007	129/309	123/302		18.48%	1.03[0.85,1.24]
Subtotal (95% CI)	**556**	**542**		**64%**	**0.51[0.31,0.85]**
Total events: 167 (Progesterone), 210 (Placebo)					
Heterogeneity: Tau²=0.29; Chi²=22.11, df=5(P=0); I²=77.39%					
Test for overall effect: Z=2.57(P=0.01)					
Total (95% CI)	**930**	**770**		**100%**	**0.54[0.4,0.74]**
Total events: 296 (Progesterone), 336 (Placebo)					
Heterogeneity: Tau²=0.12; Chi²=29.37, df=8(P=0); I²=72.76%					
Test for overall effect: Z=3.89(P=0)					
Test for subgroup differences: Chi²=0.22, df=1 (P=0.64), I²=0%					



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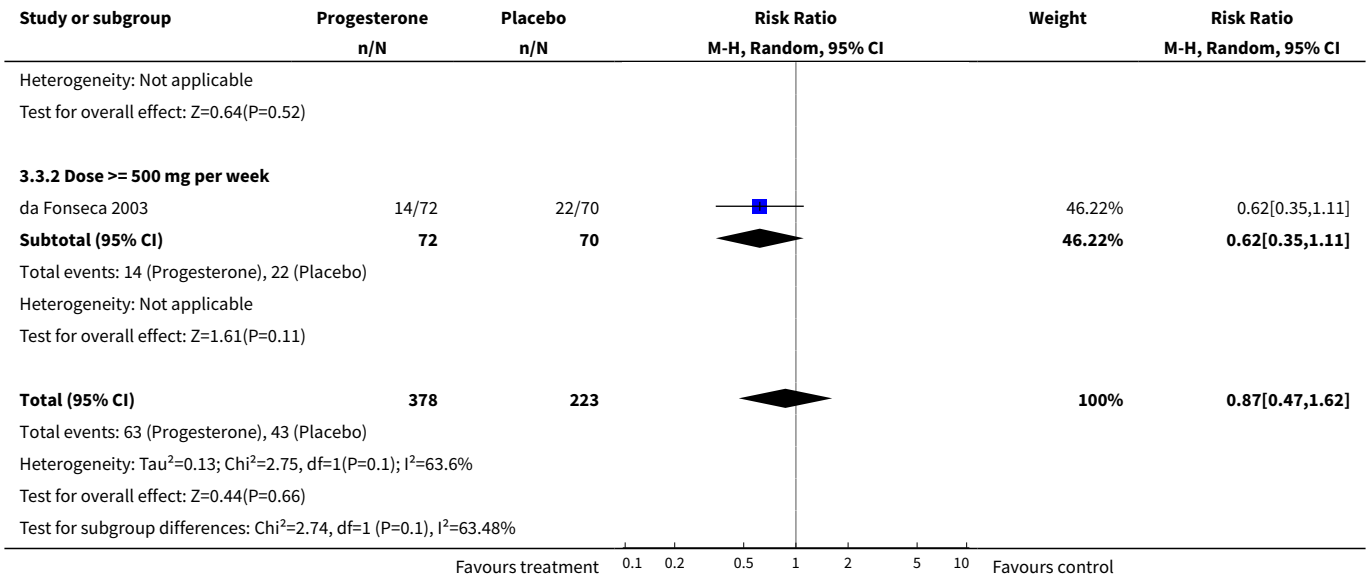
Analysis 3.3. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 3 Threatened preterm labour.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Dose < 500 mg per week					
Meis 2003	49/306	21/153		53.78%	1.17[0.73,1.87]
Subtotal (95% CI)	**306**	**153**		**53.78%**	**1.17[0.73,1.87]**
Total events: 49 (Progesterone), 21 (Placebo)					

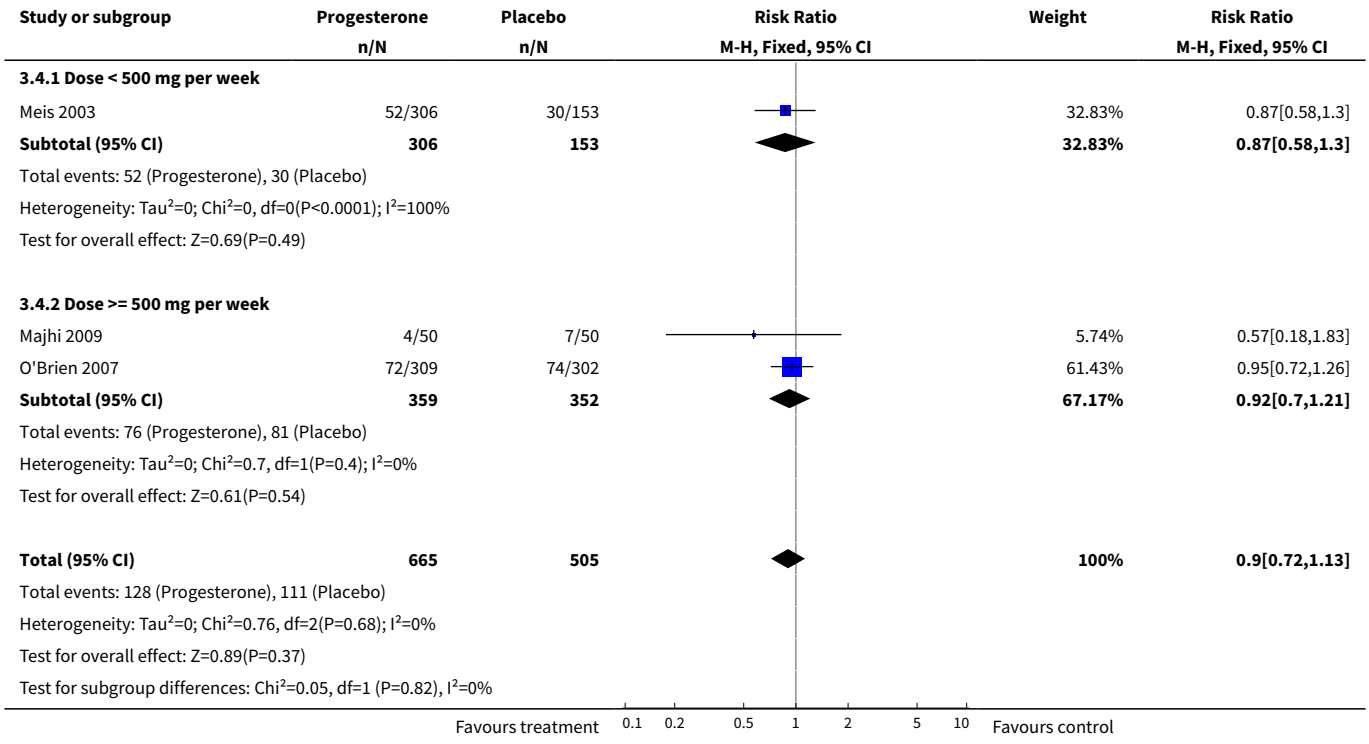


Favours treatment — Favours control

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Analysis 3.4. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 4 Caesarean section.



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Analysis 3.5. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 5 Antenatal corticosteroids.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Dose < 500 mg per week					
Meis 2003	52/306	30/153		34.83%	0.87[0.58,1.3]
Subtotal (95% CI)	**306**	**153**		**34.83%**	**0.87[0.58,1.3]**
Total events: 52 (Progesterone), 30 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.69(P=0.49)					
3.5.2 Dose >= 500 mg per week					
O'Brien 2007	72/309	74/302		65.17%	0.95[0.72,1.26]
Subtotal (95% CI)	**309**	**302**		**65.17%**	**0.95[0.72,1.26]**
Total events: 72 (Progesterone), 74 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.35(P=0.73)					
Total (95% CI)	**615**	**455**		**100%**	**0.92[0.73,1.16]**
Total events: 124 (Progesterone), 104 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%					
Test for overall effect: Z=0.69(P=0.49)					
Test for subgroup differences: Chi^2=0.14, df=1 (P=0.71), I^2=0%					



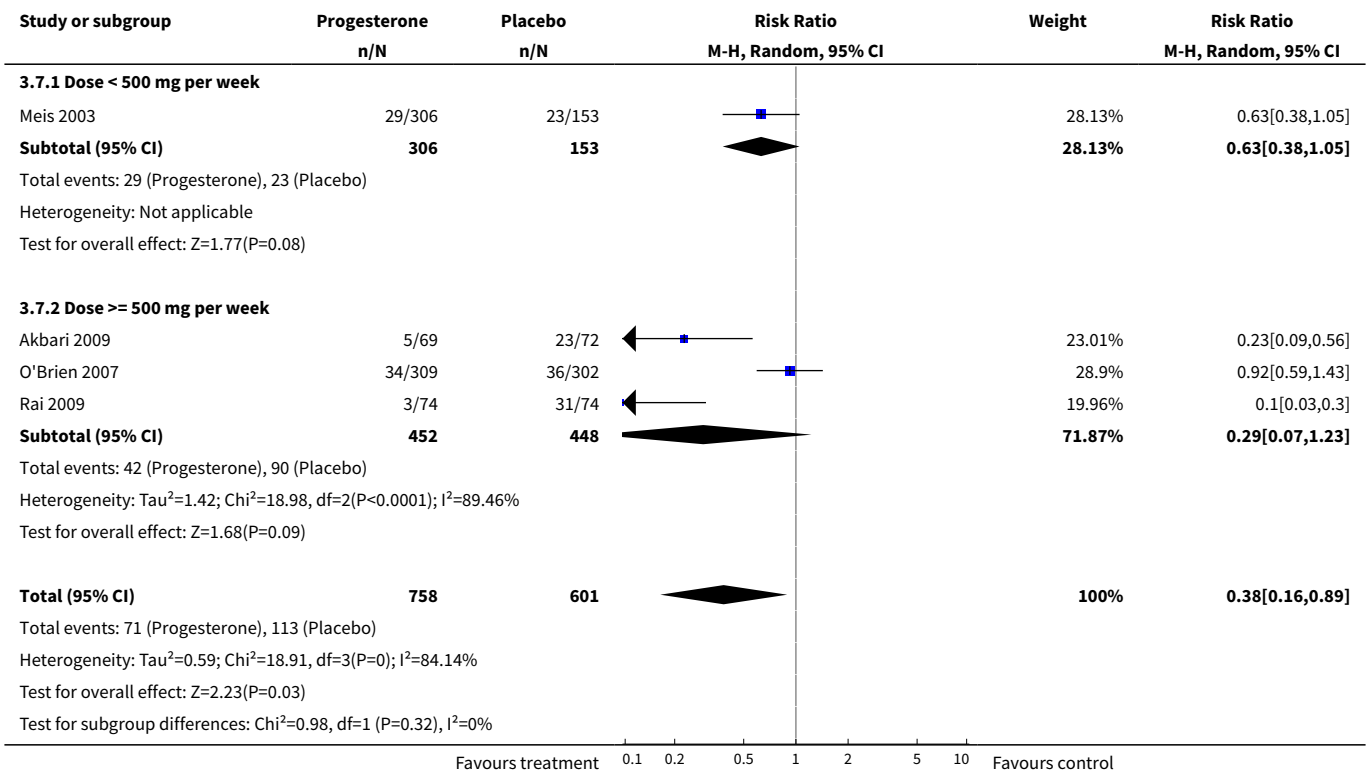
Analysis 3.6. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 6 Need for tocolysis.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 Dose < 500 mg per week					
Johnson 1975	2/18	2/26		2.52%	1.44[0.22,9.33]
Meis 2003	53/306	24/153		49.24%	1.1[0.71,1.72]
Subtotal (95% CI)	**324**	**179**		**51.76%**	**1.12[0.73,1.72]**
Total events: 55 (Progesterone), 26 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%					
Test for overall effect: Z=0.52(P=0.6)					
3.6.2 Dose >= 500 mg per week					
O'Brien 2007	35/309	31/302		48.24%	1.1[0.7,1.74]
Subtotal (95% CI)	**309**	**302**		**48.24%**	**1.1[0.7,1.74]**
Total events: 35 (Progesterone), 31 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.42(P=0.67)					
Total (95% CI)	**633**	**481**		**100%**	**1.11[0.81,1.52]**
Total events: 90 (Progesterone), 57 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=2(P=0.96); I^2=0%					
Test for overall effect: Z=0.67(P=0.5)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.96), I^2=0%					

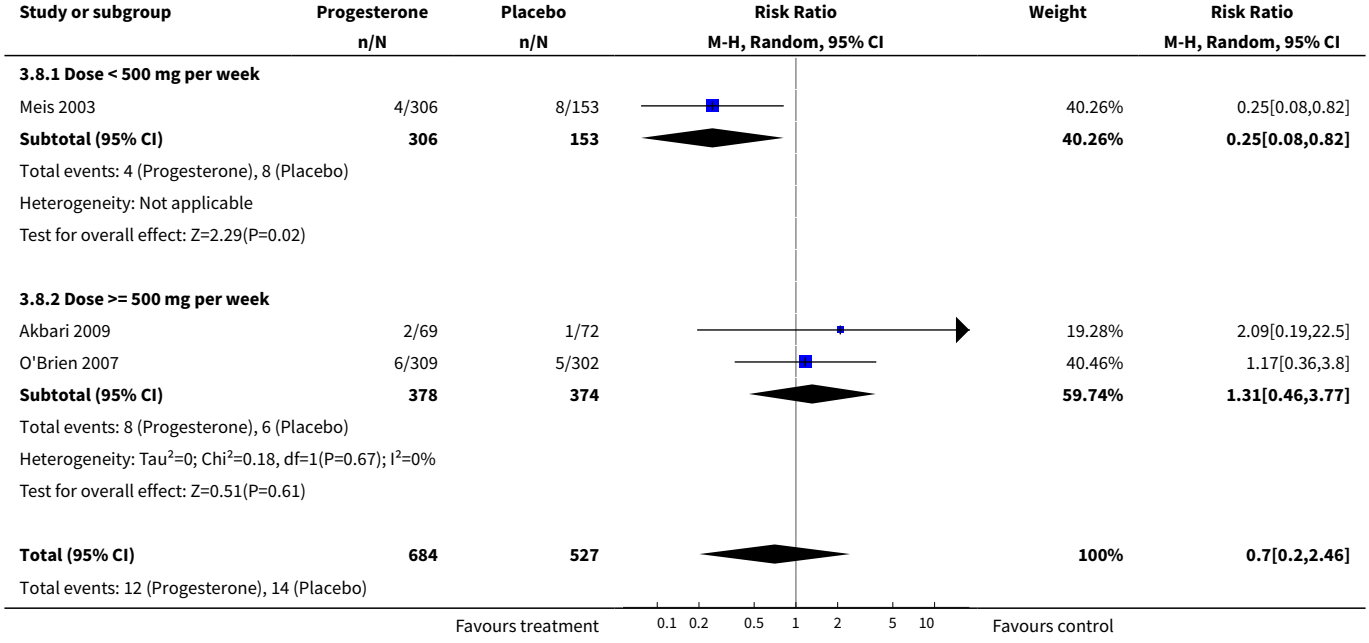


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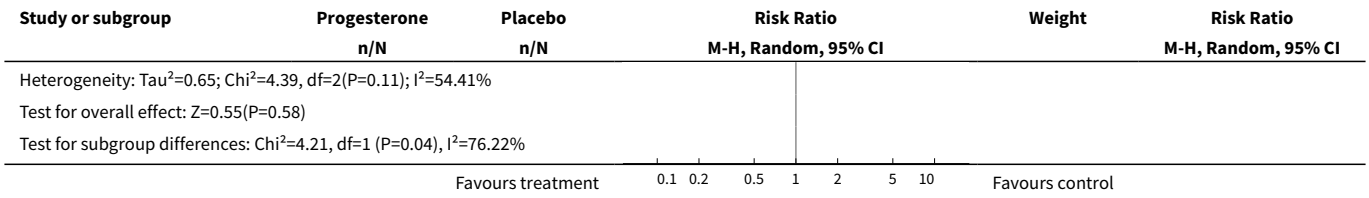
Analysis 3.7. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 7 Respiratory distress syndrome.



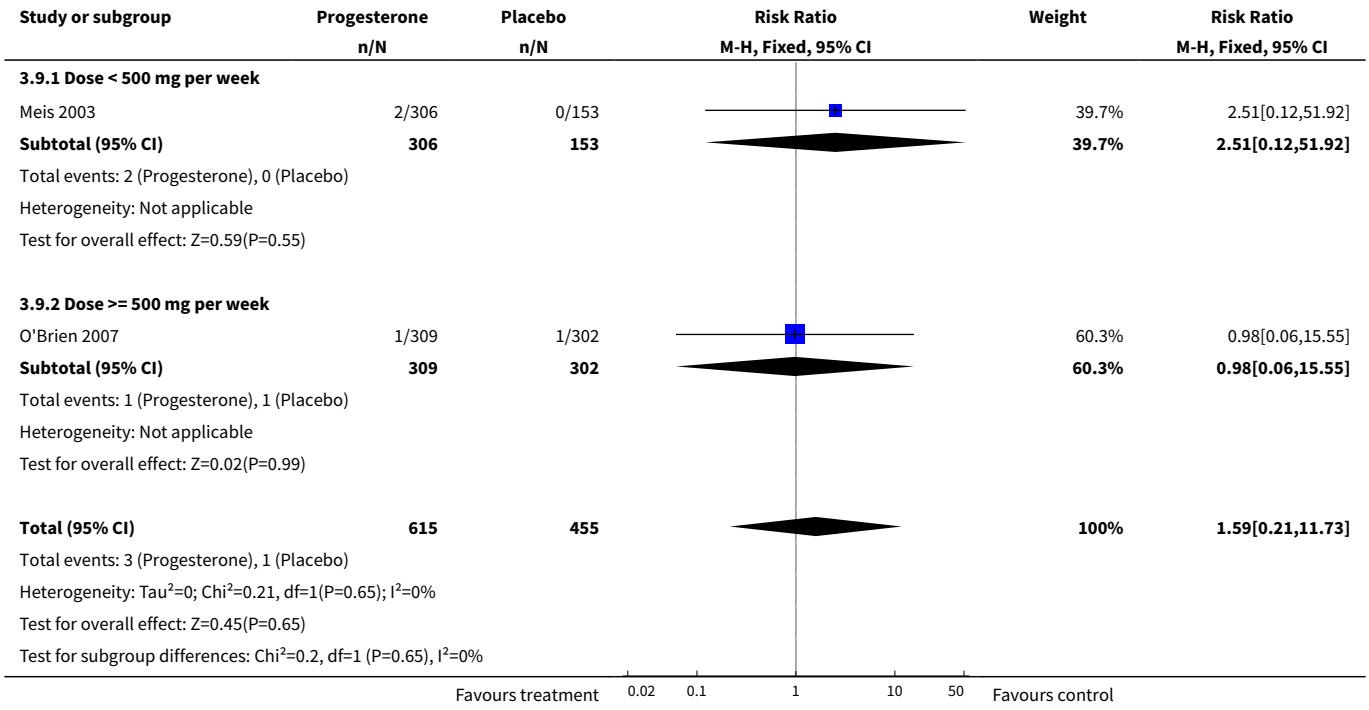
Analysis 3.8. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 8 Intraventricular haemorrhage - all grades.



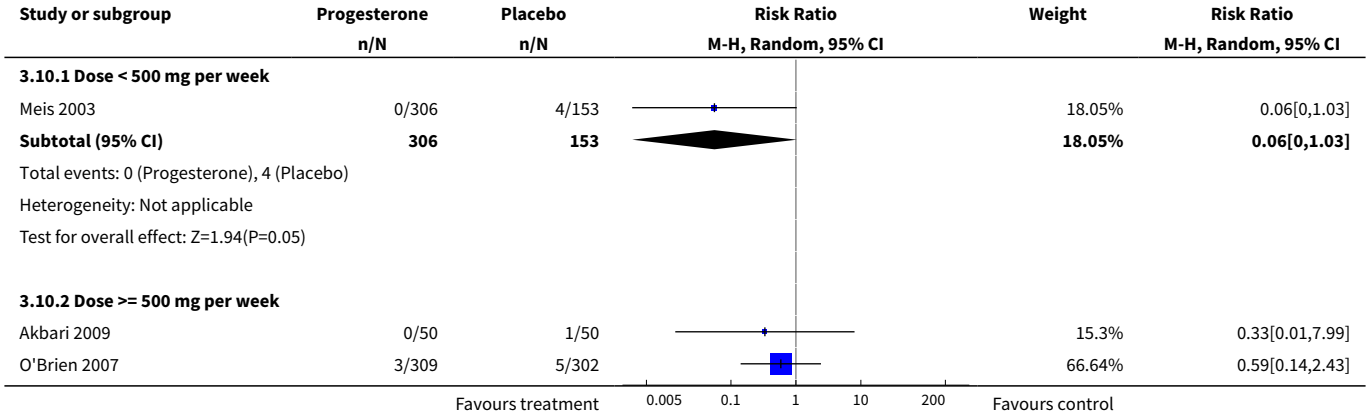
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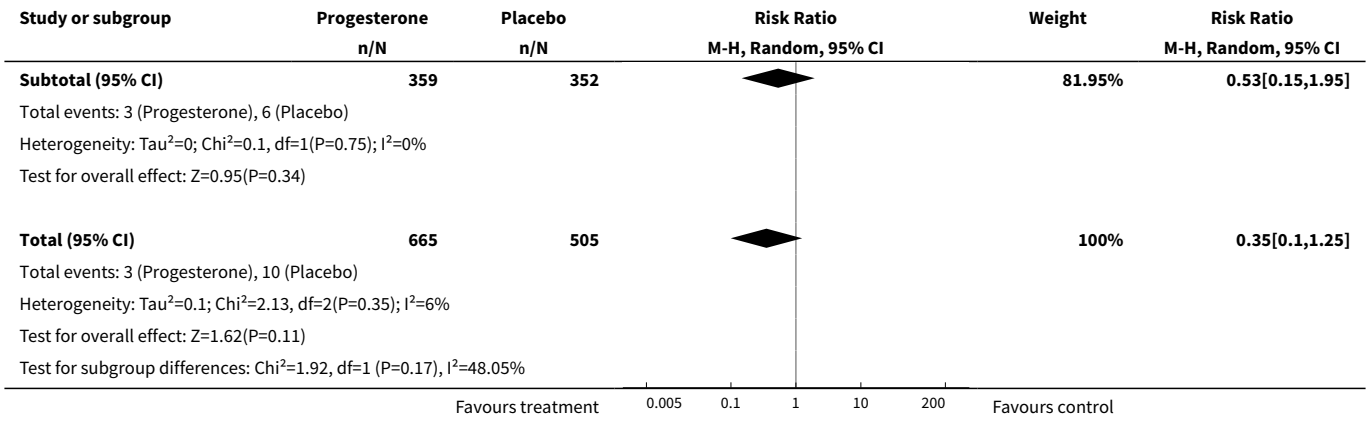
Analysis 3.9. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 9 Intraventricular haemorrhage - grade III or IV.



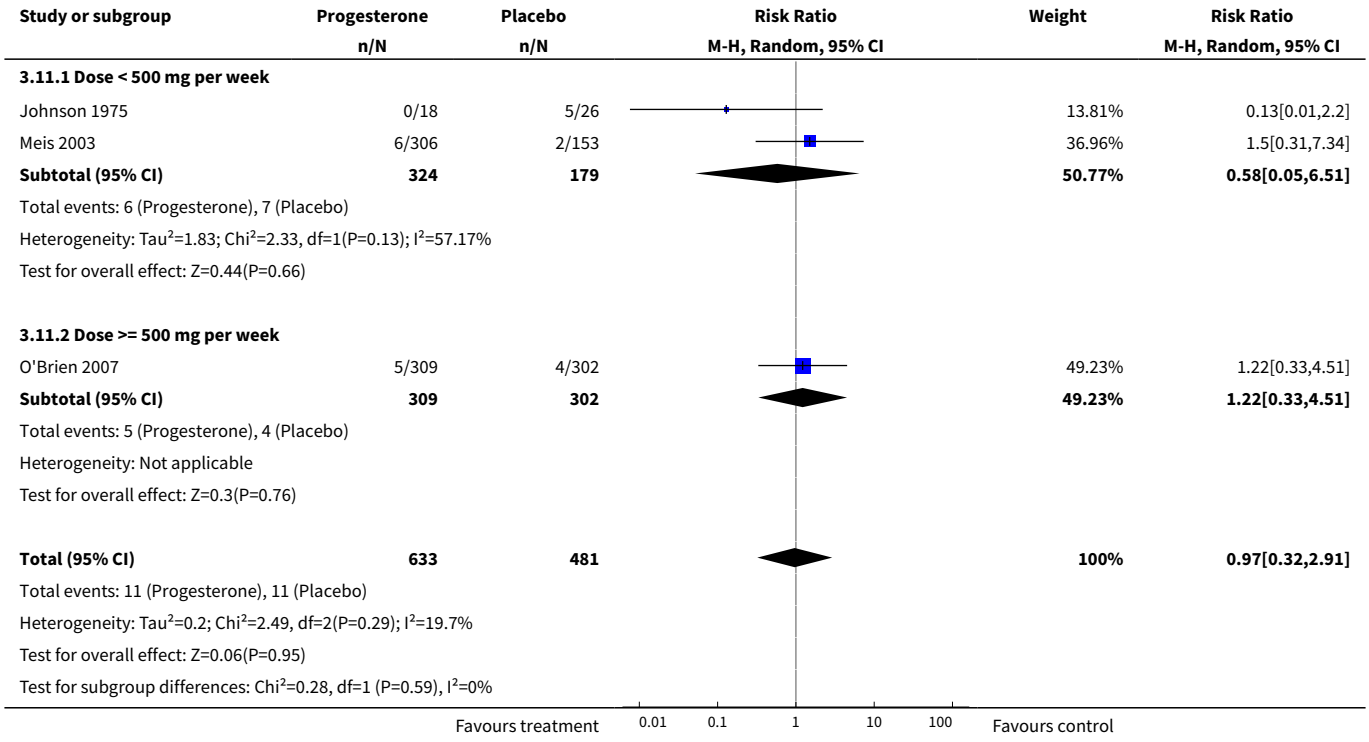
Analysis 3.10. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 10 Necrotising enterocolitis.



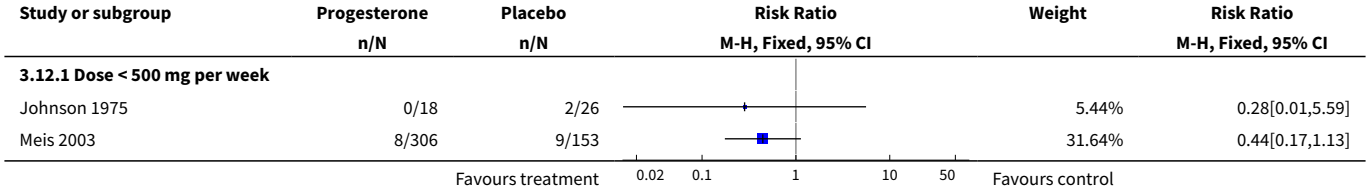
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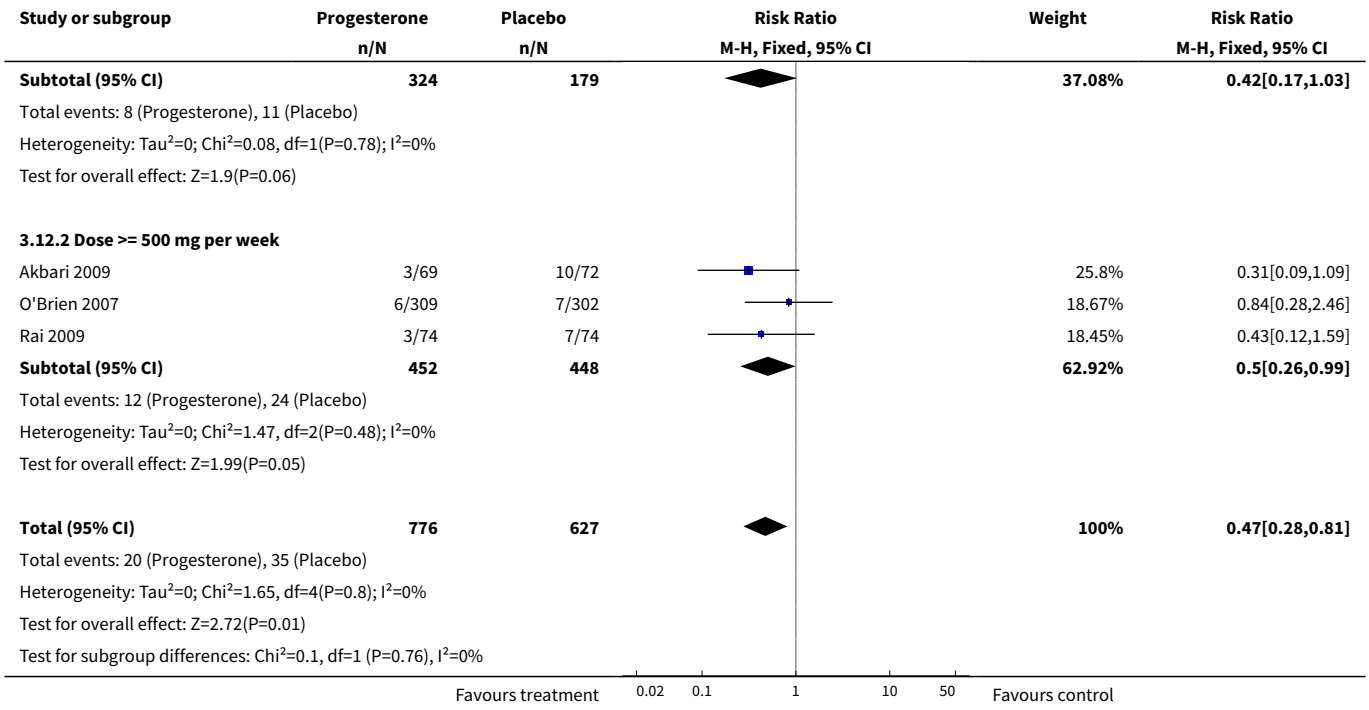
Analysis 3.11. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 11 Intrauterine fetal death.



Analysis 3.12. Comparison 3 Progesterone versus placebo/no treatment: previous history spontaneous preterm birth by cumulative weekly dose (< 500 mg v >= 500 mg, singletons), Outcome 12 Neonatal death.



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Comparison 4. Progesterone versus placebo: ultrasound identified short cervix, singletons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	3	1389	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.42, 1.29]
1.1 Vaginal	2	732	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.27, 1.17]
1.2 Intramuscular	1	657	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.46, 2.72]
2 Preterm birth less than 34 weeks	2	438	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.45, 0.90]
2.1 Vaginal	1	250	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.38, 0.87]
2.2 Intramuscular	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.43, 1.46]
3 Preterm labour	1	188	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.63, 1.74]
3.1 Intramuscular	1	188	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.63, 1.74]
4 Prelabour spontaneous rupture of membranes	2	845	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.68, 2.62]
4.1 Intramuscular	2	845	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.68, 2.62]
5 Side effects (any)	2	842	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.92, 1.13]
5.1 Intramuscular	2	842	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.92, 1.13]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Side effects (injection site)	1	654	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.93, 1.17]
6.1 Intramuscular	1	654	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.93, 1.17]
7 Side effects (urticaria)	1	654	Risk Ratio (M-H, Fixed, 95% CI)	5.03 [1.11, 22.78]
7.1 Intramuscular	1	654	Risk Ratio (M-H, Fixed, 95% CI)	5.03 [1.11, 22.78]
8 Side effects (nausea)	1	654	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.27, 1.83]
8.1 Intramuscular	1	654	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.27, 1.83]
9 Pregnancy prolongation (days)	1	188	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-10.29, 6.29]
9.1 Intramuscular	1	188	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-10.29, 6.29]
10 Caesarean section	2	838	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.79, 1.40]
10.1 Intramuscular	2	838	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.79, 1.40]
11 Antenatal tocolysis	2	828	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.60, 1.11]
11.1 Intramuscular	2	828	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.60, 1.11]
12 Preterm birth less than 37 weeks	3	1303	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.15]
12.1 Vaginal	1	458	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.68, 1.16]
12.2 Intramuscular	2	845	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.28]
13 Preterm birth less than 28 weeks	2	1115	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.37, 0.93]
13.1 Vaginal	1	458	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.25, 0.97]
13.2 Intramuscular	1	657	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.36, 1.30]
14 Infant birthweight less than 2500 g	3	1379	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.78, 1.09]
14.1 Vaginal	2	728	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.09]
14.2 Intramuscular	1	651	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.73, 1.30]
15 Respiratory distress syndrome	4	1556	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.48, 1.00]
15.1 Vaginal	2	732	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.29, 0.85]
15.2 Intramuscular	2	824	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.58, 1.58]

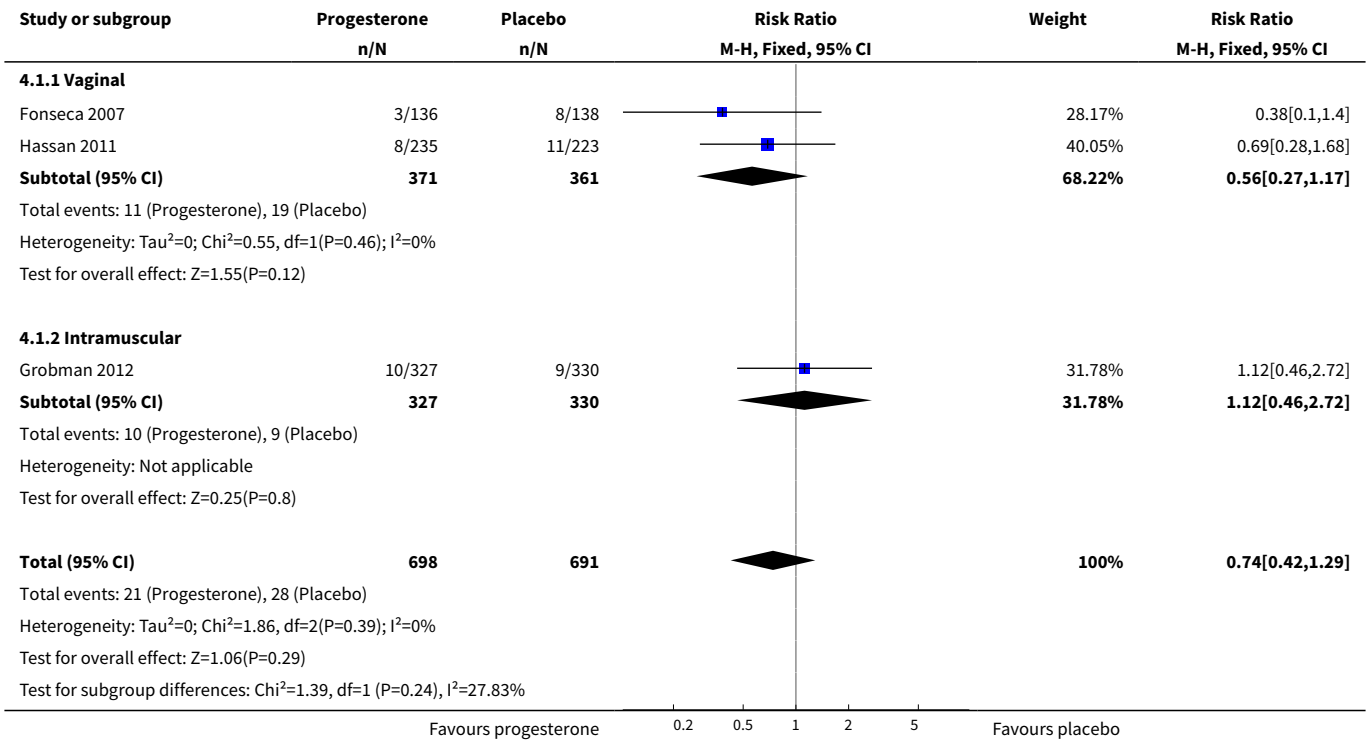
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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Apgar score < 7	1	651	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.41, 1.55]
16.1 Intramuscular	1	651	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.41, 1.55]
17 Need for assisted ventilation	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.36, 1.16]
17.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.36, 1.16]
18 Intraventricular haemorrhage - all grades	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.53]
18.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.53]
19 Intraventricular haemorrhage - grades III or IV	2	1100	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.17, 5.60]
19.1 Vaginal	1	458	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.73]
19.2 Intramuscular	1	642	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.18, 22.08]
20 Periventricular leucomalacia	3	1282	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.38, 8.24]
20.1 Vaginal	1	458	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Intramuscular	2	824	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.38, 8.24]
21 Retinopathy of prematurity	2	916	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.23, 4.42]
21.1 Vaginal	1	274	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 104.70]
21.2 Intramuscular	1	642	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.04, 3.21]
22 Necrotising enterocolitis	3	1374	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.27, 1.78]
22.1 Vaginal	2	732	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.30, 3.11]
22.2 Intramuscular	1	642	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.06]
23 Neonatal sepsis	3	1374	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.18, 1.20]
23.1 Vaginal	2	732	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.15, 2.25]
23.2 Intramuscular	1	642	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.08, 0.97]
24 Intrauterine fetal death	3	1389	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.48, 3.04]
24.1 Vaginal	2	732	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.28, 2.42]
24.2 Intramuscular	1	657	Risk Ratio (M-H, Fixed, 95% CI)	4.04 [0.45, 35.92]

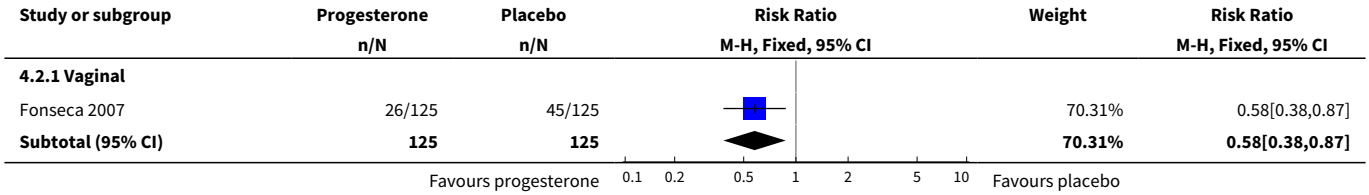
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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25 Neonatal death	4	1571	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.26, 1.13]
25.1 Vaginal	2	732	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.15, 1.15]
25.2 Intramuscular	2	839	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.27, 2.16]
26 Admission to neonatal intensive care unit	2	834	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.35]
26.1 Intramuscular	2	834	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.35]

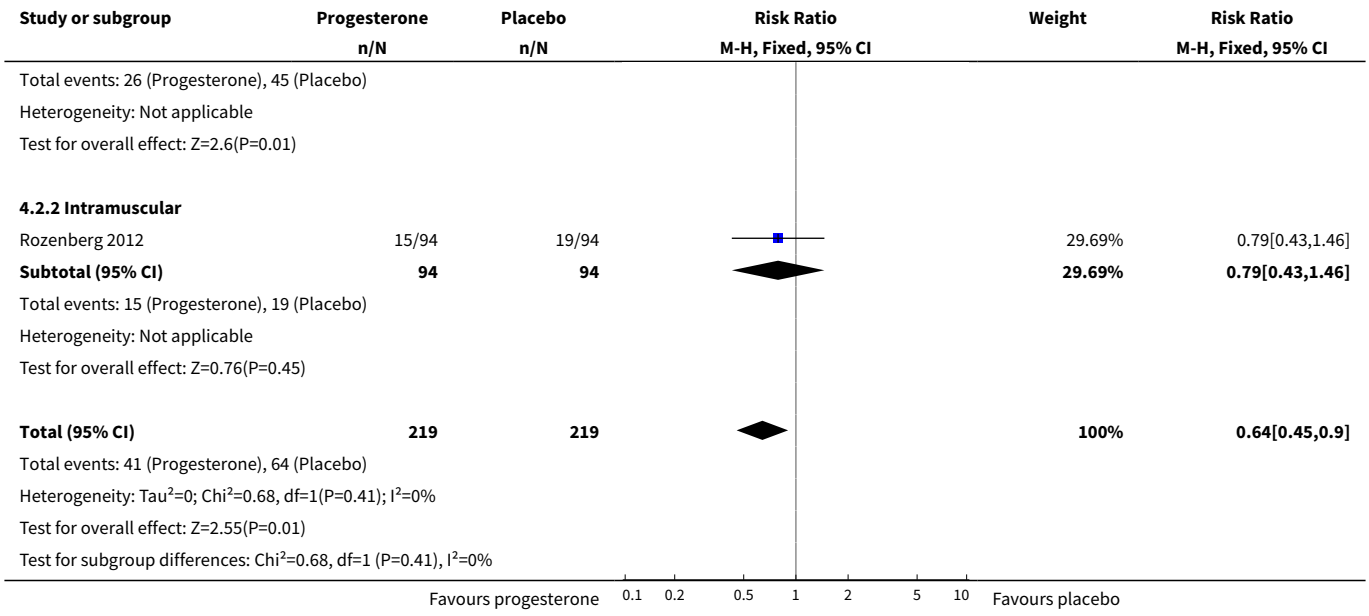
Analysis 4.1. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 1 Perinatal death.



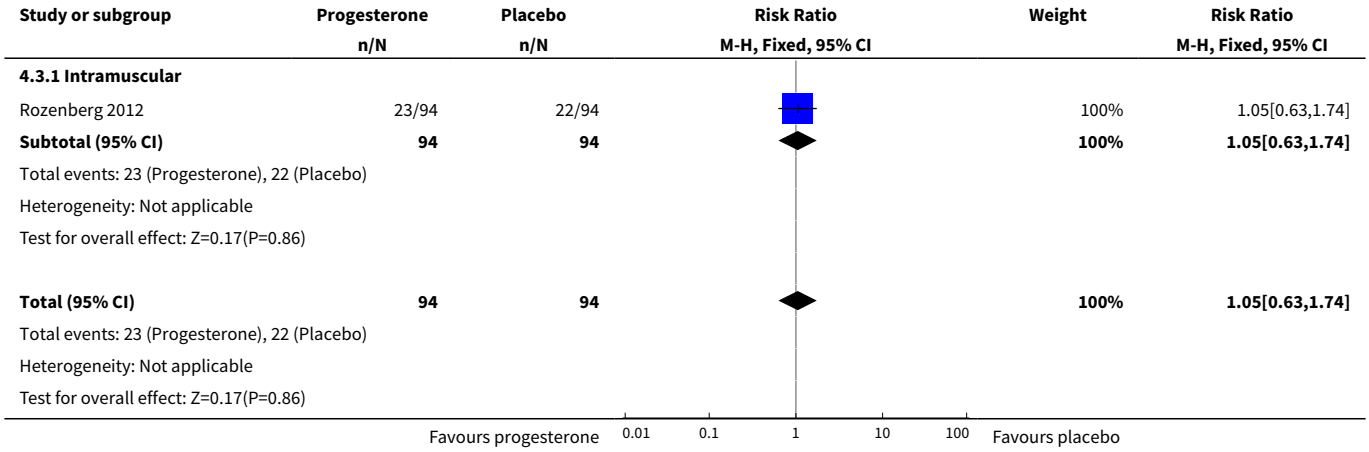
Analysis 4.2. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 2 Preterm birth less than 34 weeks.



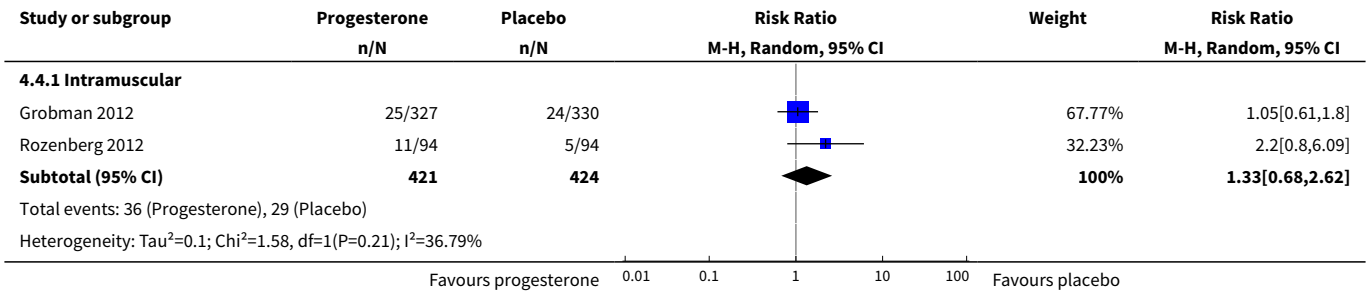
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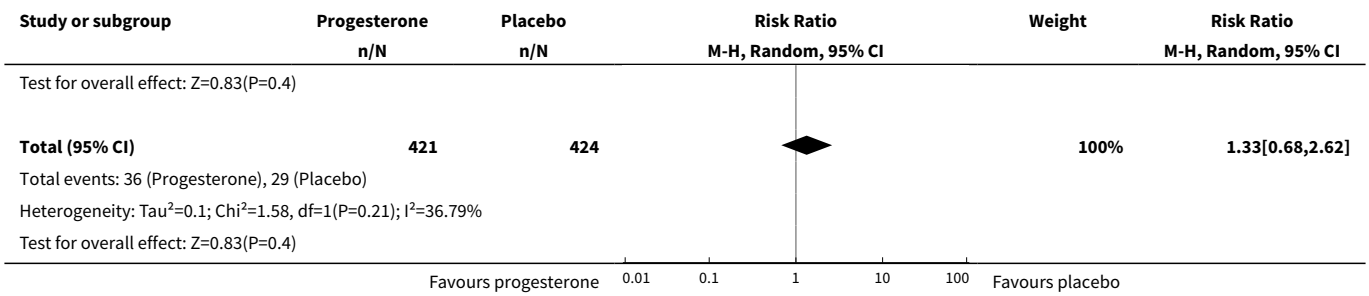
Analysis 4.3. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 3 Preterm labour.



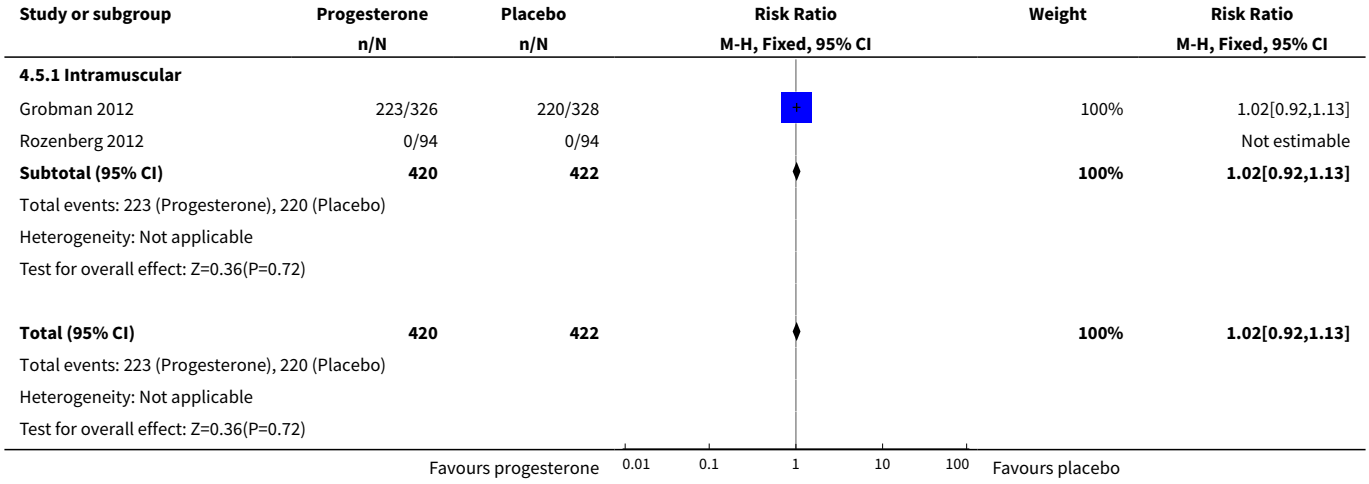
Analysis 4.4. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 4 Prelabour spontaneous rupture of membranes.



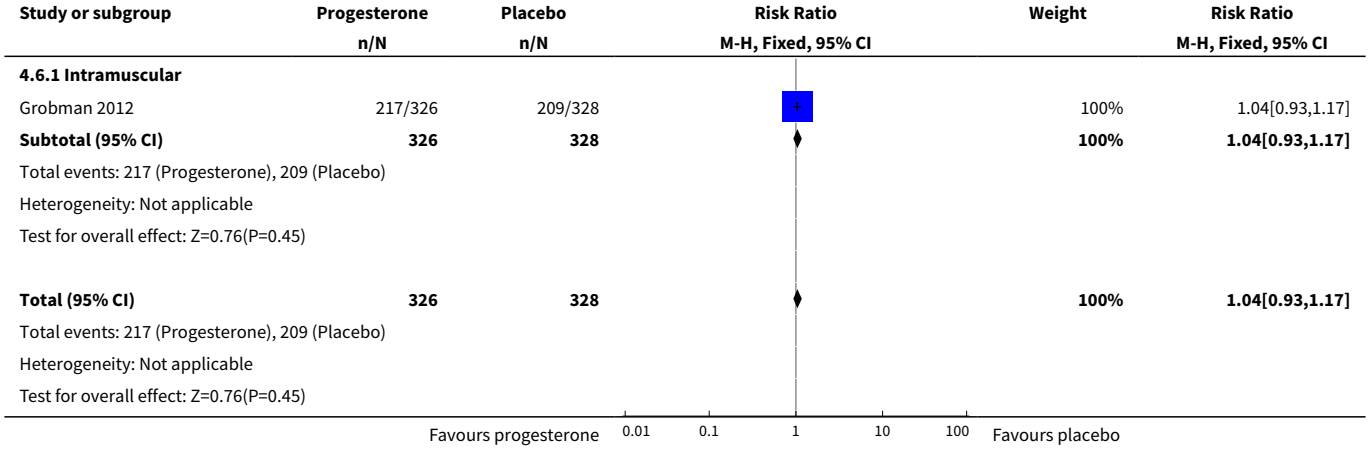
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Analysis 4.5. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 5 Side effects (any).

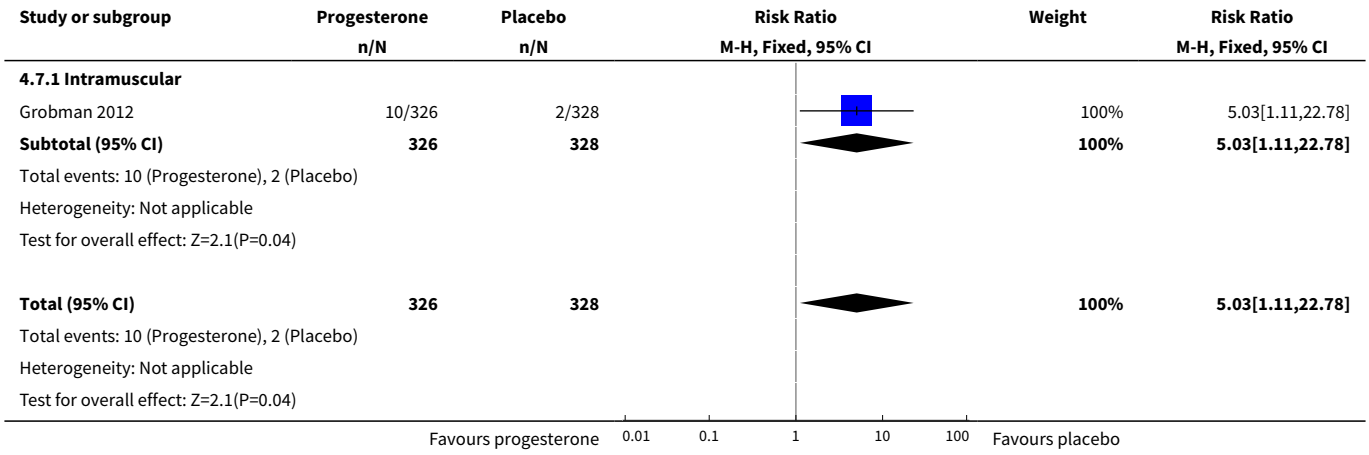


Analysis 4.6. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 6 Side effects (injection site).

