Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in twin gestations: a systematic review and meta-analysis

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OBJECTIVE: To evaluate the efficacy of vaginal progesterone for the prevention of preterm birth and adverse perinatal outcomes in twin gestations.

DATA SOURCES: MEDLINE, Embase, LILACS, and CINAHL (from their inception to January 31, 2023), Cochrane databases, Google Scholar, bibliographies, and conference proceedings.

STUDY ELIGIBILITY CRITERIA: Randomized controlled trials that compared vaginal progesterone to placebo or no treatment in asymptomatic women with a twin gestation.

METHODS: The systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions. The primary outcome was preterm birth <34 weeks of gestation. Secondary outcomes included adverse perinatal outcomes. Pooled relative risks with 95% confidence intervals were calculated. We assessed the risk of bias in each included study, heterogeneity, publication bias, and quality of evidence, and performed subgroup and sensitivity analyses.

RESULTS: Eleven studies (3401 women and 6802 fetuses/infants) fulfilled the inclusion criteria. Among all twin gestations, there were no significant differences between the vaginal progesterone and placebo or no treatment groups in the risk of preterm birth <34 weeks (relative risk, 0.99; 95% confidence interval, 0.84—1.17; high-quality evidence), <37 weeks (relative risk, 0.99; 95% confidence interval, 0.92—1.06; high-quality evidence), and <28 weeks (relative risk, 1.00; 95% confidence interval, 0.64—1.55; moderate-quality evidence), and spontaneous preterm birth <34 weeks of gestation (relative risk, 0.97; 95% confidence interval, 0.80—1.18; high-quality evidence). Vaginal progesterone had no significant effect on any of the perinatal outcomes evaluated. Subgroup analyses showed that there was no evidence of a different effect of vaginal progesterone on preterm birth <34 weeks of gestation related to chorionicity, type of conception, history of spontaneous preterm birth, daily dose of vaginal progesterone, and gestational age at initiation of treatment. The frequencies of preterm birth <37, <34, <32, <30, and <28 weeks of gestation and adverse perinatal outcomes did not significantly differ between the vaginal progesterone and placebo or no treatment groups in unselected twin gestations (8 studies; 3274 women and 6548 fetuses/infants). Among twin gestations with a transvaginal sonographic cervical length <30 mm (6 studies; 306 women and 612 fetuses/infants), vaginal progesterone was associated with a significant decrease in the risk of preterm birth occurring at <28 to <32 gestational weeks (relative risks, 0.48—0.65; moderate- to high-quality evidence), neonatal death (relative risk, 0.32; 95% confidence interval, 0.11—0.92; moderate-quality evidence), and birthweight <1500 g (relative risk, 0.60; 95% confidence interval, 0.39—0.88; high-quality evidence). Vaginal progesterone significantly reduced the risk of preterm birth occurring at <28 to <34 gestational weeks (relative risks, 0.41—0.68), composite neonatal morbidity and mortality (relative risk, 0.59; 95% confidence interval, 0.33—0.98), and birthweight <1500 g (relative risk, 0.55; 95% confidence interval, 0.33—0.94) in twin gestations with a transvaginal sonographic cervical length ≤25 mm (6 studies; 95 women and 190 fetuses/infants). The quality of evidence was moderate for all these outcomes.

CONCLUSION: Vaginal progesterone does not prevent preterm birth, nor does it improve perinatal outcomes in unselected twin gestations, but it appears to reduce the risk of preterm birth occurring at early gestational ages and of neonatal morbidity and mortality in twin gestations with a sonographic short cervix. However, more evidence is needed before recommending this intervention to this subset of patients.

Key words: cervical length, multiple gestation, neonatal morbidity, neonatal mortality, prematurity, preterm delivery, progestins, progestogens, transvaginal ultrasound

Introduction

An estimated 15 million infants are born preterm worldwide every year.[1] In 2019, preterm birth complications were the leading cause of death in newborns aged <28 days, accounting for 36% of all neonatal deaths.[2] In 2021, the rate of preterm birth in the United States was 10.49%, the highest level reported since at least 2007.[3] Surviving preterm infants are at increased risk for short-term complications such as respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and intraventricular hemorrhage, among others, and long-term adverse health outcomes such as cerebral palsy, behavioral and cognitive disorders, mental health conditions, and

AJOG at a Glance

Why was this study conducted?

The efficacy of vaginal progesterone in preventing preterm birth in twin gestations remains inconclusive.