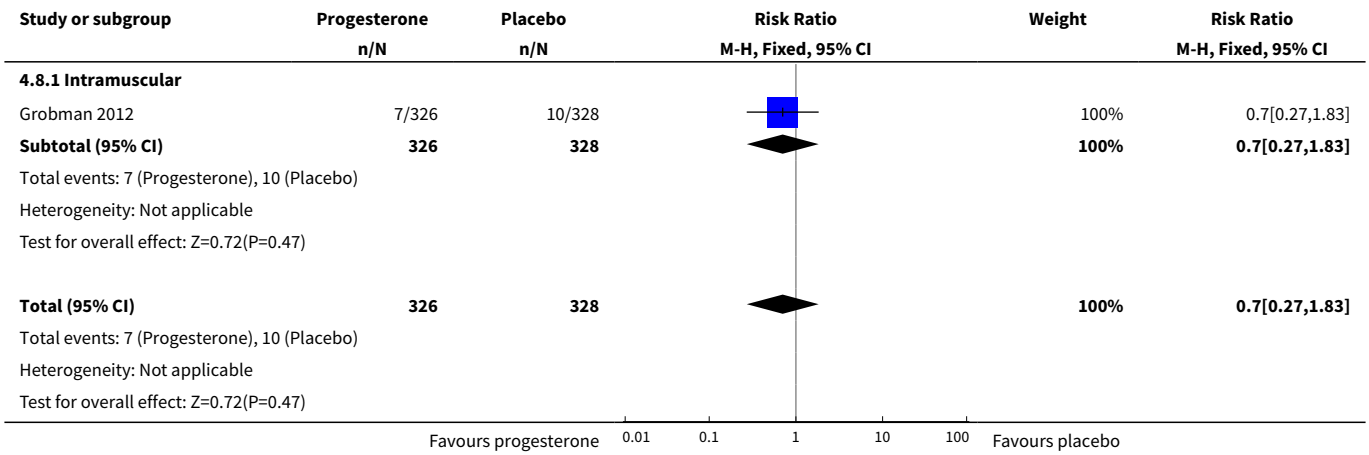


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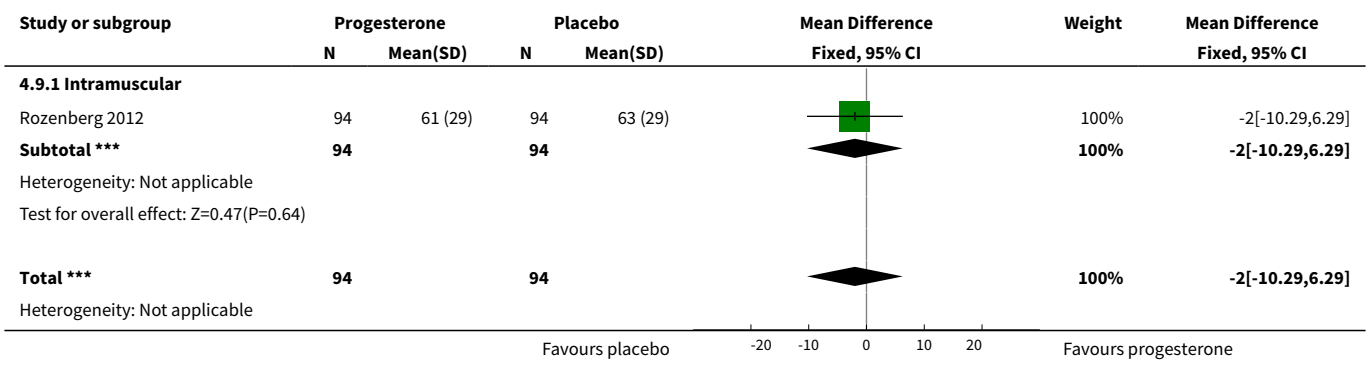
Analysis 4.7. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 7 Side effects (urticaria).



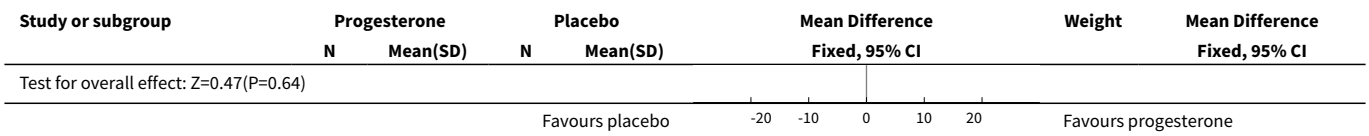
Analysis 4.8. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 8 Side effects (nausea).



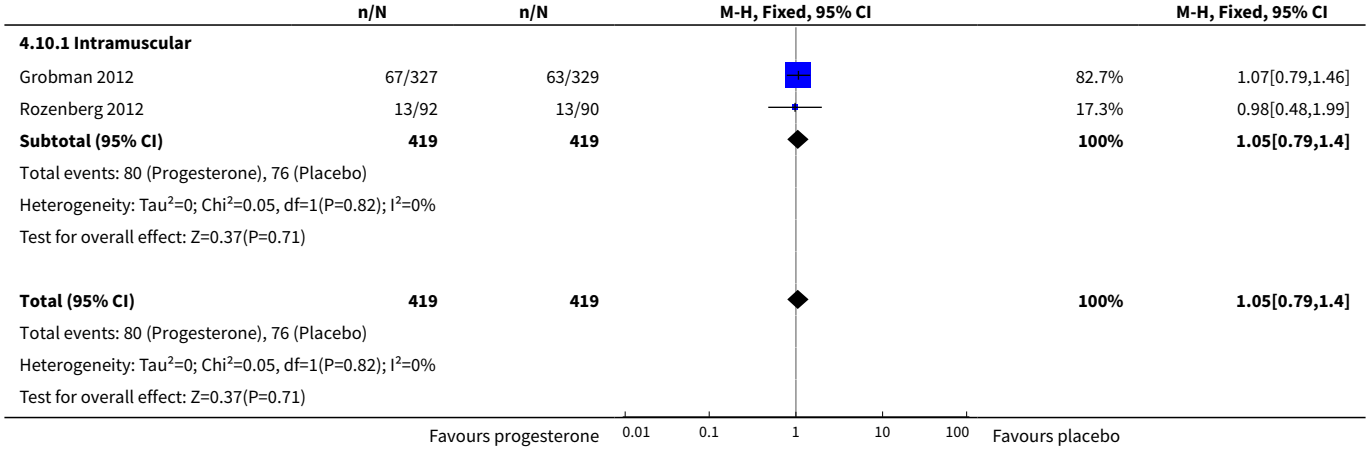
Analysis 4.9. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 9 Pregnancy prolongation (days).



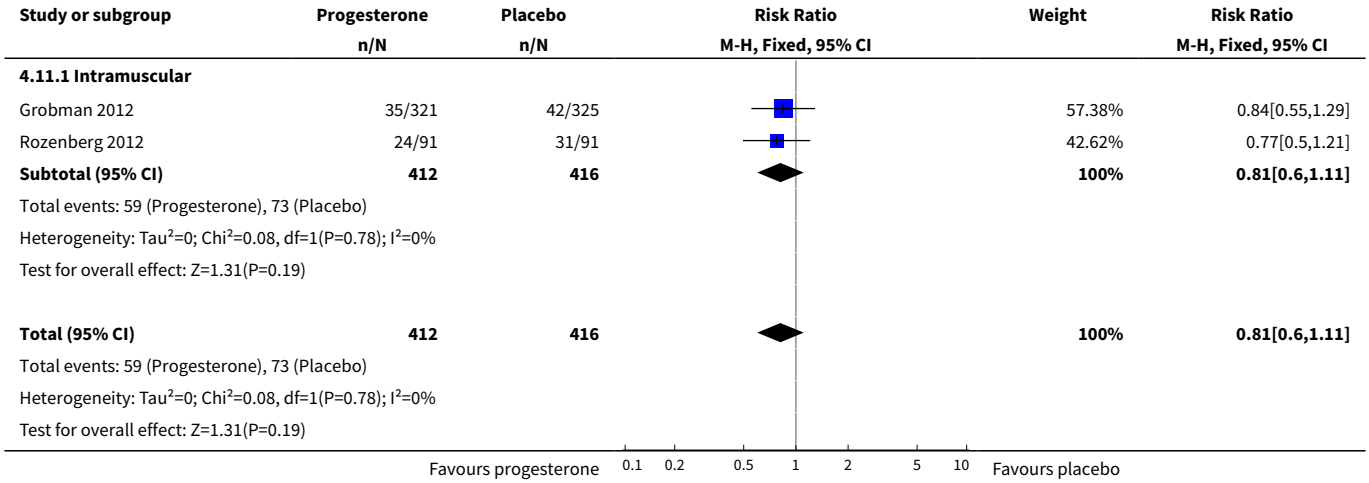
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Analysis 4.10. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 10 Caesarean section.

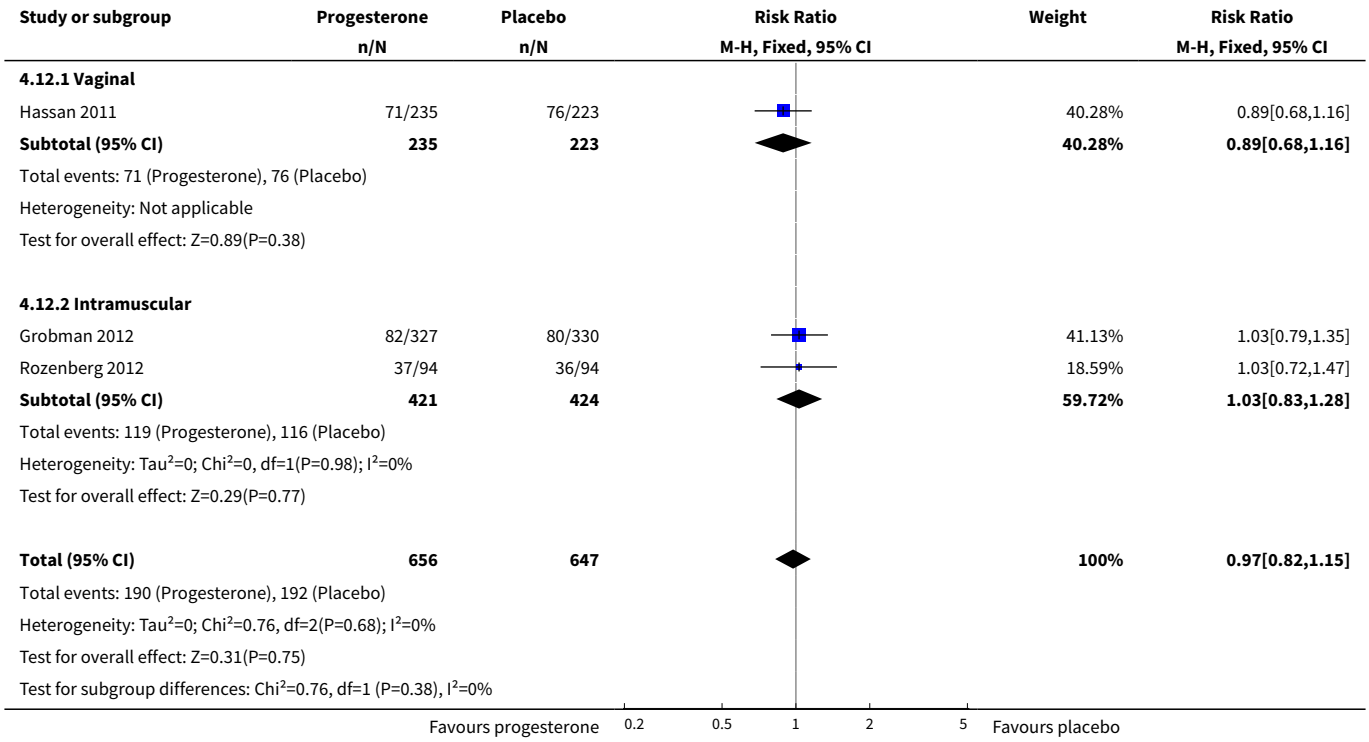


Analysis 4.11. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 11 Antenatal tocolysis.

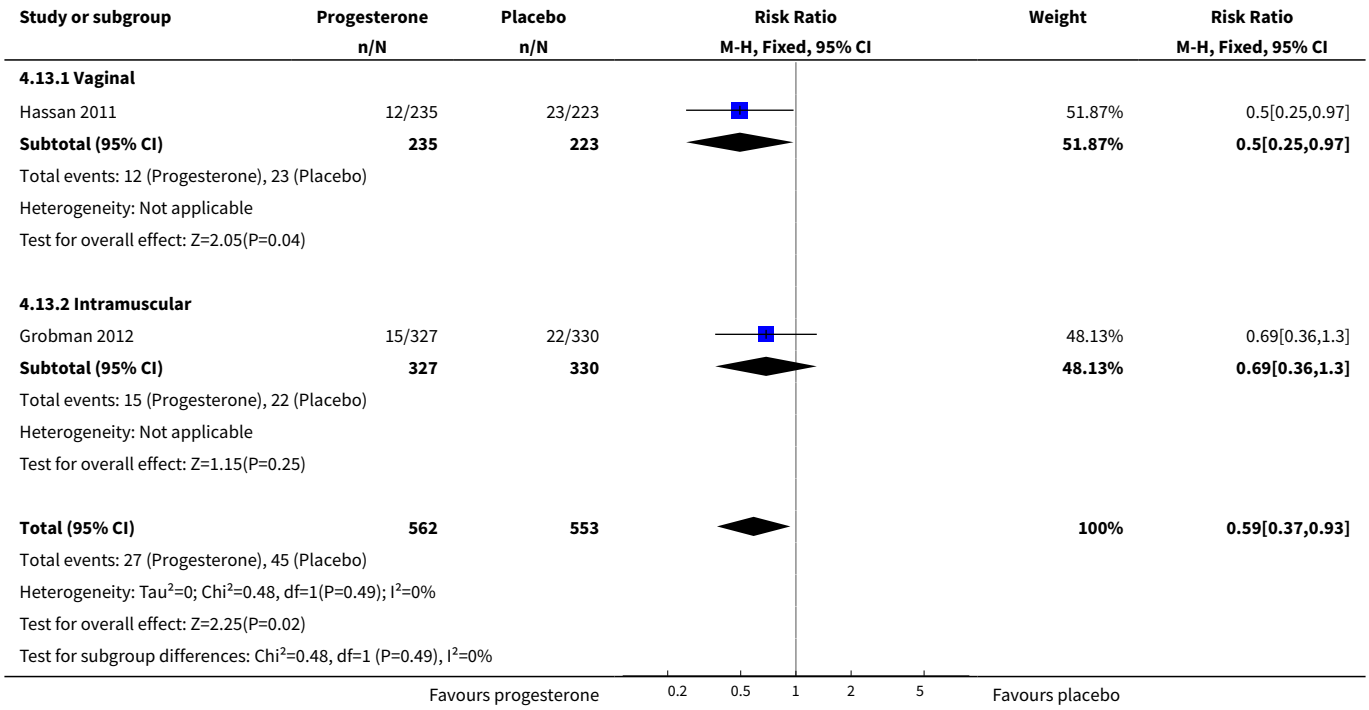


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Analysis 4.12. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 12 Preterm birth less than 37 weeks.



Analysis 4.13. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 13 Preterm birth less than 28 weeks.



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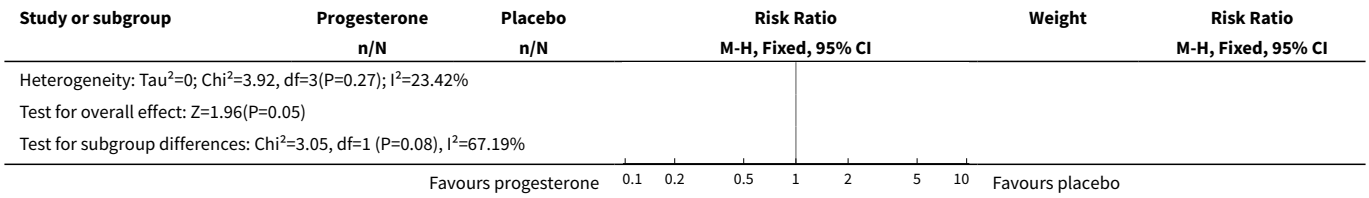
Analysis 4.14. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 14 Infant birthweight less than 2500 g.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.14.1 Vaginal					
Fonseca 2007	56/136	59/138		28.84%	0.96[0.73,1.27]
Hassan 2011	60/234	68/220		34.52%	0.83[0.62,1.11]
Subtotal (95% CI)	**370**	**358**		**63.35%**	**0.89[0.73,1.09]**
Total events: 116 (Progesterone), 127 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.53, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=1.12(P=0.26)					
4.14.2 Intramuscular					
Grobman 2012	72/323	75/328		36.65%	0.97[0.73,1.3]
Subtotal (95% CI)	**323**	**328**		**36.65%**	**0.97[0.73,1.3]**
Total events: 72 (Progesterone), 75 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.18(P=0.86)					
Total (95% CI)	**693**	**686**		**100%**	**0.92[0.78,1.09]**
Total events: 188 (Progesterone), 202 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.74, df=2(P=0.69); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					
Test for subgroup differences: Chi^2=0.26, df=1 (P=0.61), I^2=0%					

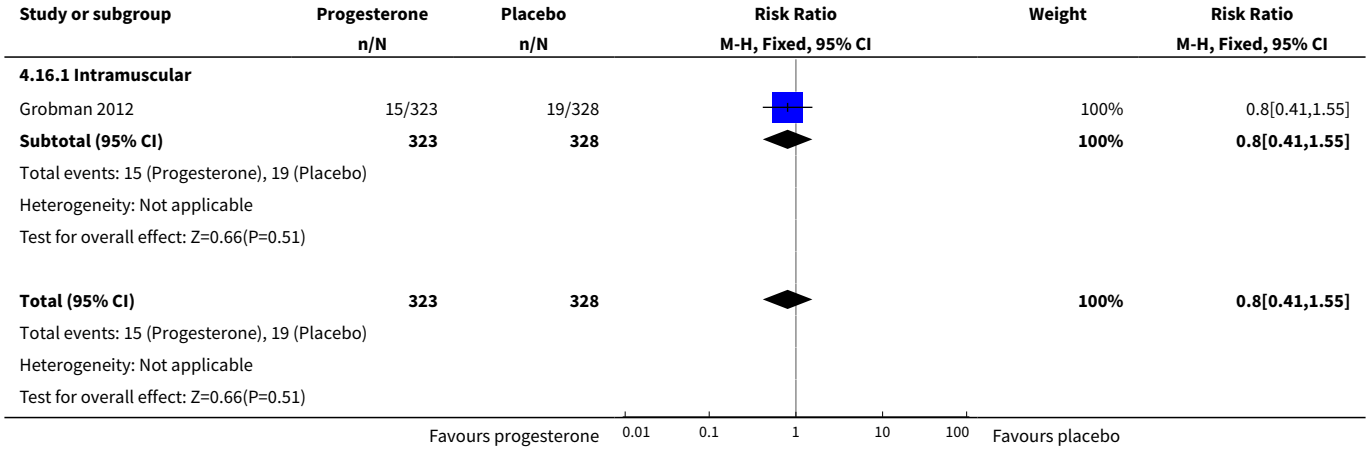
Analysis 4.15. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 15 Respiratory distress syndrome.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.15.1 Vaginal					
Fonseca 2007	11/136	19/138		29.27%	0.59[0.29,1.19]
Hassan 2011	7/235	17/223		27.08%	0.39[0.17,0.92]
Subtotal (95% CI)	**371**	**361**		**56.35%**	**0.49[0.29,0.85]**
Total events: 18 (Progesterone), 36 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.52, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=2.55(P=0.01)					
4.15.2 Intramuscular					
Grobman 2012	13/320	16/323		24.72%	0.82[0.4,1.68]
Rozenberg 2012	14/92	12/89		18.93%	1.13[0.55,2.3]
Subtotal (95% CI)	**412**	**412**		**43.65%**	**0.95[0.58,1.58]**
Total events: 27 (Progesterone), 28 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.38, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=0.18(P=0.85)					
Total (95% CI)	**783**	**773**		**100%**	**0.69[0.48,1]**
Total events: 45 (Progesterone), 64 (Placebo)					

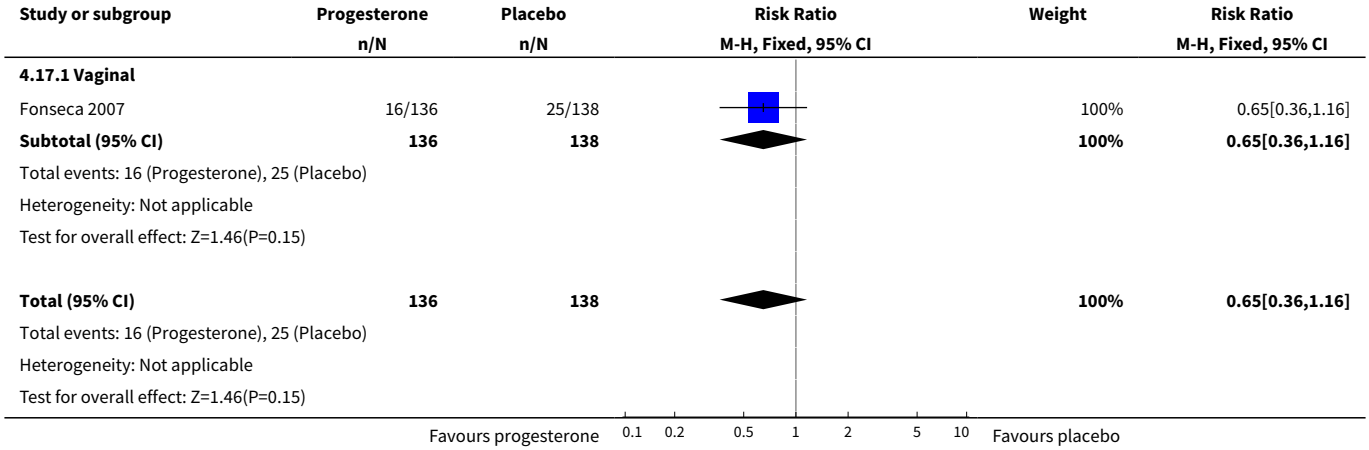
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Analysis 4.16. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 16 Apgar score < 7.

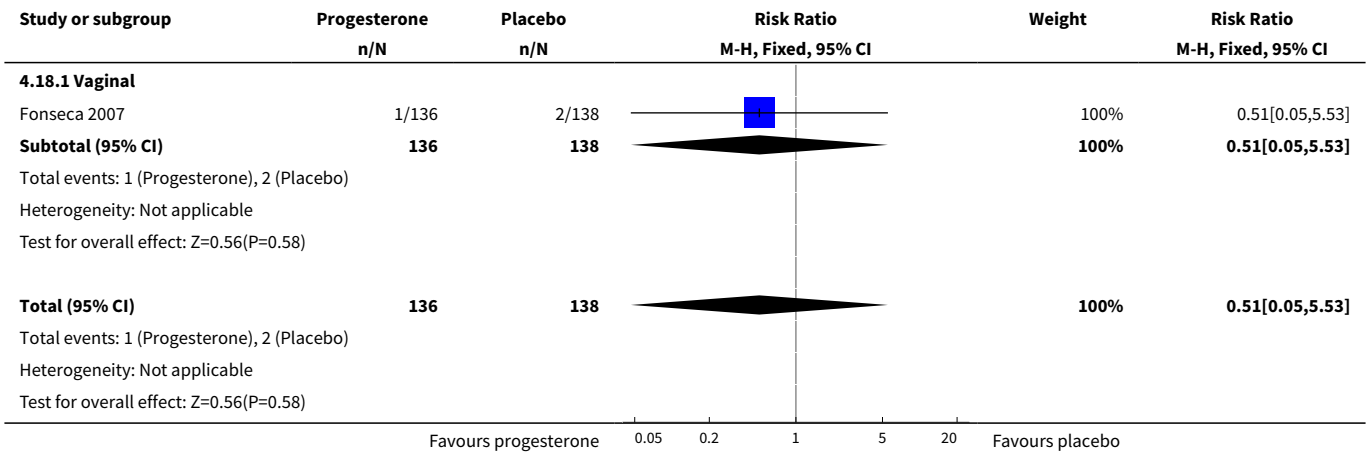


Analysis 4.17. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 17 Need for assisted ventilation.

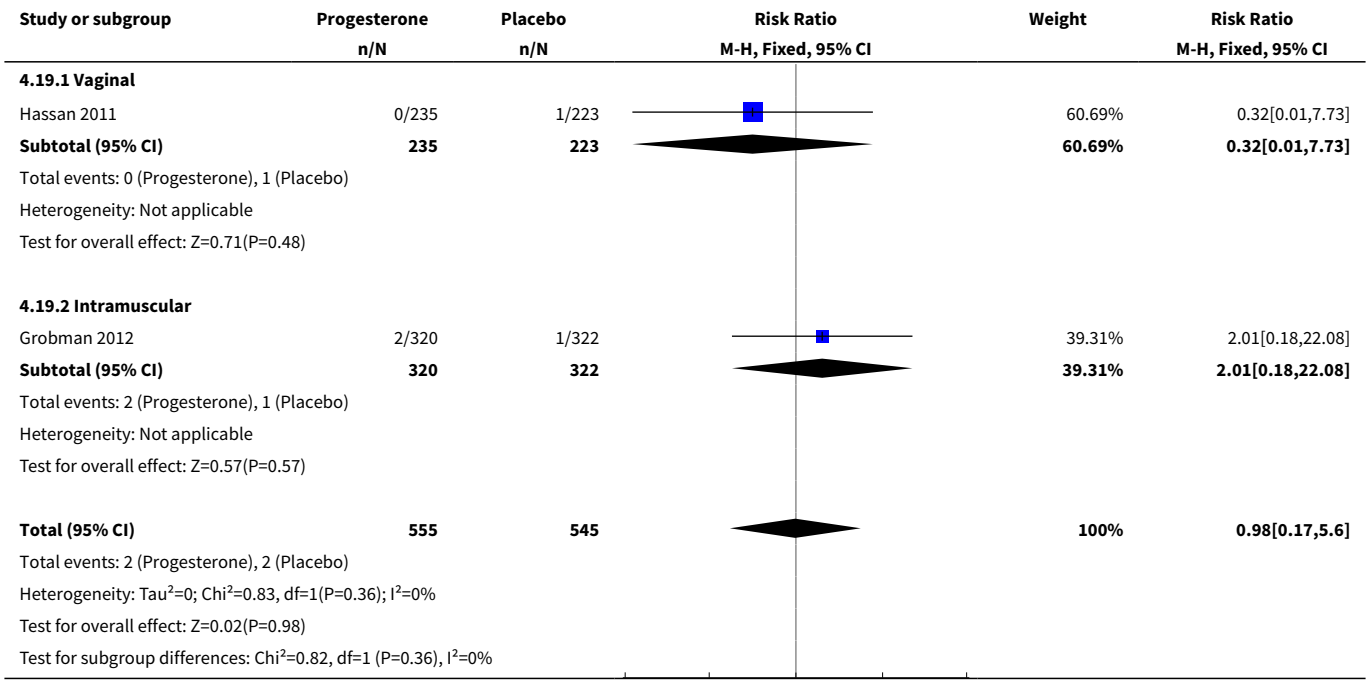


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Analysis 4.18. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 18 Intraventricular haemorrhage - all grades.

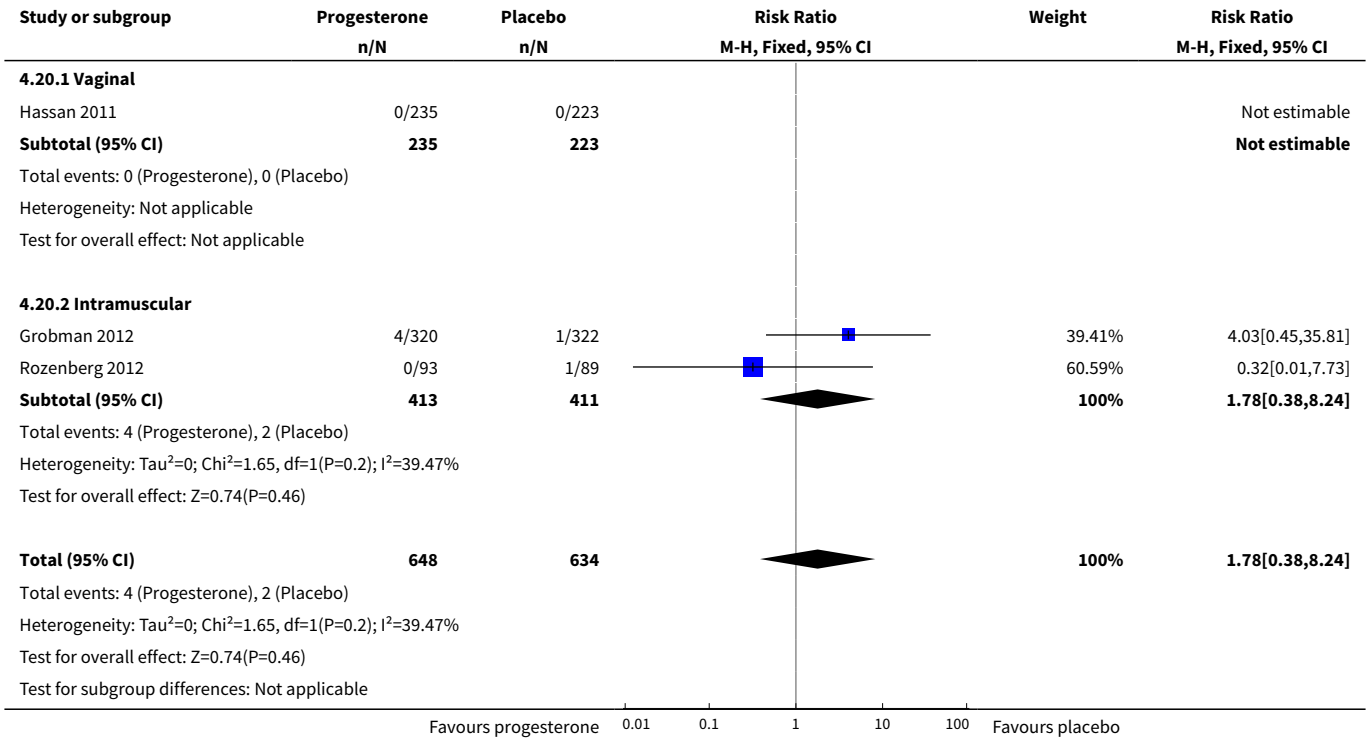


Analysis 4.19. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 19 Intraventricular haemorrhage - grades III or IV.

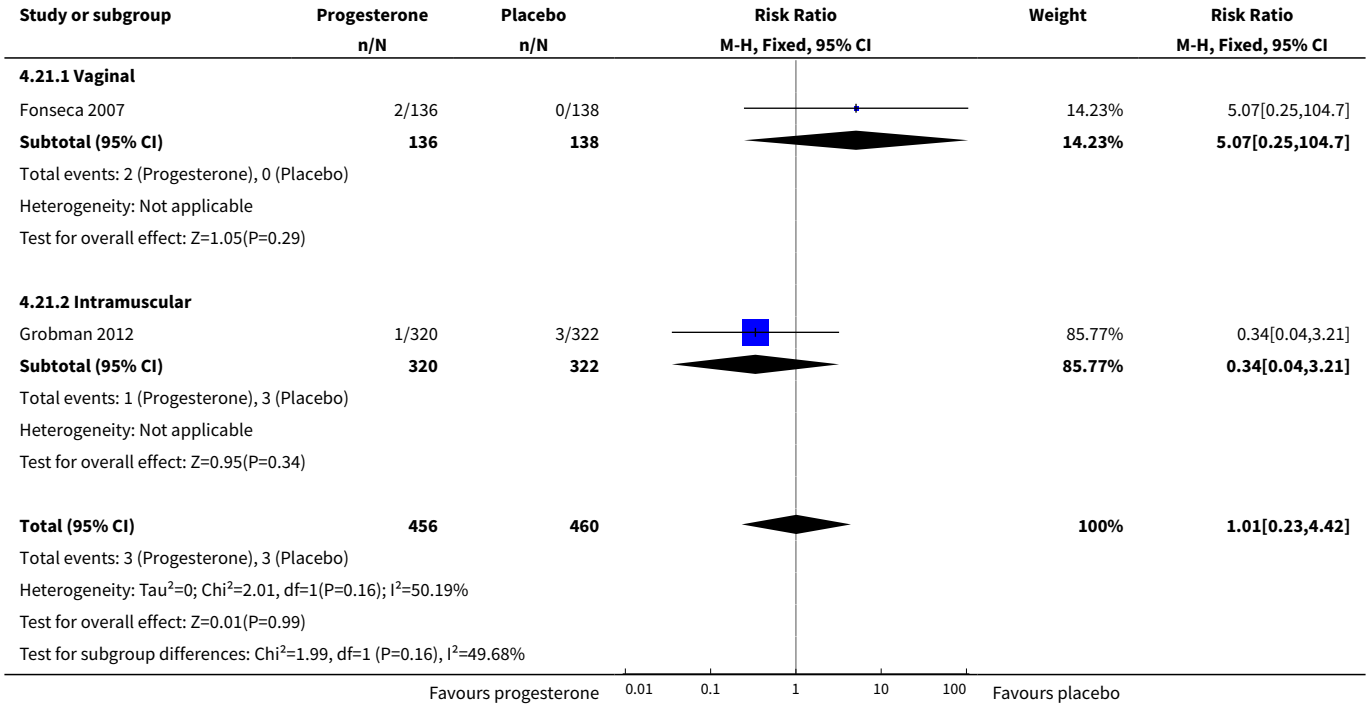


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Analysis 4.20. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 20 Periventricular leucomalacia.

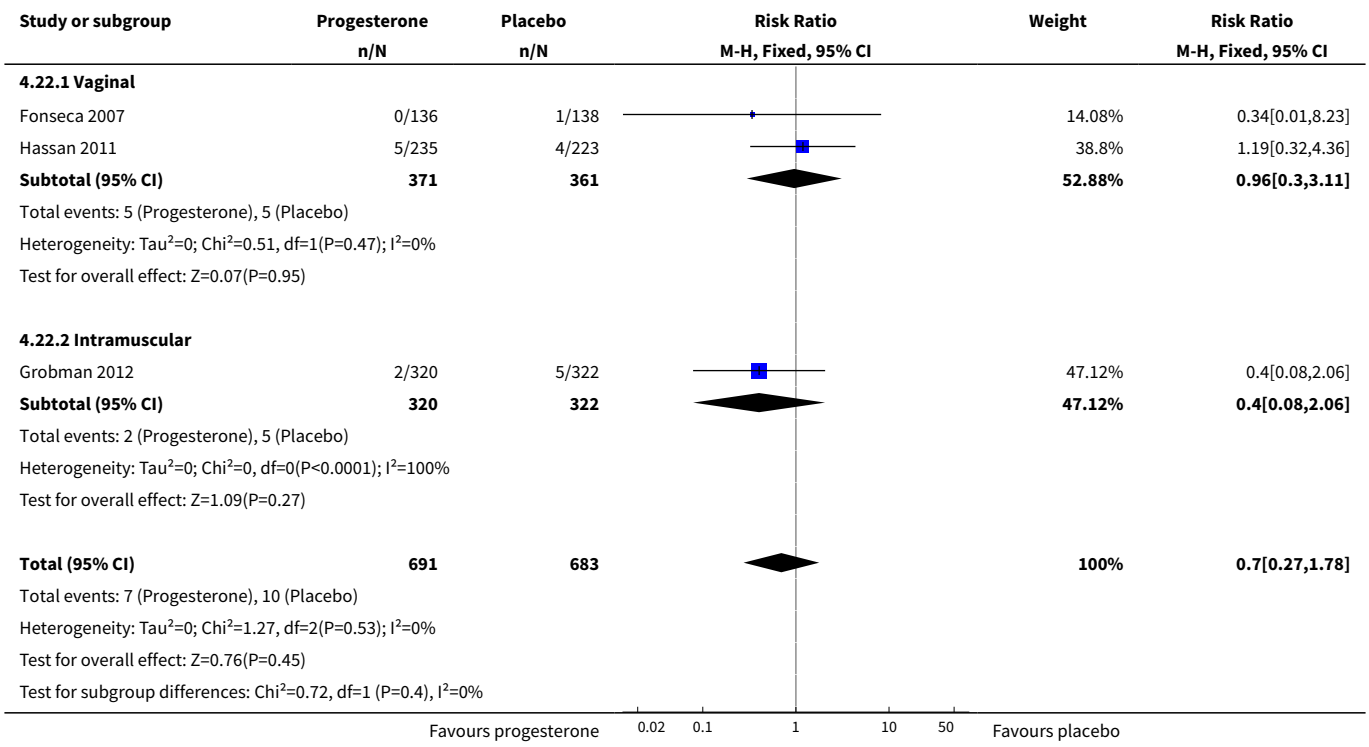


Analysis 4.21. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 21 Retinopathy of prematurity.

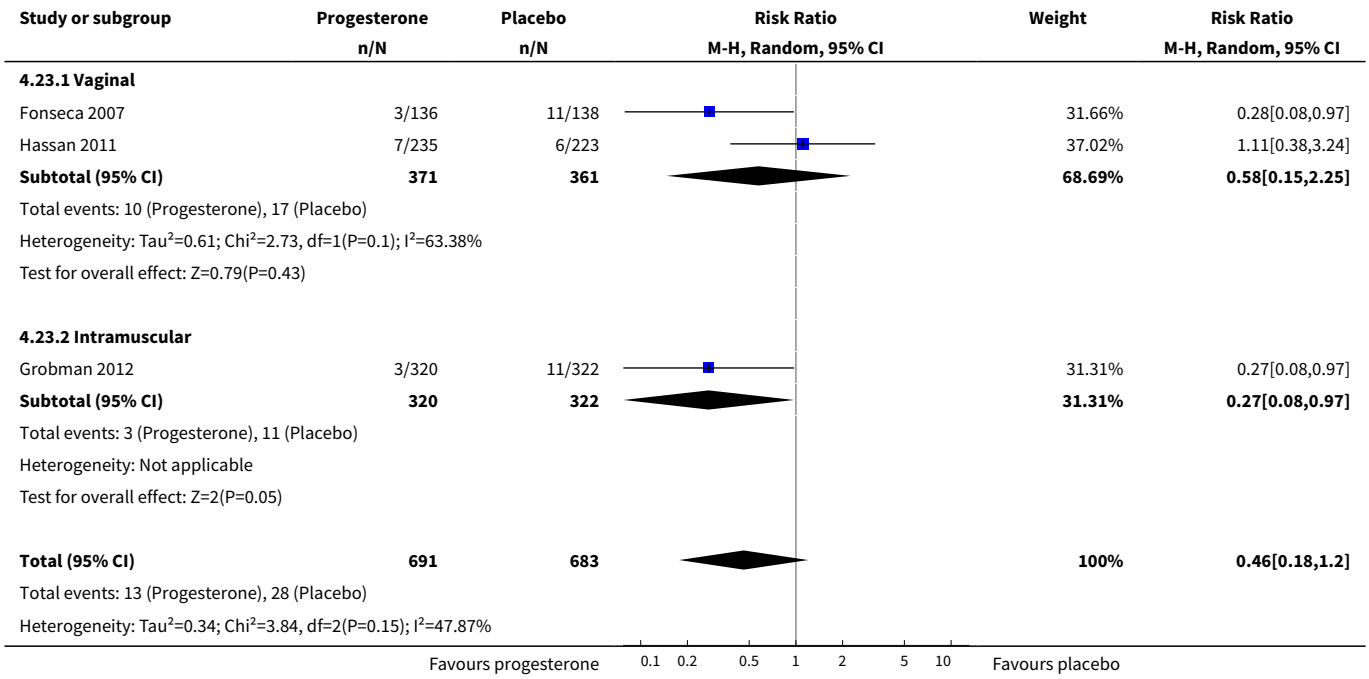


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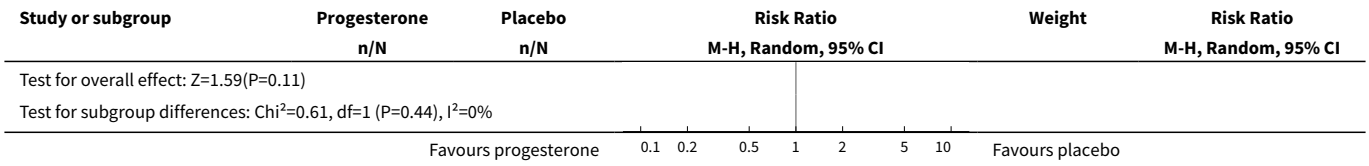
Analysis 4.22. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 22 Necrotising enterocolitis.



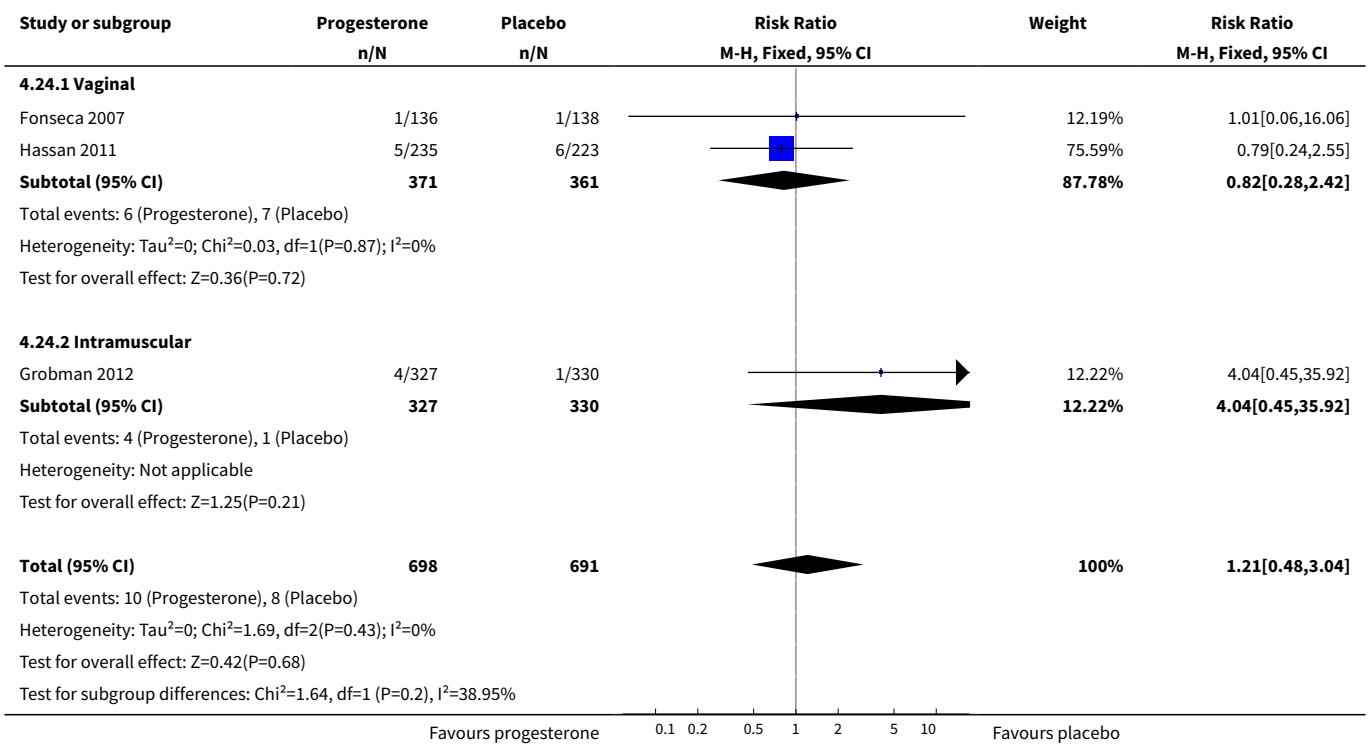
Analysis 4.23. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 23 Neonatal sepsis.



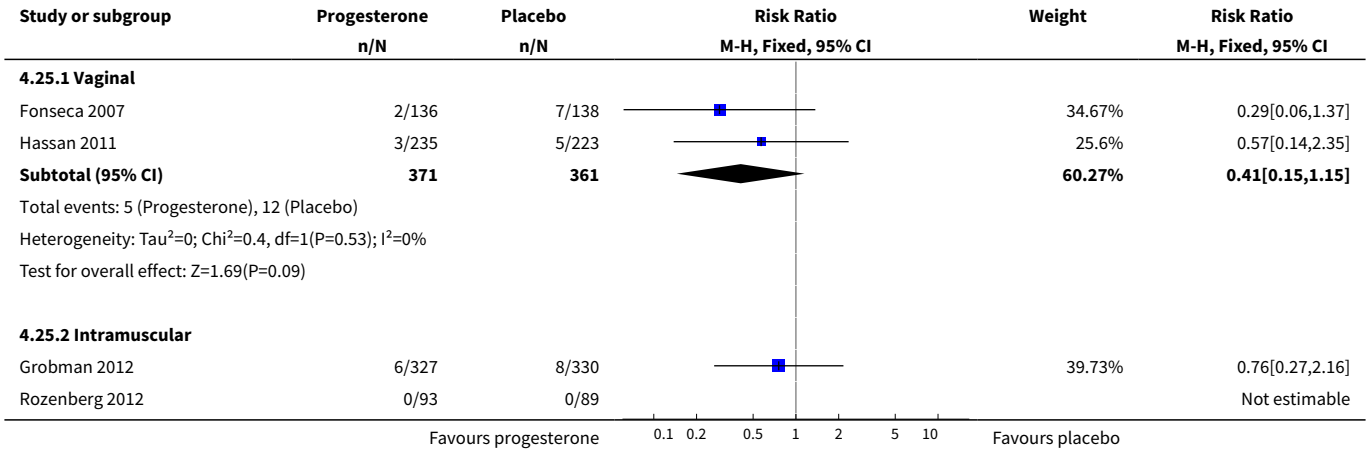
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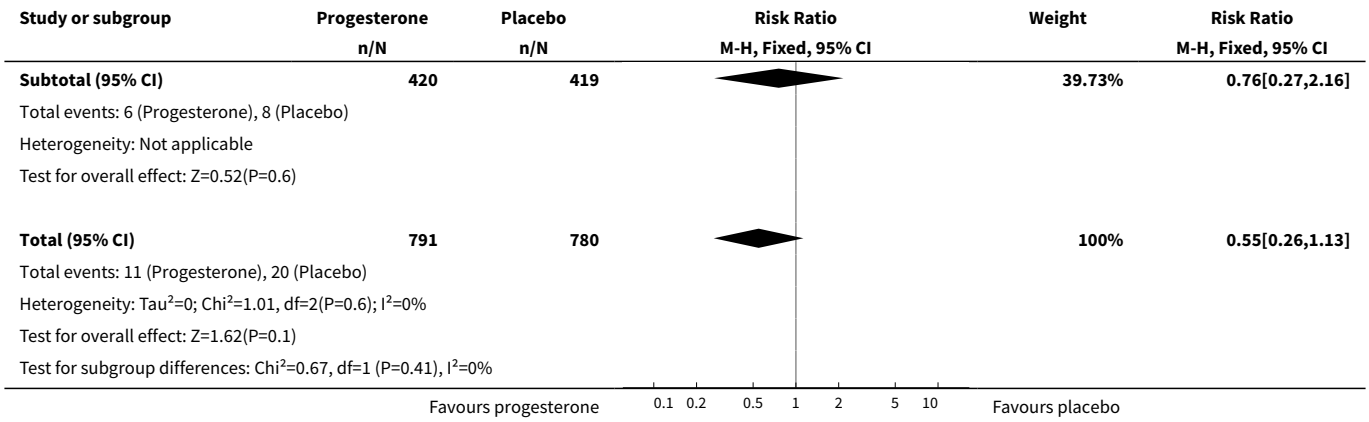
Analysis 4.24. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 24 Intrauterine fetal death.



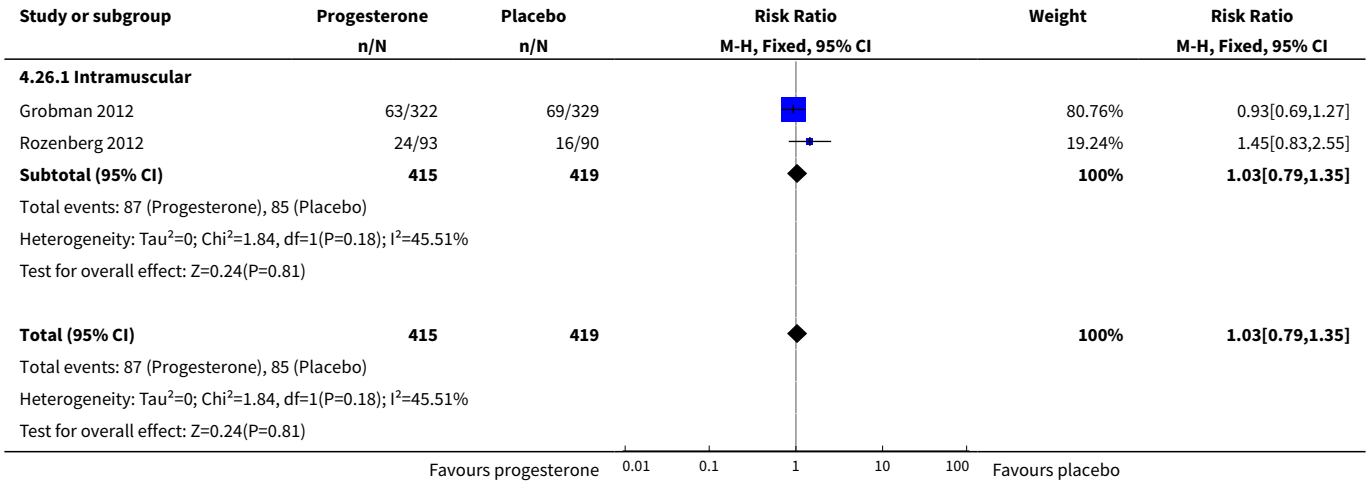
Analysis 4.25. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 25 Neonatal death.



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Analysis 4.26. Comparison 4 Progesterone versus placebo: ultrasound identified short cervix, singletons, Outcome 26 Admission to neonatal intensive care unit.



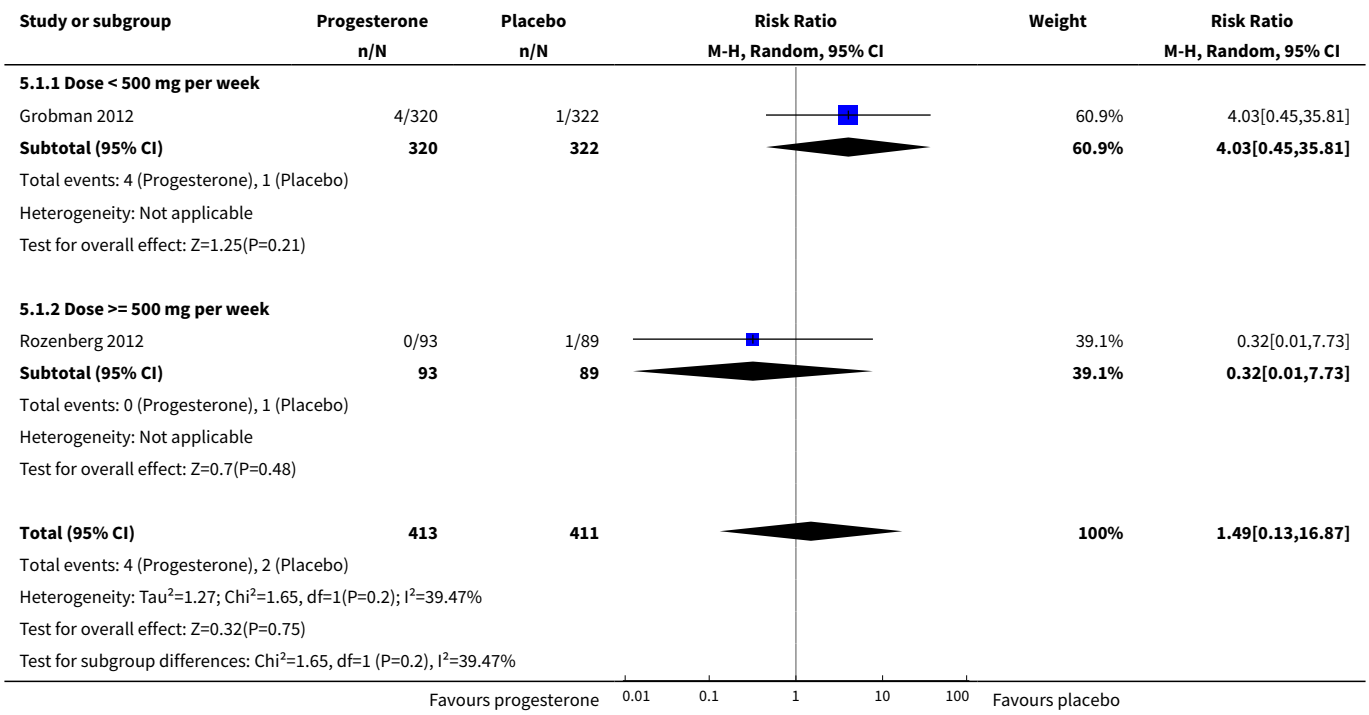
Comparison 5. Progesterone versus placebo: ultrasound identified short cervix, singletons by cumulative weekly dose (<500 mg v >=500 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Periventricular leucomalacia	2	824	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.13, 16.87]
1.1 Dose < 500 mg per week	1	642	Risk Ratio (M-H, Random, 95% CI)	4.03 [0.45, 35.81]
1.2 Dose >= 500 mg per week	1	182	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.73]
2 Admission to neonatal intensive care unit	2	834	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.72, 1.65]
2.1 Dose < 500 mg per week	1	651	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.69, 1.27]

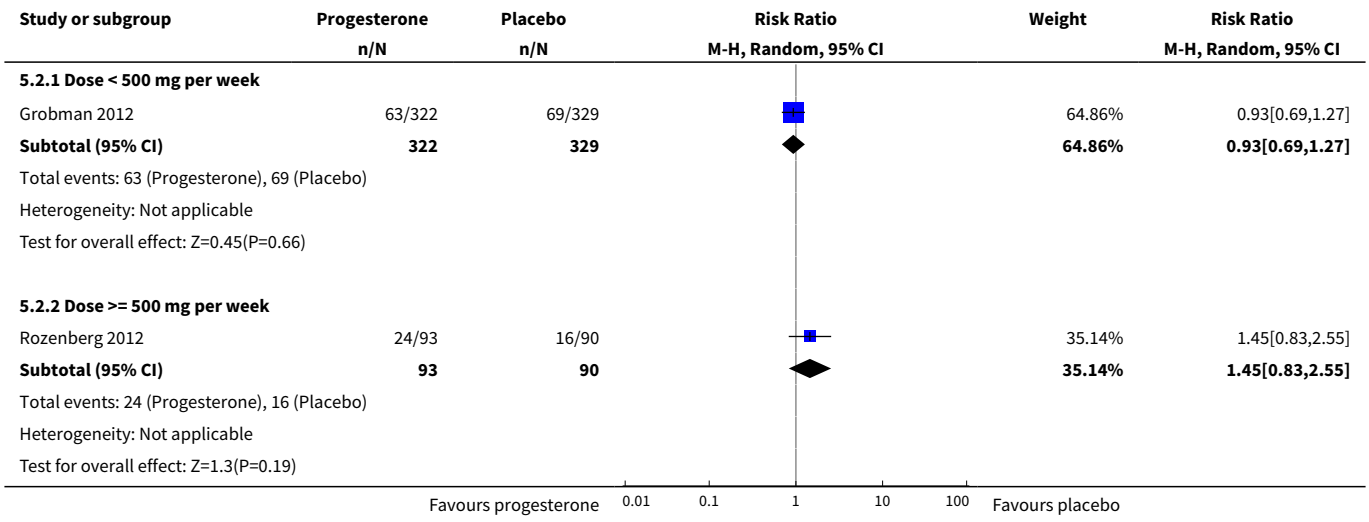
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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Dose >= 500 mg per week	1	183	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.83, 2.55]

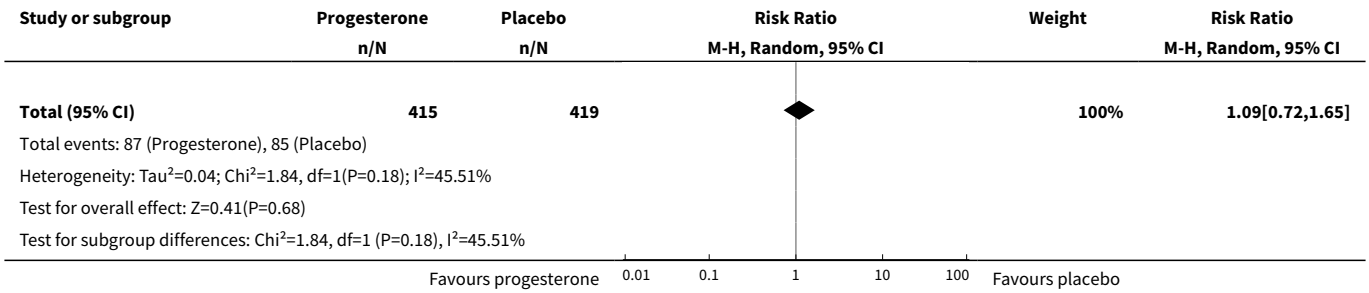
Analysis 5.1. Comparison 5 Progesterone versus placebo: ultrasound identified short cervix, singletons by cumulative weekly dose (<500 mg v >=500 mg), Outcome 1 Periventricular leucomalacia.



Analysis 5.2. Comparison 5 Progesterone versus placebo: ultrasound identified short cervix, singletons by cumulative weekly dose (<500 mg v >=500 mg), Outcome 2 Admission to neonatal intensive care unit.



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Comparison 6. Progesterone versus placebo: multiple pregnancy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	7	4136	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.45, 1.94]
1.1 Intramuscular	4	2228	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.30, 3.71]
1.2 Vaginal	3	1908	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.24, 2.41]
2 Preterm birth less than 34 weeks	6	1758	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.74, 1.27]
2.1 Vaginal	5	1520	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.69, 1.23]
2.2 Intramuscular	1	238	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.73, 2.59]
3 Preterm PROM	3	995	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.74, 1.70]
3.1 Intramuscular	2	802	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.72, 1.71]
3.2 Vaginal	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.30, 5.74]
4 Adverse drug reaction	2	1162	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.19]
4.1 Intramuscular	1	668	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.54, 1.01]
4.2 Vaginal	1	494	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.08]
5 Caesarean section	8	3136	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.91, 1.02]
5.1 Intramuscular	5	1773	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.09]
5.2 Vaginal	3	1363	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.84, 0.98]
6 Spontaneous birth	2	1168	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.62, 2.38]
6.1 Intramuscular	1	668	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.75, 1.04]
6.2 Vaginal	1	500	Risk Ratio (M-H, Random, 95% CI)	1.74 [1.21, 2.49]
7 Assisted birth	2	1168	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.57, 1.76]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Intramuscular	1	668	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.86, 1.99]
7.2 Vaginal	1	500	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.44, 1.24]
8 Satisfaction with therapy	1	494	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.35, 0.35]
8.1 Vaginal	1	494	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.35, 0.35]
9 Antenatal tocolysis	7	2642	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.80, 1.10]
9.1 Intramuscular	5	1775	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.17]
9.2 Vaginal	2	867	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.03]
10 Antenatal corticosteroids	2	847	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.77, 1.26]
10.1 Intramuscular	1	654	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.70, 1.17]
10.2 Vaginal	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.81, 3.49]
11 Preterm birth less than 37 weeks	8	2674	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.95, 1.14]
11.1 Intramuscular	4	1638	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.96, 1.22]
11.2 Vaginal	4	1036	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.85, 1.13]
12 Preterm birth less than 28 weeks	5	1855	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.75, 1.95]
12.1 Intramuscular	3	987	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.68, 2.07]
12.2 Vaginal	2	868	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.51, 3.19]
13 Infant birthweight less than 2500 g	7	5404	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
13.1 Intramuscular	4	3502	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.14]
13.2 Vaginal	3	1902	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.80, 0.94]
14 Apgar score < 7 at 5 minutes	4	3451	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.66, 1.21]
14.1 Intramuscular	2	1750	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.70, 1.38]
14.2 Vaginal	2	1701	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.28, 1.23]
15 Respiratory distress syndrome	6	5065	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.94, 1.35]
15.1 Intramuscular	5	3732	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.42]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.2 Vaginal	1	1333	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.79, 1.48]
16 Use of assisted ventilation	4	3392	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.16]
16.1 Intramuscular	2	1675	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.80, 1.22]
16.2 Vaginal	2	1717	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.45, 1.36]
17 Intraventricular haemorrhage - grades III or IV	4	2368	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.45, 1.92]
17.1 Intramuscular	4	2368	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.45, 1.92]
18 Intraventricular haemorrhage - all grades	2	2688	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [0.75, 4.21]
18.1 Intramuscular	1	1355	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [0.36, 10.77]
18.2 Vaginal	1	1333	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.62, 4.66]
19 Periventricular leucomalacia	3	1091	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.05, 3.02]
19.1 Intramuscular	3	1091	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.05, 3.02]
20 Retinopathy of prematurity	5	3668	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.32, 1.91]
20.1 Intramuscular	4	2335	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.20, 2.06]
20.2 Vaginal	1	1333	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.26, 4.07]
21 Chronic lung disease	2	681	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.13, 27.80]
21.1 Intramuscular	2	681	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.13, 27.80]
22 Necrotising enterocolitis	6	5059	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.50, 1.75]
22.1 Intramuscular	5	3726	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.52, 1.88]
22.2 Vaginal	1	1333	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.63]
23 Neonatal sepsis	6	5065	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.62]
23.1 Intramuscular	5	3732	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.87, 1.72]
23.2 Vaginal	1	1333	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.61, 2.13]
24 Fetal death	6	4788	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.71, 2.09]
24.1 Intramuscular	3	2074	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.77, 3.12]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.2 Vaginal	3	2714	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.35, 1.95]
25 Neonatal death	7	5170	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.48, 2.10]
25.1 Intramuscular	4	2456	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.31, 2.10]
25.2 Vaginal	3	2714	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.36, 4.95]
26 Admission to NICU	5	4251	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.76, 1.18]
26.1 Vaginal	4	2896	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
26.2 Intramuscular	1	1355	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.05, 1.62]
27 Perinatal death	7	4133	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.61, 2.08]
27.1 Intramuscular	4	2228	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.30, 3.71]
27.2 Vaginal	3	1905	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.67, 2.35]
28 Preterm birth less than 34 weeks	6	1758	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.71, 1.24]
28.1 Vaginal	5	1520	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.65, 1.19]
28.2 Intramuscular	1	238	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.73, 2.59]
29 Preterm PROM	3	995	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]
29.1 Intramuscular	2	802	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.72, 1.71]
29.2 Vaginal	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.12]
30 Caesarean section	8	3136	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.91, 1.01]
30.1 Intramuscular	5	1773	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.09]
30.2 Vaginal	3	1363	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.98]
31 Antenatal tocolysis	7	2642	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.80, 1.10]
31.1 Intramuscular	5	1775	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.17]
31.2 Vaginal	2	867	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.05]
32 Antenatal corticosteroids	2	847	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.76, 1.24]
32.1 Intramuscular	1	654	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.70, 1.17]
32.2 Vaginal	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.76, 3.31]
33 Preterm birth less than 37 weeks	8	2674	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.95, 1.13]

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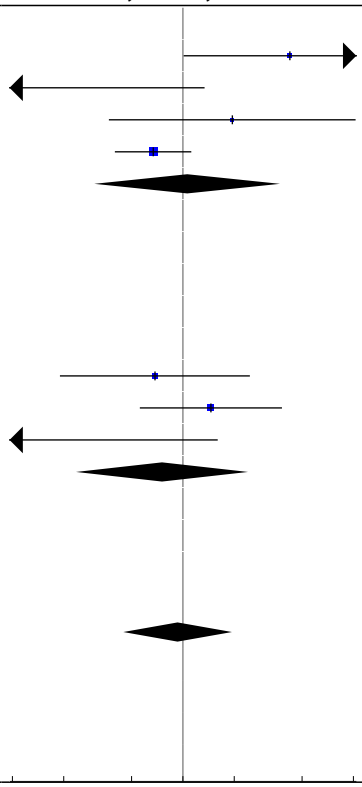
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.1 Intramuscular	4	1638	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.96, 1.22]
33.2 Vaginal	4	1036	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.84, 1.11]
34 Preterm birth less than 28 weeks	5	1855	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.80, 2.04]
34.1 Intramuscular	3	987	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.68, 2.07]
34.2 Vaginal	2	868	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.63, 3.69]
35 Infant birthweight less than 2500 g	7	5401	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.89, 1.04]
35.1 Intramuscular	4	3502	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.14]
35.2 Vaginal	3	1899	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.82, 0.96]
36 Apgar score < 7 at 5 minutes	4	3448	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.70, 1.27]
36.1 Intramuscular	2	1750	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.70, 1.38]
36.2 Vaginal	2	1698	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.41, 1.58]
37 Use of assisted ventilation	4	3389	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.19]
37.1 Intramuscular	2	1675	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.80, 1.22]
37.2 Vaginal	2	1714	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.55, 1.59]
38 Fetal death	6	4785	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.79, 2.29]
38.1 Intramuscular	3	2074	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.77, 3.12]
38.2 Vaginal	3	2711	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.49, 2.48]
39 Neonatal death	7	5167	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.62, 2.21]
39.1 Intramuscular	4	2456	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.31, 2.10]
39.2 Vaginal	3	2711	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.84, 3.72]
40 Admission to NICU	5	4248	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.17]
40.1 Vaginal	4	2893	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.07]
40.2 Intramuscular	1	1355	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.05, 1.62]
41 Sensitivity analysis for perinatal death (assuming total non-independence)	7	2068	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.43, 1.65]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
41.1 Intramuscular	4	1114	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.29, 3.36]
41.2 Vaginal	3	954	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.28, 2.07]
42 Sensitivity analysis for perinatal death (assuming 1% non-independence)	7	4091	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.44, 1.90]
42.1 Intramuscular	4	2203	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.29, 3.58]
42.2 Vaginal	3	1888	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.24, 2.41]

Analysis 6.1. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 1 Perinatal death.

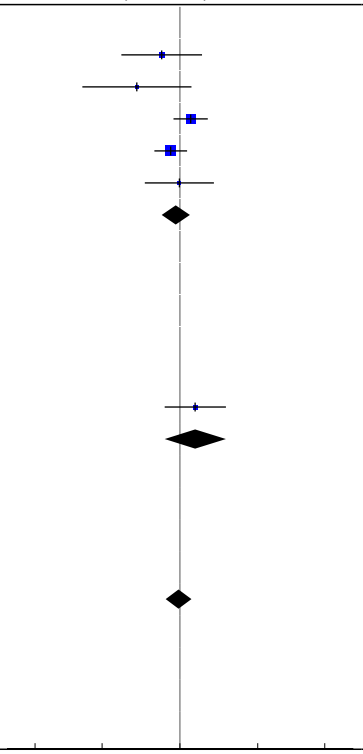
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Intramuscular					
Combs 2010	19/168	2/75		14.26%	4.24[1.01,17.75]
Combs 2011	0/320	3/156		5.14%	0.07[0,1.34]
Hartikainen 1980	4/78	2/76		11.94%	1.95[0.37,10.33]
Lim 2011	23/681	34/674		27%	0.67[0.4,1.12]
Subtotal (95% CI)	**1247**	**981**		**58.34%**	**1.06[0.3,3.71]**
Total events: 46 (Progesterone), 41 (Placebo)					
Heterogeneity: Tau^2=1.02; Chi^2=9.42, df=3(P=0.02); I^2=68.17%					
Test for overall effect: Z=0.09(P=0.93)					
6.1.2 Vaginal					
Aboulghar 2012	4/98	5/84		15.98%	0.69[0.19,2.47]
Rode 2011	10/664	7/678		20.34%	1.46[0.56,3.81]
Serra 2013	0/194	5/190		5.35%	0.09[0,1.6]
Subtotal (95% CI)	**956**	**952**		**41.66%**	**0.75[0.24,2.41]**
Total events: 14 (Progesterone), 17 (Placebo)					
Heterogeneity: Tau^2=0.49; Chi^2=3.78, df=2(P=0.15); I^2=47.09%					
Test for overall effect: Z=0.48(P=0.63)					
Total (95% CI)	**2203**	**1933**		**100%**	**0.93[0.45,1.94]**
Total events: 60 (Progesterone), 58 (Placebo)					
Heterogeneity: Tau^2=0.45; Chi^2=13.01, df=6(P=0.04); I^2=53.9%					
Test for overall effect: Z=0.19(P=0.85)					
Test for subgroup differences: Chi^2=0.15, df=1 (P=0.7), I^2=0%					



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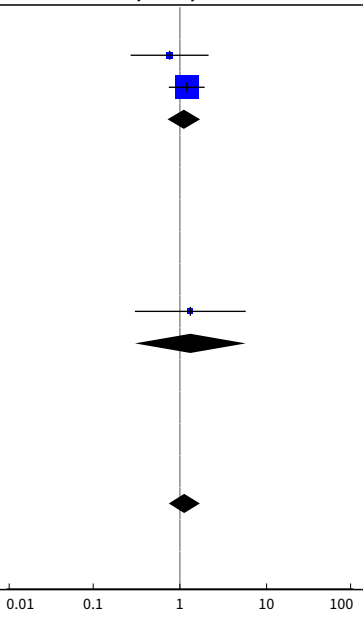
Analysis 6.2. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 2 Preterm birth less than 34 weeks.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Vaginal					
Aboulghar 2012	8/49	10/42		8.74%	0.69[0.3,1.58]
Cetingoz 2011	4/39	7/28		5.09%	0.41[0.13,1.27]
Norman 2009	55/247	44/247		29.71%	1.25[0.88,1.78]
Rode 2011	51/334	63/341		31.36%	0.83[0.59,1.16]
Serra 2013	13/97	13/96		11.32%	0.99[0.48,2.02]
Subtotal (95% CI)	**766**	**754**		**86.21%**	**0.92[0.69,1.23]**
Total events: 131 (Progesterone), 137 (Placebo)					
Heterogeneity: Tau^2=0.03; Chi^2=5.68, df=4(P=0.22); I^2=29.57%					
Test for overall effect: Z=0.59(P=0.56)					
6.2.2 Intramuscular					
Combs 2011	31/160	11/78		13.79%	1.37[0.73,2.59]
Subtotal (95% CI)	**160**	**78**		**13.79%**	**1.37[0.73,2.59]**
Total events: 31 (Progesterone), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.98(P=0.32)					
Total (95% CI)	**926**	**832**		**100%**	**0.97[0.74,1.27]**
Total events: 162 (Progesterone), 148 (Placebo)					
Heterogeneity: Tau^2=0.03; Chi^2=6.88, df=5(P=0.23); I^2=27.27%					
Test for overall effect: Z=0.22(P=0.83)					
Test for subgroup differences: Chi^2=1.3, df=1 (P=0.25), I^2=22.9%					

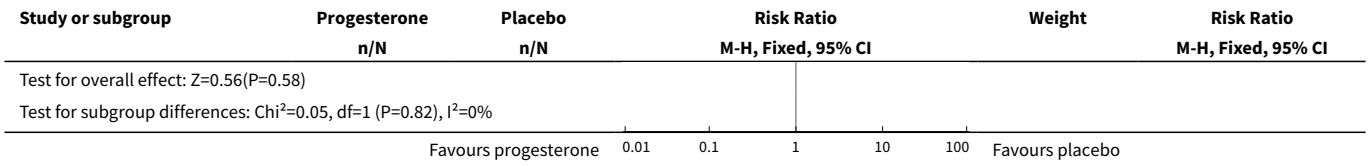


Analysis 6.3. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 3 Preterm PROM.

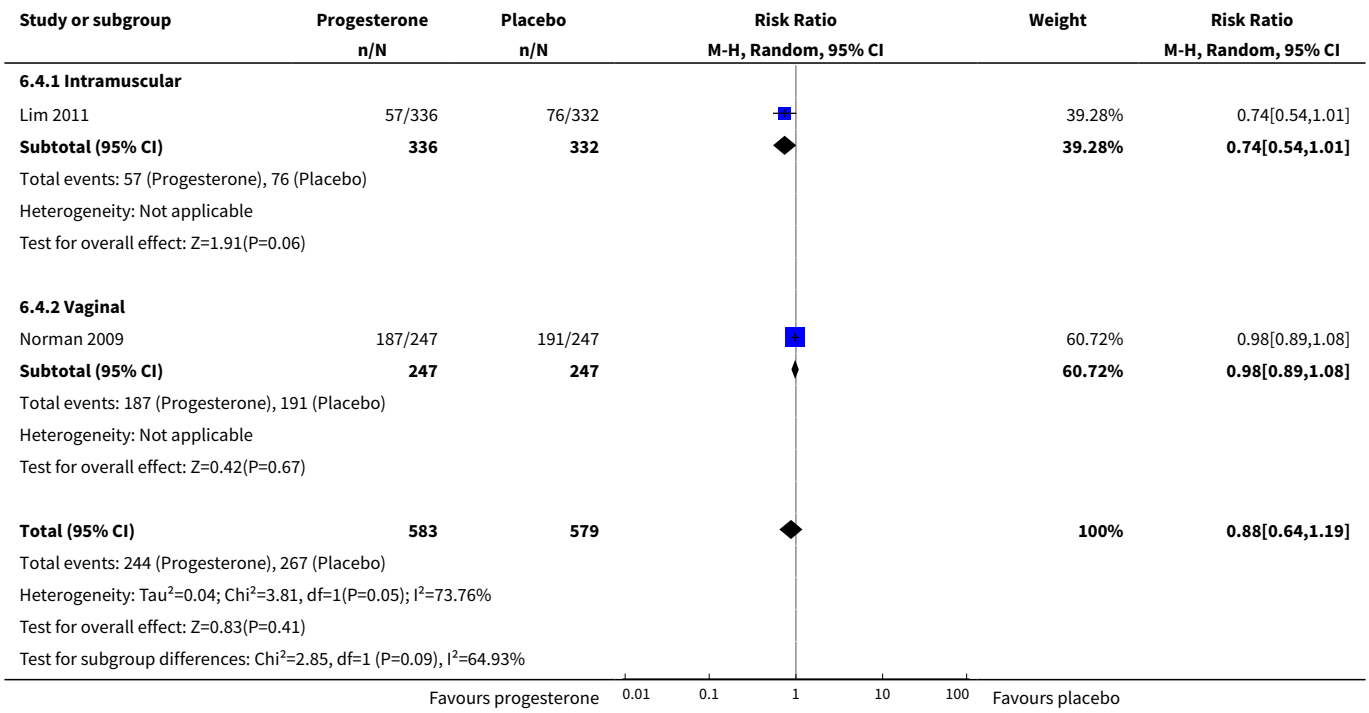
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 Intramuscular					
Caritis 2009	6/71	7/63		19.22%	0.76[0.27,2.14]
Lim 2011	34/336	28/332		72.97%	1.2[0.74,1.93]
Subtotal (95% CI)	**407**	**395**		**92.19%**	**1.11[0.72,1.71]**
Total events: 40 (Progesterone), 35 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.61, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=0.47(P=0.64)					
6.3.2 Vaginal					
Serra 2013	4/97	3/96		7.81%	1.32[0.3,5.74]
Subtotal (95% CI)	**97**	**96**		**7.81%**	**1.32[0.3,5.74]**
Total events: 4 (Progesterone), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					
Total (95% CI)	**504**	**491**		**100%**	**1.12[0.74,1.7]**
Total events: 44 (Progesterone), 38 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.66, df=2(P=0.72); I^2=0%					



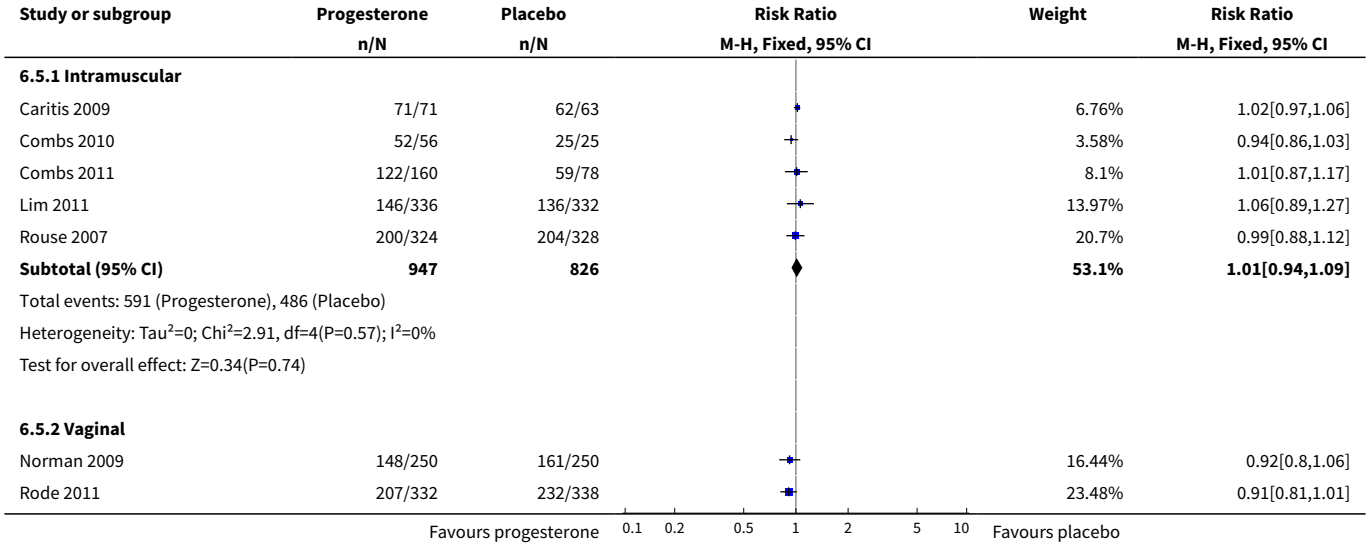
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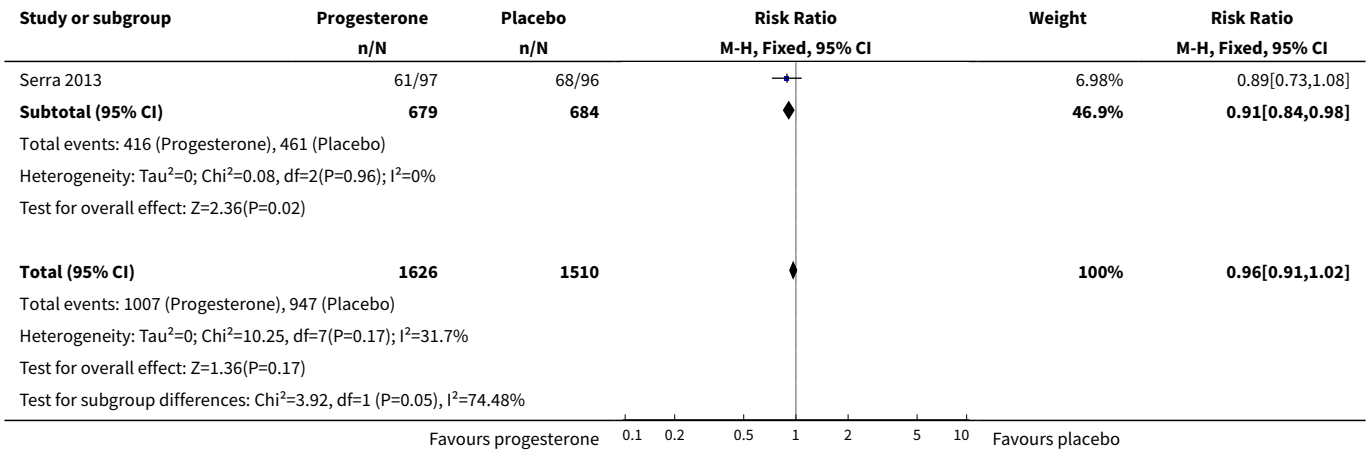
Analysis 6.4. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 4 Adverse drug reaction.



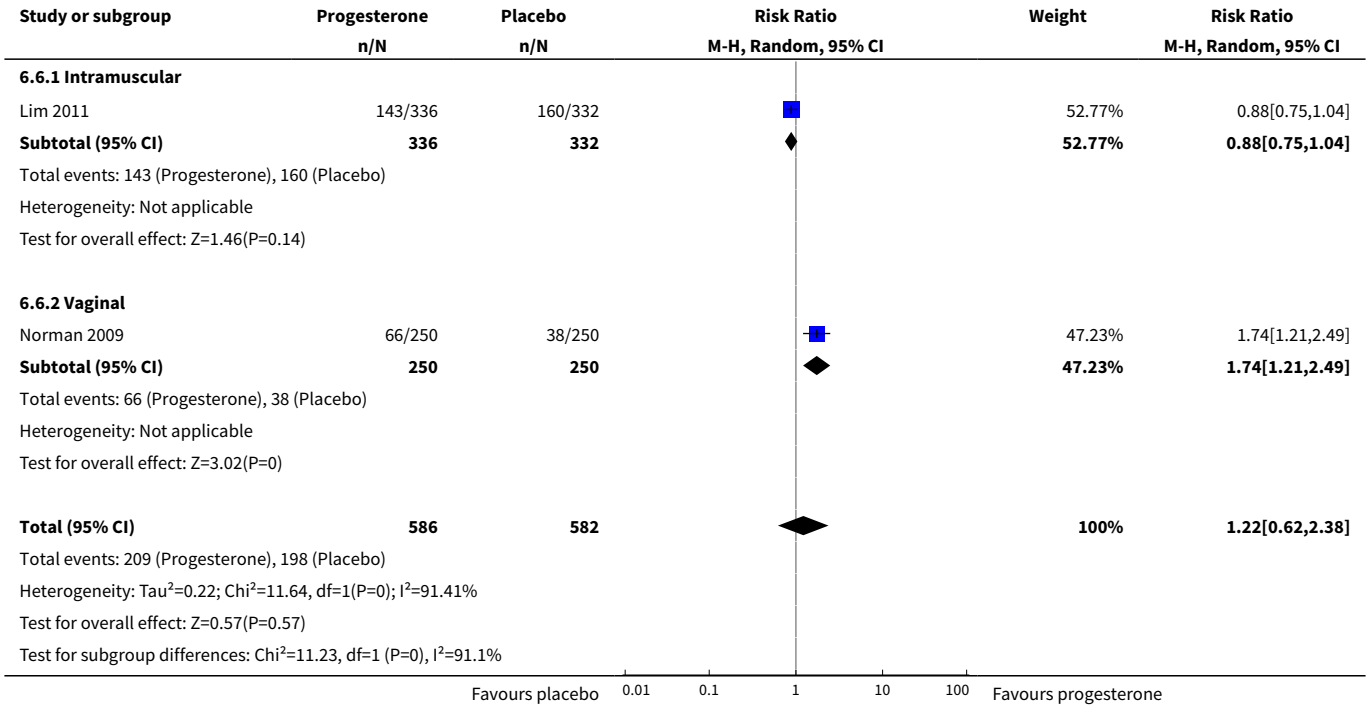
Analysis 6.5. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 5 Caesarean section.



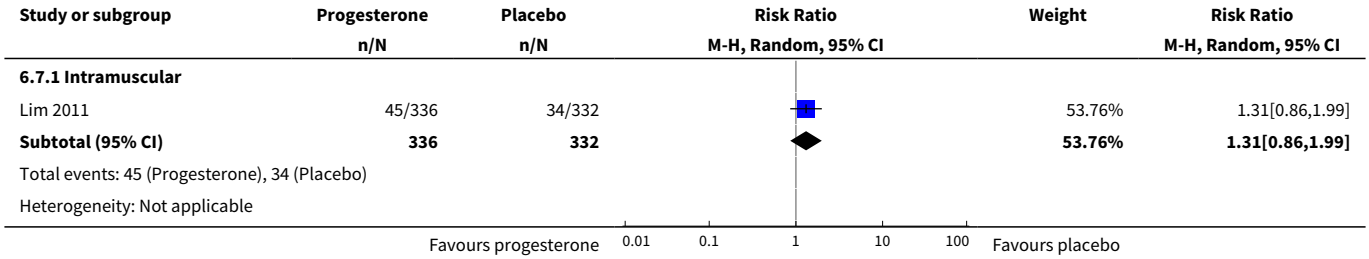
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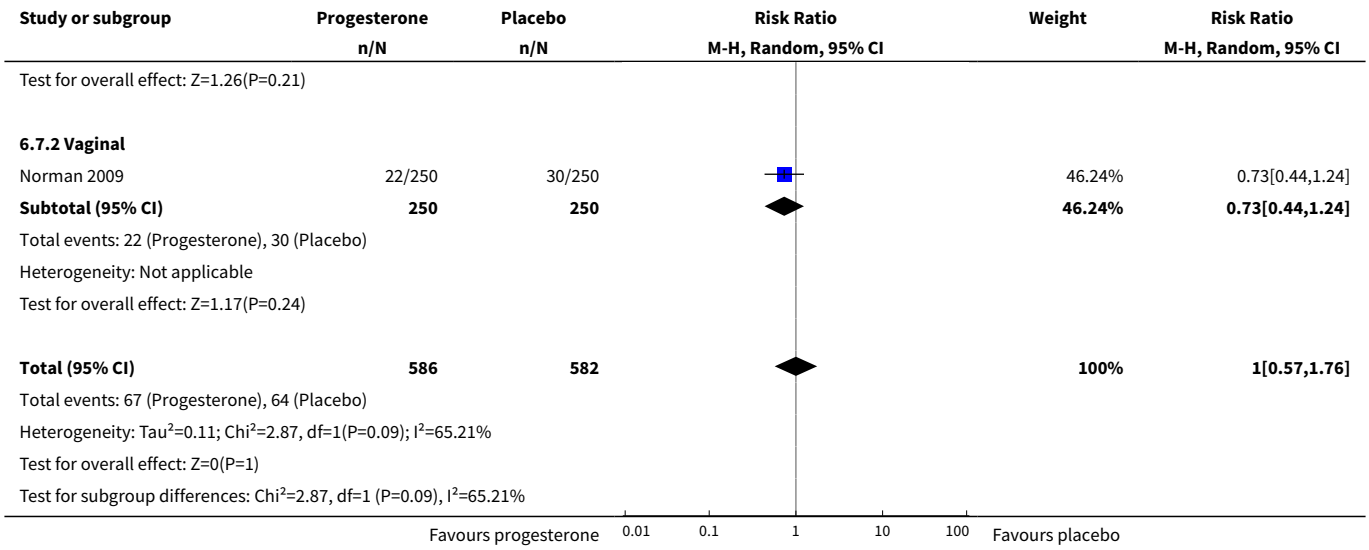
Analysis 6.6. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 6 Spontaneous birth.



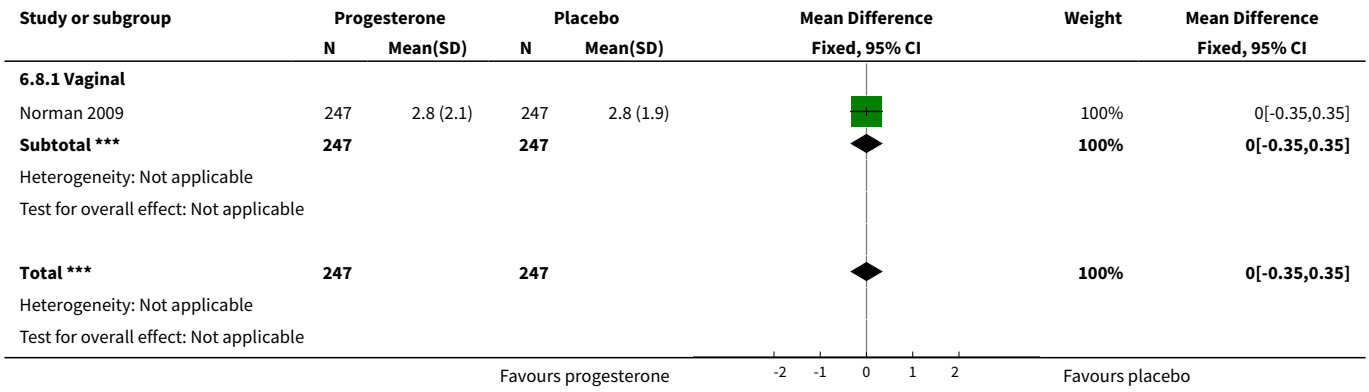
Analysis 6.7. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 7 Assisted birth.



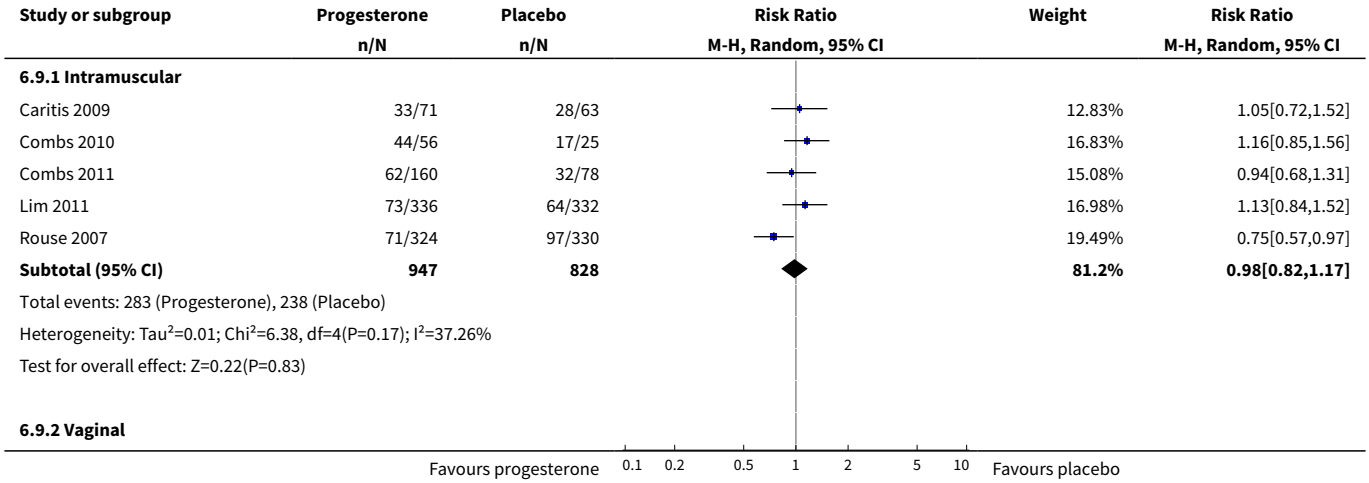
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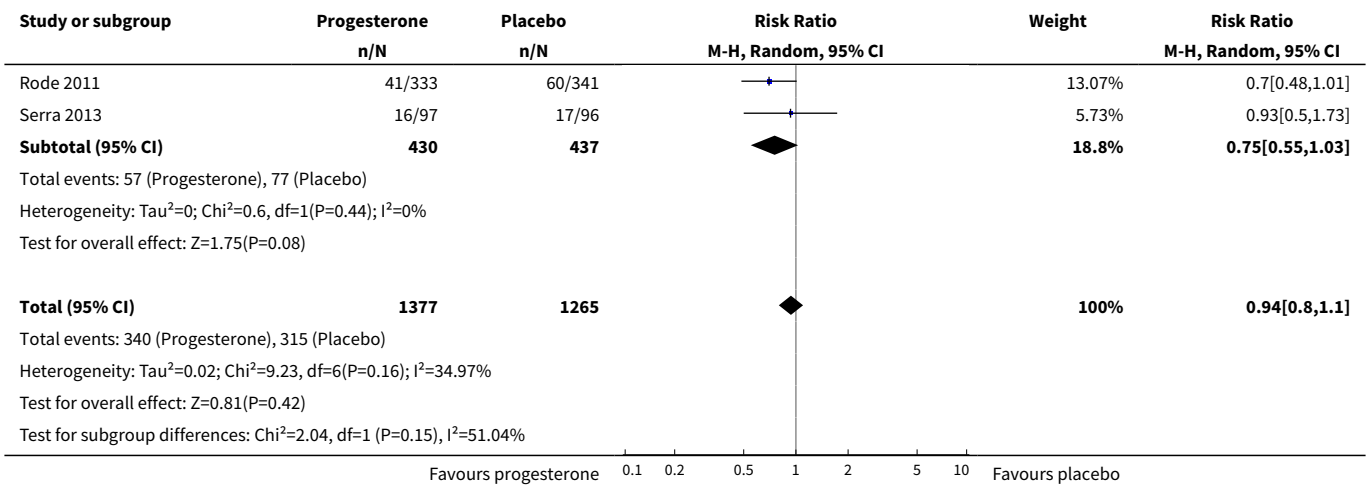
Analysis 6.8. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 8 Satisfaction with therapy.



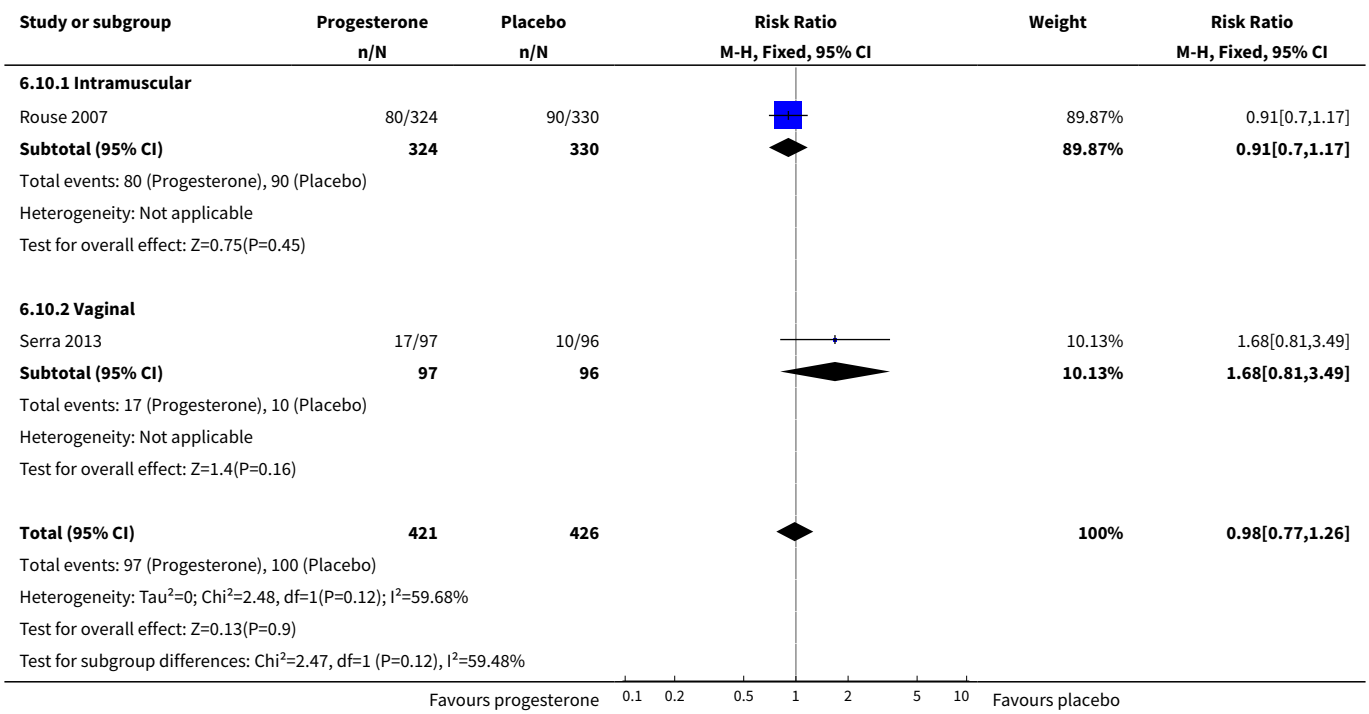
Analysis 6.9. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 9 Antenatal tocolysis.



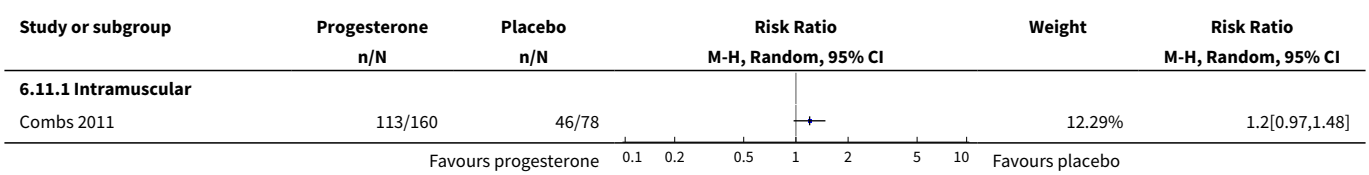
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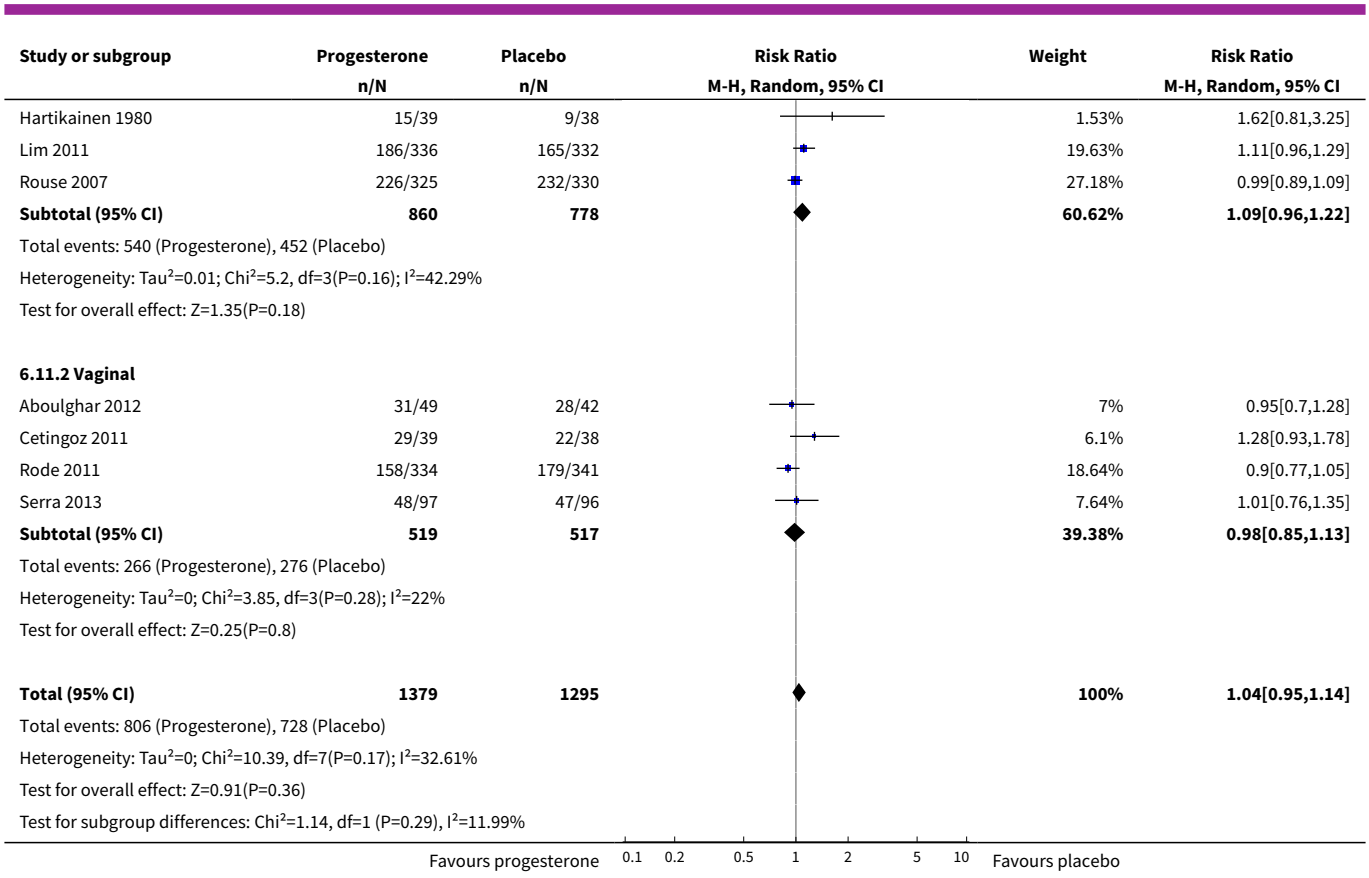
Analysis 6.10. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 10 Antenatal corticosteroids.



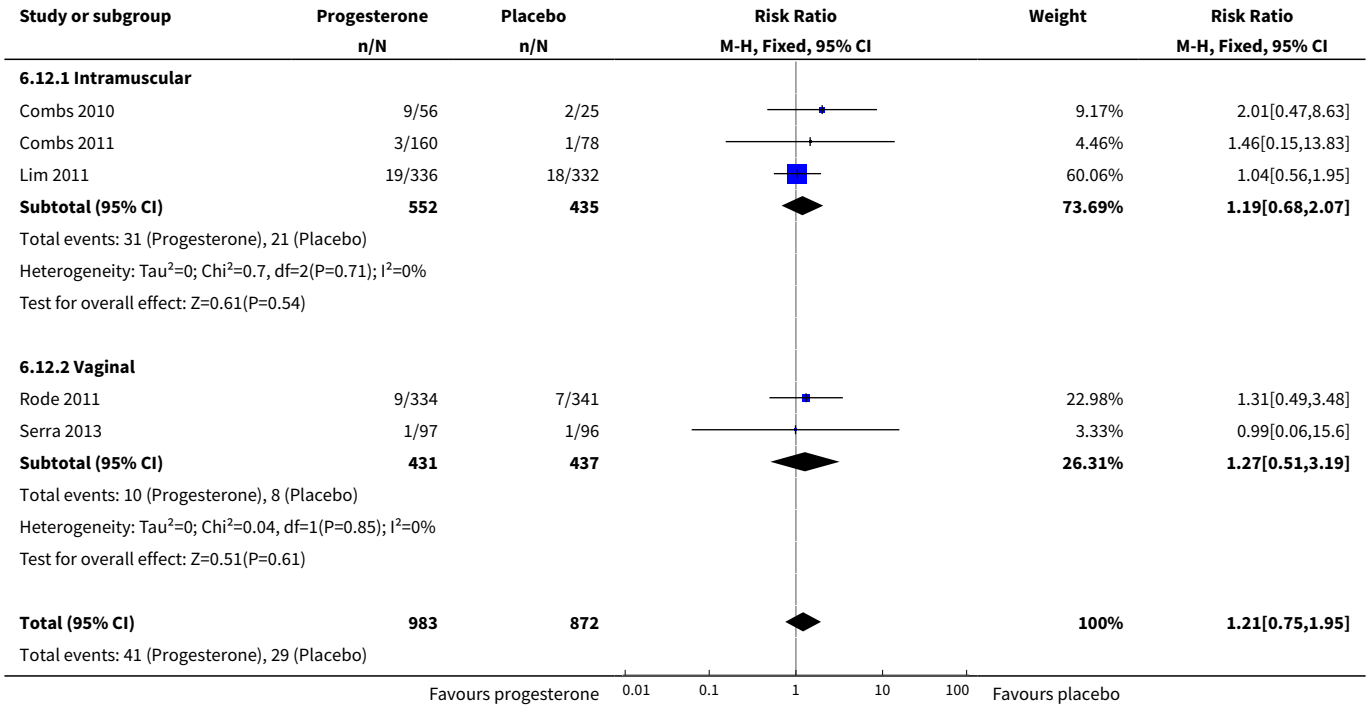
Analysis 6.11. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 11 Preterm birth less than 37 weeks.



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Analysis 6.12. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 12 Preterm birth less than 28 weeks.



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Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.76, df=4(P=0.94); I²=0%					
Test for overall effect: Z=0.79(P=0.43)					
Test for subgroup differences: Chi²=0.02, df=1 (P=0.9), I²=0%					

Favours progesterone 0.01 0.1 1 10 100 Favours placebo

Analysis 6.13. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 13 Infant birthweight less than 2500 g.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.13.1 Intramuscular					
Caritis 2009	191/212	175/183		20.6%	0.94[0.89,0.99]
Combs 2011	195/320	70/156		9.45%	1.36[1.12,1.65]
Lim 2011	363/681	355/674		16.62%	1.01[0.92,1.12]
Rouse 2007	377/628	415/648		17.91%	0.94[0.86,1.02]
Subtotal (95% CI)	**1841**	**1661**		**64.58%**	**1.02[0.91,1.14]**
Total events: 1126 (Progesterone), 1015 (Placebo)					
Heterogeneity: Tau²=0.01; Chi²=16.56, df=3(P=0); I²=81.88%					
Test for overall effect: Z=0.3(P=0.76)					
6.13.2 Vaginal					
Aboulghar 2012	58/98	62/84		8.73%	0.8[0.65,0.99]
Rode 2011	306/659	357/677		15.86%	0.88[0.79,0.98]
Serra 2013	104/194	117/190		10.82%	0.87[0.73,1.03]
Subtotal (95% CI)	**951**	**951**		**35.42%**	**0.86[0.8,0.94]**
Total events: 468 (Progesterone), 536 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.63, df=2(P=0.73); I²=0%					
Test for overall effect: Z=3.38(P=0)					
Total (95% CI)	**2792**	**2612**		**100%**	**0.95[0.88,1.03]**
Total events: 1594 (Progesterone), 1551 (Placebo)					
Heterogeneity: Tau²=0.01; Chi²=20.29, df=6(P=0); I²=70.43%					
Test for overall effect: Z=1.19(P=0.23)					
Test for subgroup differences: Chi²=5.22, df=1 (P=0.02), I²=80.85%					

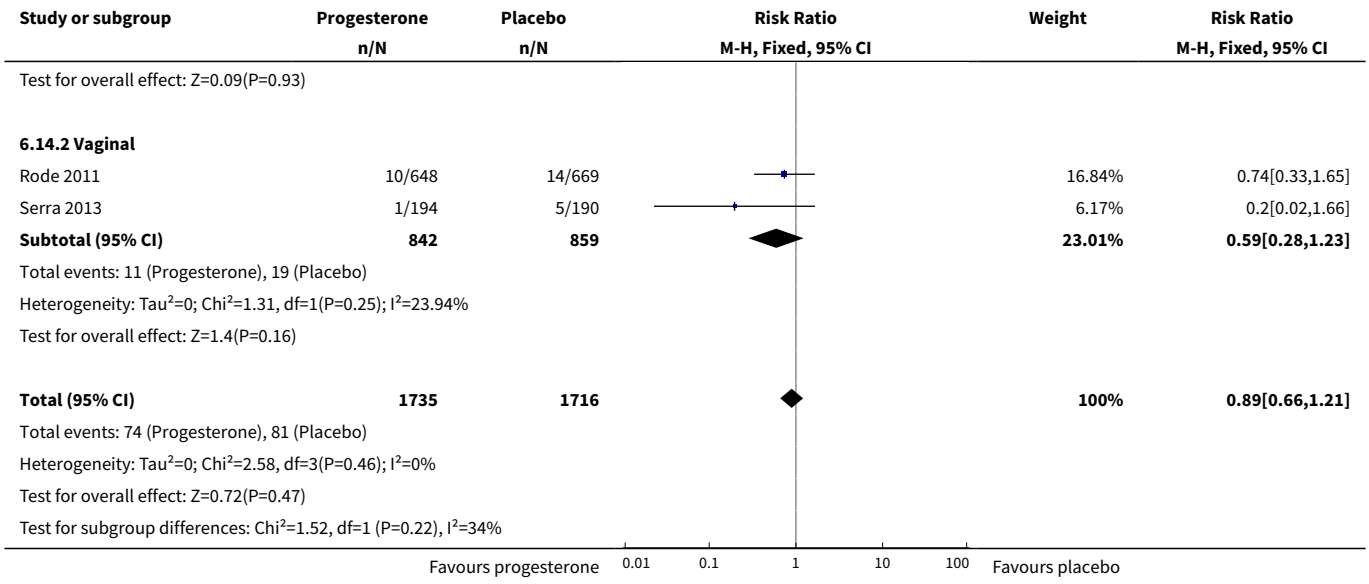
Favours progesterone 0.1 0.2 0.5 1 2 5 10 Favours placebo

Analysis 6.14. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 14 Apgar score < 7 at 5 minutes.

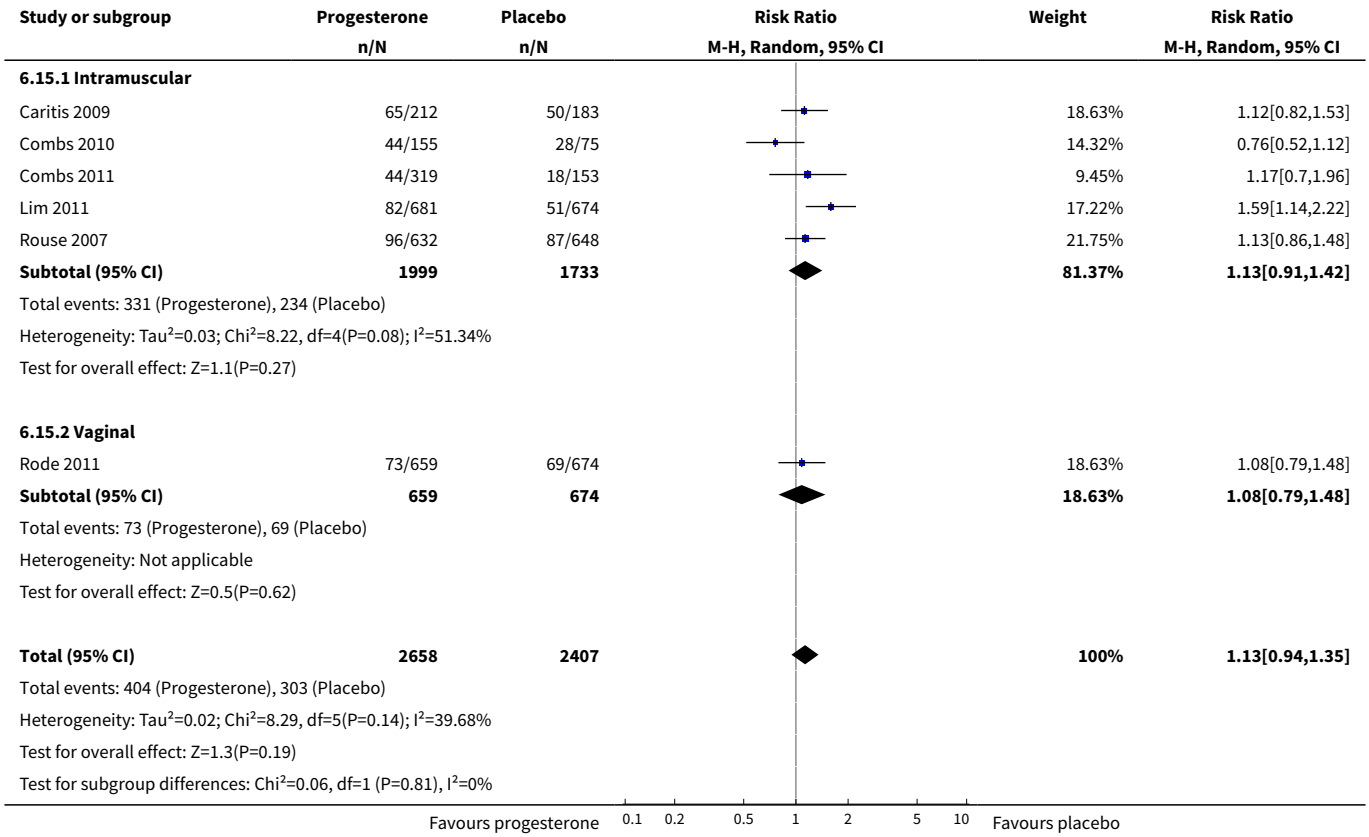
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.14.1 Intramuscular					
Caritis 2009	10/212	10/183		13.12%	0.86[0.37,2.03]
Lim 2011	53/681	52/674		63.87%	1.01[0.7,1.46]
Subtotal (95% CI)	**893**	**857**		**76.99%**	**0.98[0.7,1.38]**
Total events: 63 (Progesterone), 62 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.11, df=1(P=0.74); I²=0%					

Favours progesterone 0.01 0.1 1 10 100 Favours placebo

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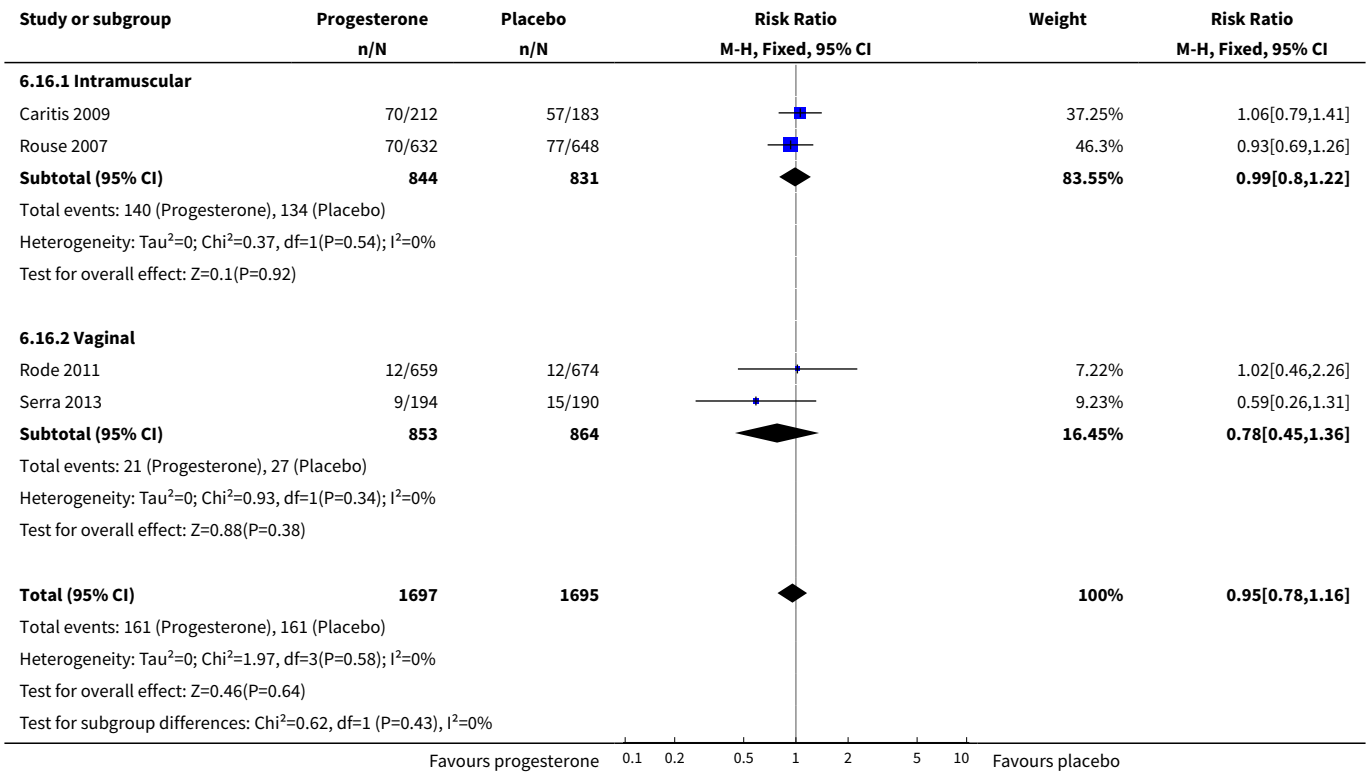


Analysis 6.15. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 15 Respiratory distress syndrome.

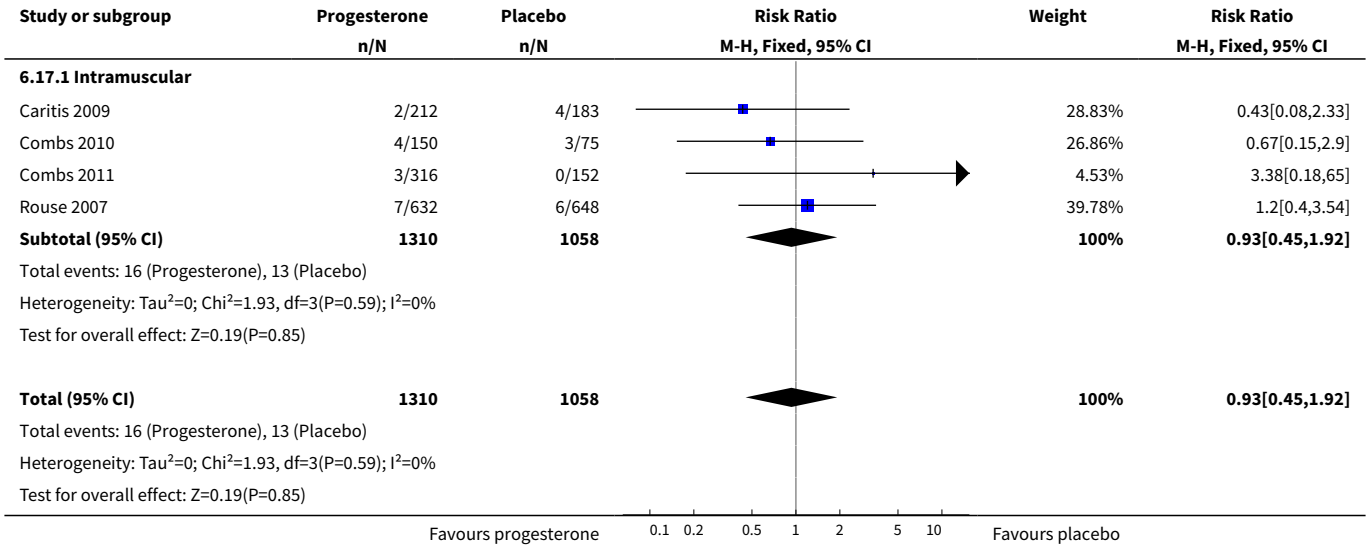


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Analysis 6.16. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 16 Use of assisted ventilation.

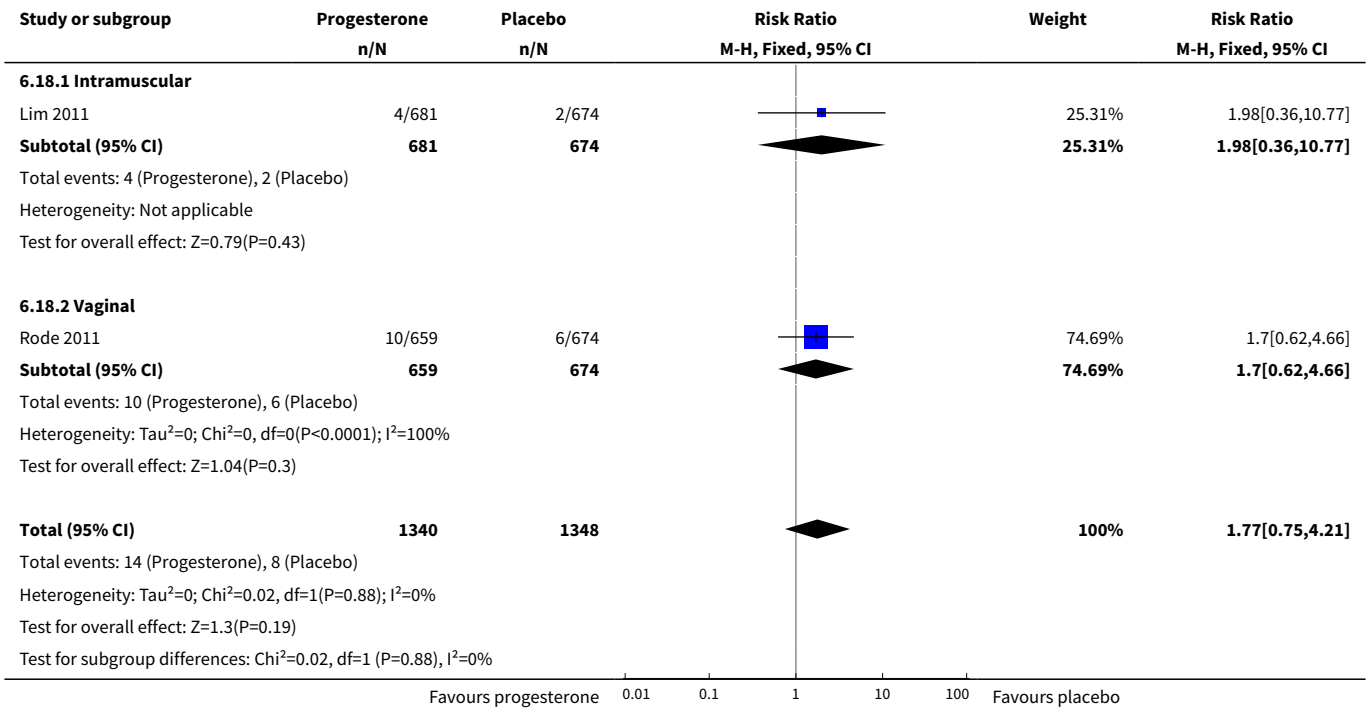


Analysis 6.17. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 17 Intraventricular haemorrhage - grades III or IV.

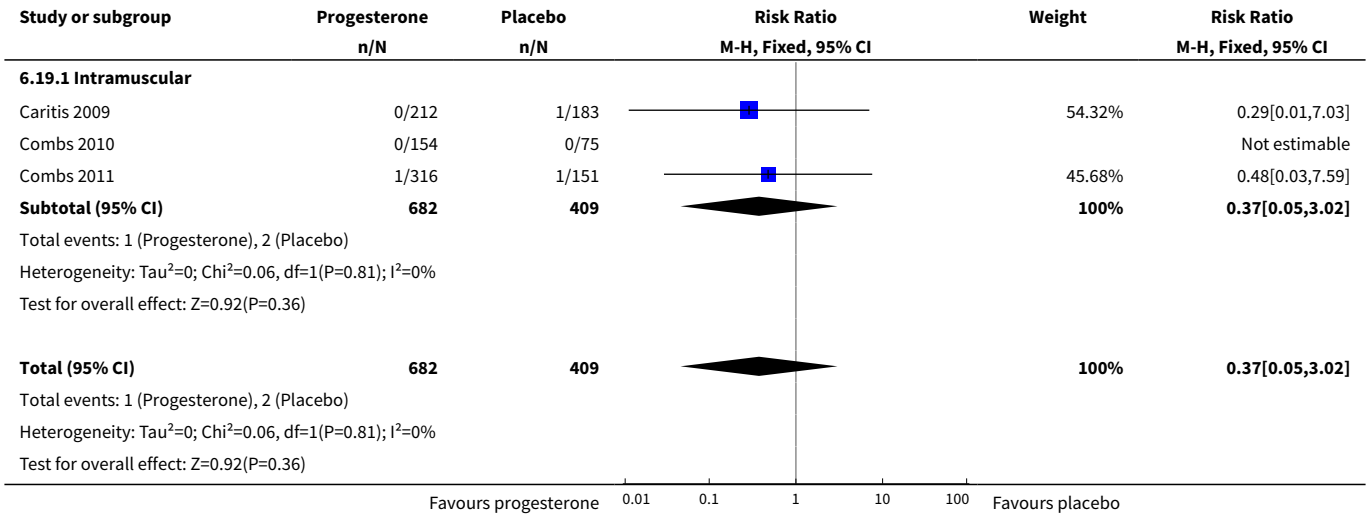


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Analysis 6.18. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 18 Intraventricular haemorrhage - all grades.

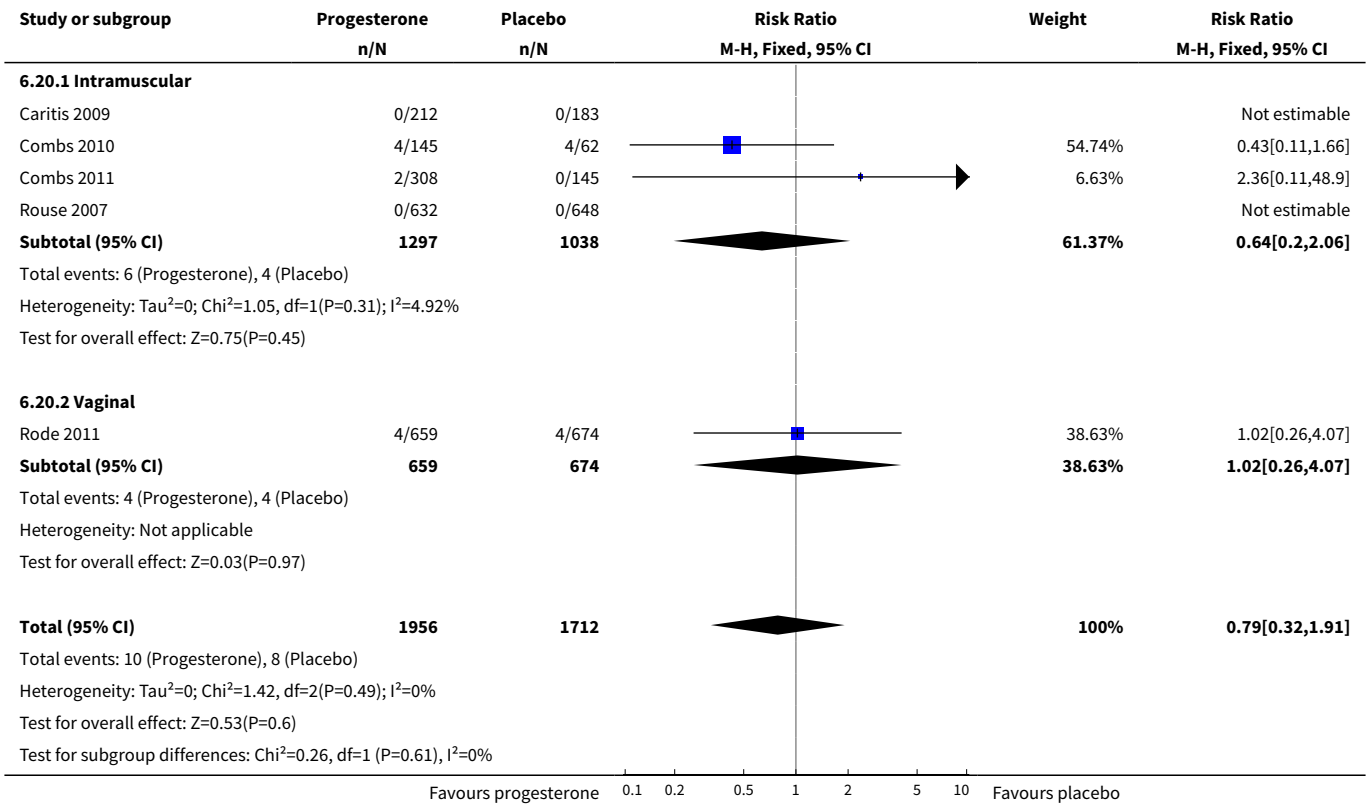


Analysis 6.19. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 19 Periventricular leucomalacia.

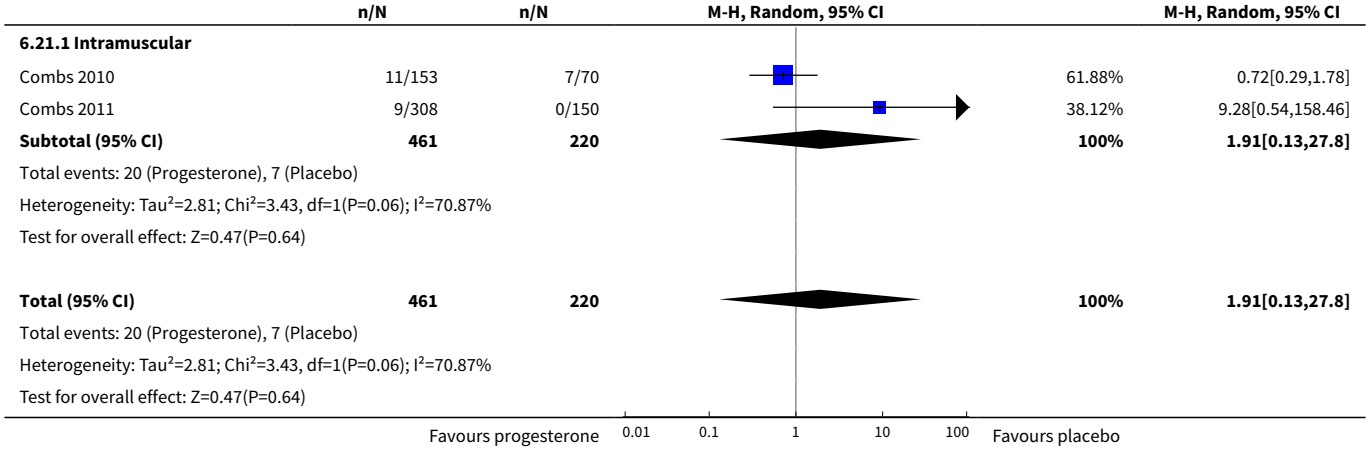


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Analysis 6.20. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 20 Retinopathy of prematurity.



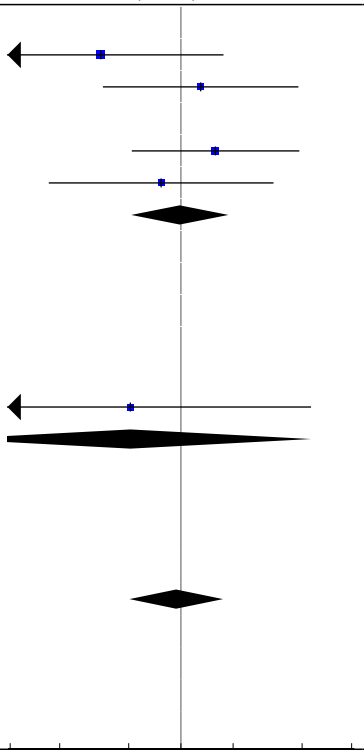
Analysis 6.21. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 21 Chronic lung disease.



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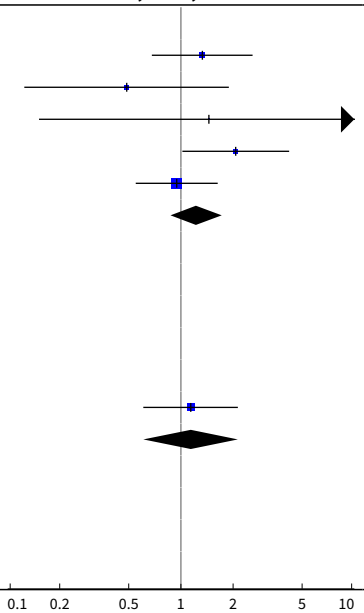
Analysis 6.22. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 22 Necrotising enterocolitis.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.22.1 Intramuscular					
Caritis 2009	2/212	5/183		26.37%	0.35[0.07,1.76]
Combs 2010	8/154	3/75		19.82%	1.3[0.35,4.76]
Combs 2011	0/315	0/152			Not estimable
Lim 2011	8/681	5/674		24.69%	1.58[0.52,4.82]
Rouse 2007	3/632	4/648		19.41%	0.77[0.17,3.42]
Subtotal (95% CI)	**1994**	**1732**		**90.29%**	**0.98[0.52,1.88]**
Total events: 21 (Progesterone), 17 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.57, df=3(P=0.46); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					
6.22.2 Vaginal					
Rode 2011	1/659	2/674		9.71%	0.51[0.05,5.63]
Subtotal (95% CI)	**659**	**674**		**9.71%**	**0.51[0.05,5.63]**
Total events: 1 (Progesterone), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.55(P=0.58)					
Total (95% CI)	**2653**	**2406**		**100%**	**0.94[0.5,1.75]**
Total events: 22 (Progesterone), 19 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.85, df=4(P=0.58); I²=0%					
Test for overall effect: Z=0.2(P=0.84)					
Test for subgroup differences: Chi²=0.27, df=1 (P=0.61), I²=0%					

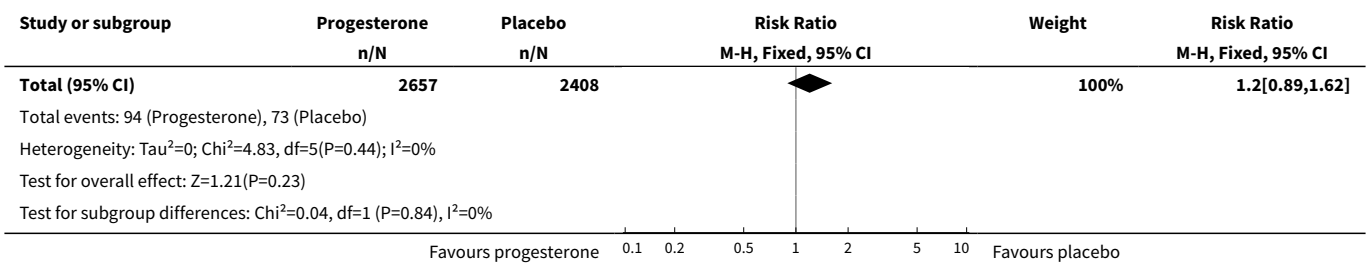


Analysis 6.23. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 23 Neonatal sepsis.

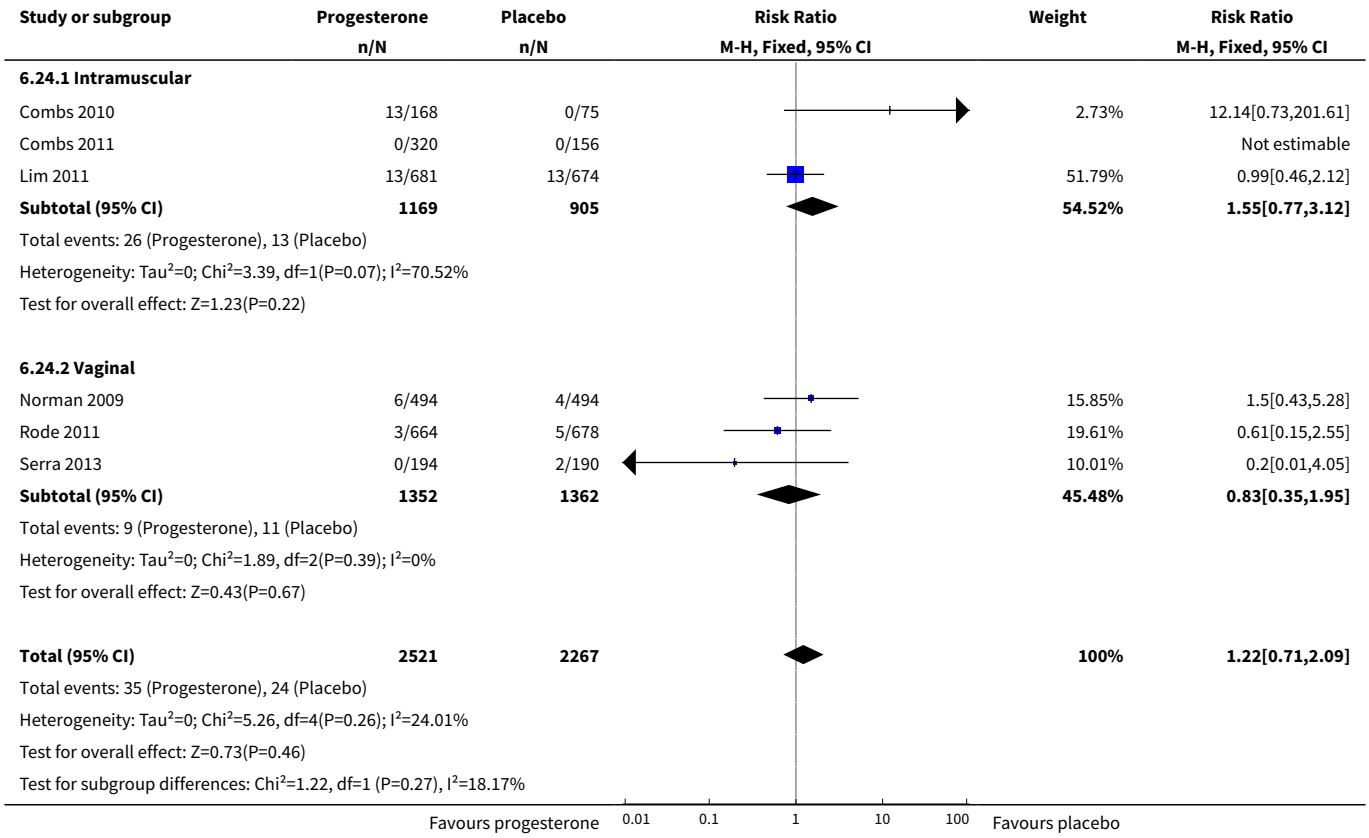
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.23.1 Intramuscular					
Caritis 2009	20/212	13/183		18.55%	1.33[0.68,2.59]
Combs 2010	4/154	4/75		7.15%	0.49[0.13,1.89]
Combs 2011	3/319	1/154		1.79%	1.45[0.15,13.81]
Lim 2011	23/681	11/674		14.7%	2.07[1.02,4.21]
Rouse 2007	24/632	26/648		34.14%	0.95[0.55,1.63]
Subtotal (95% CI)	**1998**	**1734**		**76.34%**	**1.22[0.87,1.72]**
Total events: 74 (Progesterone), 55 (Placebo)					
Heterogeneity: Tau²=0; Chi²=4.8, df=4(P=0.31); I²=16.74%					
Test for overall effect: Z=1.16(P=0.24)					
6.23.2 Vaginal					
Rode 2011	20/659	18/674		23.66%	1.14[0.61,2.13]
Subtotal (95% CI)	**659**	**674**		**23.66%**	**1.14[0.61,2.13]**
Total events: 20 (Progesterone), 18 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					



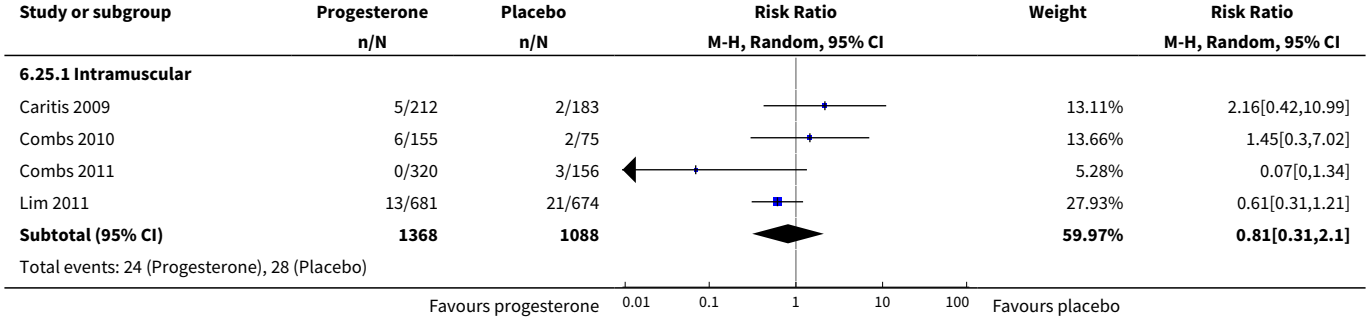
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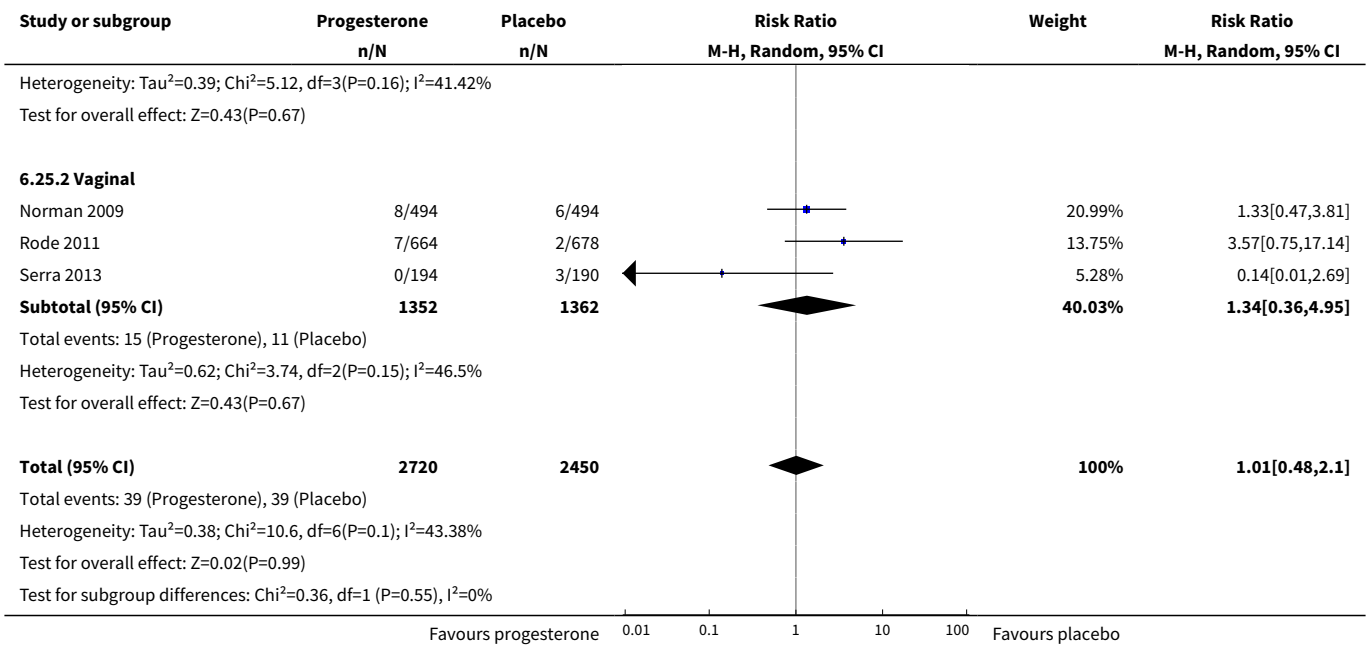
Analysis 6.24. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 24 Fetal death.



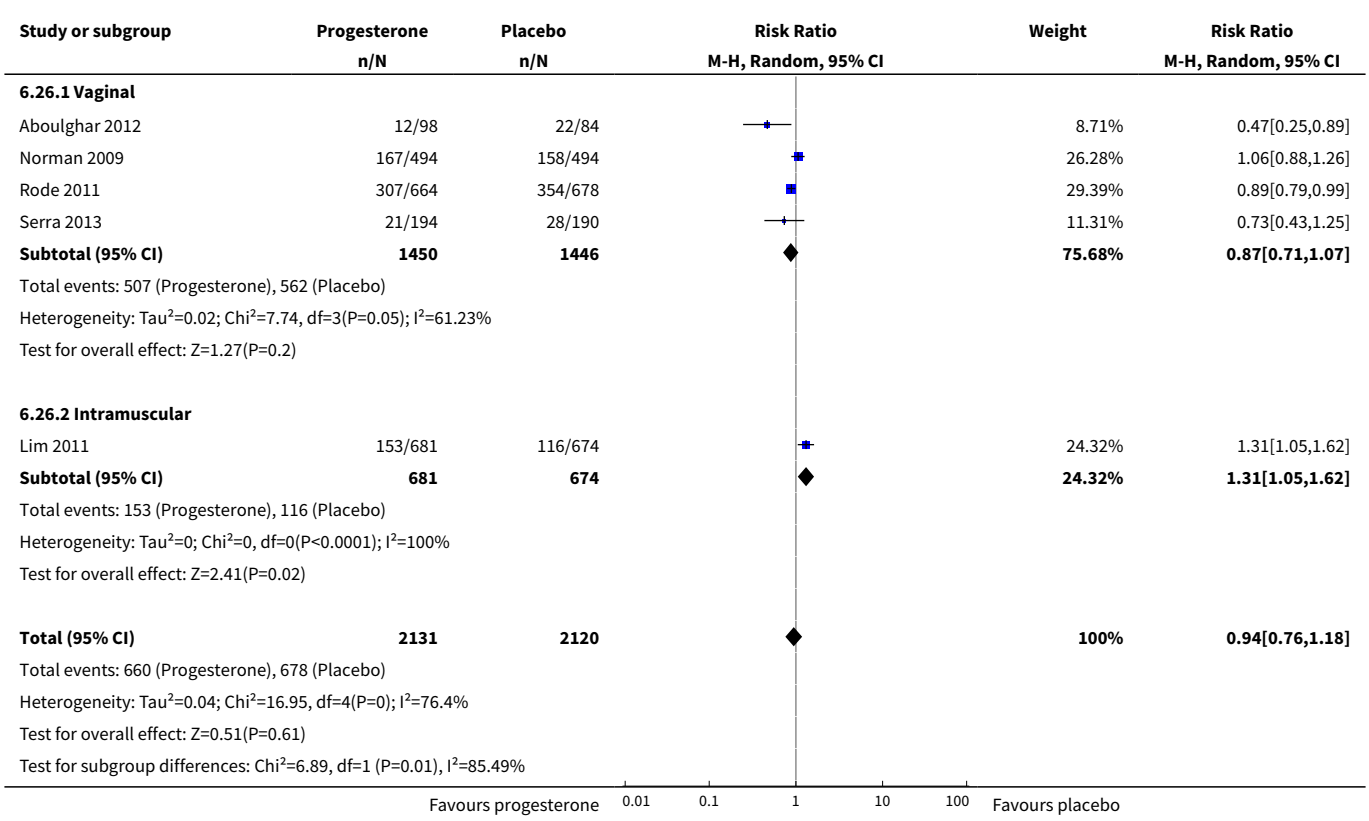
Analysis 6.25. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 25 Neonatal death.



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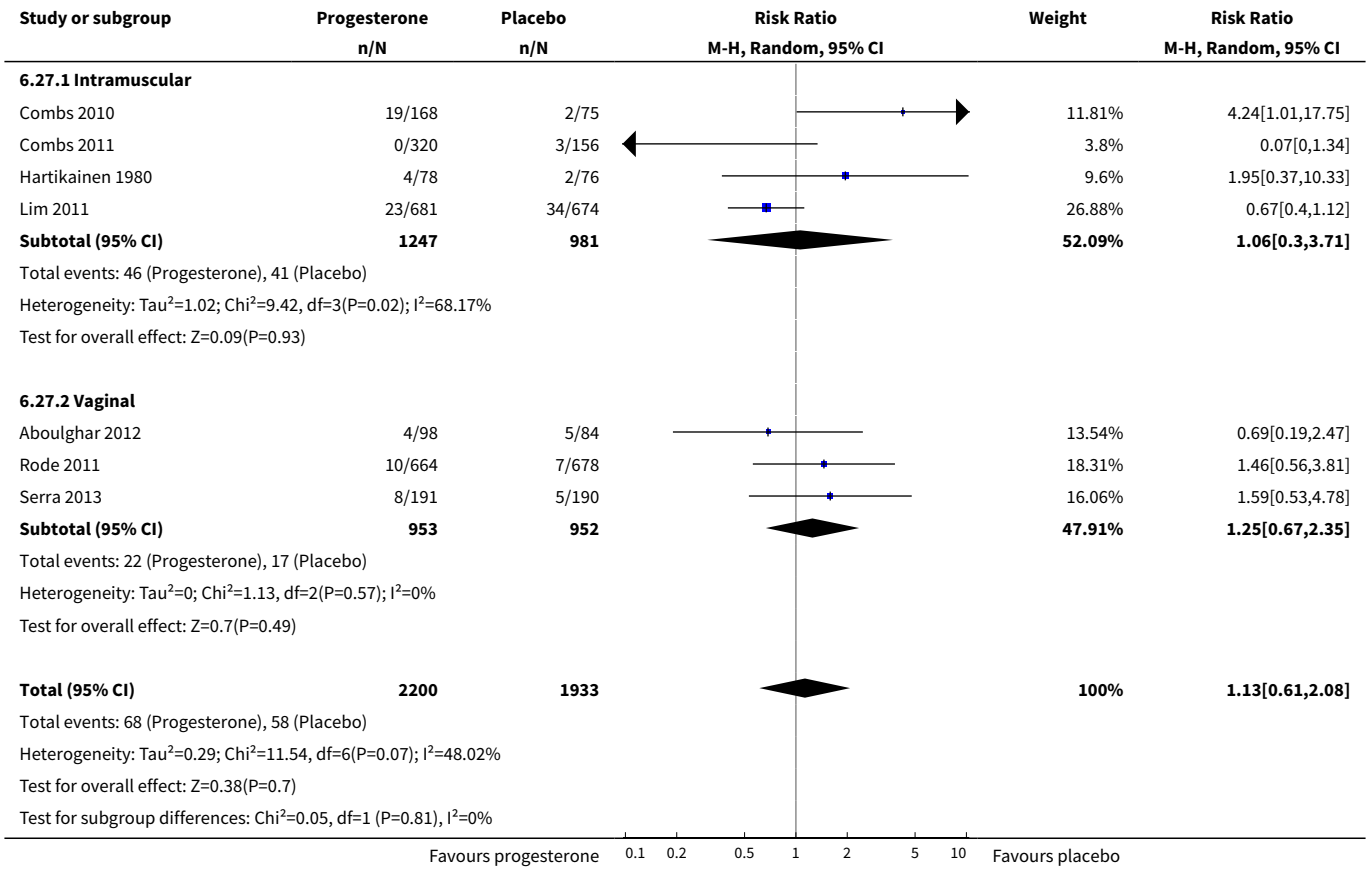


Analysis 6.26. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 26 Admission to NICU.

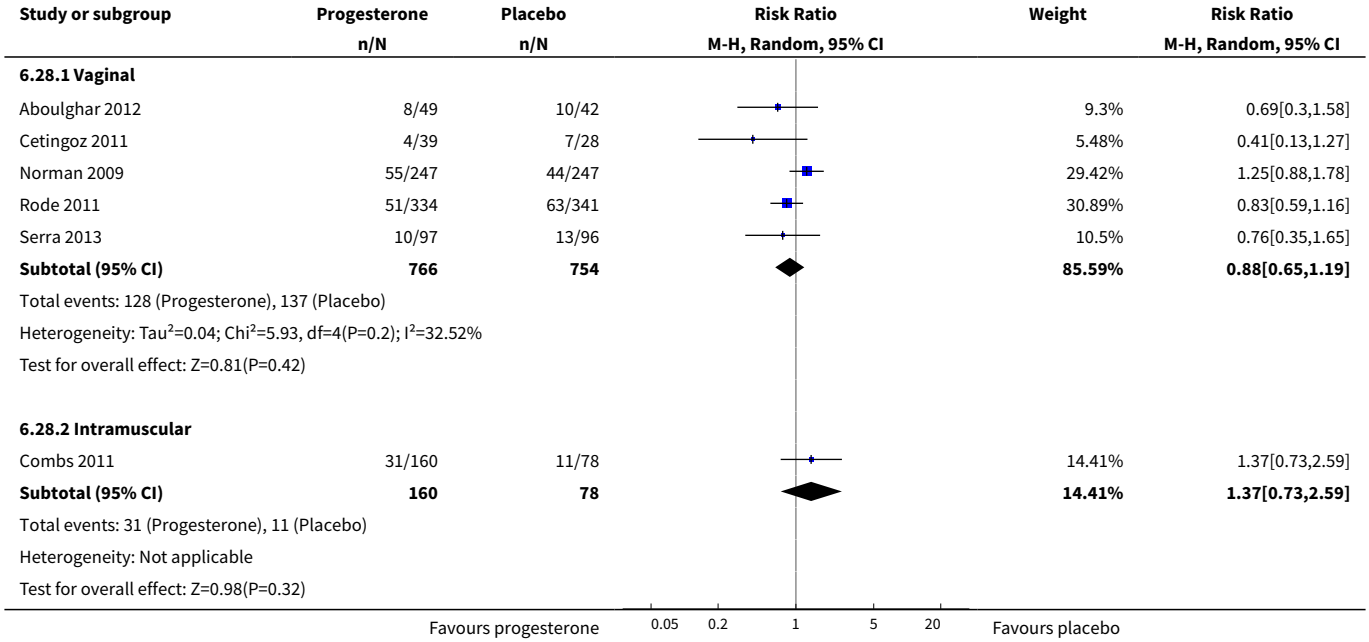


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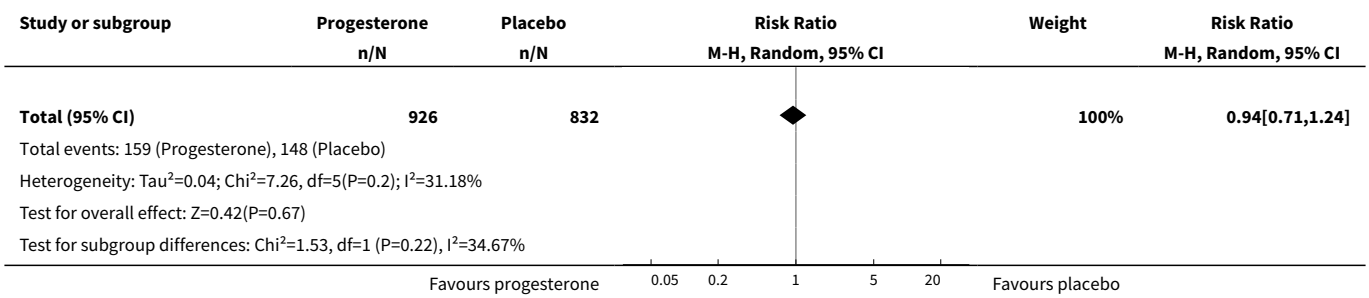
Analysis 6.27. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 27 Perinatal death.



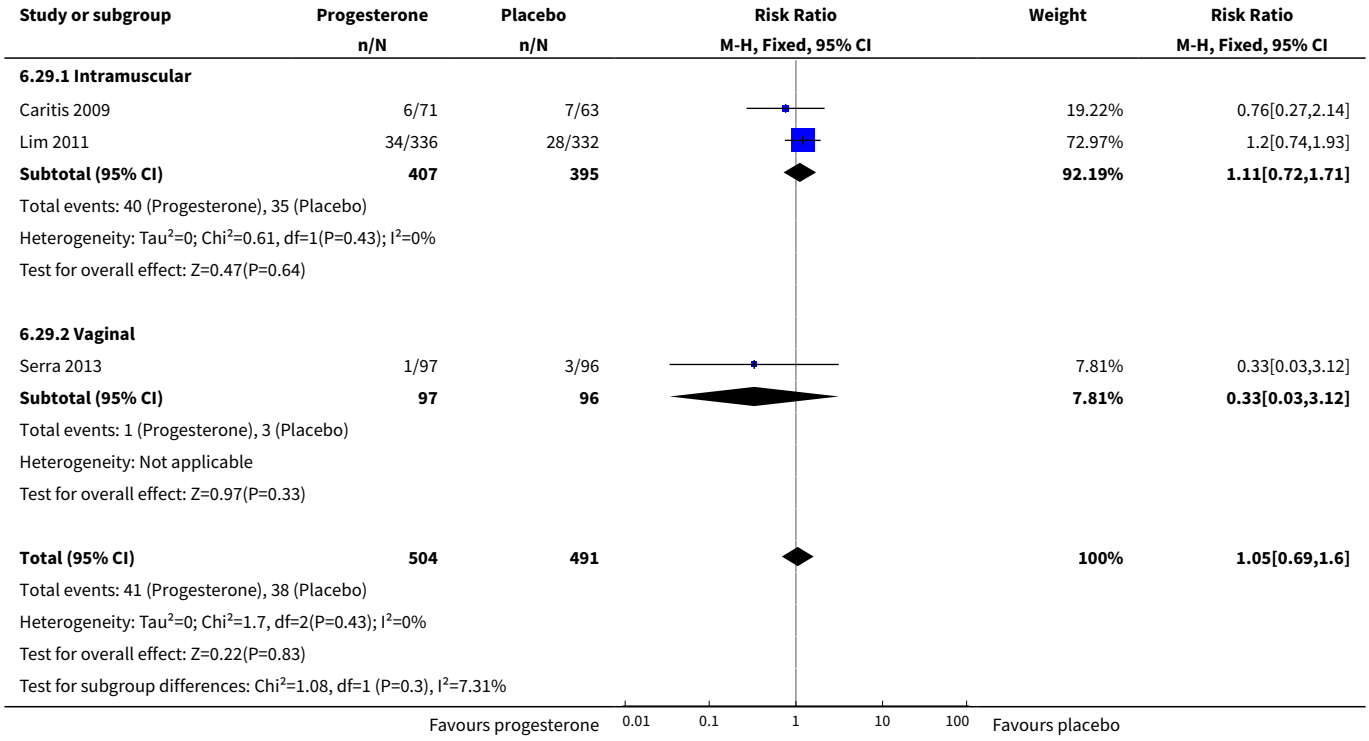
Analysis 6.28. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 28 Preterm birth less than 34 weeks.



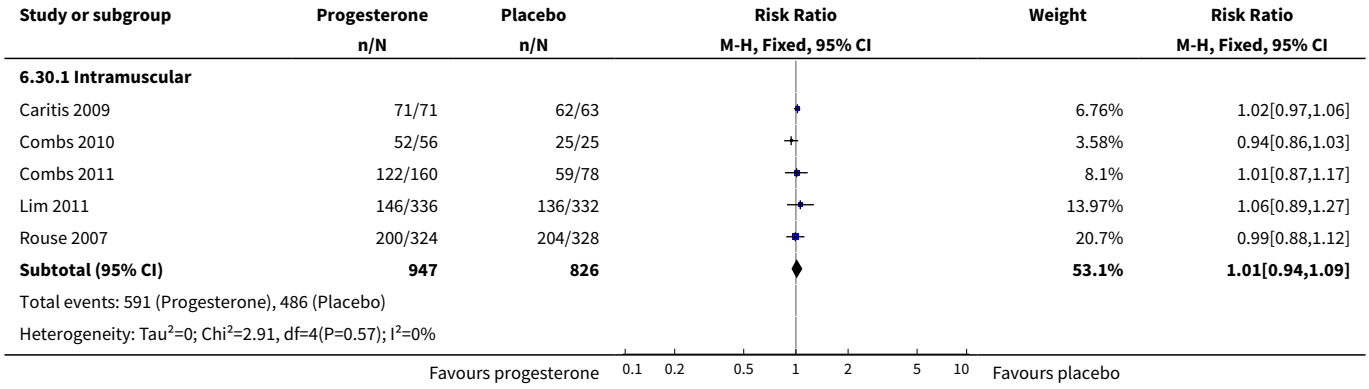
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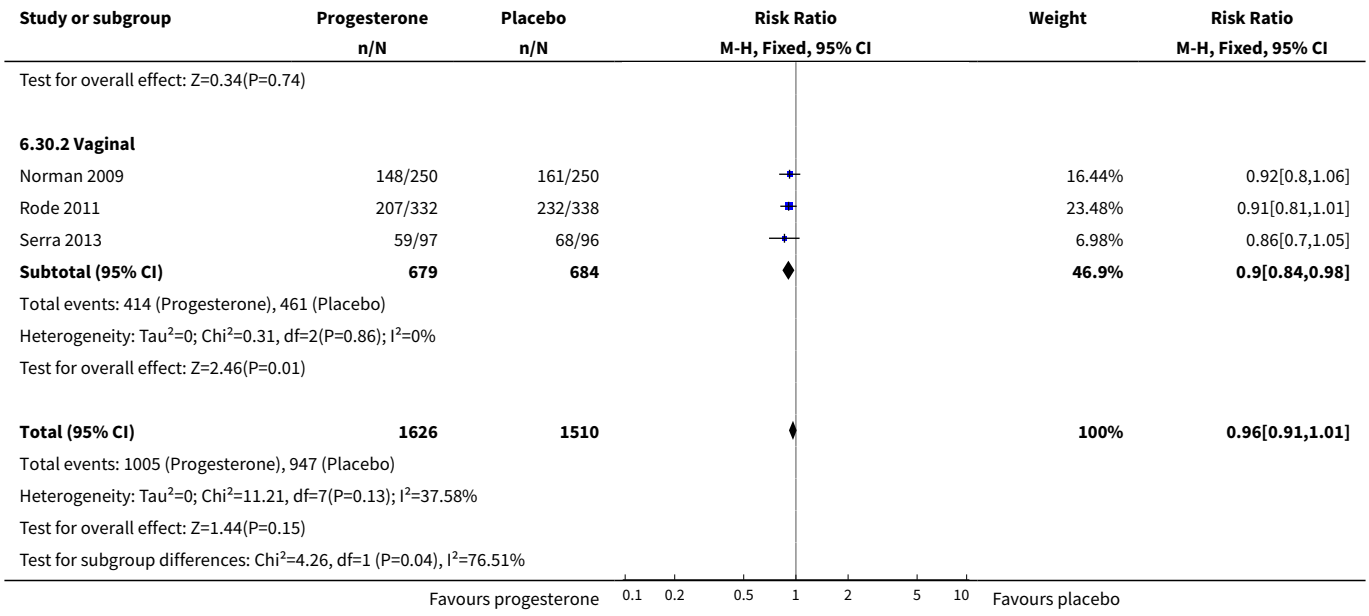
Analysis 6.29. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 29 Preterm PROM.



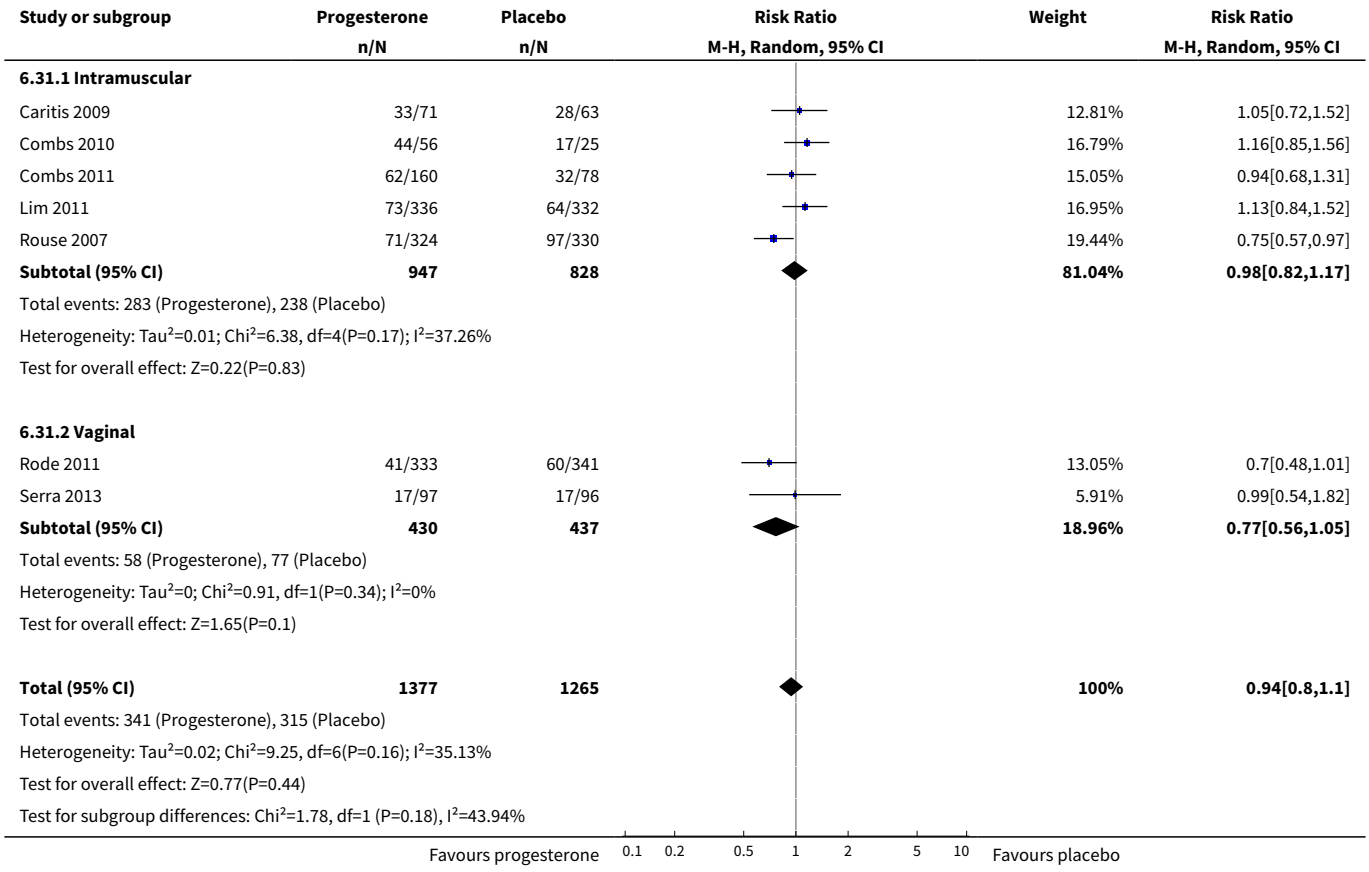
Analysis 6.30. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 30 Caesarean section.



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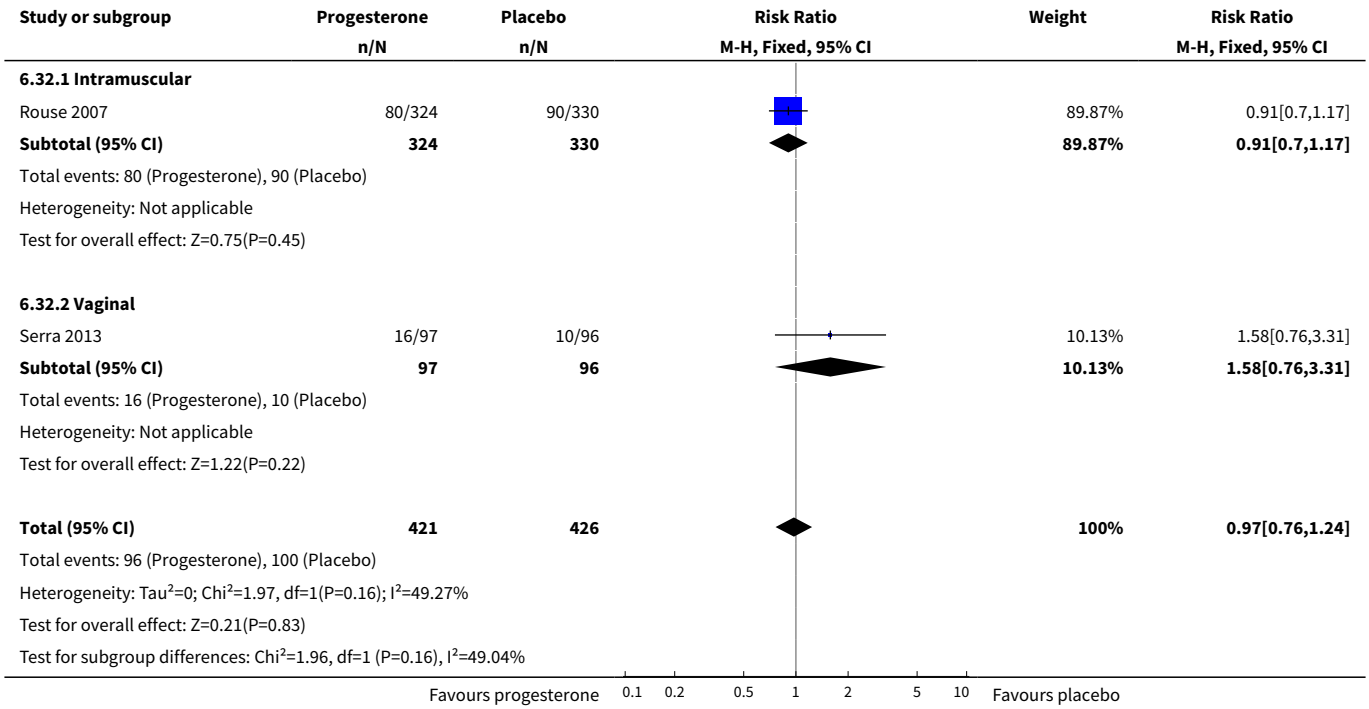


Analysis 6.31. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 31 Antenatal tocolysis.

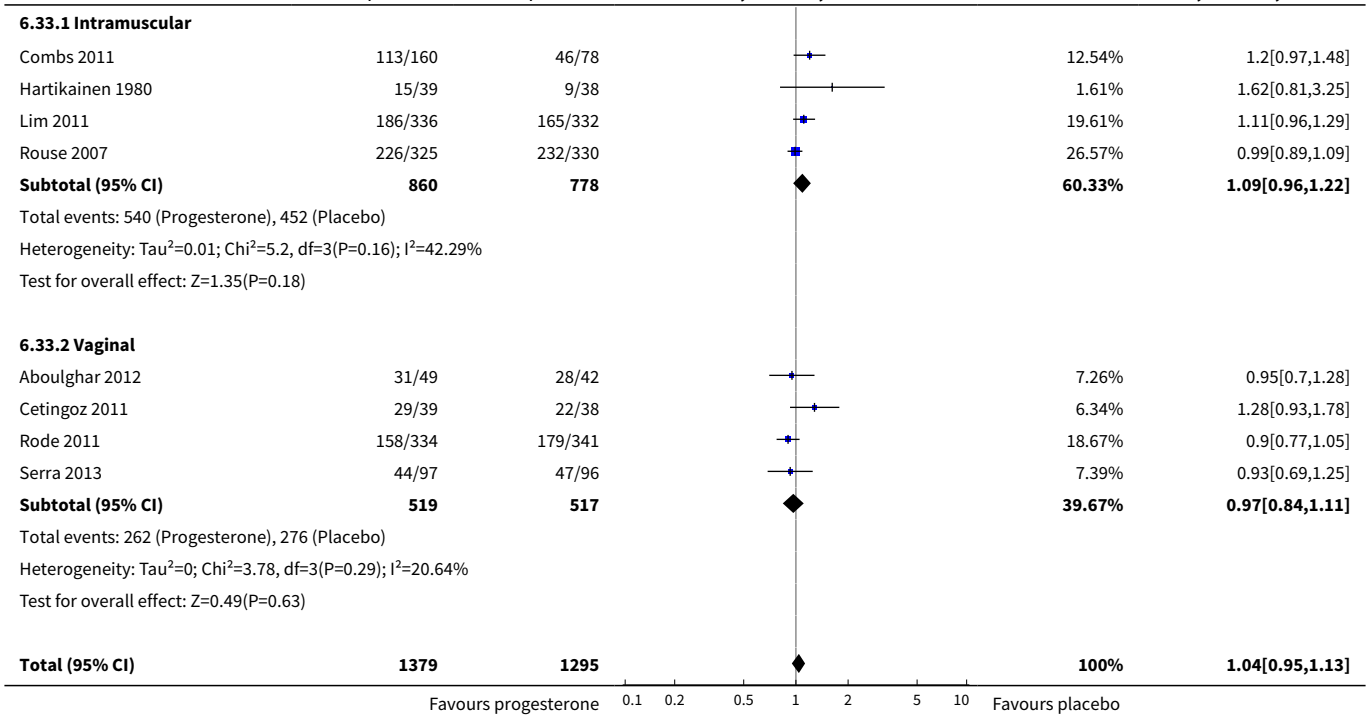


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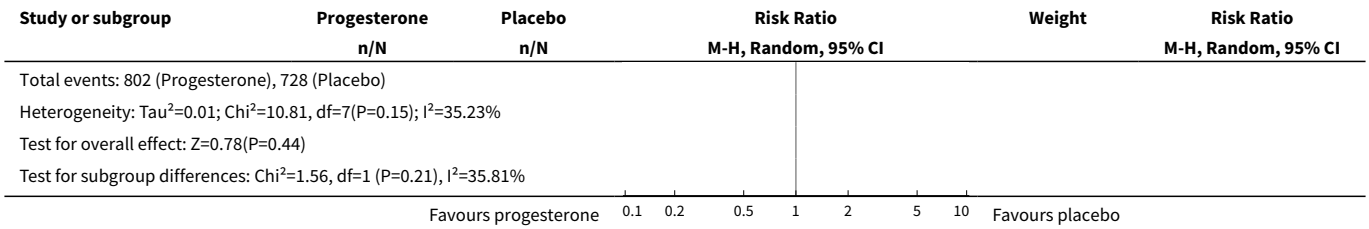
Analysis 6.32. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 32 Antenatal corticosteroids.



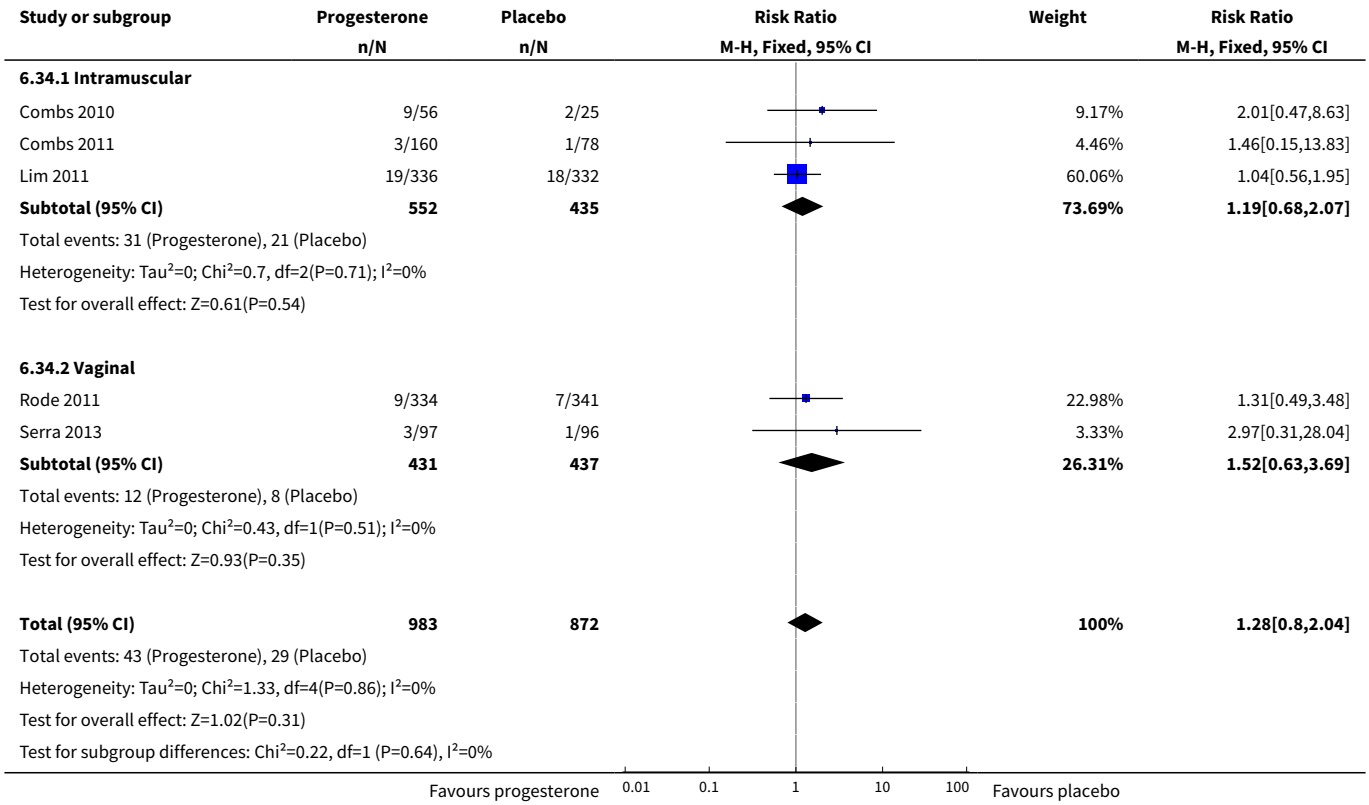
Analysis 6.33. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 33 Preterm birth less than 37 weeks.



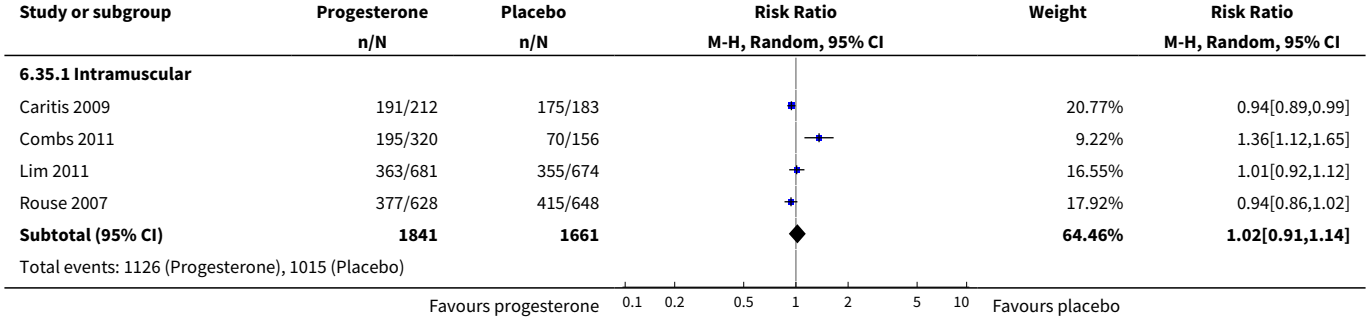
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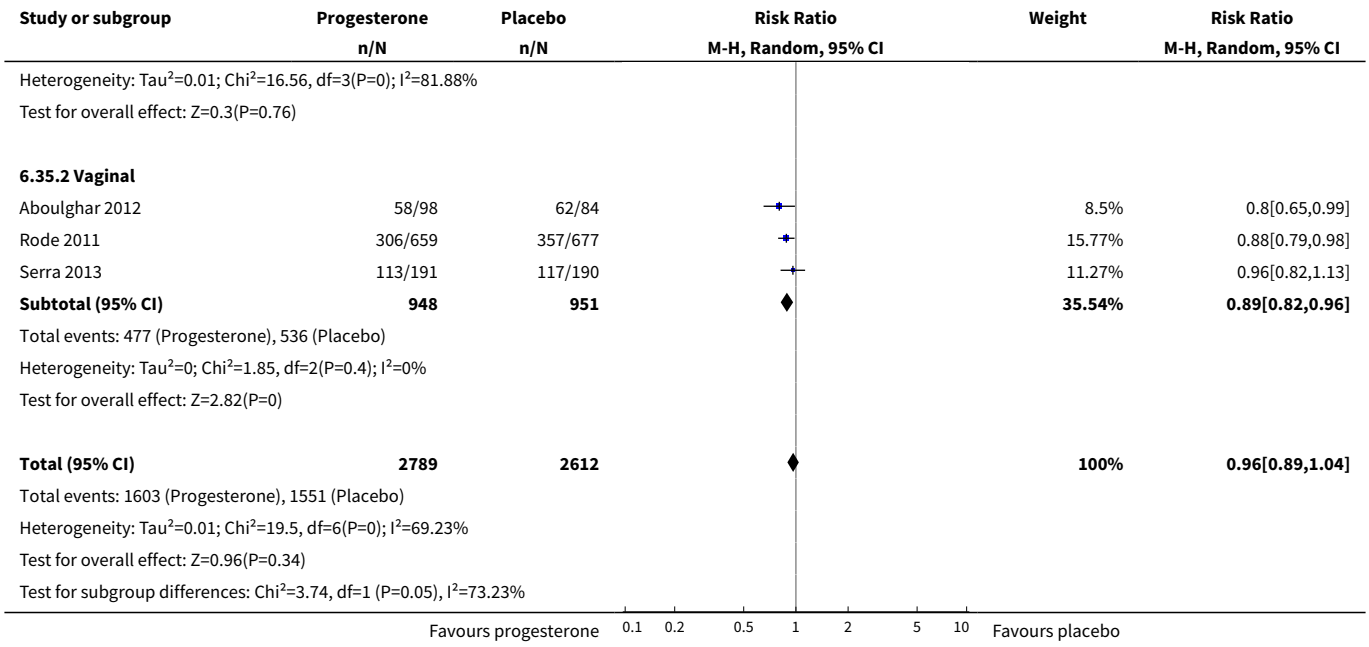
Analysis 6.34. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 34 Preterm birth less than 28 weeks.



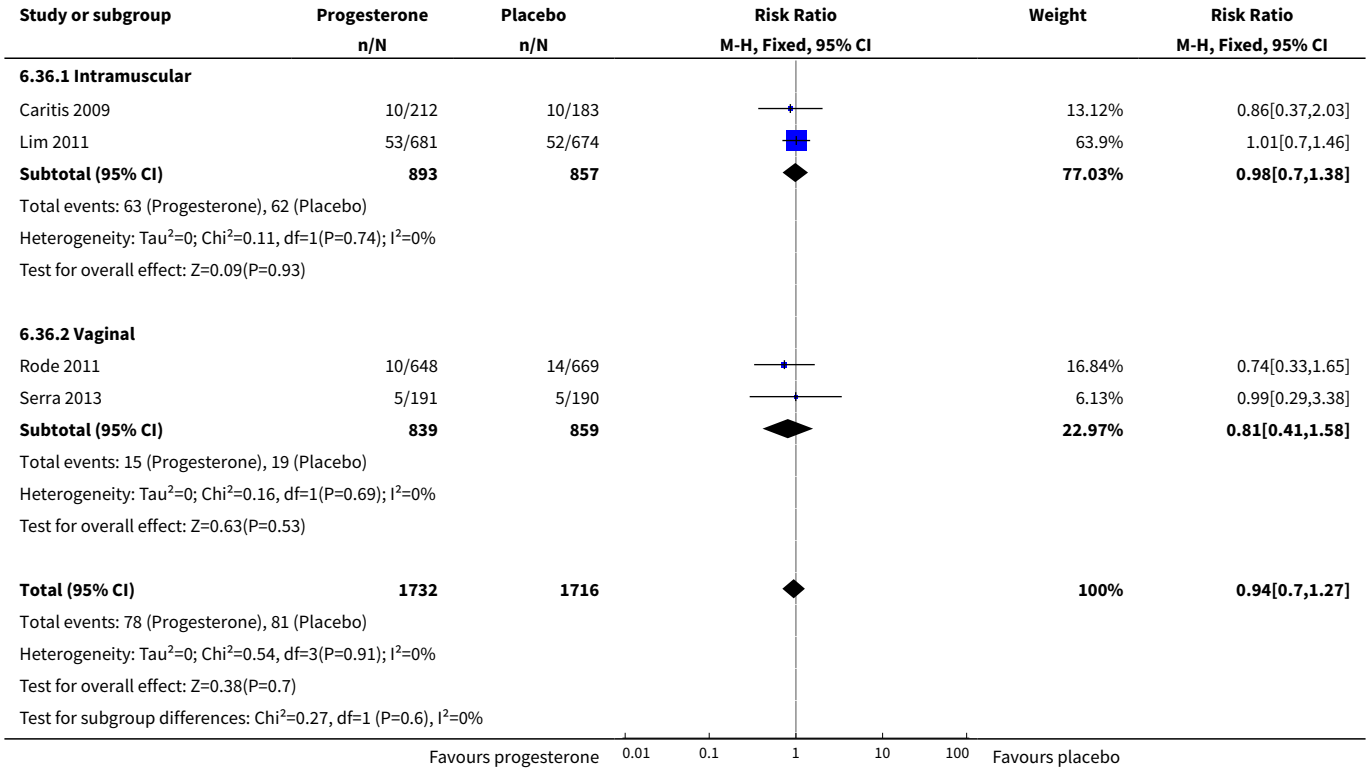
Analysis 6.35. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 35 Infant birthweight less than 2500 g.



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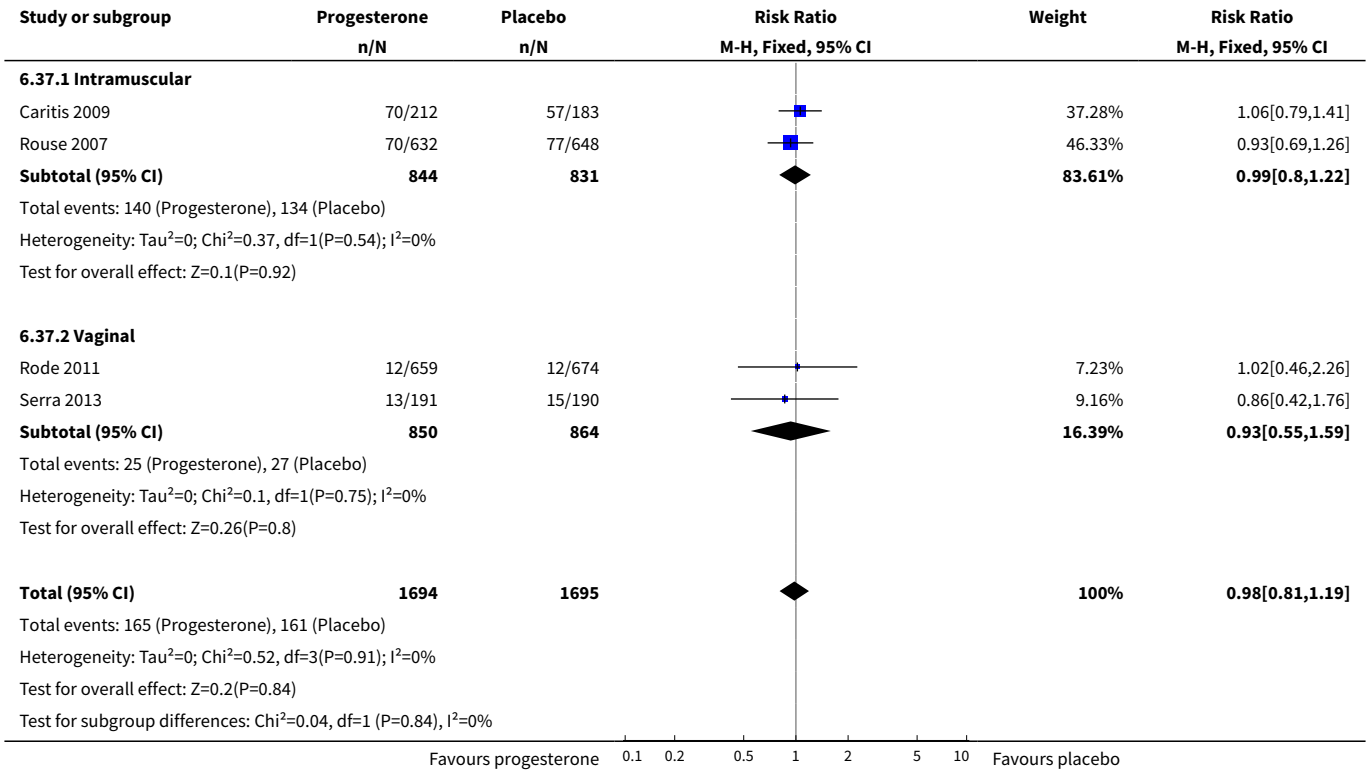


Analysis 6.36. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 36 Apgar score < 7 at 5 minutes.

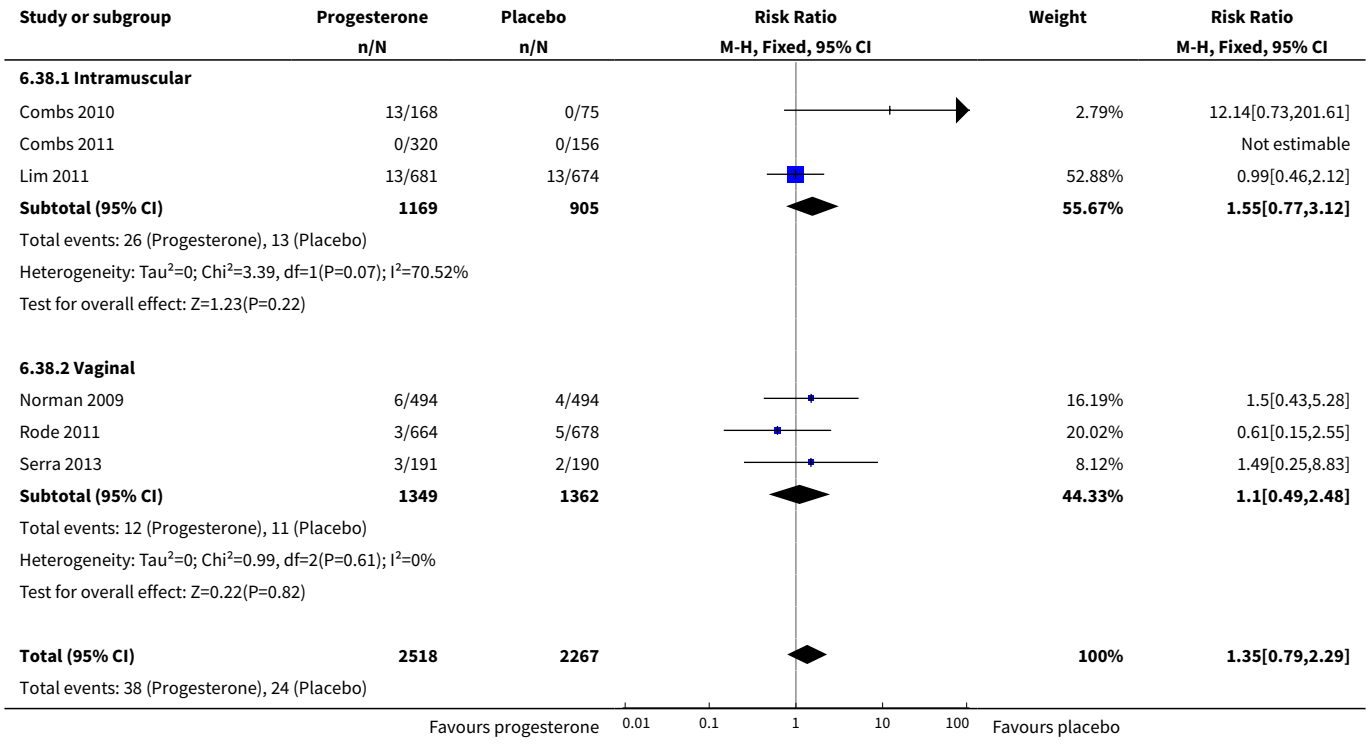


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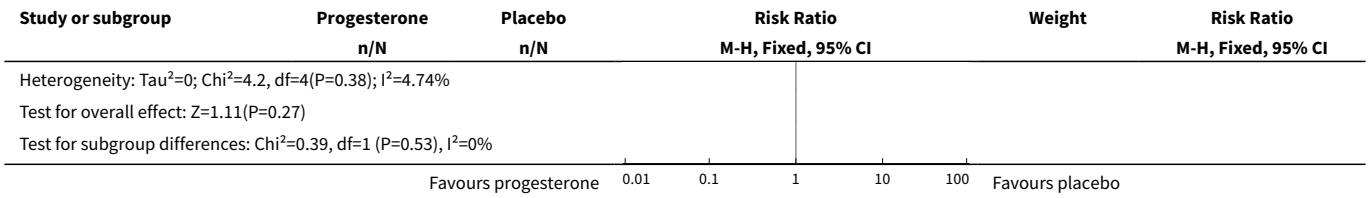
Analysis 6.37. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 37 Use of assisted ventilation.



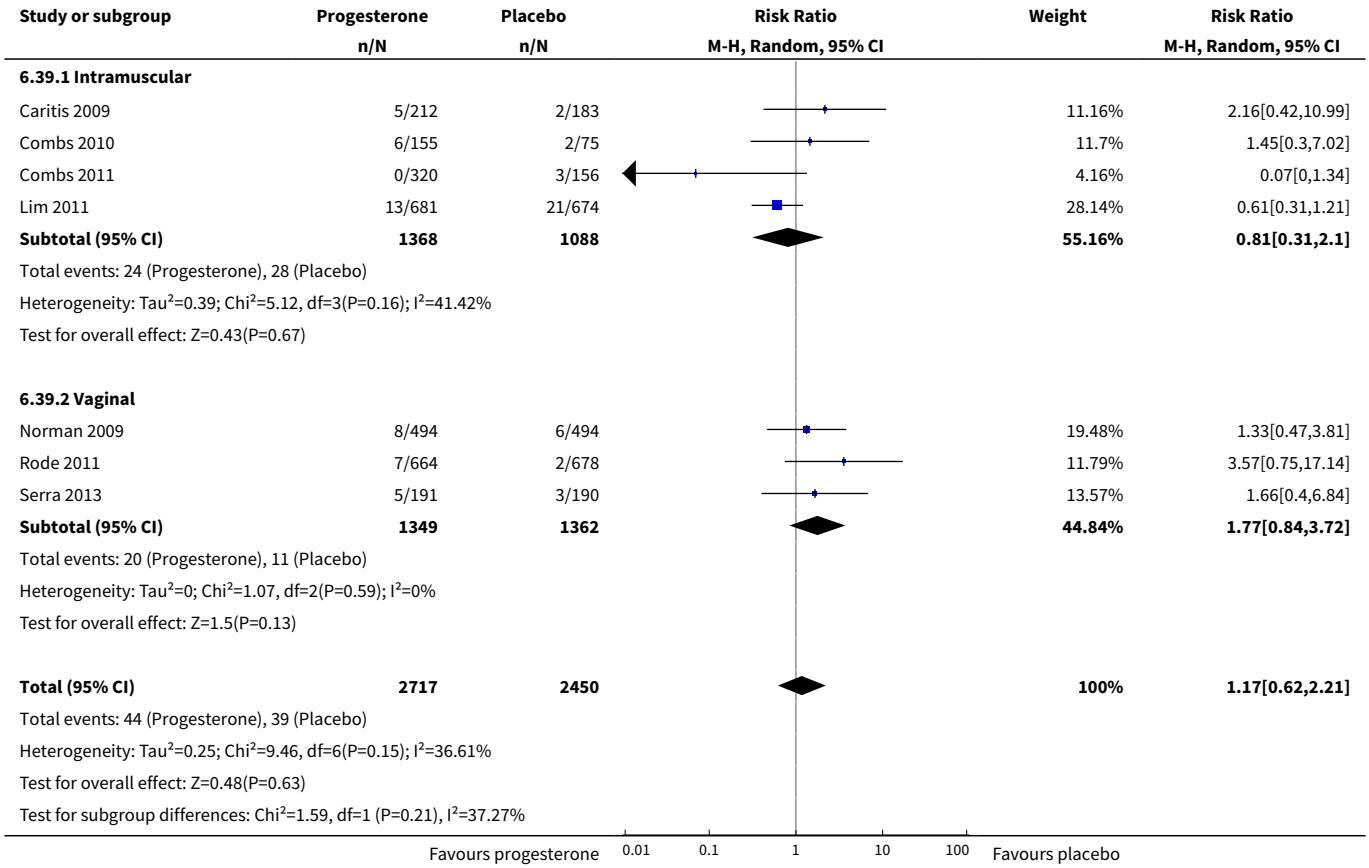
Analysis 6.38. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 38 Fetal death.



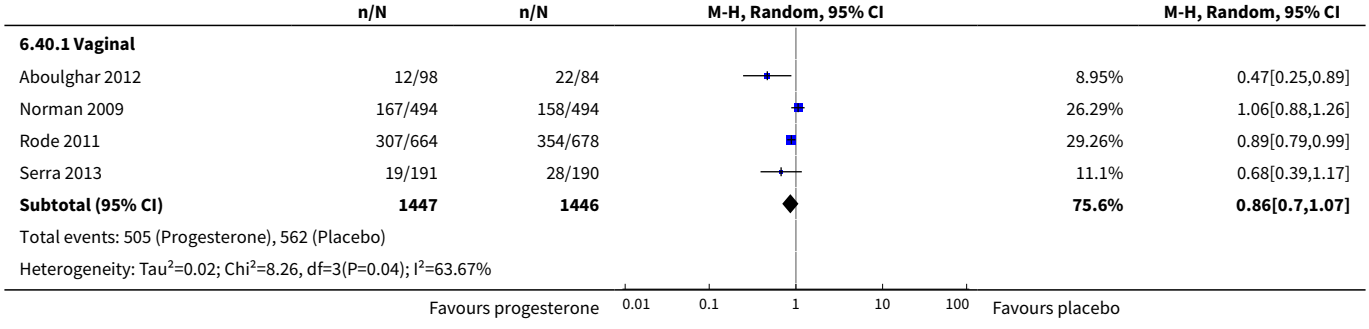
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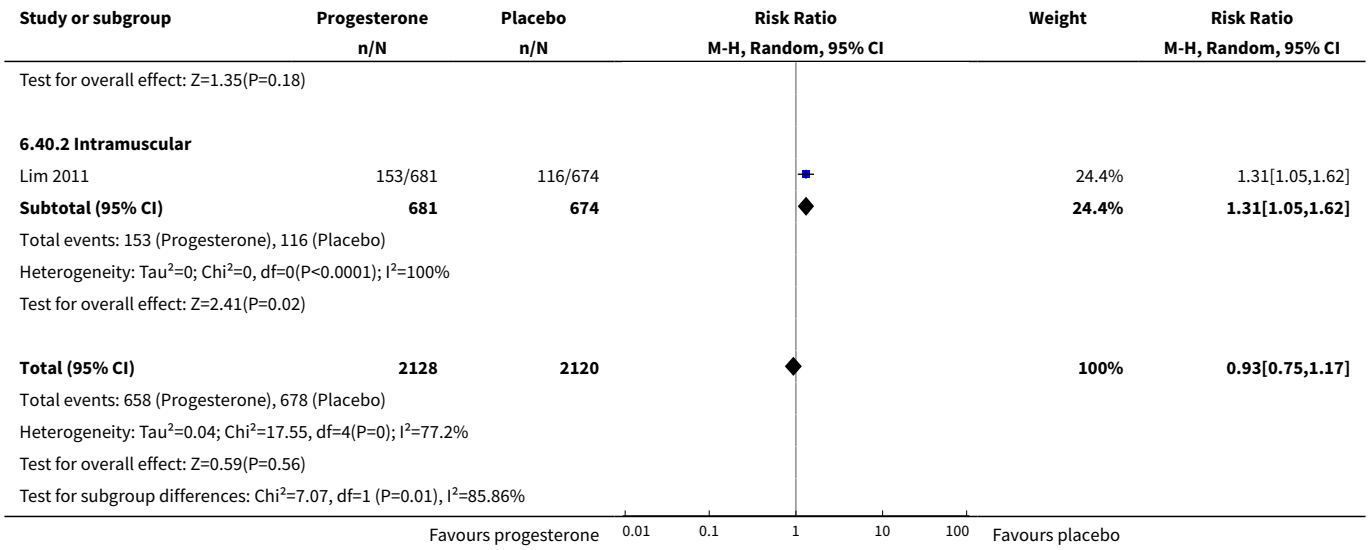
Analysis 6.39. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 39 Neonatal death.



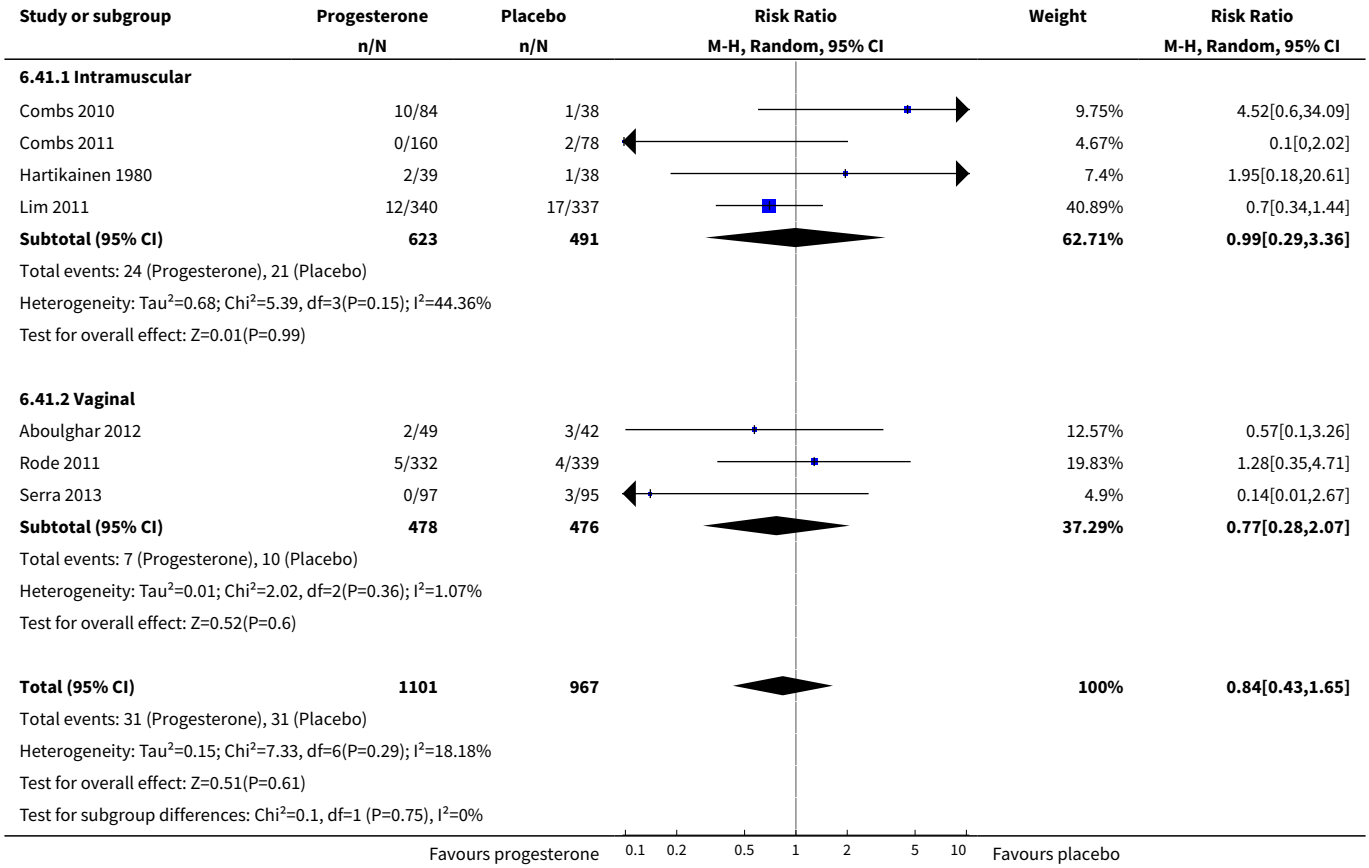
Analysis 6.40. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 40 Admission to NICU.



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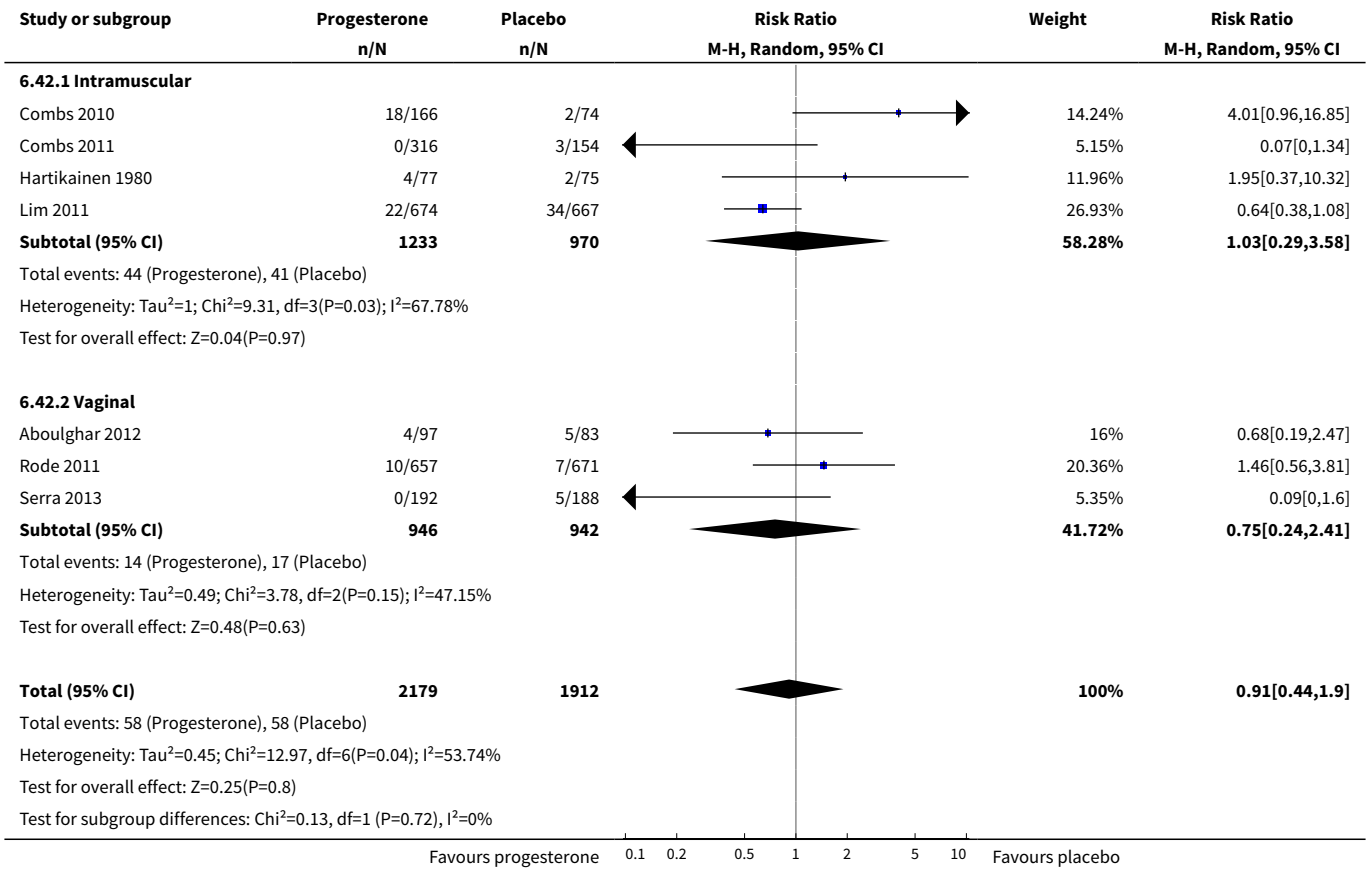


Analysis 6.41. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 41 Sensitivity analysis for perinatal death (assuming total non-independence).



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Analysis 6.42. Comparison 6 Progesterone versus placebo: multiple pregnancy, Outcome 42 Sensitivity analysis for perinatal death (assuming 1% non-independence).



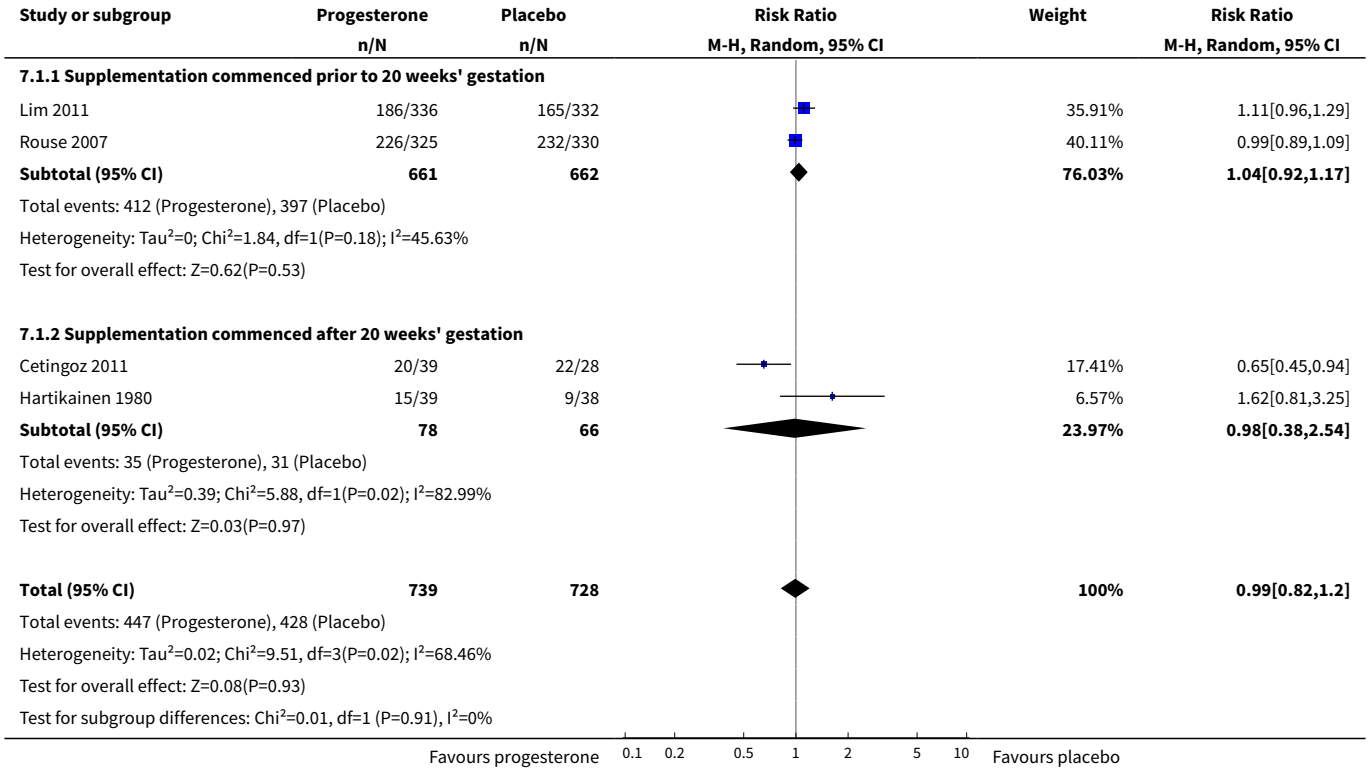
Comparison 7. Progesterone versus placebo: multiple pregnancy, by timing of commencement (< 20 wk v > 20 wk)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth < 37 weeks	4	1467	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.82, 1.20]
1.1 Supplementation commenced prior to 20 weeks' gestation	2	1323	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.17]
1.2 Supplementation commenced after 20 weeks' gestation	2	144	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.38, 2.54]
2 Neonatal death	3	2738	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.47, 1.93]
2.1 Supplementation commenced prior to 20 weeks' gestation	2	1750	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.29, 2.91]
2.2 Supplementation commenced after 20 weeks' gestation	1	988	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.47, 3.81]

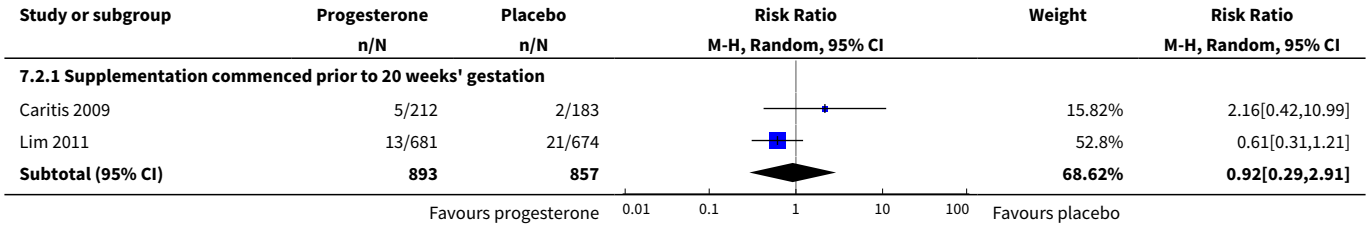
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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Admission to NICU	2	2343	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.95, 1.43]
3.1 Supplementation commenced prior to 20 weeks' gestation	1	988	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.88, 1.26]
3.2 Supplementation commenced after 20 weeks' gestation	1	1355	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.05, 1.62]

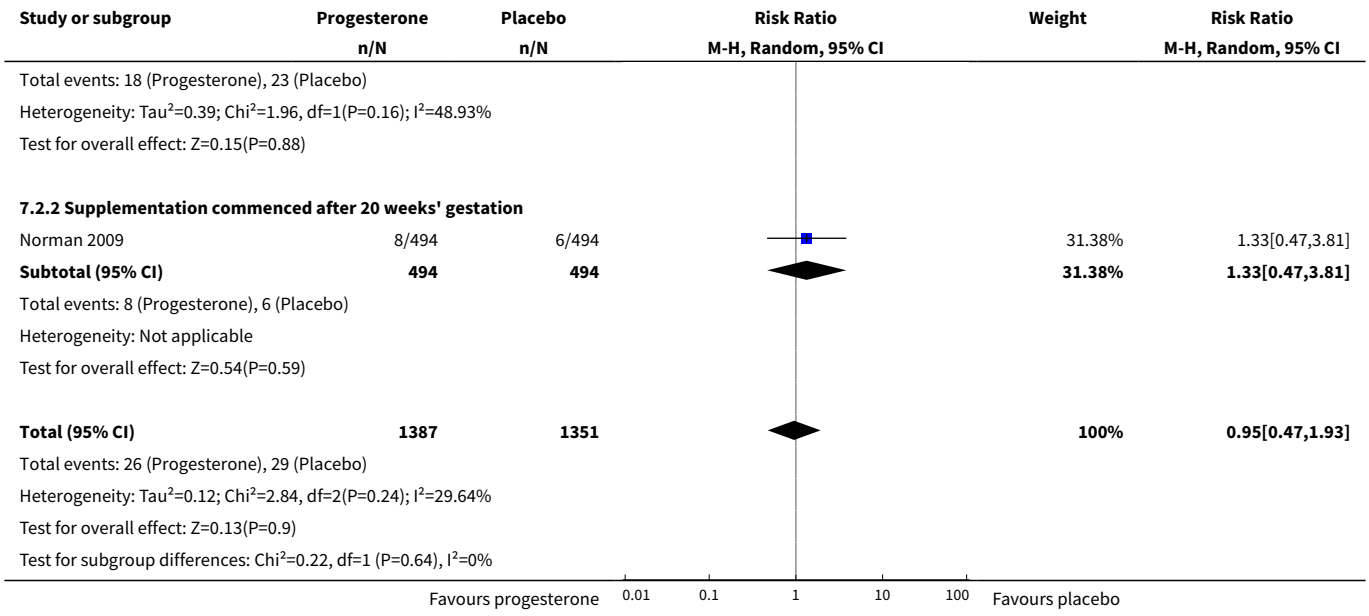
Analysis 7.1. Comparison 7 Progesterone versus placebo: multiple pregnancy, by timing of commencement (< 20 wk v > 20 wk), Outcome 1 Preterm birth < 37 weeks.



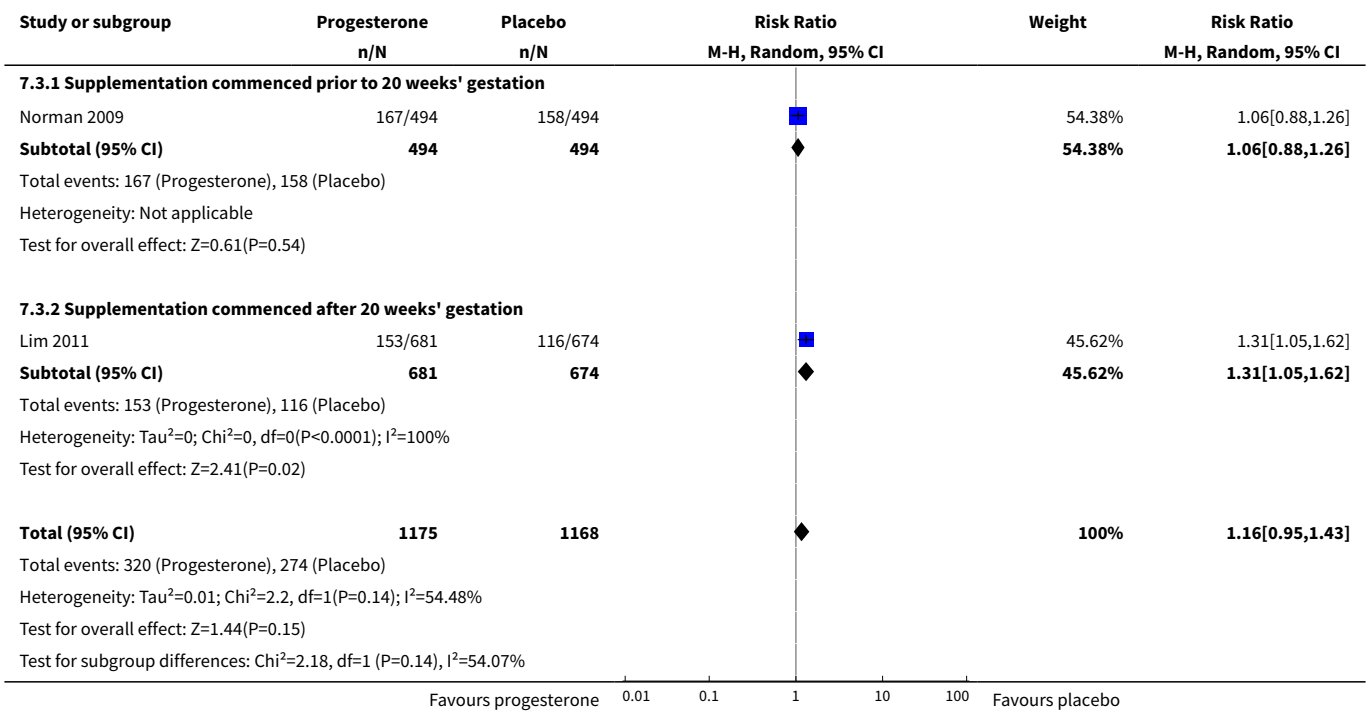
Analysis 7.2. Comparison 7 Progesterone versus placebo: multiple pregnancy, by timing of commencement (< 20 wk v > 20 wk), Outcome 2 Neonatal death.



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Analysis 7.3. Comparison 7 Progesterone versus placebo: multiple pregnancy, by timing of commencement (< 20 wk v > 20 wk), Outcome 3 Admission to NICU.



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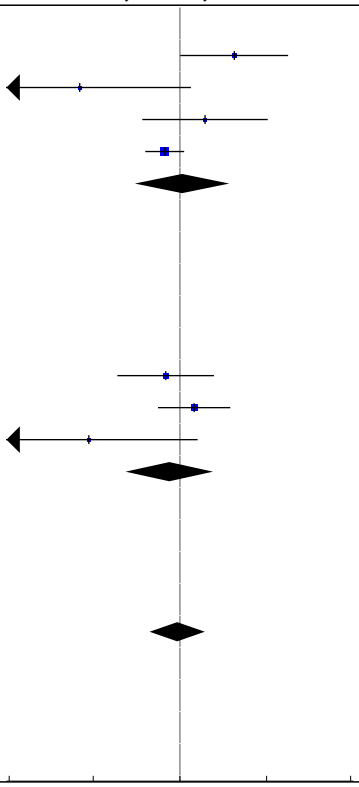
Comparison 8. Progesterone versus placebo: multiple pregnancy by cumulative weekly dose (< 500 mg v >= 500 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	7	4136	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.45, 1.94]
1.1 Dose < 500 mg per week	4	2228	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.30, 3.71]
1.2 Dose >= 500 mg per week	3	1908	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.24, 2.41]
2 Preterm birth less than 34 weeks	6	1758	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.74, 1.27]
2.1 Dose < 500 mg per week	1	238	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.73, 2.59]
2.2 Dose > 500 mg per week	5	1520	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.69, 1.23]
3 Antenatal tocolysis	7	2642	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.80, 1.10]
3.1 Dose < 500 mg per week	5	1775	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.17]
3.2 Dose >= 500 mg per week	2	867	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.03]
4 Preterm birth less than 37 weeks	8	3489	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.06]
4.1 Dose < 500 mg per week	6	2380	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.88, 1.15]
4.2 Dose >= 500 mg per week	4	1109	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
5 Infant birthweight less than 2500 g	7	5404	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
5.1 Dose < 500 mg per week	4	3502	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.14]
5.2 Dose >= 500 mg per week	3	1902	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.80, 0.94]
6 Respiratory distress syndrome	6	5065	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.94, 1.35]
6.1 Dose < 500 mg per week	5	3732	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.42]
6.2 Dose >= 500 mg per week	1	1333	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.79, 1.48]
7 Fetal death	6	4788	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.51, 2.23]
7.1 Dose < 500 mg per week	3	2074	Risk Ratio (M-H, Random, 95% CI)	2.52 [0.19, 33.68]
7.2 Dose >= 500 mg per week	3	2714	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.36, 2.16]
8 Admission to NICU	5	4251	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.76, 1.18]
8.1 Dose < 500 mg per week	1	1355	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.05, 1.62]
8.2 Dose >= 500 mg per week	4	2896	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]

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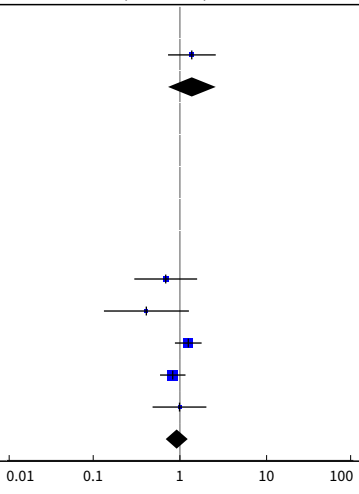
Analysis 8.1. Comparison 8 Progesterone versus placebo: multiple pregnancy by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 1 Perinatal death.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Dose < 500 mg per week					
Combs 2010	19/168	2/75		14.26%	4.24[1.01,17.75]
Combs 2011	0/320	3/156		5.14%	0.07[0,1.34]
Hartikainen 1980	4/78	2/76		11.94%	1.95[0.37,10.33]
Lim 2011	23/681	34/674		27%	0.67[0.4,1.12]
Subtotal (95% CI)	**1247**	**981**		**58.34%**	**1.06[0.3,3.71]**
Total events: 46 (Progesterone), 41 (Placebo)					
Heterogeneity: Tau^2=1.02; Chi^2=9.42, df=3(P=0.02); I^2=68.17%					
Test for overall effect: Z=0.09(P=0.93)					
8.1.2 Dose >= 500 mg per week					
Aboulghar 2012	4/98	5/84		15.98%	0.69[0.19,2.47]
Rode 2011	10/664	7/678		20.34%	1.46[0.56,3.81]
Serra 2013	0/194	5/190		5.35%	0.09[0,1.6]
Subtotal (95% CI)	**956**	**952**		**41.66%**	**0.75[0.24,2.41]**
Total events: 14 (Progesterone), 17 (Placebo)					
Heterogeneity: Tau^2=0.49; Chi^2=3.78, df=2(P=0.15); I^2=47.09%					
Test for overall effect: Z=0.48(P=0.63)					
Total (95% CI)	**2203**	**1933**		**100%**	**0.93[0.45,1.94]**
Total events: 60 (Progesterone), 58 (Placebo)					
Heterogeneity: Tau^2=0.45; Chi^2=13.01, df=6(P=0.04); I^2=53.9%					
Test for overall effect: Z=0.19(P=0.85)					
Test for subgroup differences: Chi^2=0.15, df=1 (P=0.7), I^2=0%					



Analysis 8.2. Comparison 8 Progesterone versus placebo: multiple pregnancy by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 2 Preterm birth less than 34 weeks.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.2.1 Dose < 500 mg per week					
Combs 2011	31/160	11/78		13.79%	1.37[0.73,2.59]
Subtotal (95% CI)	**160**	**78**		**13.79%**	**1.37[0.73,2.59]**
Total events: 31 (Progesterone), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.98(P=0.32)					
8.2.2 Dose > 500 mg per week					
Aboulghar 2012	8/49	10/42		8.74%	0.69[0.3,1.58]
Cetingoz 2011	4/39	7/28		5.09%	0.41[0.13,1.27]
Norman 2009	55/247	44/247		29.71%	1.25[0.88,1.78]
Rode 2011	51/334	63/341		31.36%	0.83[0.59,1.16]
Serra 2013	13/97	13/96		11.32%	0.99[0.48,2.02]
Subtotal (95% CI)	**766**	**754**		**86.21%**	**0.92[0.69,1.23]**



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Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 131 (Progesterone), 137 (Placebo)					
Heterogeneity: Tau²=0.03; Chi²=5.68, df=4(P=0.22); I²=29.57%					
Test for overall effect: Z=0.59(P=0.56)					
Total (95% CI)	**926**	**832**		**100%**	**0.97[0.74,1.27]**
Total events: 162 (Progesterone), 148 (Placebo)					
Heterogeneity: Tau²=0.03; Chi²=6.88, df=5(P=0.23); I²=27.27%					
Test for overall effect: Z=0.22(P=0.83)					
Test for subgroup differences: Chi²=1.3, df=1 (P=0.25), I²=22.9%					

Favours progesterone 0.01 0.1 1 10 100 Favours placebo

Analysis 8.3. Comparison 8 Progesterone versus placebo: multiple pregnancy by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 3 Antenatal tocolysis.

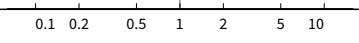
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.3.1 Dose < 500 mg per week					
Caritis 2009	33/71	28/63		12.83%	1.05[0.72,1.52]
Combs 2010	44/56	17/25		16.83%	1.16[0.85,1.56]
Combs 2011	62/160	32/78		15.08%	0.94[0.68,1.31]
Lim 2011	73/336	64/332		16.98%	1.13[0.84,1.52]
Rouse 2007	71/324	97/330		19.49%	0.75[0.57,0.97]
Subtotal (95% CI)	**947**	**828**		**81.2%**	**0.98[0.82,1.17]**
Total events: 283 (Progesterone), 238 (Placebo)					
Heterogeneity: Tau²=0.01; Chi²=6.38, df=4(P=0.17); I²=37.26%					
Test for overall effect: Z=0.22(P=0.83)					
8.3.2 Dose >= 500 mg per week					
Rode 2011	41/333	60/341		13.07%	0.7[0.48,1.01]
Serra 2013	16/97	17/96		5.73%	0.93[0.5,1.73]
Subtotal (95% CI)	**430**	**437**		**18.8%**	**0.75[0.55,1.03]**
Total events: 57 (Progesterone), 77 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.6, df=1(P=0.44); I²=0%					
Test for overall effect: Z=1.75(P=0.08)					
Total (95% CI)	**1377**	**1265**		**100%**	**0.94[0.8,1.1]**
Total events: 340 (Progesterone), 315 (Placebo)					
Heterogeneity: Tau²=0.02; Chi²=9.23, df=6(P=0.16); I²=34.97%					
Test for overall effect: Z=0.81(P=0.42)					
Test for subgroup differences: Chi²=2.04, df=1 (P=0.15), I²=51.04%					

Favours progesterone 0.01 0.1 1 10 100 Favours placebo

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Analysis 8.4. Comparison 8 Progesterone versus placebo: multiple pregnancy by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 4 Preterm birth less than 37 weeks.

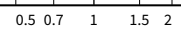
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.4.1 Dose < 500 mg per week					
Cetingoz 2011	20/39	22/28		5.48%	0.65[0.45,0.94]
Combs 2011	113/160	46/78		10.86%	1.2[0.97,1.48]
Hartikainen 1980	15/39	9/38		1.82%	1.62[0.81,3.25]
Lim 2011	186/336	165/332		14.75%	1.11[0.96,1.29]
Rode 2011	158/334	179/341		14.3%	0.9[0.77,1.05]
Rouse 2007	226/325	232/330		17.7%	0.99[0.89,1.09]
Subtotal (95% CI)	**1233**	**1147**		**64.91%**	**1.01[0.88,1.15]**
Total events: 718 (Progesterone), 653 (Placebo)					
Heterogeneity: Tau²=0.01; Chi²=14.01, df=5(P=0.02); I²=64.31%					
Test for overall effect: Z=0.08(P=0.93)					
8.4.2 Dose >= 500 mg per week					
Aboulghar 2012	31/49	28/42		7.09%	0.95[0.7,1.28]
Cetingoz 2011	32/80	40/70		6.1%	0.7[0.5,0.98]
Rode 2011	158/334	179/341		14.3%	0.9[0.77,1.05]
Serra 2013	48/97	47/96		7.6%	1.01[0.76,1.35]
Subtotal (95% CI)	**560**	**549**		**35.09%**	**0.9[0.8,1.01]**
Total events: 269 (Progesterone), 294 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.89, df=3(P=0.41); I²=0%					
Test for overall effect: Z=1.83(P=0.07)					
Total (95% CI)	**1793**	**1696**		**100%**	**0.97[0.88,1.06]**
Total events: 987 (Progesterone), 947 (Placebo)					
Heterogeneity: Tau²=0.01; Chi²=19.68, df=9(P=0.02); I²=54.26%					
Test for overall effect: Z=0.71(P=0.48)					
Test for subgroup differences: Chi²=1.6, df=1 (P=0.21), I²=37.62%					



Favours progesterone — Favours placebo

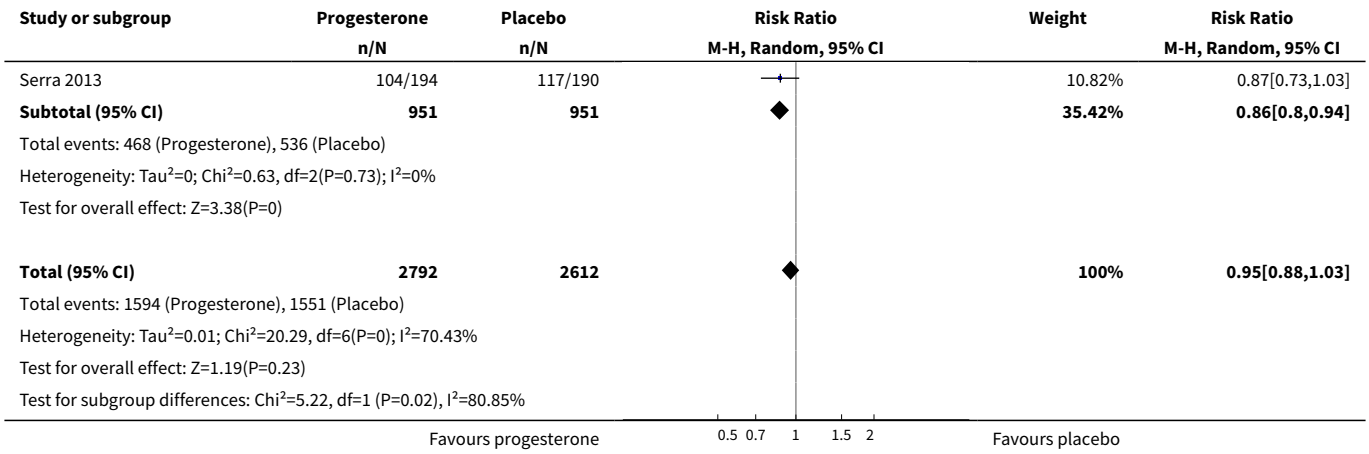
Analysis 8.5. Comparison 8 Progesterone versus placebo: multiple pregnancy by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 5 Infant birthweight less than 2500 g.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.5.1 Dose < 500 mg per week					
Caritis 2009	191/212	175/183		20.6%	0.94[0.89,0.99]
Combs 2011	195/320	70/156		9.45%	1.36[1.12,1.65]
Lim 2011	363/681	355/674		16.62%	1.01[0.92,1.12]
Rouse 2007	377/628	415/648		17.91%	0.94[0.86,1.02]
Subtotal (95% CI)	**1841**	**1661**		**64.58%**	**1.02[0.91,1.14]**
Total events: 1126 (Progesterone), 1015 (Placebo)					
Heterogeneity: Tau²=0.01; Chi²=16.56, df=3(P=0); I²=81.88%					
Test for overall effect: Z=0.3(P=0.76)					
8.5.2 Dose >= 500 mg per week					
Aboulghar 2012	58/98	62/84		8.73%	0.8[0.65,0.99]
Rode 2011	306/659	357/677		15.86%	0.88[0.79,0.98]

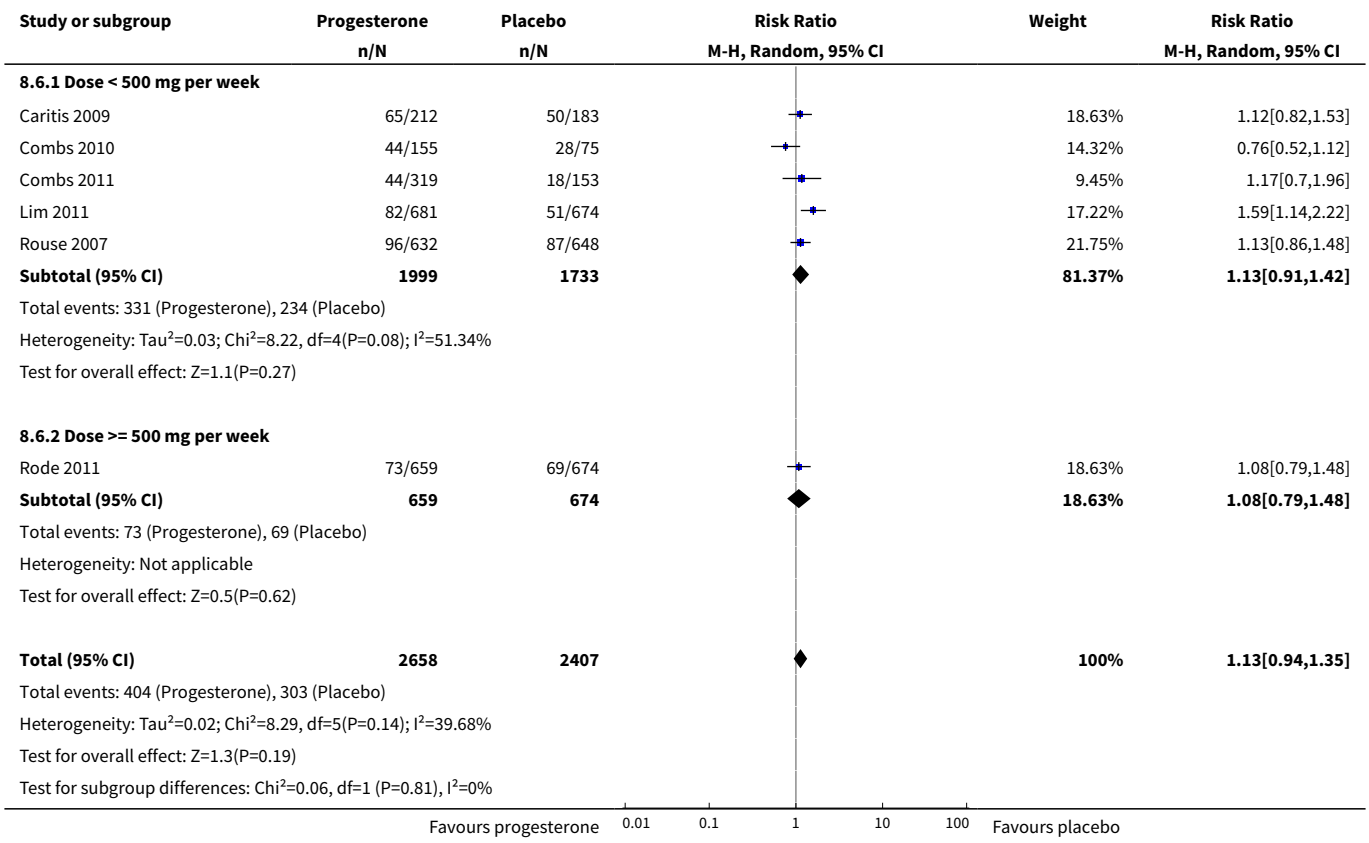


Favours progesterone — Favours placebo

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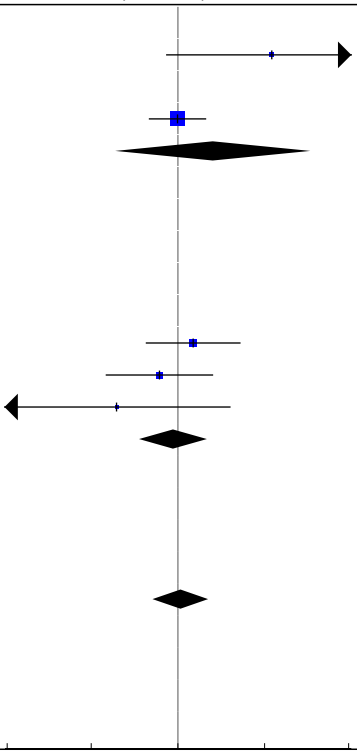
Analysis 8.6. Comparison 8 Progesterone versus placebo: multiple pregnancy by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 6 Respiratory distress syndrome.



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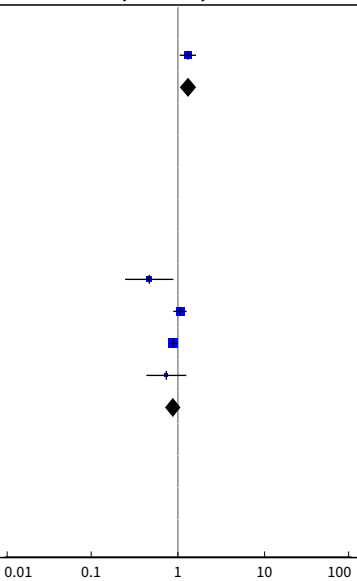
Analysis 8.7. Comparison 8 Progesterone versus placebo: multiple pregnancy by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 7 Fetal death.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.7.1 Dose < 500 mg per week					
Combs 2010	13/168	0/75		6.36%	12.14[0.73,201.61]
Combs 2011	0/320	0/156			Not estimable
Lim 2011	13/681	13/674		43.75%	0.99[0.46,2.12]
Subtotal (95% CI)	**1169**	**905**		**50.12%**	**2.52[0.19,33.68]**
Total events: 26 (Progesterone), 13 (Placebo)					
Heterogeneity: Tau^2=2.64; Chi^2=3.39, df=1(P=0.07); I^2=70.52%					
Test for overall effect: Z=0.7(P=0.48)					
8.7.2 Dose >= 500 mg per week					
Norman 2009	6/494	4/494		24.2%	1.5[0.43,5.28]
Rode 2011	3/664	5/678		20.15%	0.61[0.15,2.55]
Serra 2013	0/194	2/190		5.53%	0.2[0.01,4.05]
Subtotal (95% CI)	**1352**	**1362**		**49.88%**	**0.88[0.36,2.16]**
Total events: 9 (Progesterone), 11 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.89, df=2(P=0.39); I^2=0%					
Test for overall effect: Z=0.29(P=0.77)					
Total (95% CI)	**2521**	**2267**		**100%**	**1.07[0.51,2.23]**
Total events: 35 (Progesterone), 24 (Placebo)					
Heterogeneity: Tau^2=0.17; Chi^2=5.26, df=4(P=0.26); I^2=24.01%					
Test for overall effect: Z=0.17(P=0.87)					
Test for subgroup differences: Chi^2=0.57, df=1 (P=0.45), I^2=0%					

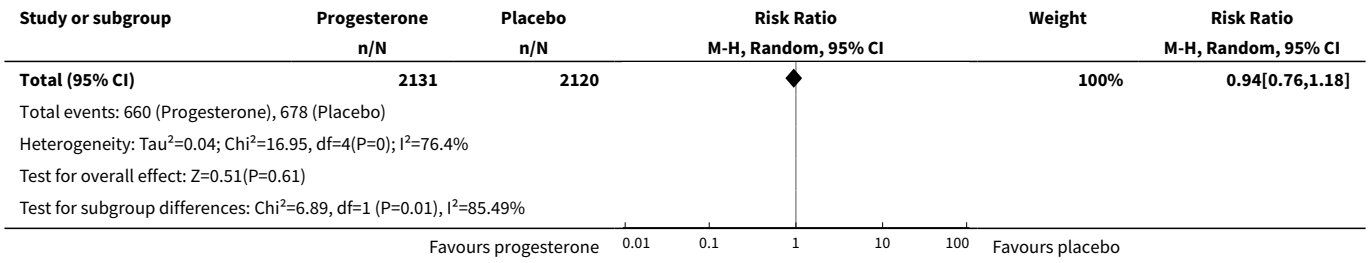


Analysis 8.8. Comparison 8 Progesterone versus placebo: multiple pregnancy by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 8 Admission to NICU.

Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.8.1 Dose < 500 mg per week					
Lim 2011	153/681	116/674		24.32%	1.31[1.05,1.62]
Subtotal (95% CI)	**681**	**674**		**24.32%**	**1.31[1.05,1.62]**
Total events: 153 (Progesterone), 116 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.41(P=0.02)					
8.8.2 Dose >= 500 mg per week					
Aboulghar 2012	12/98	22/84		8.71%	0.47[0.25,0.89]
Norman 2009	167/494	158/494		26.28%	1.06[0.88,1.26]
Rode 2011	307/664	354/678		29.39%	0.89[0.79,0.99]
Serra 2013	21/194	28/190		11.31%	0.73[0.43,1.25]
Subtotal (95% CI)	**1450**	**1446**		**75.68%**	**0.87[0.71,1.07]**
Total events: 507 (Progesterone), 562 (Placebo)					
Heterogeneity: Tau^2=0.02; Chi^2=7.74, df=3(P=0.05); I^2=61.23%					
Test for overall effect: Z=1.27(P=0.2)					



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Comparison 9. Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	1	12	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.16, 24.33]
1.1 Intramuscular	1	12	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.16, 24.33]
2 Preterm birth less than 34 weeks' gestation	2	175	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.55, 1.65]
2.1 Intramuscular	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.72, 1.39]
2.2 Vaginal	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.37, 2.27]
3 Pregnancy prolongation (days)	2	232	Mean Difference (IV, Random, 95% CI)	1.88 [-8.42, 12.17]
3.1 Intramuscular	1	69	Mean Difference (IV, Random, 95% CI)	-3.30 [-7.41, 0.81]
3.2 Vaginal	1	163	Mean Difference (IV, Random, 95% CI)	7.21 [2.39, 12.03]
4 Pregnancy prolongation - less than 1 week	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.07, 2.37]
4.1 Intramuscular	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.07, 2.37]
5 Pregnancy prolongation - 1.0 to 1.9 weeks	1	12	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.16, 24.33]
5.1 Intramuscular	1	12	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.16, 24.33]
6 Pregnancy prolongation - 2 weeks or more	1	12	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.42, 9.42]
6.1 Intramuscular	1	12	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.42, 9.42]
7 Spontaneous birth	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.80, 1.49]
7.1 Intramuscular	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.80, 1.49]
8 Caesarean section	2	81	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.51, 1.60]

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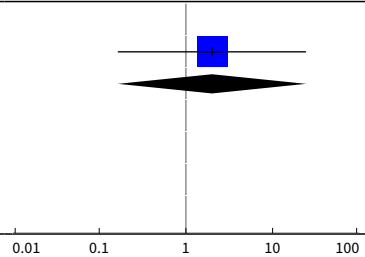
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Intramuscular	2	81	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.51, 1.60]
9 Use of tocolysis	2	205	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.58, 1.65]
9.1 Intramuscular	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.55, 2.62]
9.2 Vaginal	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.50, 1.73]
10 Preterm birth less than 37 weeks' gestation	2	223	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.20, 1.31]
10.1 Vaginal	1	163	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.55, 1.06]
10.2 Intramuscular	1	60	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.12, 0.69]
11 Infant birthweight less than 2500 g	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.28, 0.98]
11.1 Vaginal	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.28, 0.98]
12 Respiratory distress syndrome	4	314	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.49, 1.10]
12.1 Vaginal	2	233	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.20, 1.15]
12.2 Intramuscular	2	81	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.66, 1.12]
13 Intraventricular haemorrhage grade III or IV	1	12	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.53, 152.93]
13.1 Intramuscular	1	12	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.53, 152.93]
14 Periventricular leucomalacia	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.1 Intramuscular	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Use of assisted ventilation	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.37]
15.1 Vaginal	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.37]
16 Necrotizing enterocolitis	2	81	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.50, 18.69]
16.1 Intramuscular	2	81	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.50, 18.69]
17 Neonatal sepsis	4	314	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.17, 1.68]
17.1 Vaginal	2	233	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.07, 1.00]
17.2 Intramuscular	2	81	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.39, 3.05]
18 Fetal death	2	81	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.07, 16.75]

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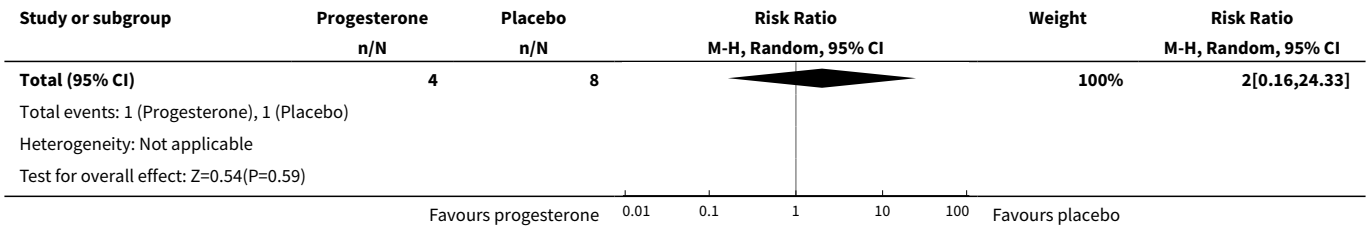
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Intramuscular	2	81	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.07, 16.75]
19 Neonatal death	2	175	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.05, 6.24]
19.1 Intramuscular	1	12	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.16, 24.33]
19.2 Vaginal	1	163	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.40]
20 Neonatal length of hospital stay (days)	2	81	Mean Difference (IV, Fixed, 95% CI)	-2.16 [-15.84, 11.53]
20.1 Intramuscular	2	81	Mean Difference (IV, Fixed, 95% CI)	-2.16 [-15.84, 11.53]
21 Apgar score less than seven at five minutes	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.27]
21.1 Vaginal	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.27]
22 Prelabour spontaneous rupture of membranes	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.19, 1.45]
22.1 Vaginal	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.19, 1.45]
23 Preterm birth less than 28 weeks' gestation	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 15.60]
23.1 Vaginal	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 15.60]
24 Apgar score less than seven at five minutes	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.27]
24.1 Vaginal	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.27]
25 Admission to neonatal intensive care unit	1	163	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.27, 9.07]
25.1 Vaginal	1	163	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.27, 9.07]

Analysis 9.1. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 1 Perinatal death.

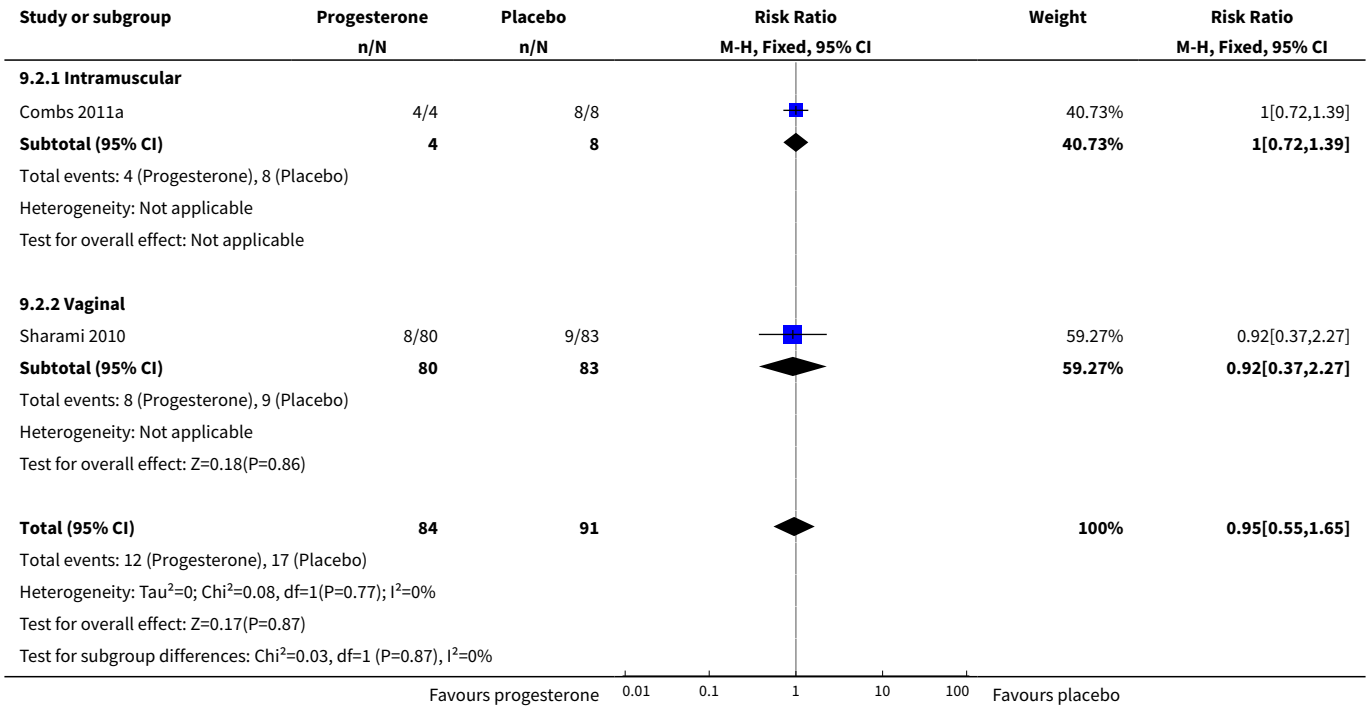
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 Intramuscular					
Combs 2011a	1/4	1/8		100%	2[0.16,24.33]
Subtotal (95% CI)	**4**	**8**		**100%**	**2[0.16,24.33]**
Total events: 1 (Progesterone), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					



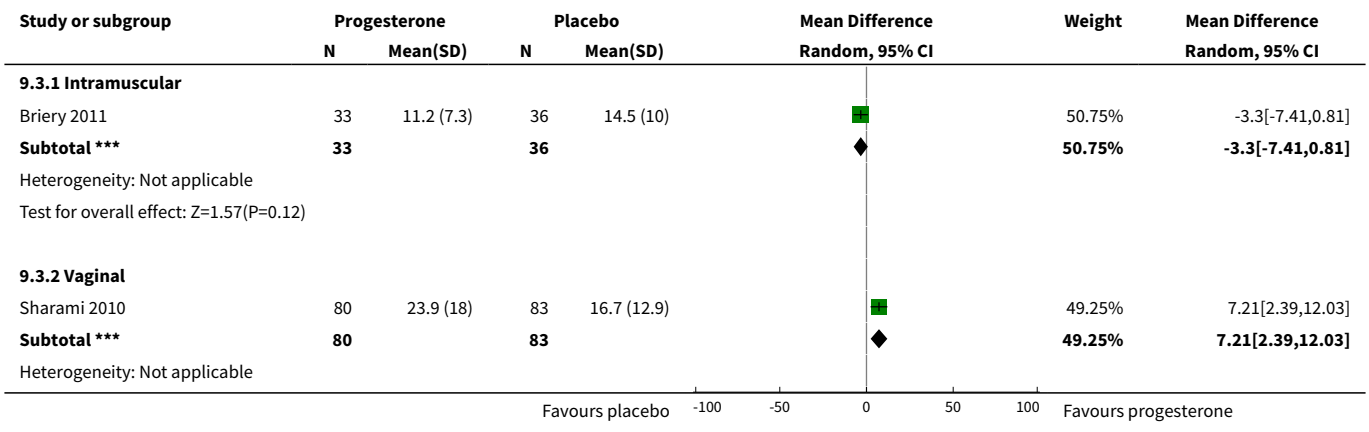
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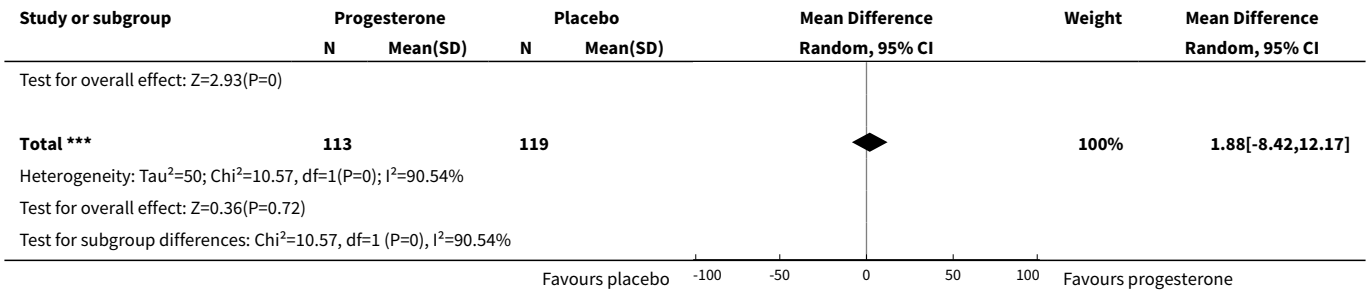
Analysis 9.2. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 2 Preterm birth less than 34 weeks' gestation.



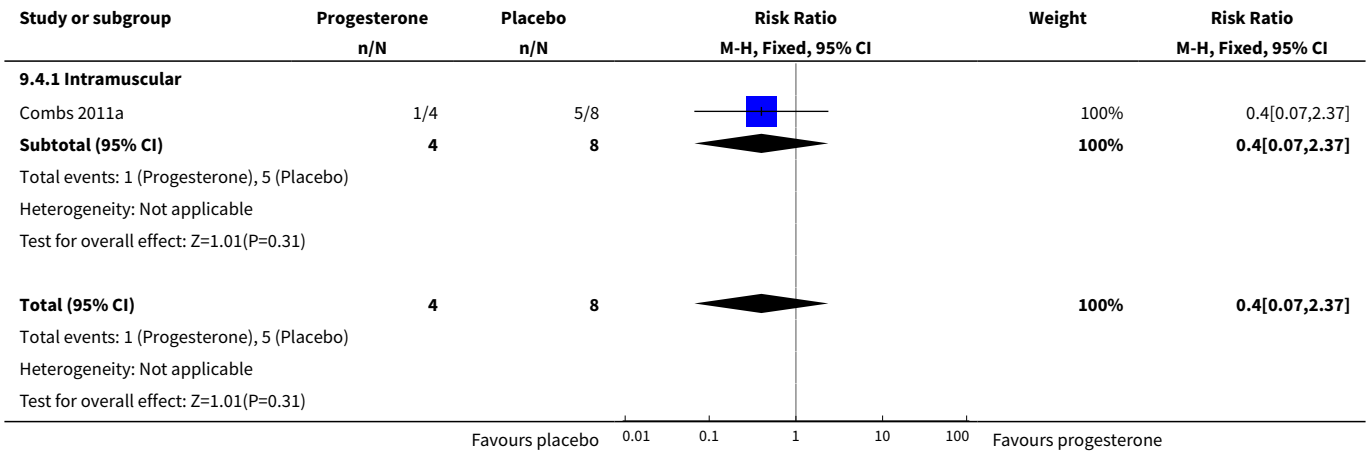
Analysis 9.3. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 3 Pregnancy prolongation (days).



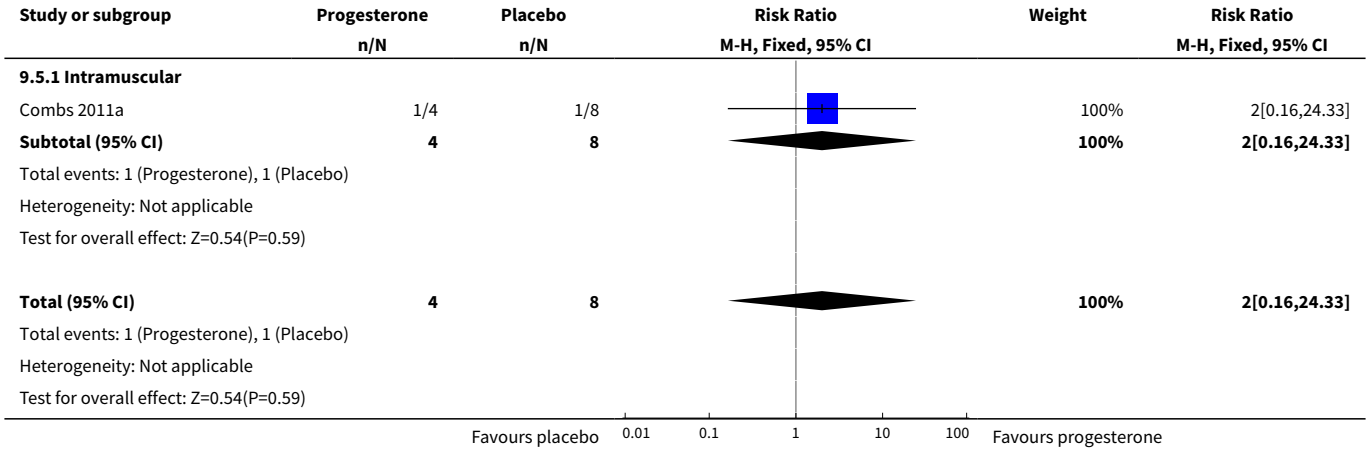
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Analysis 9.4. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 4 Pregnancy prolongation - less than 1 week.

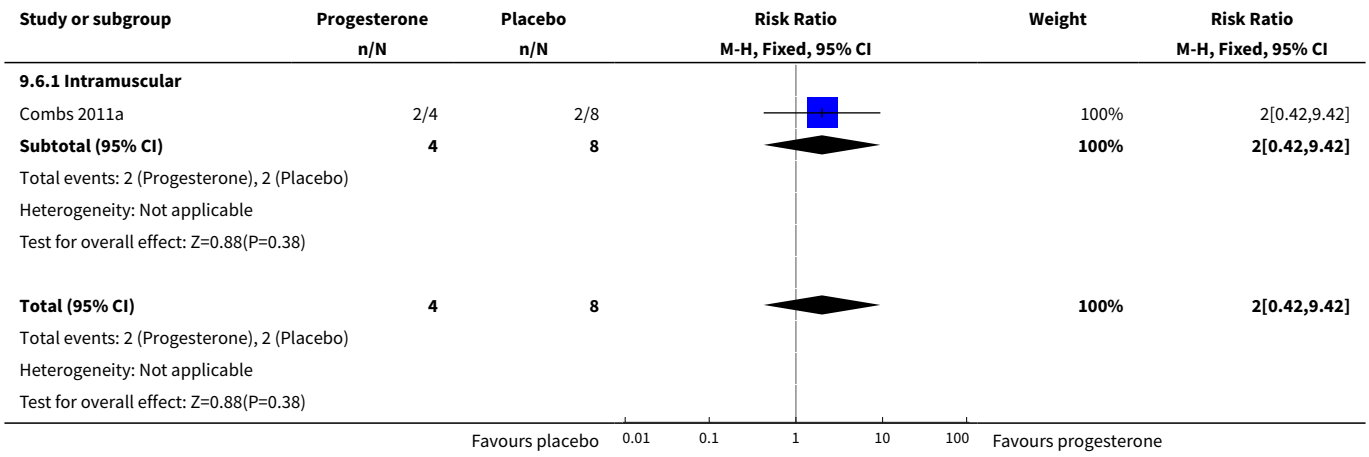


Analysis 9.5. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 5 Pregnancy prolongation - 1.0 to 1.9 weeks.

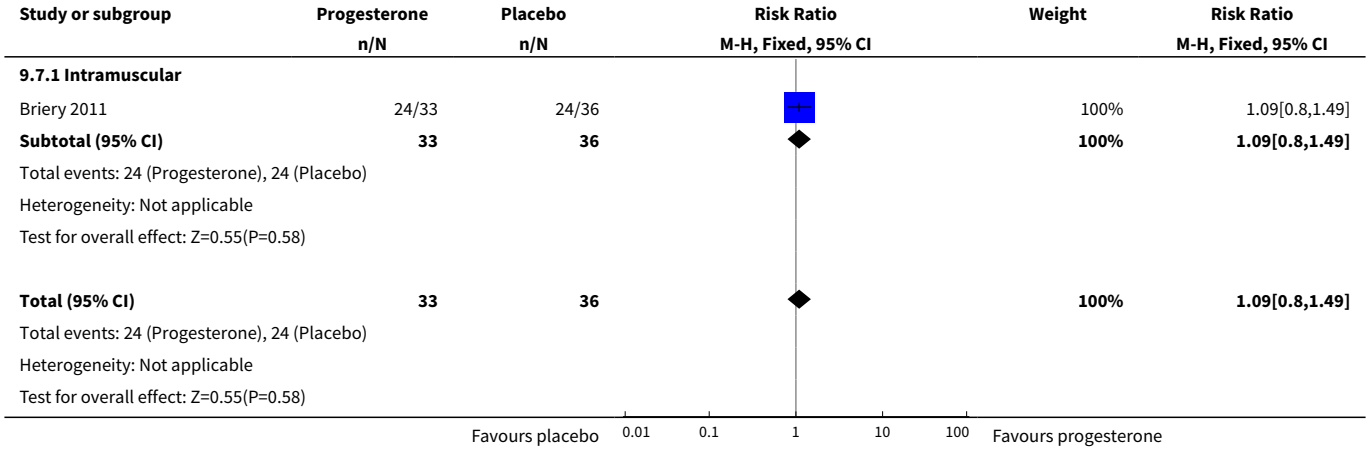


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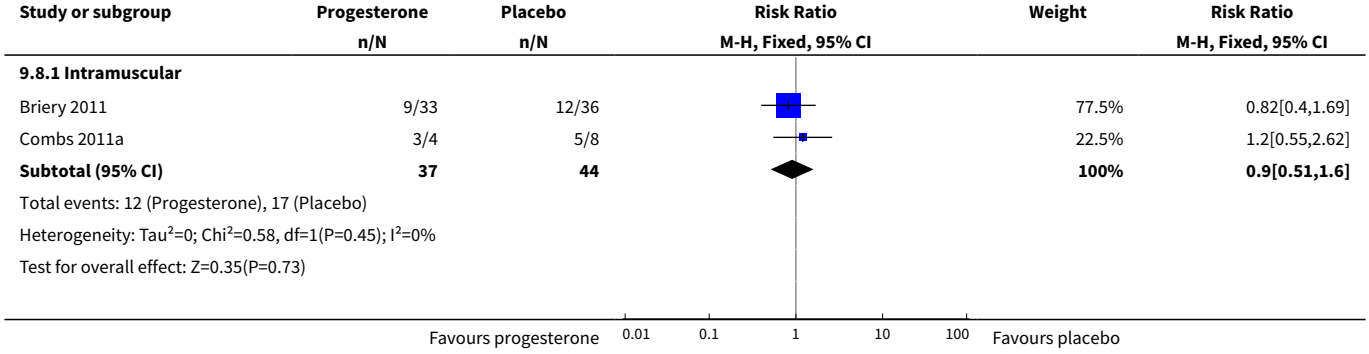
Analysis 9.6. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 6 Pregnancy prolongation - 2 weeks or more.



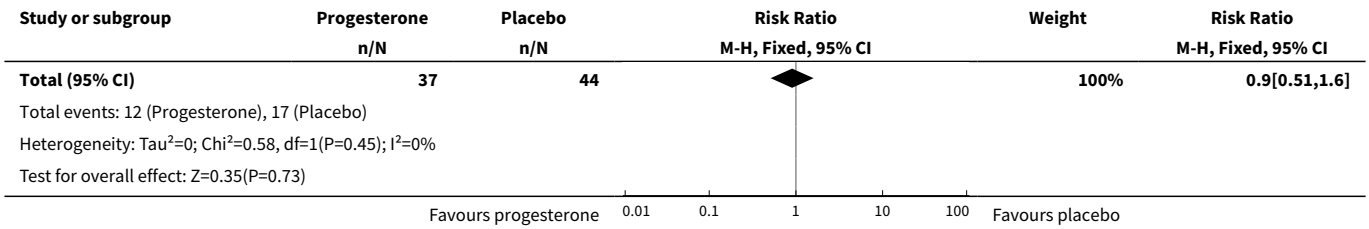
Analysis 9.7. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 7 Spontaneous birth.



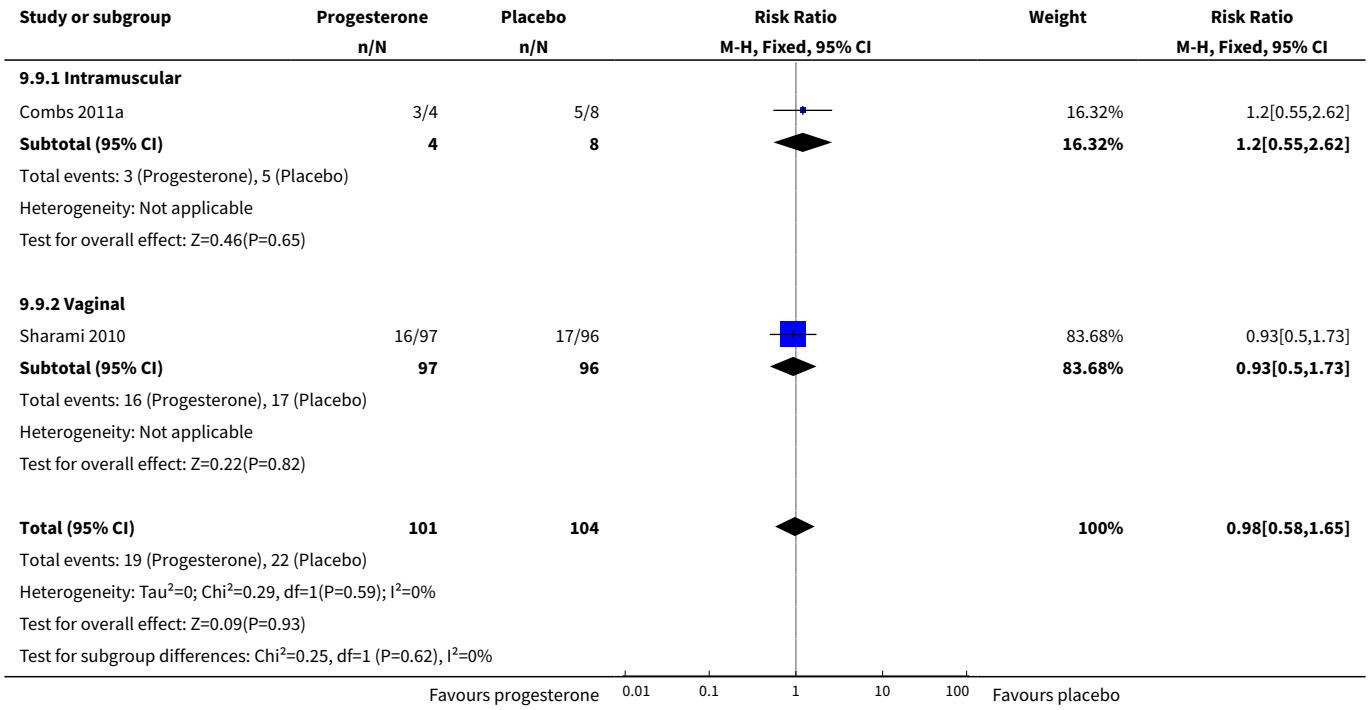
Analysis 9.8. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 8 Caesarean section.



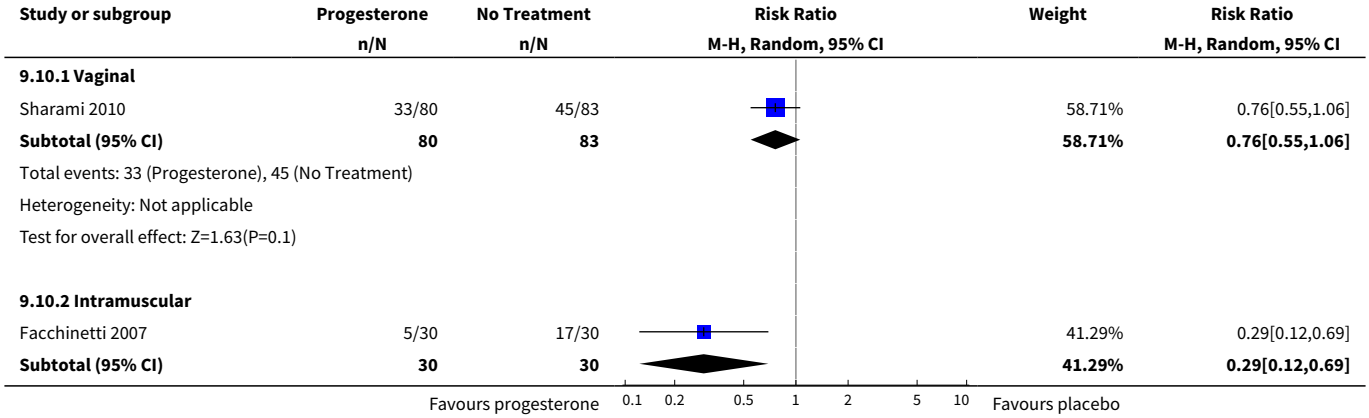
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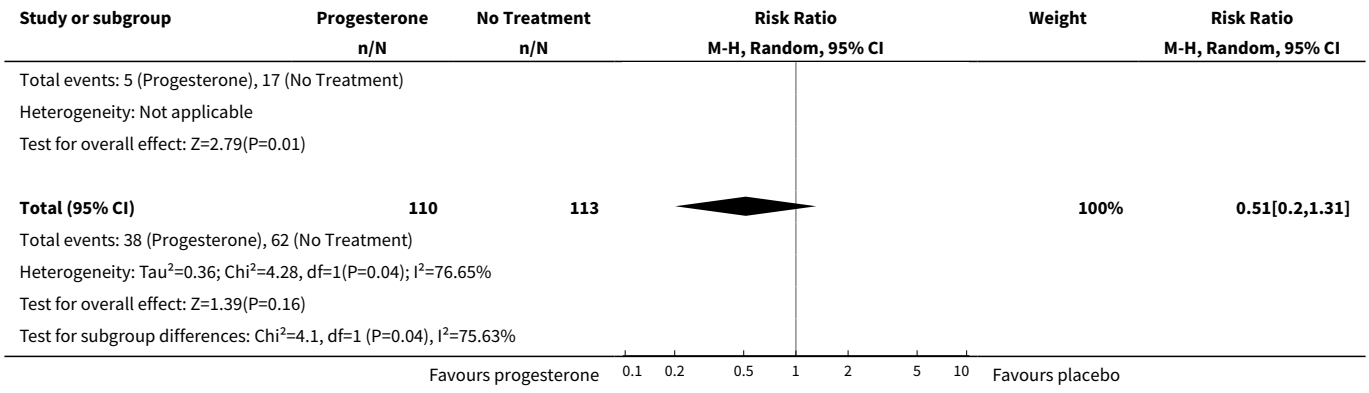
Analysis 9.9. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 9 Use of tocolysis.



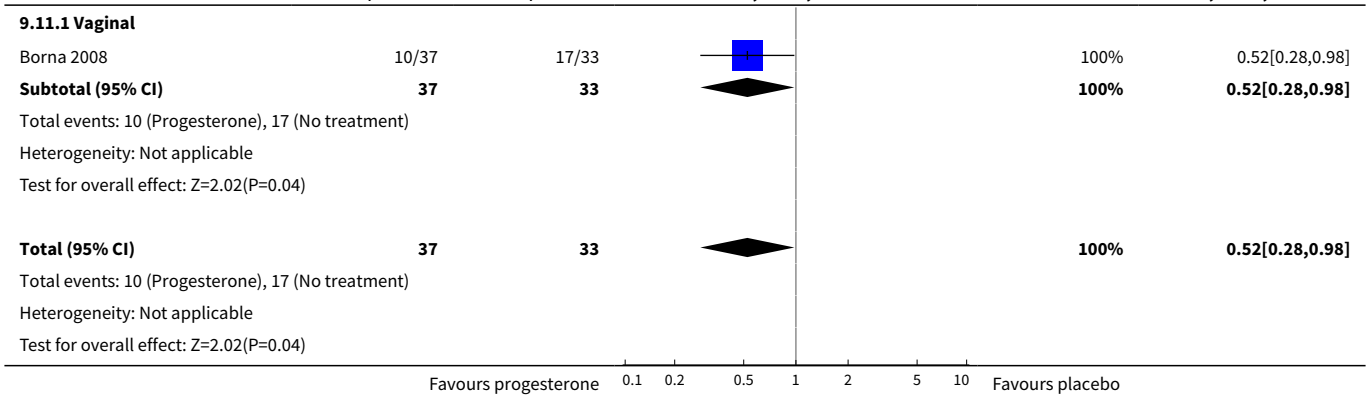
Analysis 9.10. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 10 Preterm birth less than 37 weeks' gestation.



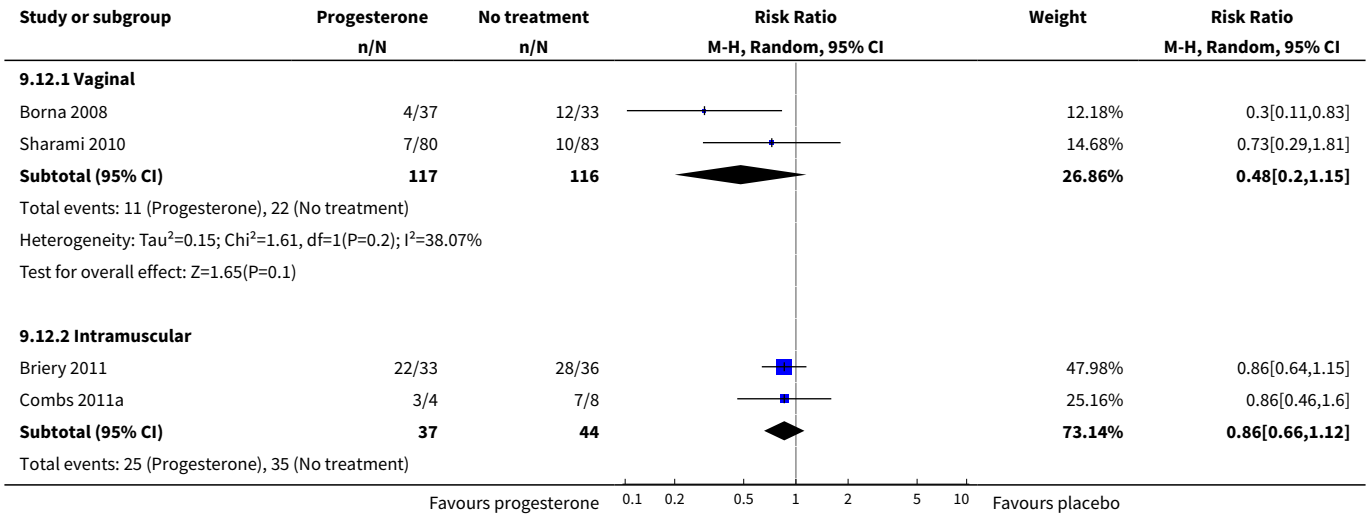
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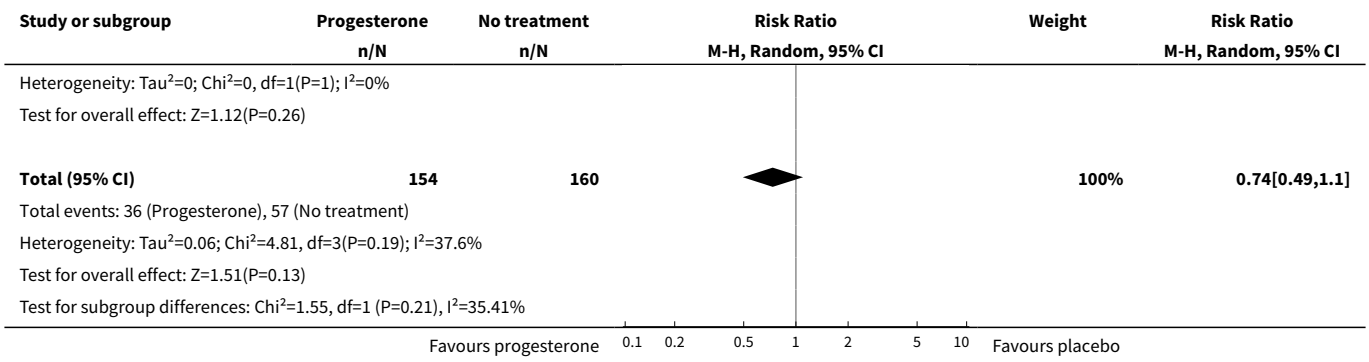
Analysis 9.11. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 11 Infant birthweight less than 2500 g.



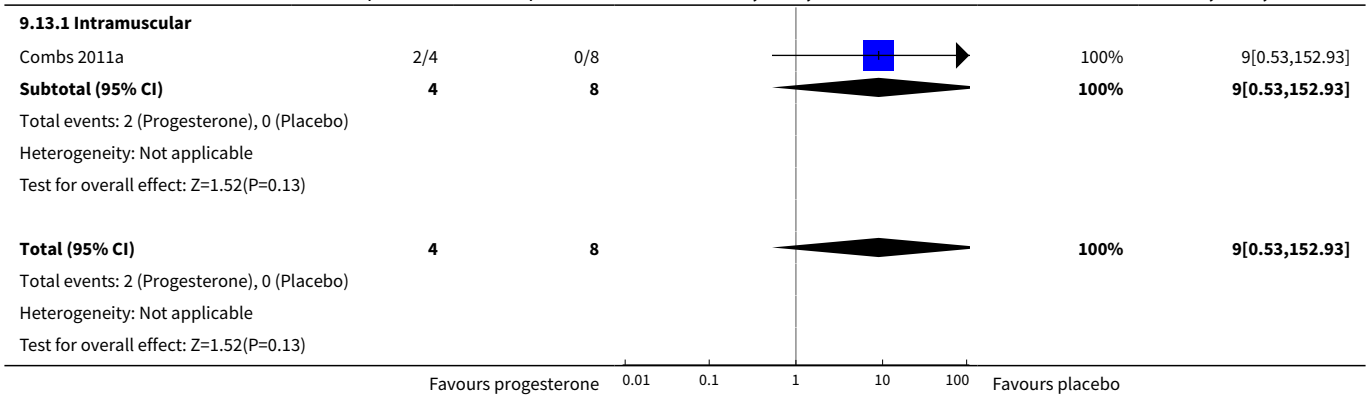
Analysis 9.12. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 12 Respiratory distress syndrome.



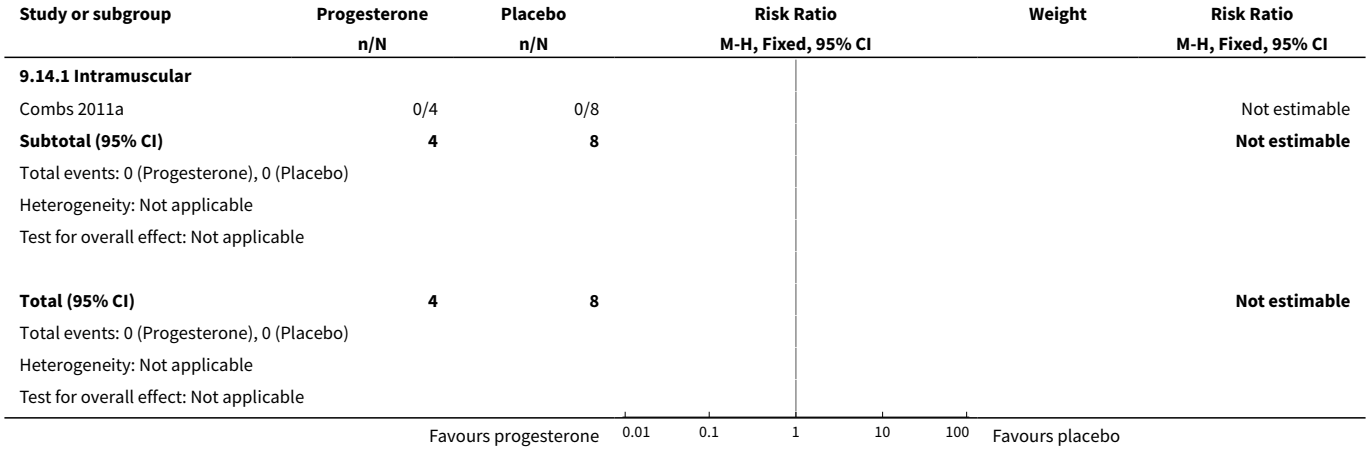
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Analysis 9.13. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 13 Intraventricular haemorrhage grade III or IV.

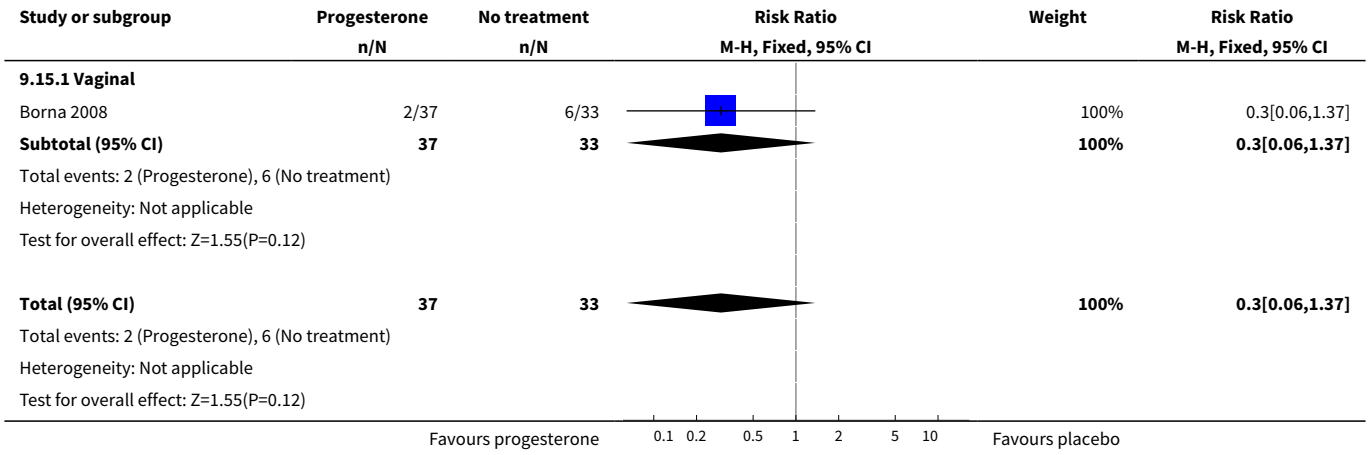


Analysis 9.14. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 14 Periventricular leucomalacia.

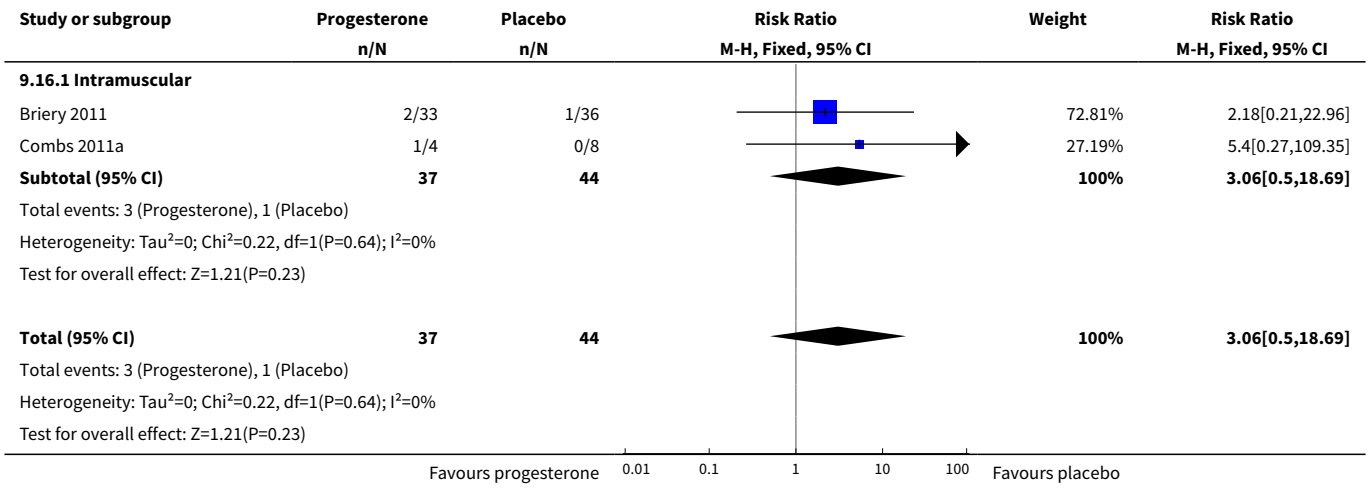


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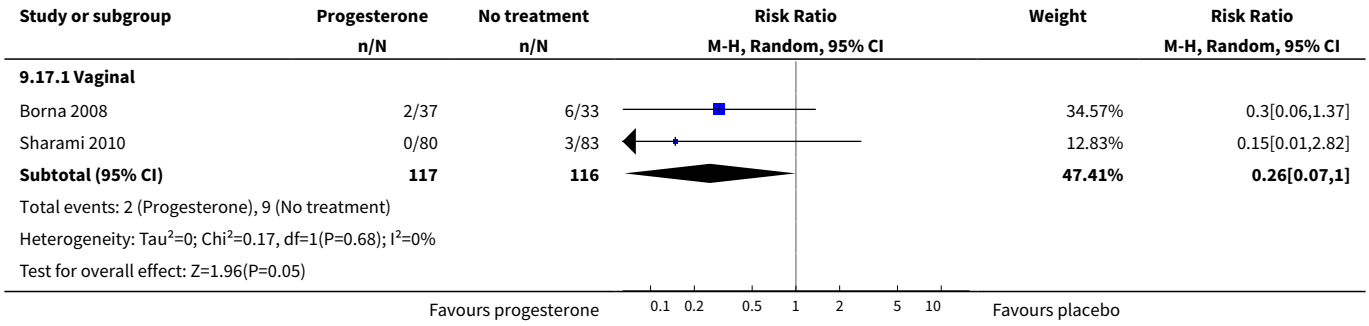
Analysis 9.15. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 15 Use of assisted ventilation.



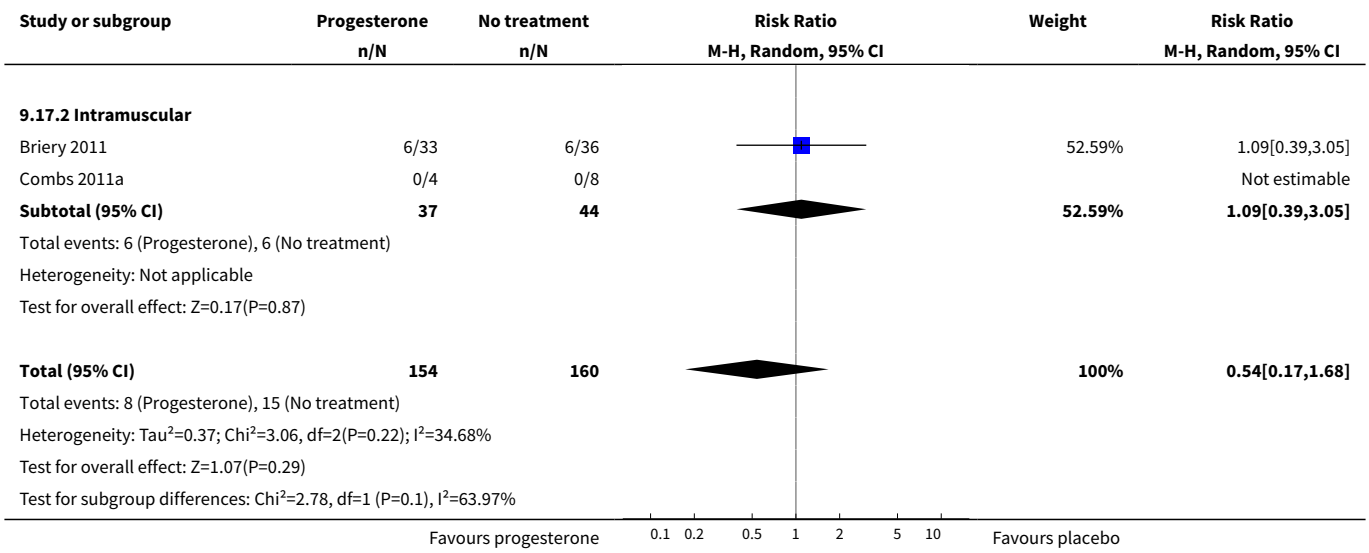
Analysis 9.16. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 16 Necrotizing enterocolitis.



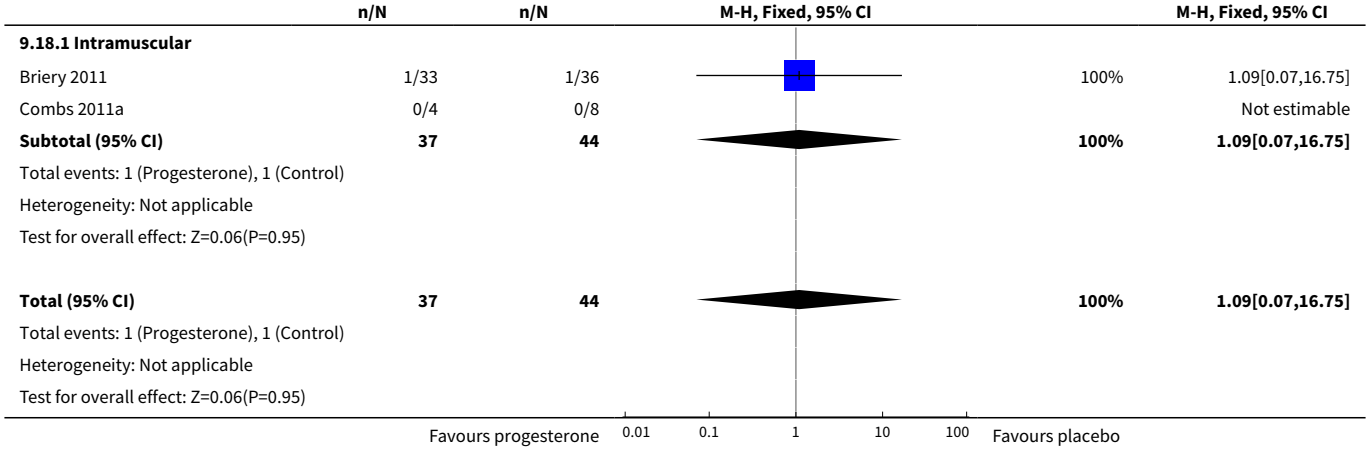
Analysis 9.17. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 17 Neonatal sepsis.



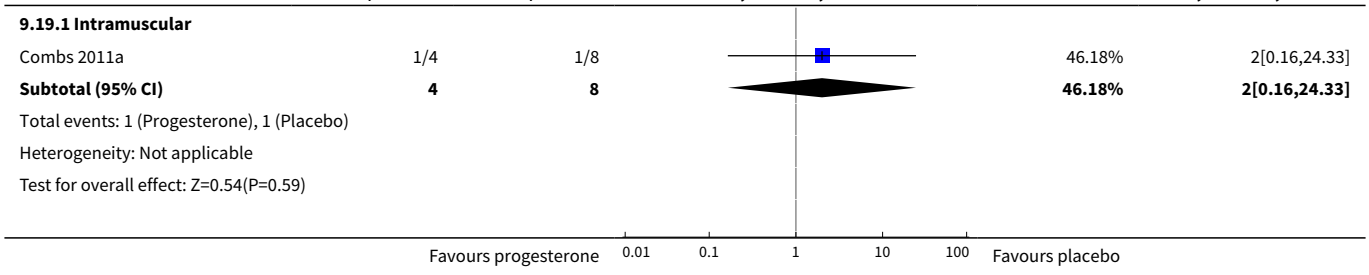
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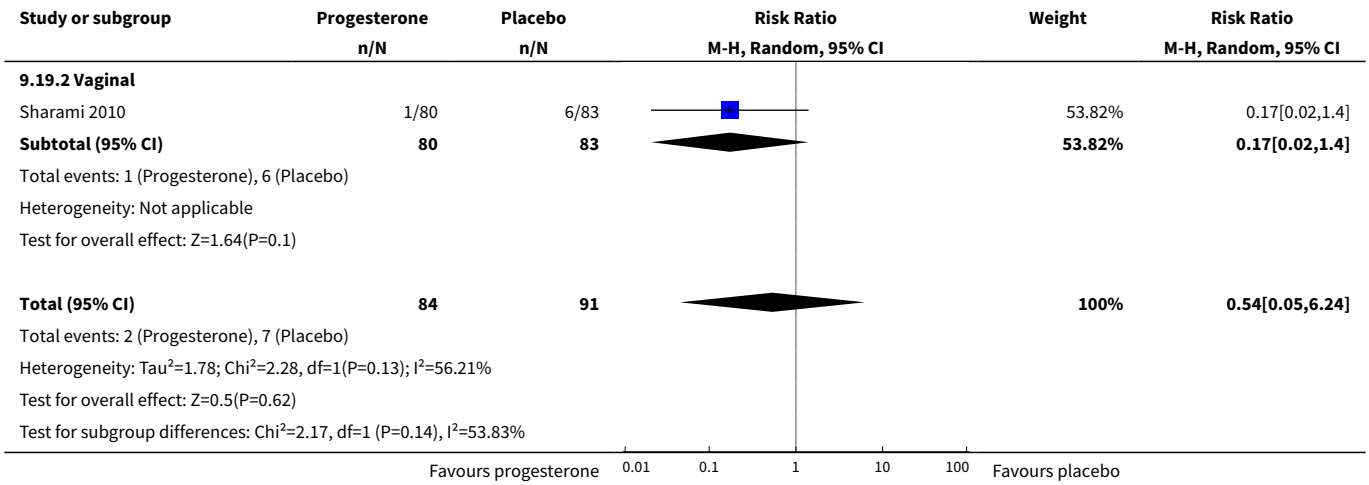
Analysis 9.18. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 18 Fetal death.



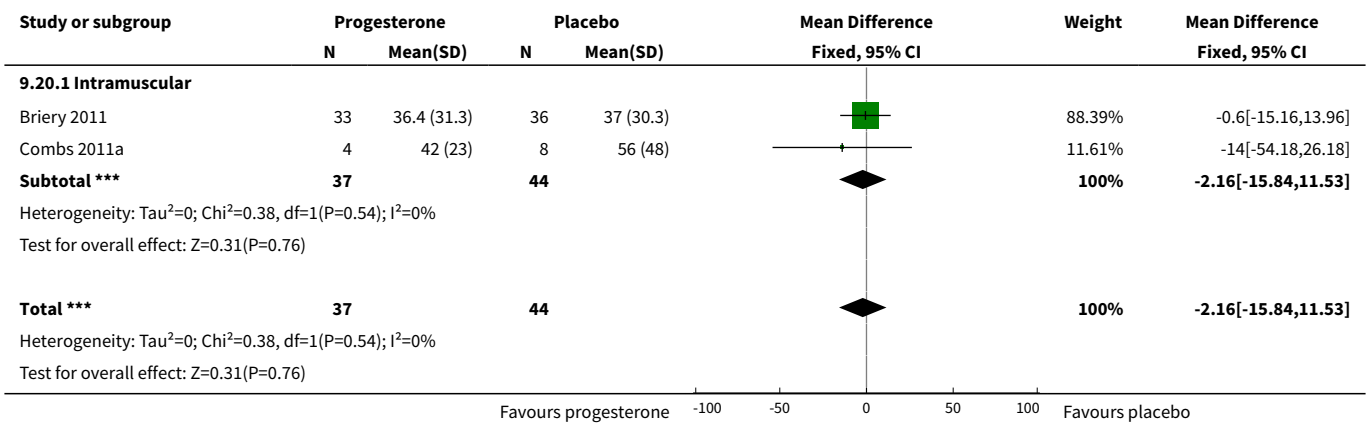
Analysis 9.19. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 19 Neonatal death.



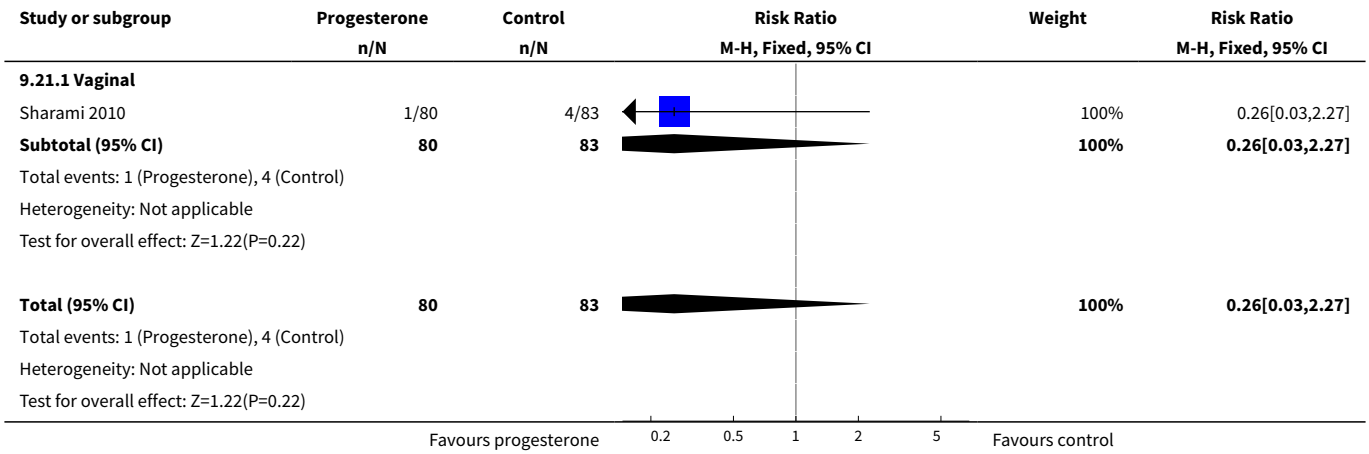
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Analysis 9.20. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 20 Neonatal length of hospital stay (days).

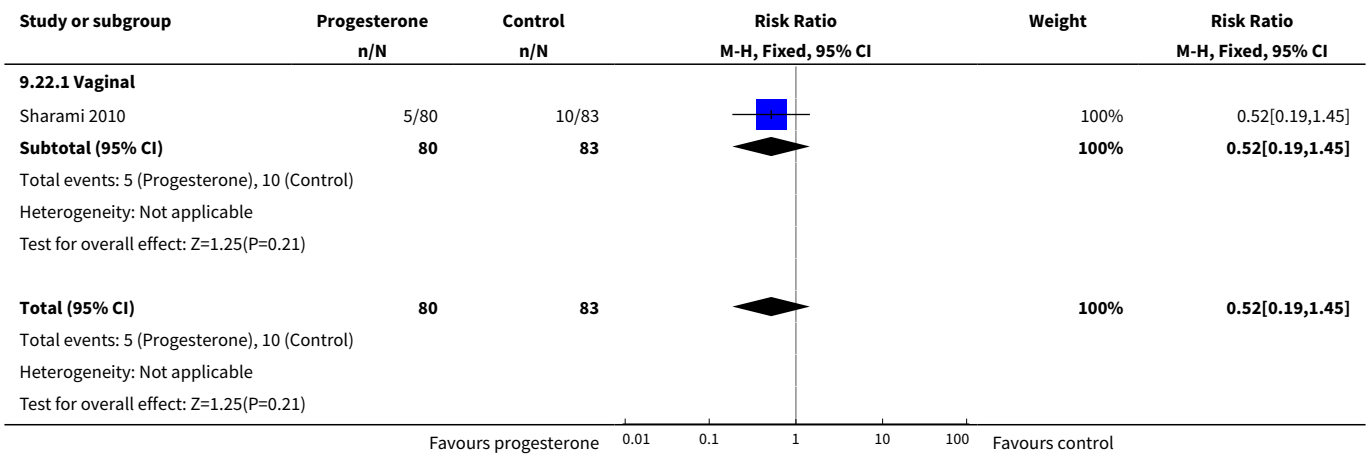


Analysis 9.21. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 21 Apgar score less than seven at five minutes.

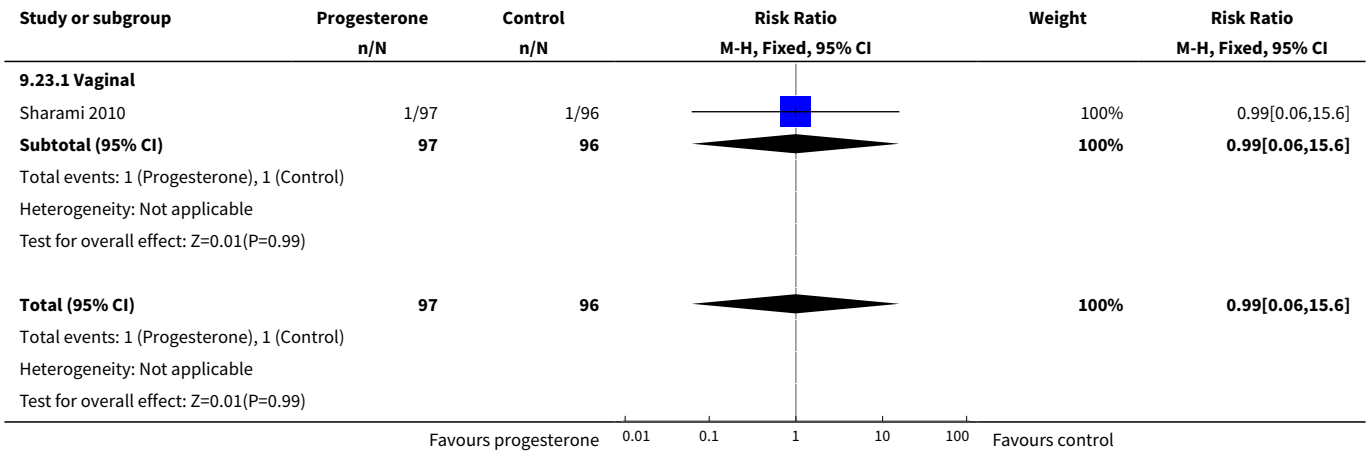


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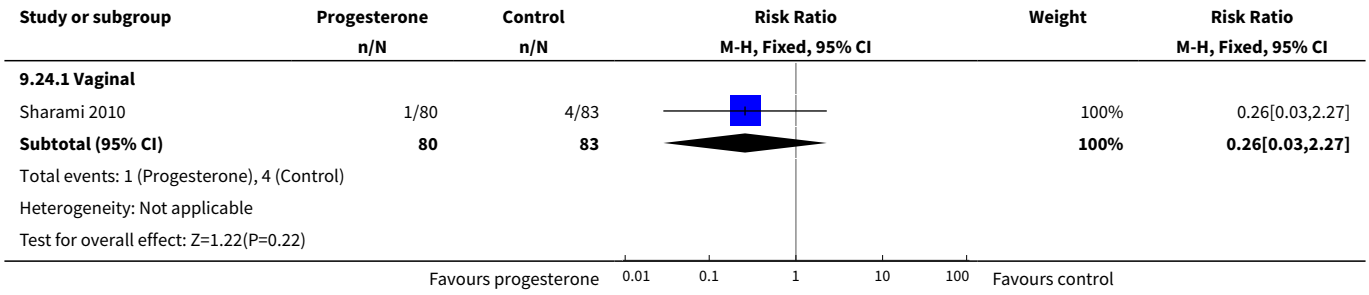
Analysis 9.22. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 22 Prelabour spontaneous rupture of membranes.



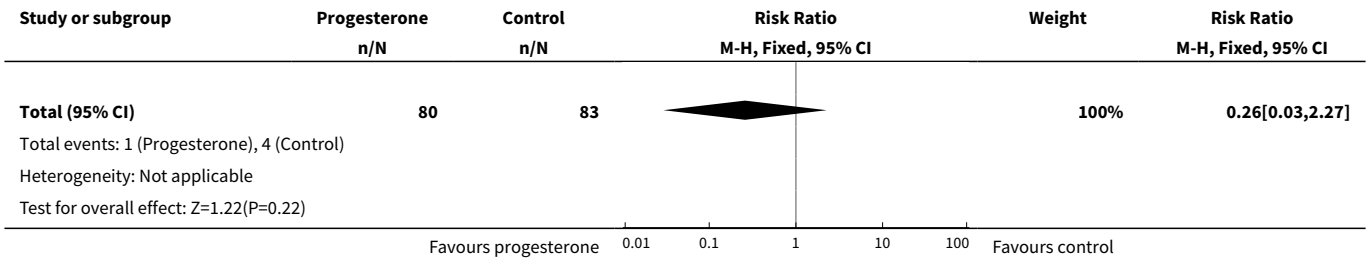
Analysis 9.23. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 23 Preterm birth less than 28 weeks' gestation.



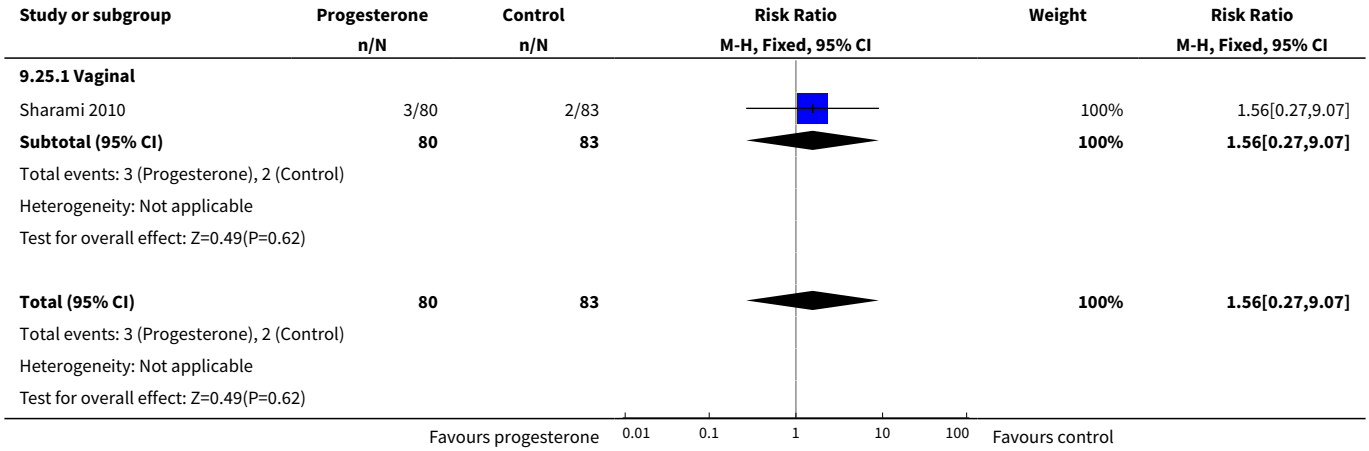
Analysis 9.24. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 24 Apgar score less than seven at five minutes.



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Analysis 9.25. Comparison 9 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, Outcome 25 Admission to neonatal intensive care unit.



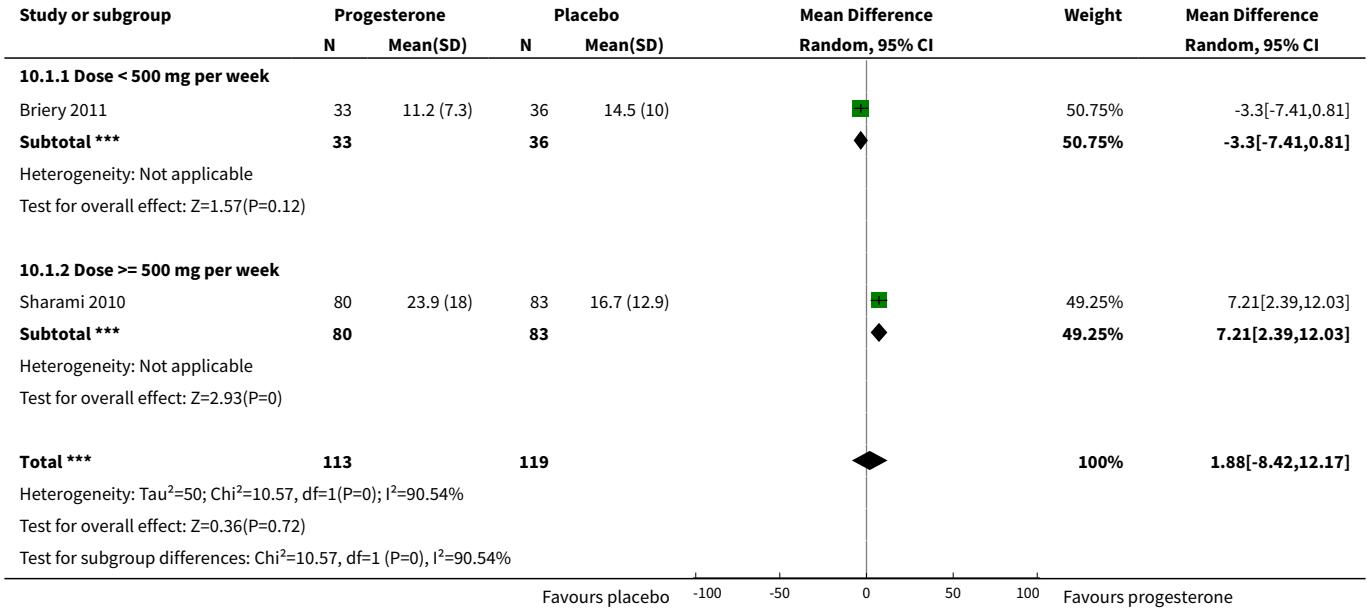
Comparison 10. Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, by cumulative weekly dose (< 500 mg v >= 500 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy prolongation (days)	2	232	Mean Difference (IV, Random, 95% CI)	1.88 [-8.42, 12.17]
1.1 Dose < 500 mg per week	1	69	Mean Difference (IV, Random, 95% CI)	-3.30 [-7.41, 0.81]
1.2 Dose >= 500 mg per week	1	163	Mean Difference (IV, Random, 95% CI)	7.21 [2.39, 12.03]
2 Preterm birth less than 37 weeks' gestation	2	223	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.20, 1.31]
2.1 Dose >=500 mg per week	1	163	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.55, 1.06]
2.2 Dose <500 mg per week	1	60	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.12, 0.69]
3 Respiratory distress syndrome	4	314	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.49, 1.10]

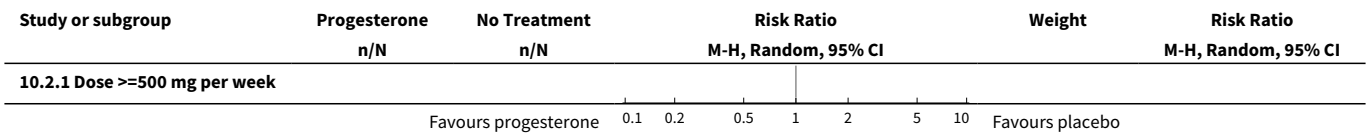
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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Dose >=500 mg per week	2	233	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.20, 1.15]
3.2 Dose <500 mg per week	2	81	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.66, 1.12]
4 Neonatal sepsis	4	314	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.17, 1.68]
4.1 Dose >=500 mg per week	2	233	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.07, 1.00]
4.2 Dose <500 mg per week	2	81	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.39, 3.05]
5 Neonatal death	2	175	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.05, 6.24]
5.1 Dose <500 mg per week	1	12	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.16, 24.33]
5.2 Dose >=500 mg per week	1	163	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.40]

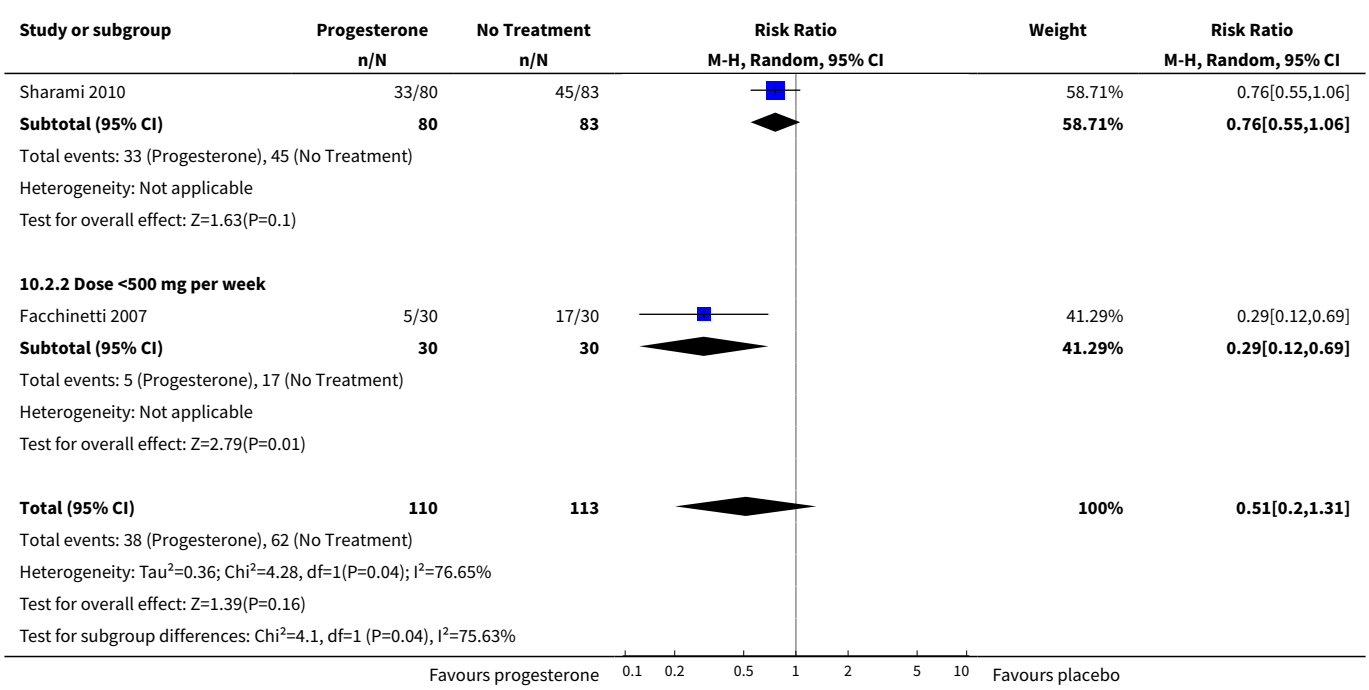
Analysis 10.1. Comparison 10 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 1 Pregnancy prolongation (days).



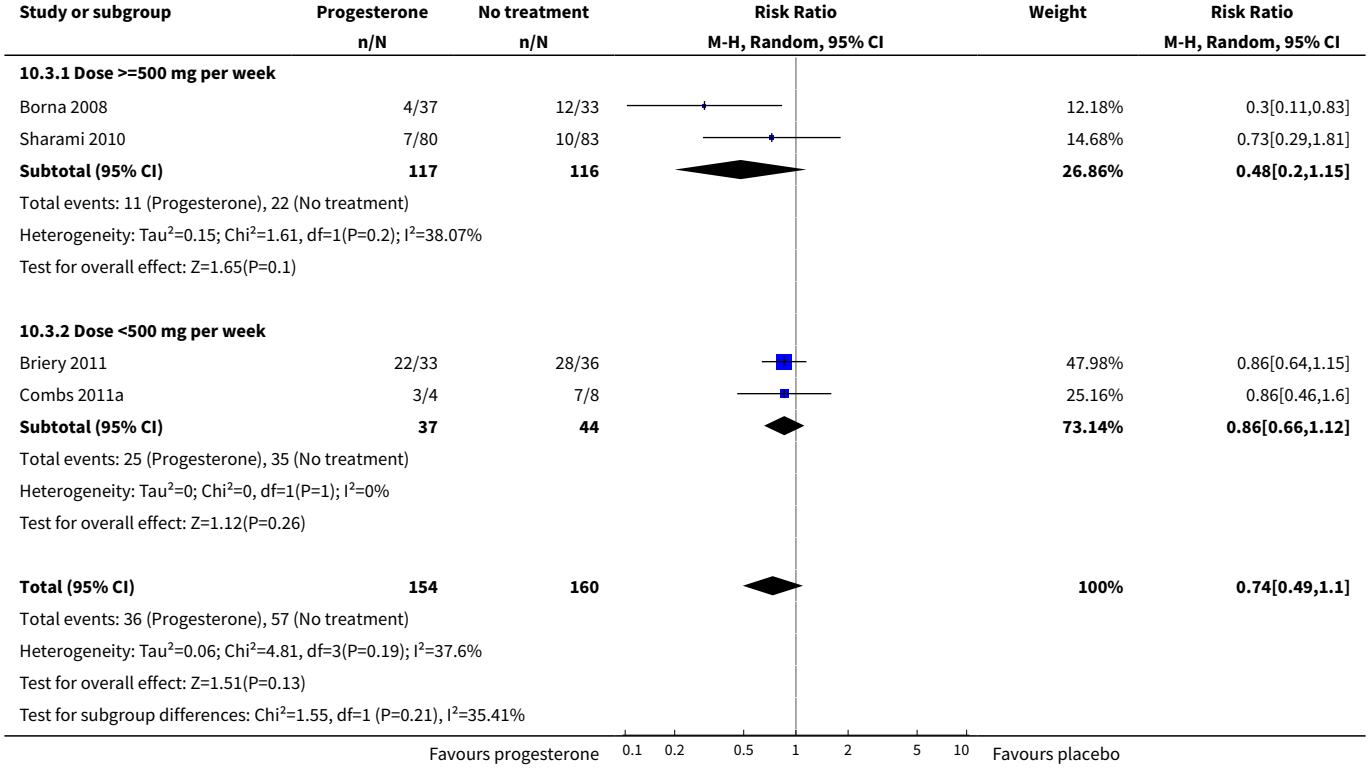
Analysis 10.2. Comparison 10 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 2 Preterm birth less than 37 weeks' gestation.



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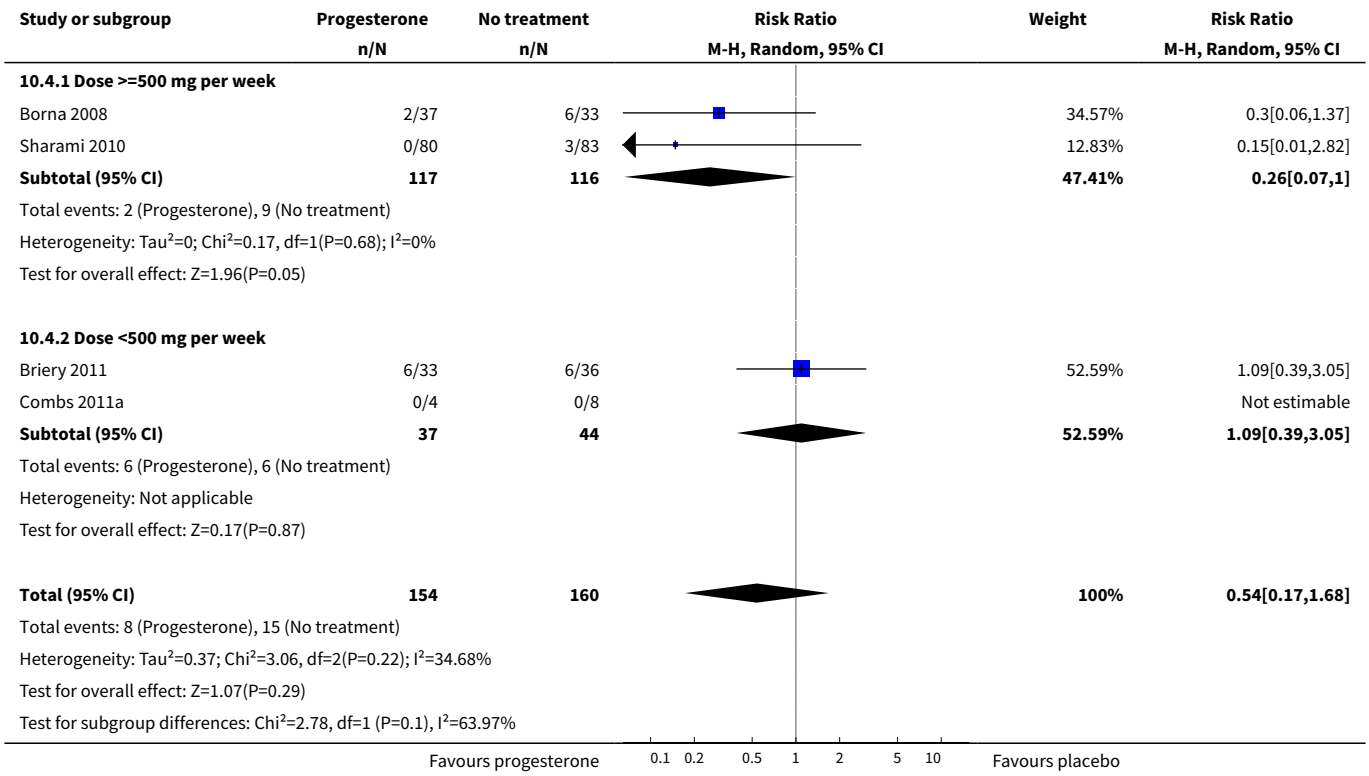


Analysis 10.3. Comparison 10 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 3 Respiratory distress syndrome.

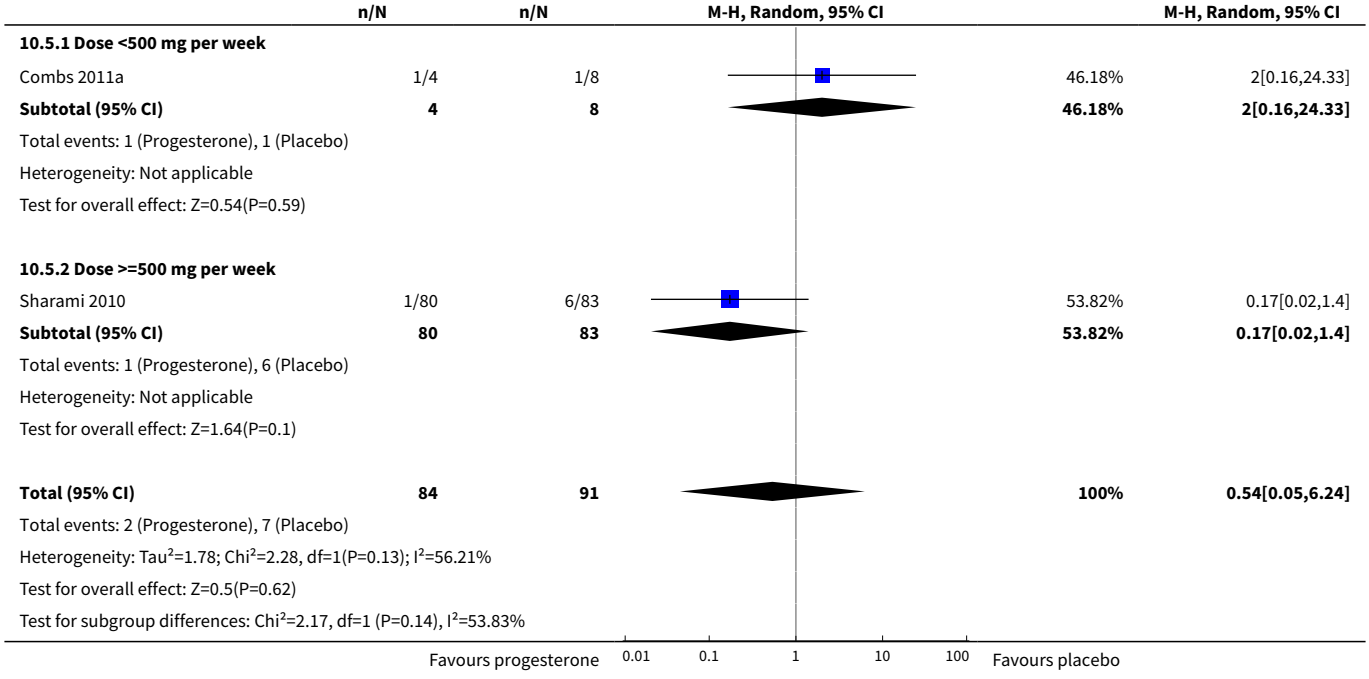


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Analysis 10.4. Comparison 10 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 4 Neonatal sepsis.



Analysis 10.5. Comparison 10 Progesterone versus placebo/no treatment: prior threatened preterm labour, singletons, by cumulative weekly dose (< 500 mg v >= 500 mg), Outcome 5 Neonatal death.



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Comparison 11. Progesterone versus placebo: other reason at risk of preterm birth, singletons

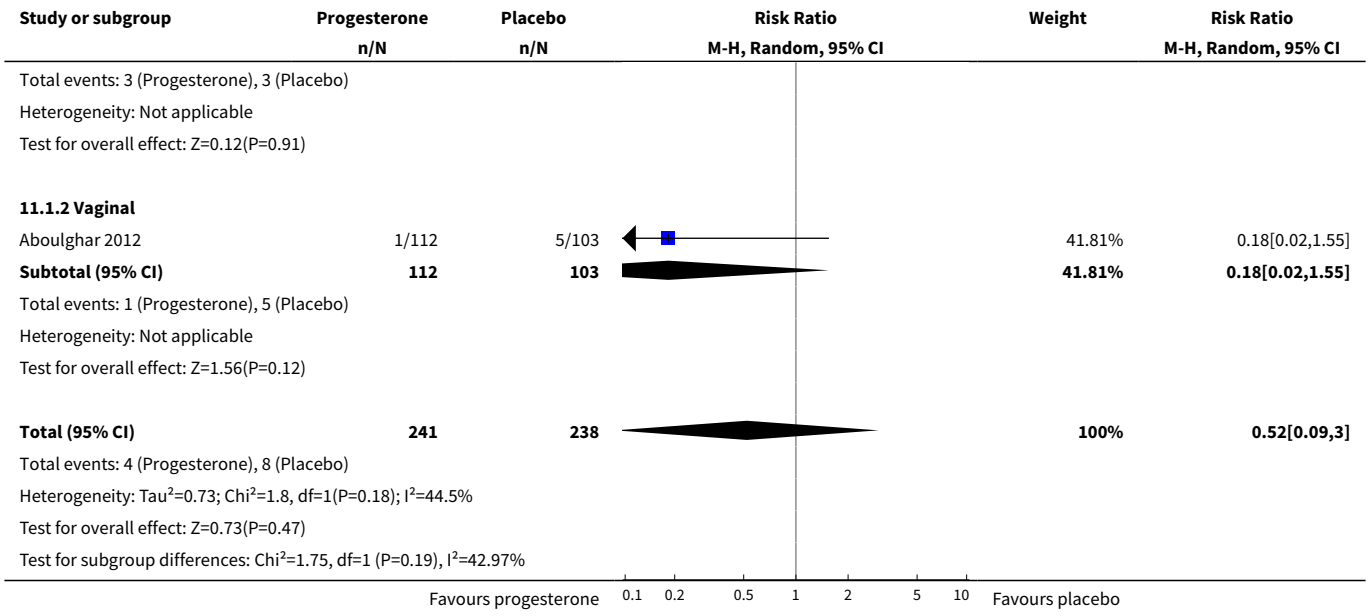
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	3	479	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.09, 3.00]
1.1 Intramuscular	2	264	Risk Ratio (M-H, Random, 95% CI)	1.1 [0.23, 5.29]
1.2 Vaginal	1	215	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.02, 1.55]
2 Preterm birth less than 34 weeks	1	215	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.16, 3.01]
2.1 Vaginal	1	215	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.16, 3.01]
3 Preterm birth less than 37 weeks	3	482	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.32, 1.13]
3.1 Intramuscular	2	267	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.11, 2.56]
3.2 Vaginal	1	215	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.40, 0.98]
4 Infant birthweight less than 2500 g	3	482	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.25, 0.91]
4.1 Intramuscular	2	267	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.23, 1.18]
4.2 Vaginal	1	215	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.15, 1.16]
5 Intrauterine fetal death	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.04, 3.45]
5.1 Intramuscular	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.04, 3.45]
6 Neonatal death	1	168	Risk Ratio (M-H, Fixed, 95% CI)	5.49 [0.27, 112.73]
6.1 Intramuscular	1	168	Risk Ratio (M-H, Fixed, 95% CI)	5.49 [0.27, 112.73]
7 Admission to neonatal intensive care unit	1	215	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.71, 4.11]
7.1 Vaginal	1	215	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.71, 4.11]

Analysis 11.1. Comparison 11 Progesterone versus placebo: other reason at risk of preterm birth, singletons, Outcome 1 Perinatal death.

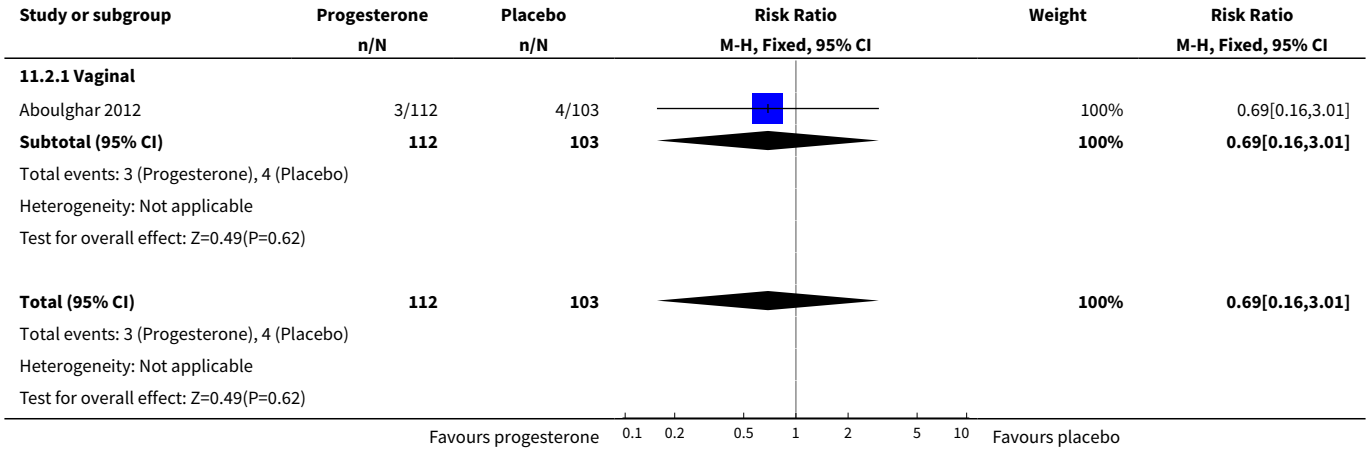
Study or subgroup	Progesterone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
11.1.1 Intramuscular					
Hauth 1983	3/80	3/88		58.19%	1.1[0.23,5.29]
Papiernik 1970	0/49	0/47			Not estimable
Subtotal (95% CI)	**129**	**135**		**58.19%**	**1.1[0.23,5.29]**

Favours progesterone — Favours placebo

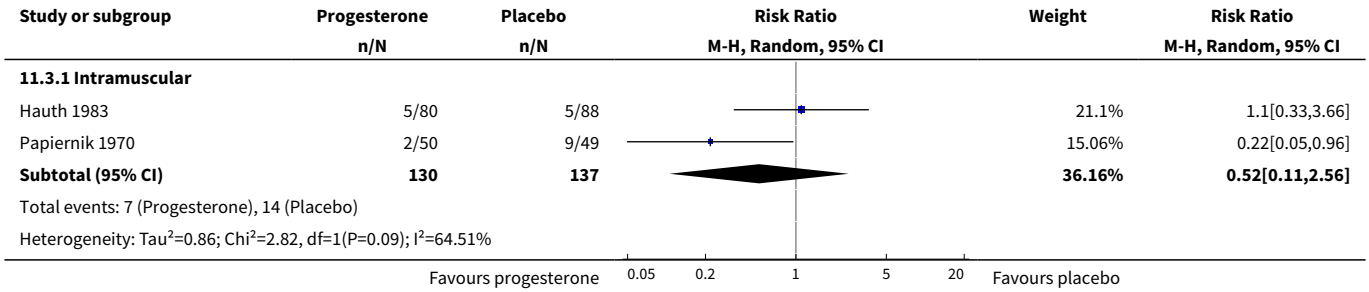
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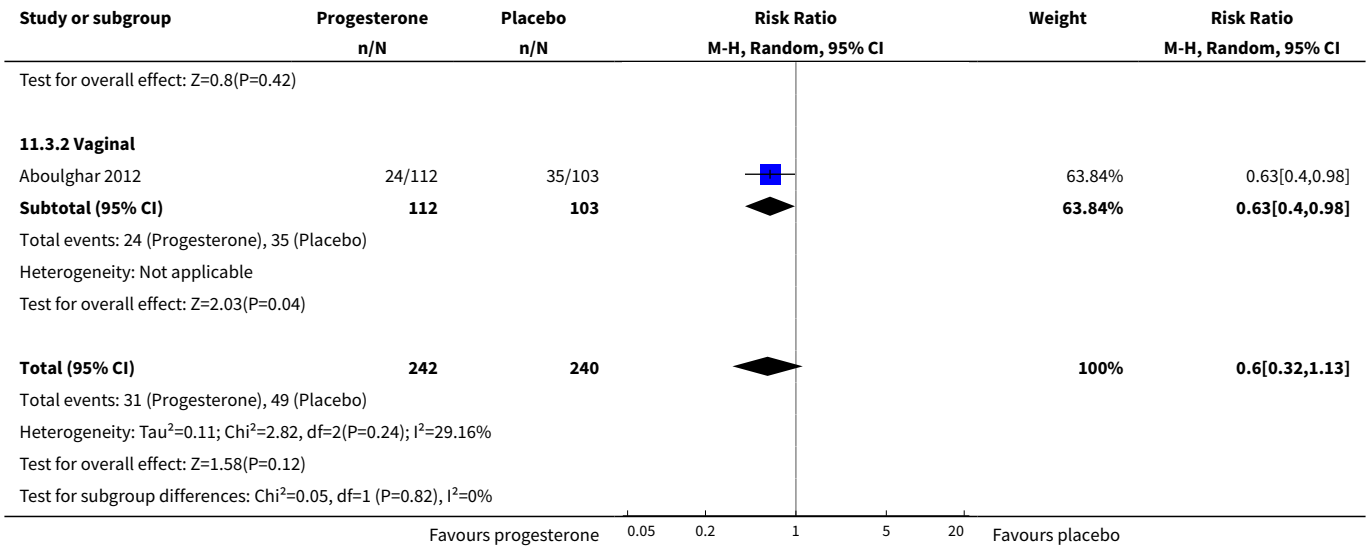
Analysis 11.2. Comparison 11 Progesterone versus placebo: other reason at risk of preterm birth, singletons, Outcome 2 Preterm birth less than 34 weeks.



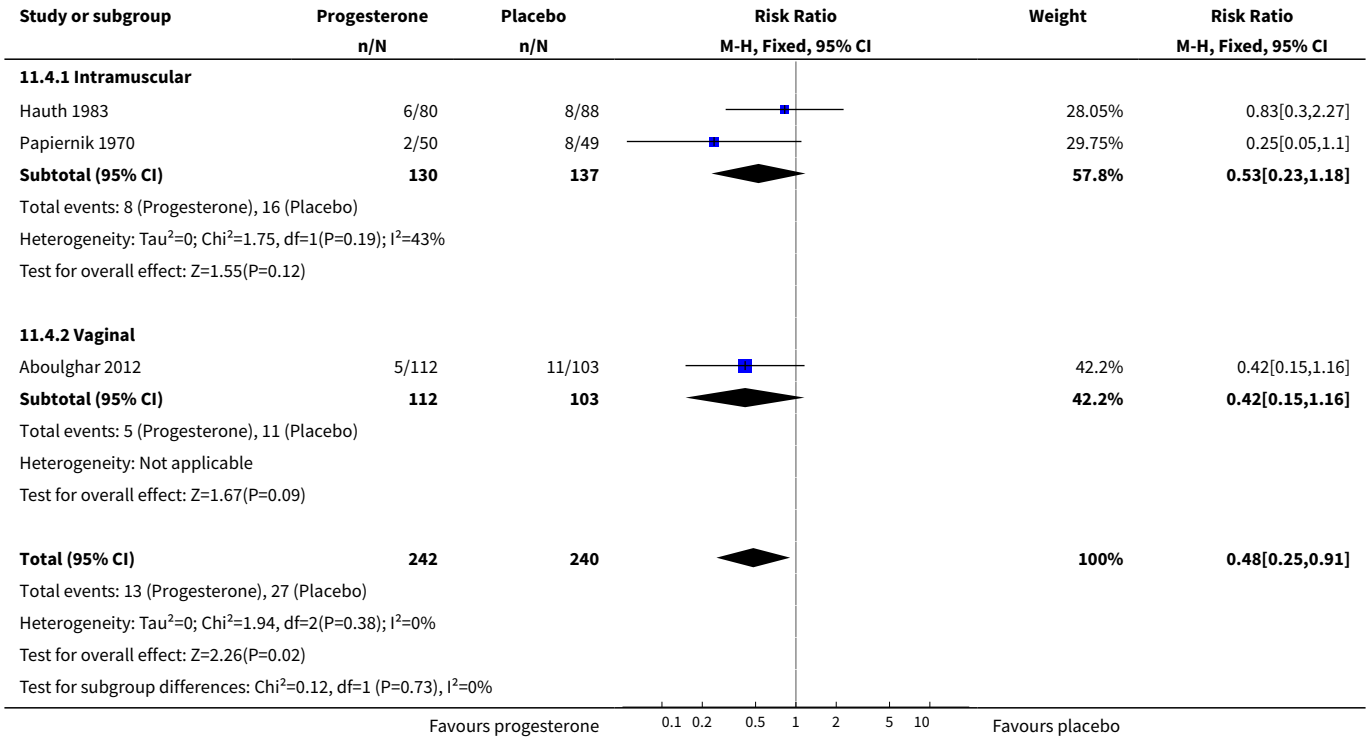
Analysis 11.3. Comparison 11 Progesterone versus placebo: other reason at risk of preterm birth, singletons, Outcome 3 Preterm birth less than 37 weeks.



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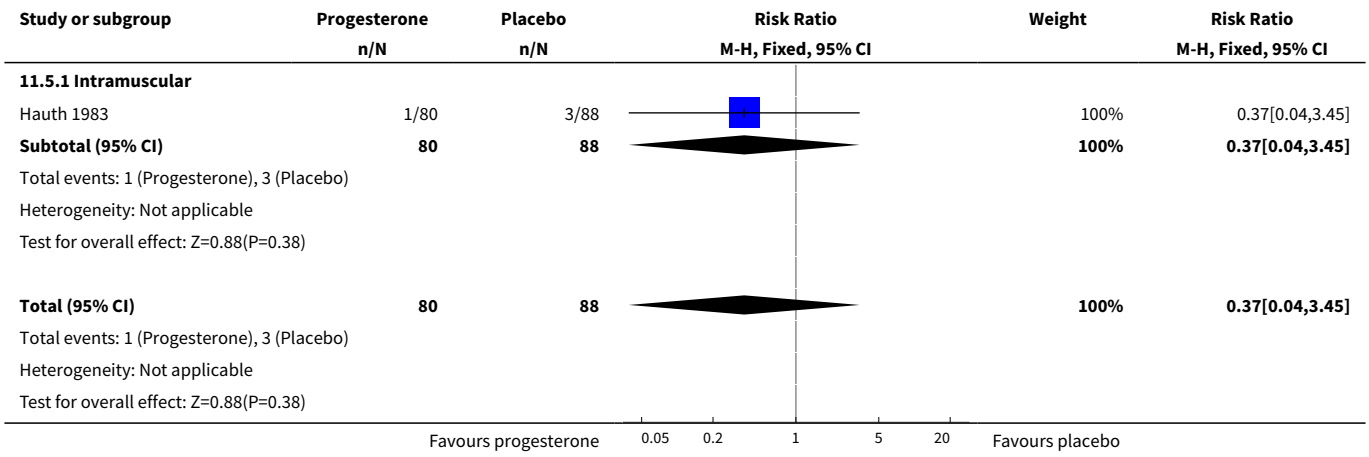


Analysis 11.4. Comparison 11 Progesterone versus placebo: other reason at risk of preterm birth, singletons, Outcome 4 Infant birthweight less than 2500 g.

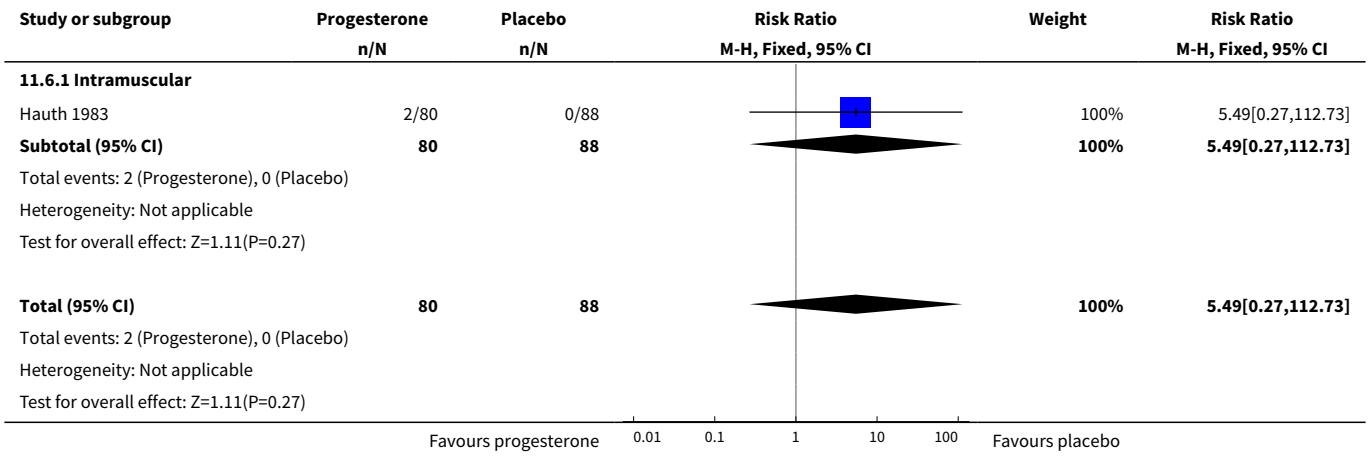


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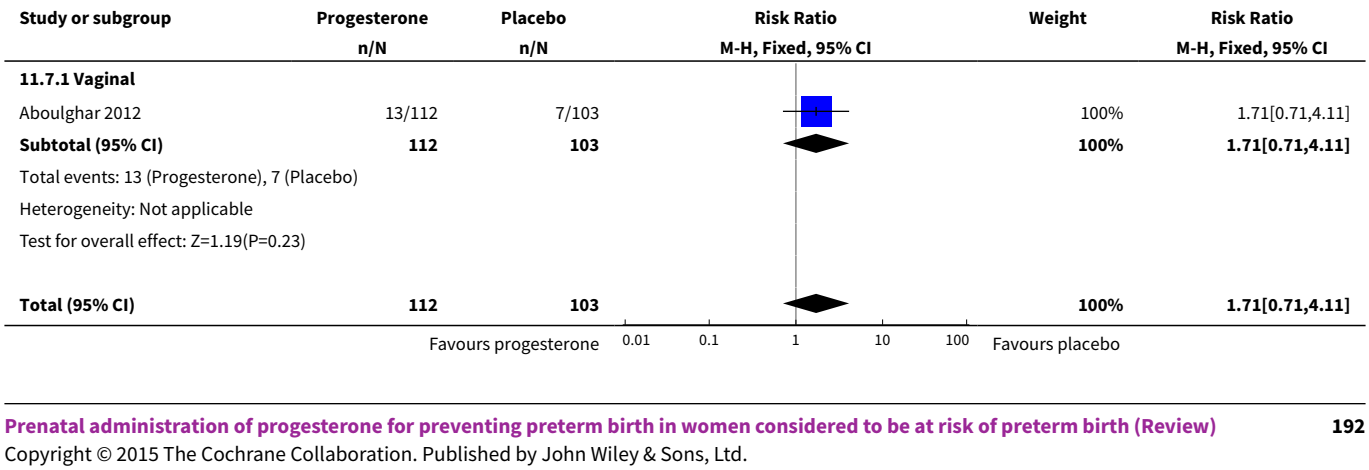
Analysis 11.5. Comparison 11 Progesterone versus placebo: other reason at risk of preterm birth, singletons, Outcome 5 Intrauterine fetal death.



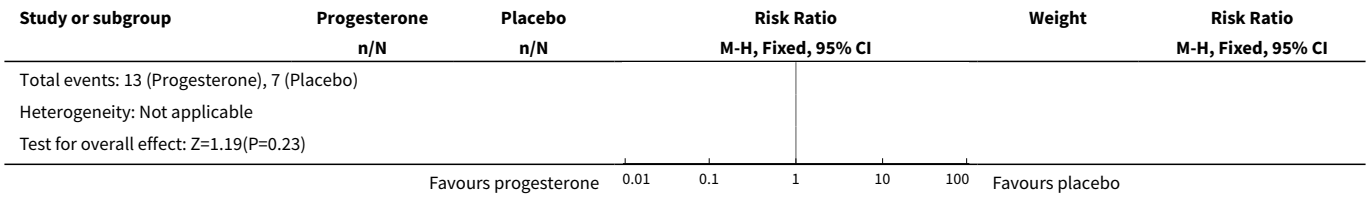
Analysis 11.6. Comparison 11 Progesterone versus placebo: other reason at risk of preterm birth, singletons, Outcome 6 Neonatal death.



Analysis 11.7. Comparison 11 Progesterone versus placebo: other reason at risk of preterm birth, singletons, Outcome 7 Admission to neonatal intensive care unit.



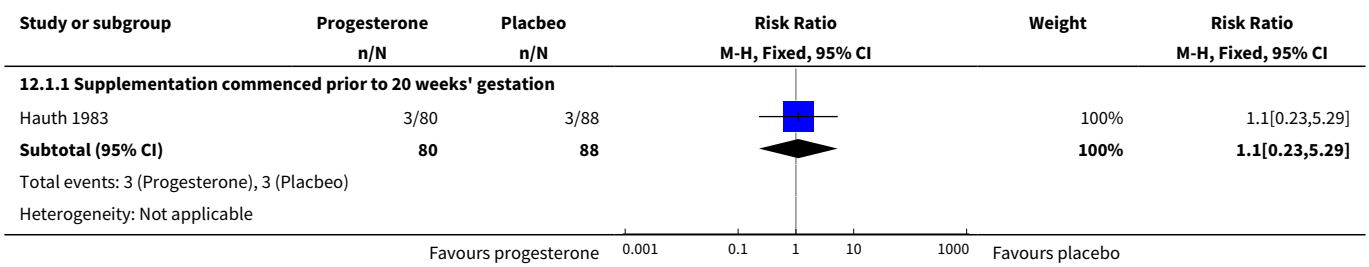
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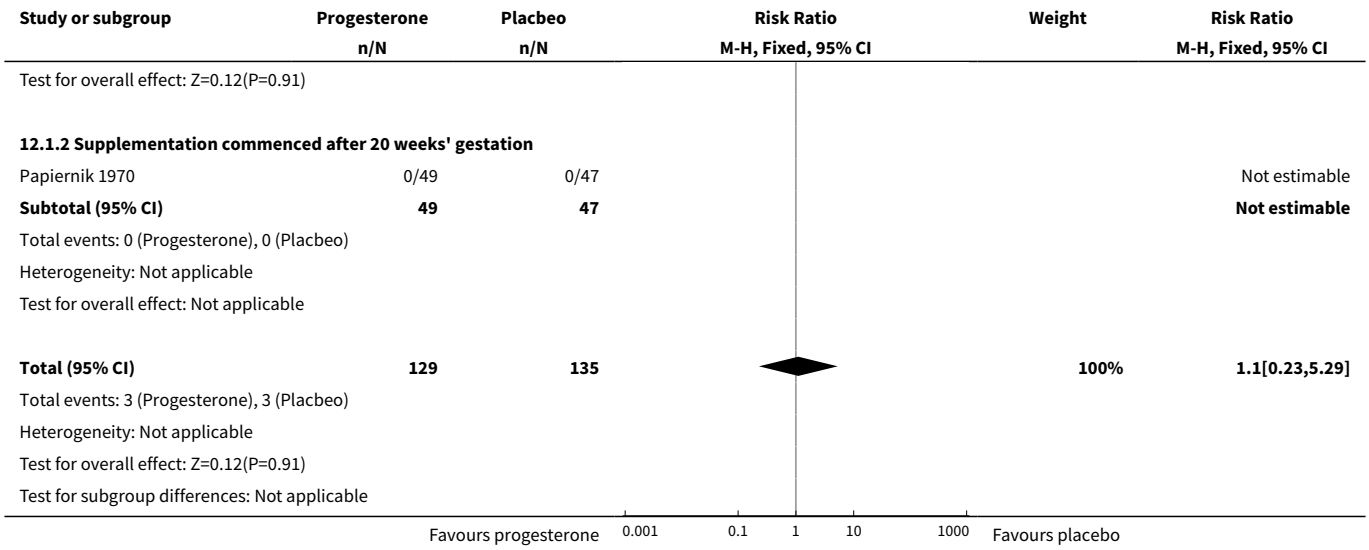
Comparison 12. Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk, singletons)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	2	264	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.23, 5.29]
1.1 Supplementation commenced prior to 20 weeks' gestation	1	168	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.23, 5.29]
1.2 Supplementation commenced after 20 weeks' gestation	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Preterm birth less than 37 weeks	2	267	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.11, 2.56]
2.1 Supplementation commenced prior to 20 weeks' gestation	1	168	Risk Ratio (M-H, Random, 95% CI)	1.1 [0.33, 3.66]
2.2 Supplementation commenced after 20 weeks' gestation	1	99	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.05, 0.96]
3 Infant birthweight less than 2500 g	2	267	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.16, 1.65]
3.1 Supplementation commenced prior to 20 weeks' gestation	1	168	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.30, 2.27]
3.2 Supplementation commenced after 20 weeks' gestation	1	99	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.05, 1.10]

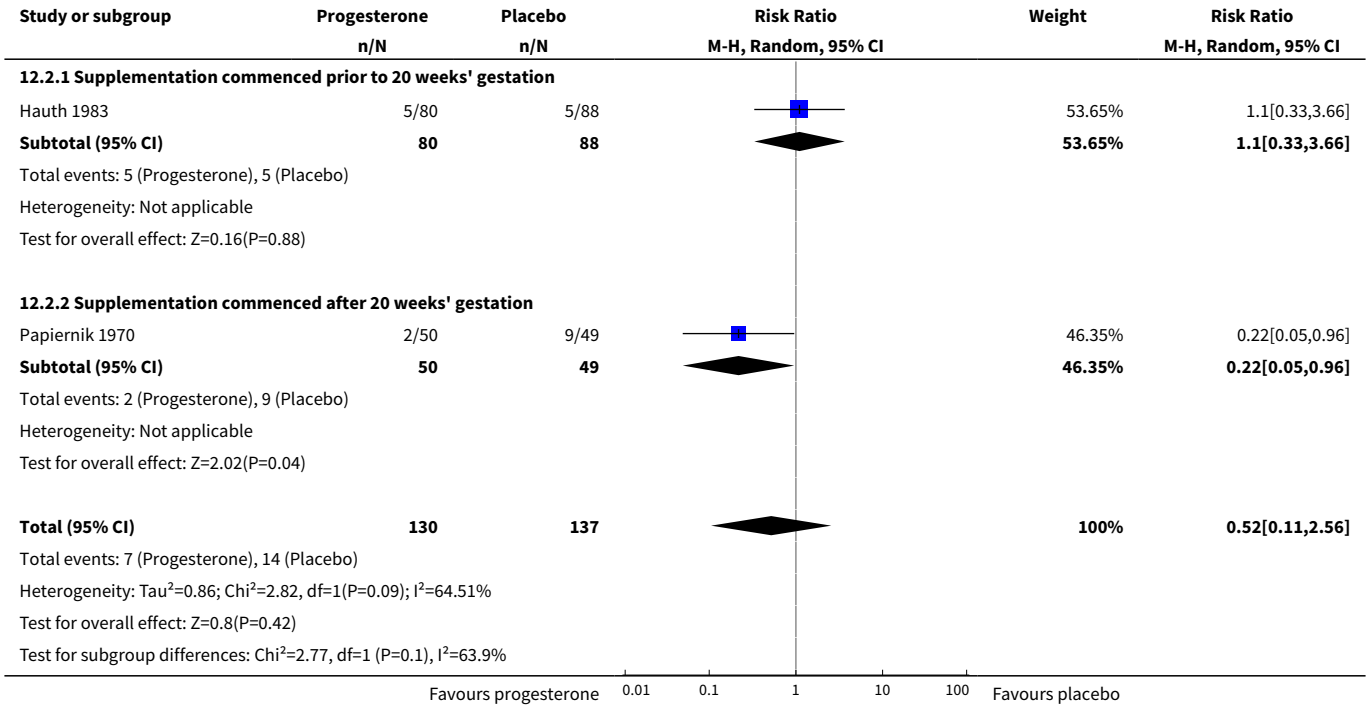
Analysis 12.1. Comparison 12 Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk, singletons), Outcome 1 Perinatal death.



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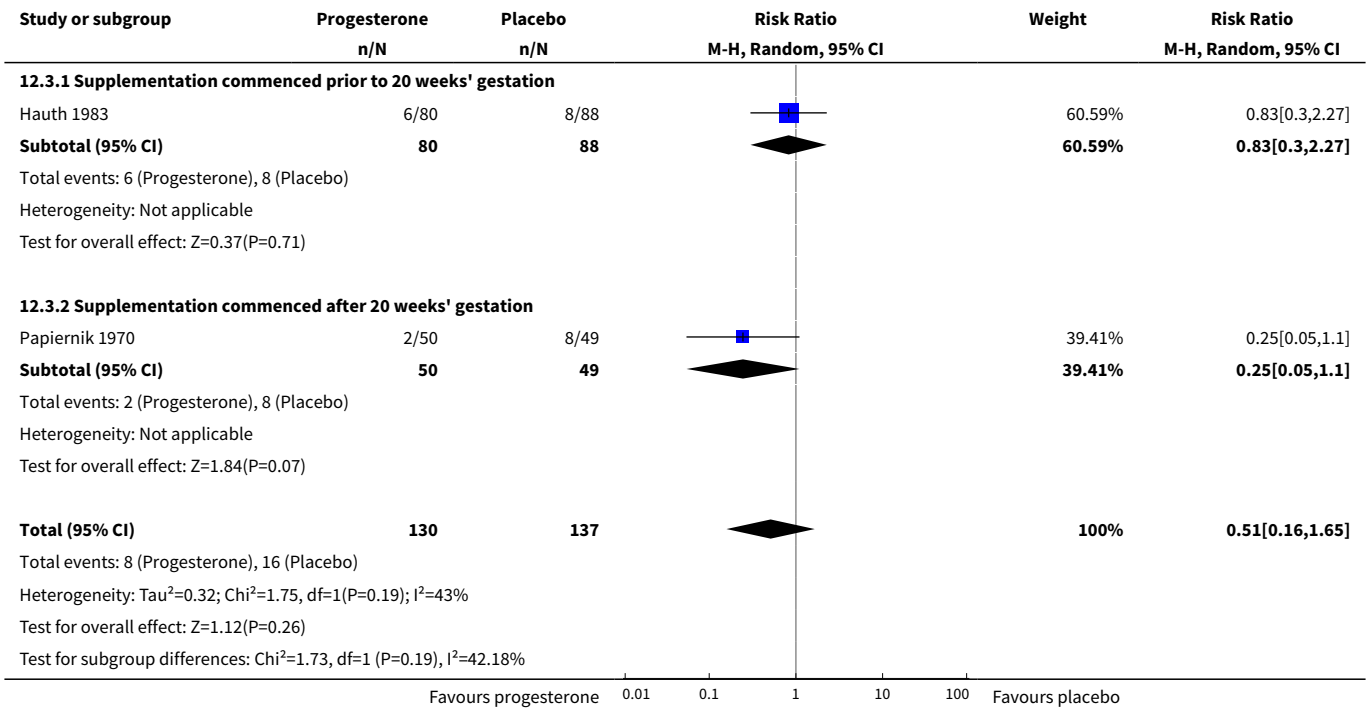


Analysis 12.2. Comparison 12 Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk, singletons), Outcome 2 Preterm birth less than 37 weeks.



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Analysis 12.3. Comparison 12 Progesterone versus placebo: other reason at risk of preterm birth, by timing of commencement (< 20 wk v > 20 wk, singletons), Outcome 3 Infant birthweight less than 2500 g.



APPENDICES

Appendix 1. Search methods used for previous version of this review

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (December 2008).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched CENTRAL (*The Cochrane LIbrary* 2008, Issue 1). *See* below for search terms.

We did not apply any language restrictions.

Searching other resources

We also manually cross referenced key publications.

We did not apply any language restrictions.

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We searched the International Clinical Trials Register (using the terms pregnancy, progesterone and ante/prenatal) to identify ongoing registered clinical trials.

Search terms for CENTRAL

Search terms included free text terms pregnancy, preterm birth, progesterone, progestogen, intramuscular, vaginal, oral, perinatal morbidity, perinatal mortality, and randomis(z)ed controlled trial. Please contact review author for exact strategy.

Appendix 2. Methods for the previous version of this review

We used the standard methods of The Cochrane Collaboration (Higgins 2008). Review authors independently assessed trials for inclusion in the review and extracted the data. Any differences were resolved by discussion with all co-authors.

Assessment of risk of bias in included studies

The methodology used to assess risk of bias of studies included in the previous version of this review is given in Appendix 2.

For this update, the following methods were used.

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- adequate (any truly random process, e.g., random number table; computer random number generator);
- inadequate (any non random process, e.g.,, odd or even date of birth; hospital or clinic record number);
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- adequate (e.g., telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Studies will be judged at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results. Blinding will be assessed separately for different outcomes or classes of outcomes.

We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or was supplied by the trial authors, we re-included missing data in the analyses which we undertook. We assessed methods as:

- adequate;
- inadequate:
- unclear;

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where 'adequate' is less than 20% losses to follow-up.

(5) Selective reporting bias

We describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We describe for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2008). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses.

Data management and analysis

We conducted data management and analysis using RevMan software (RevMan 2008). V Flenady, R Cincotta and J Dodd independently extracted data. Results are reported as mean differences for continuous variables, and risk ratios for categorical outcomes, both with 95% confidence intervals.

We conducted the meta-analysis using the fixed-effect model, and assessed heterogeneity by visual inspection of the outcomes tables and by using two statistics (H and I^2 test) of heterogeneity (Higgins 2002). Where we discovered statistical heterogeneity, this was explored.

Results are presented by reason women were considered to be at risk of preterm birth, including:

- past history of spontaneous preterm birth (including preterm premature rupture of membranes);
- multiple pregnancy;
- ultrasound identified short cervical length;
- fetal fibronectin testing;
- presentation with symptoms or signs of threatened preterm labour;
- other reason for risk of preterm birth.

Planned subgroup analyses included an assessment of the effect of: (1) time of treatment commencing (before 20 weeks' gestation versus after 20 weeks' gestation); (2) route of administration (intramuscular, intravaginal, oral, intravenous); and (3) different dosage regimens (divided arbitrarily into a cumulative dose of less than 500 mg per week and a dose of greater than or equal to 500 mg per week). To evaluate the effect of subgroup comparisons, we considered confidence intervals (where non-overlap was taken to indicate a statistically significant difference).

WHAT'S NEW

Date	Event	Description
27 July 2015	Amended	Corrected spelling of included study Fonseca 2007 (was previously listed as Fonesca 2007).

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Date	Event	Description
		Text has been added to Published notes about this review being split into two reviews following two new protocols.

HISTORY

Protocol first published: Issue 4, 2004
Review first published: Issue 1, 2006

Date	Event	Description
13 August 2013	Amended	Robert Cincotta added to the byline. Contribution to this update added.
5 August 2013	Amended	Contact details amended for Caroline Crowther.
12 June 2013	New citation required and conclusions have changed	This updated review is now comprised of 36 included studies (involving 8523 women and 12,515 infants). There are now 11 ongoing studies. The results and conclusions have changed: Progesterone versus placebo for women with a history of preterm birth: now significant findings for perinatal mortality; significant findings for additional infant and maternal secondary outcomes. Progesterone versus placebo for women with a short cervix: significant findings now identified for secondary infant outcome (preterm birth less than 28 weeks' gestation) and secondary maternal outcome (adverse drug reaction (urticaria); now no significant findings for neonatal sepsis. Progesterone versus placebo for women with a multiple pregnancy: now no significant findings for any of the reported outcomes. Progesterone versus no treatment/placebo for women following presentation with threatened preterm labour: now no significant findings for two secondary infant outcomes (preterm birth less than 37 weeks' gestation; respiratory distress syndrome (RDS)). Progesterone versus placebo for women with 'other' risk factors for preterm birth: now significant findings for one secondary infant outcome (infant birthweight less than 2500 g).
14 January 2013	New search has been performed	Search updated. Data from 25 new trials incorporated into this update.
27 January 2012	Amended	Fifty-two reports for 44 trials added to Studies awaiting classification.
31 December 2008	New search has been performed	Search updated. A search in October 2007 identified 17 new trials. We included five (Borna 2008; Facchinetti 2007; Fonseca 2007; O'Brien 2007; Rouse 2007); added a follow-up report to Meis 2003; and excluded one (Walch 2005). Ten trials are ongoing (Bruinse 2007; Maurel 2007; Grobman 2007; Martinez 2007; Nassar 2007; Perlitz 2007; Rode 2007; Rozenberg 2007; Serra 2007; Wood 2007).

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Date	Event	Description
		A further updated search in December 2008 identified one more report of Borna 2008; five more reports of O'Brien 2007; six more reports of Rouse 2007; one more report of Crowther 2007; one more report of Bruinse 2007; three ongoing studies (Creasy 2008; Starkey 2008; Swaby 2007); and one study which is awaiting classification (Moghtadaei 2008a). The review's conclusions have not changed.
5 November 2008	Amended	Converted to new review format.
31 March 2005	New search has been performed	Search updated and new studies found and included or excluded.

CONTRIBUTIONS OF AUTHORS

For the update in 2013, J Dodd and L Jones assessed studies, extracted data and entered it into RevMan. L Jones wrote the first version of the results. J Dodd revised the review, discussion and conclusions. V Flenady, CA Crowther and R Cincotta commented on all drafts of the update (2013).

DECLARATIONS OF INTEREST

J Dodd, V Flenady and C Crowther are investigators in a randomised trial assessing the use of progesterone for prevention of respiratory distress syndrome (The PROGRESS Trial).

SOURCES OF SUPPORT

Internal sources

- Mater Research Support Centre, Mater Health Services Brisbane, South Brisbane, Queensland, Australia.
- Department of Maternal Fetal Medicine, Mater Mothers' Hospital, South Brisbane, Queensland, Australia.
- The University of Adelaide, Discipline of Obstetrics and Gynaecology, Australia.

External sources

- National Institute for Health Research, UK.

  NIHR Programme of centrally-managed pregnancy and childbirth systematic reviews of priority to the NHS and users of the NHS:10/4001/02

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In view of the increase in the number of trials published, along with the huge variation in the patient populations recruited, we have decided to categorise the studies by the reason women were considered to be at increased risk of preterm birth. We have also included longer-term childhood health outcomes, in recognition of the need for ongoing follow-up of children exposed antenatally to progesterone (Update 2008), and maternal quality of life (Update 2013).

NOTES

This review examines prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Women considered in this review includes women considered at high risk because of multiple pregnancy as well as women with singleton pregnancies considered at high risk for various clinical reasons (history of preterm birth, short cervix, threatened preterm labour and other risk factors). This review included 36 trials with several trials recruiting only women with multiple pregnancies. The results of this review may be easier to interpret and more clinically relevant if the results for women with multiple and singleton pregnancy are assessed and reported separately.

Consequently, this review will no longer be updated in it's current form but will be split into two separate reviews:

- Prenatal administration of progesterone for preventing preterm birth in women with a multiple pregnancy
- Prenatal administration of progesterone for preventing preterm birth in women with a singleton pregnancy

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Each of these reviews will be prepared following publication of a new protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

17-alpha-Hydroxyprogesterone [administration & dosage] [adverse effects]; Pregnancy, High-Risk; Premature Birth [*prevention & control]; Prenatal Care [methods]; Progesterone [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy

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Attachment 13

Cochrane Library

Cochrane Database of Systematic Reviews

Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology (Review)

Haas DM, Hathaway TJ, Ramsey PS

Haas DM, Hathaway TJ, Ramsey PS.
Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology.
Cochrane Database of Systematic Reviews 2019, Issue 11. Art. No.: CD003511.
DOI: 10.1002/14651858.CD003511.pub5.

www.cochranelibrary.com

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WILEY

[Intervention Review]

Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology

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Contact: David M Haas, Department of Obstetrics and Gynecology, Indiana University School of Medicine, 1001 West 10th Street, F-5, Indianapolis, Indiana, 46202, USA. dahaas@iupui.edu, dahaas@iu.edu.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: Edited (no change to conclusions), published in Issue 11, 2019.

Citation: Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. *Cochrane Database of Systematic Reviews* 2019, Issue 11. Art. No.: CD003511. DOI: 10.1002/14651858.CD003511.pub5.

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ABSTRACT

Background

Progesterone, a female sex hormone, is known to induce secretory changes in the lining of the uterus essential for successful implantation of a fertilized egg. It has been suggested that a causative factor in many cases of miscarriage may be inadequate secretion of progesterone. Therefore, clinicians use progestogens (drugs that interact with the progesterone receptors), beginning in the first trimester of pregnancy, in an attempt to prevent spontaneous miscarriage. This is an update of a review, last published in 2013.

Since publication of the 2018 update of this review, we have been advised that the Ismail 2017 study is currently the subject of an investigation by the Journal of Maternal-Fetal & Neonatal Medicine. We have now moved this study from 'included studies' to 'Characteristics of studies awaiting classification' until the outcome of the investigation is known.

Objectives

To assess the efficacy and safety of progestogens as a preventative therapy against recurrent miscarriage.

Search methods

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (6 July 2017) and reference lists from relevant articles, attempting to contact trial authors where necessary, and contacted experts in the field for unpublished works.

Selection criteria

Randomized or quasi-randomized controlled trials comparing progestogens with placebo or no treatment given in an effort to prevent miscarriage.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. Two reviewers assessed the quality of the evidence using the GRADE approach.

Main results

Twelve trials (1,856 women) met the inclusion criteria. Eight of the included trials compared treatment with placebo and the remaining four trials compared progestogen administration with no treatment. The trials were a mix of multicenter and single-center trials, conducted in India, Jordan, UK and USA. In five trials women had had three or more consecutive miscarriages and in seven trials women had suffered

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two or more consecutive miscarriages. Routes, dosage and duration of progestogen treatment varied across the trials. The majority of trials were at low risk of bias for most domains. Ten trials (1684 women) contributed data to the analyses.

The meta-analysis of all women, suggests that there may be a reduction in the number of miscarriages for women given progestogen supplementation compared to placebo/controls (average risk ratio (RR) 0.73, 95% confidence interval (CI) 0.54 to 1.00, 10 trials, 1684 women, moderate-quality evidence). A subgroup analysis comparing placebo-controlled versus non-placebo-controlled trials, trials of women with three or more prior miscarriages compared to women with two or more miscarriages and different routes of administration showed no clear differences between subgroups for miscarriage.

None of the trials reported on any secondary maternal outcomes, including severity of morning sickness, thromboembolic events, depression, admission to a special care unit, or subsequent fertility.

There was probably a slight benefit for women receiving progestogen seen in the outcome of live birth rate (RR 1.07, 95% CI 1.00 to 1.13, 6 trials, 1411 women, moderate-quality evidence). We are uncertain about the effect on the rate of preterm birth because the evidence is very low-quality (RR 1.13, 95% CI 0.53 to 2.41, 4 trials, 256 women, very low-quality evidence). No clear differences were seen for women receiving progestogen for the other secondary outcomes including neonatal death, fetal genital abnormalities or stillbirth. There may be little or no difference in the rate of low birthweight and trials did not report on the secondary child outcomes of teratogenic effects or admission to a special care unit.

Authors' conclusions

For women with unexplained recurrent miscarriages, supplementation with progestogen therapy may reduce the rate of miscarriage in subsequent pregnancies.

PLAIN LANGUAGE SUMMARY

Progestogen for preventing miscarriage

What is the issue?

Early pregnancy loss, also known as miscarriage, generally occurs in the first trimester. For some women and their partners, miscarriages can happen several times, also known as recurrent miscarriages. While there are sometimes causes for miscarriages that are found, often no clear reasons can be found. The hormone called progesterone prepares the womb (uterus) to receive and support the newly fertilized egg during the early part of pregnancy. It has been suggested that some women who miscarry may not make enough progesterone in the early part of pregnancy. Supplementing these women with medications that act like progesterone (these are called progestogens) has been suggested as a possible way to prevent recurrent miscarriage.

Since publication of the 2018 update of this review, we have been advised that one study (by Ismail 2017) is currently the subject of an investigation by the Journal of Maternal-Fetal & Neonatal Medicine. We have now moved this study from 'included studies' to 'Characteristics of studies awaiting classification' until the outcome of the investigation is known.

Why is this important?

Having miscarriages can be both physically and emotionally difficult for women and their partners. Finding a therapy to help reduce recurrent miscarriages could help them avoid a miscarriage and have a live baby.

What evidence did we find?

We searched for evidence on 6 July 2017 and identified a total of 13 trials that enrolled a total of 2556 women with a history of recurrent miscarriages. These trials found that giving progestogen medication to women with recurrent miscarriages early in their pregnancy may help lower the rates of miscarriage in that pregnancy from 27.5% to 20.1%. We believe that these findings are based on evidence of only moderate quality, so we cannot be certain about the results. We did not find that giving the progestogen medication by mouth, as a shot (injection), or in the vagina, was any better than any of the other ways. We also found that the trials showed that giving progestogen to women with prior recurrent miscarriages made the chances of having a live baby in the current pregnancy slightly higher. We are uncertain about the effect on the rate of preterm birth because the evidence is very low-quality. We did not find evidence of improvement in other outcomes such as newborn death, stillbirth, low birthweight, or newborn birth defects for women given progestogens.

What does this mean?

We found evidence from randomized controlled trials that giving progestogen medication may prevent miscarriage for women with recurrent previous miscarriages.

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