Key findings

Meta-analyses, including data from 11 trials (3401 women and 6802 fetuses/infants), showed that vaginal progesterone, regardless of the daily dose used and the gestational age at which it is initiated, does not prevent preterm birth, nor does it improve perinatal outcomes in unselected twin gestations. However, vaginal progesterone appears to reduce the risk of preterm birth occurring at early gestational ages and of neonatal morbidity and mortality in twin gestations with a sonographic short cervix (cervical length $\leq$25 mm and $<$30 mm).

What does this add to what is known?

There is no evidence supporting the use of vaginal progesterone to prevent preterm birth in unselected twin gestations. However, vaginal progesterone appears promising for reducing the risk of preterm birth and adverse perinatal outcomes in twin gestations with a sonographic short cervix.

chronic diseases and mortality in adulthood.[4–11] In addition, having a preterm infant affects families emotionally and financially.[4,12,13] It has been estimated that the annual societal economic cost (medical, educational, and lost productivity) associated with preterm birth in the United States is $25.2 billion.[14]

In 2020 and 2021, the twin birth rates in the United States were the lowest in almost 2 decades (~31.1 per 1000 births).[3] However, twin births accounted for 18.4% and 22.5% of all preterm births $<$37 and $<$34 weeks of gestation, respectively. Women with twin gestations are 7 times more likely to give birth before 37 weeks of gestation and 9 times more likely to give birth before 34 weeks of gestation than women with a singleton gestation (62.1% vs 8.8% and 20.3% vs 2.2%, respectively).[3] Moreover, twin gestations have a greater risk of fetal death, neonatal death, cerebral palsy, and long-term neurodevelopmental impairment compared to singleton gestations, primarily because of complications of prematurity.[15–26] In addition, twin gestations are associated with increased risk for adverse neonatal outcomes,[17,18,22–27] affecting not only the quality of life for parents and their children but also the use of health care resources.[28–32]

Several interventions have been proposed for the prevention of preterm birth in twin gestations such as home uterine activity monitoring,[33] bed rest,[34] specialized antenatal clinics,[35] nutritional advice,[36] prophylactic tocolysis,[37]

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This systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020205184) on September 19, 2020.

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progestogens,[38,39] cervical cerclage,[40–42] and cervical pessary.[43–47] Unfortunately, most of these interventions have been shown to be ineffective in reducing the risk of preterm birth and adverse perinatal outcomes in twin gestations.[48–52] The use of cervical cerclage and cervical pessary for preventing preterm birth among twin gestations has conflicting results.[53–59] The efficacy of the administration of vaginal progesterone in preventing preterm birth in twin gestations remains inconclusive. Therefore, an assessment of the efficacy of this intervention in such pregnancies is justified.

The aim of this systematic review and meta-analysis was to evaluate the efficacy of vaginal progesterone in preventing preterm birth and adverse perinatal outcomes in asymptomatic women with a twin gestation.

Materials and Methods

This systematic review was performed and reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[60] and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines,[61] respectively. The protocol was prospectively registered with PROSPERO (International Prospective Register of Systematic Reviews; CRD42020205184). Two of the authors (A.C.-A. and R.R.) independently retrieved and reviewed studies for eligibility, assessed their risk of bias, and extracted data. All disagreements encountered in the review process were resolved through consensus.

Eligibility criteria

We included randomized controlled trials that compared vaginal progesterone to placebo or no treatment for the prevention of preterm birth and/or adverse perinatal outcomes in asymptomatic women with a twin gestation. We excluded quasirandomized trials, trials assessing vaginal progesterone in women with threatened or arrested preterm labor, second-trimester bleeding, or premature rupture of membranes, and trials that evaluated the administration of vaginal progesterone to prevent spontaneous miscarriage. When a study assessed vaginal progesterone in singleton and multiple gestations, it was considered for inclusion in the review if data for twin gestations were reported or extractable separately.

Literature search

To identify potentially eligible studies, we searched MEDLINE, Embase, LILACS (Latin American and Caribbean Health Sciences Literature), CINAHL (Cumulative Index to Nursing and Allied Health Literature), CENTRAL (Cochrane Central Register of Controlled Trials), the World Health Organization's ICTRP (International Clinical Trials Registry Platform), and clinical trial registries (all from their inception to January 31, 2023) using key words related to *progesterone*, *preterm birth*, *randomized controlled trial*, and *twin gestation*. We also searched: Google Scholar; proceedings of congresses and scientific meetings on obstetrics, maternal-fetal medicine, and twin or multiple gestation; reference lists of identified studies; previously published systematic reviews; and review articles. No restrictions were applied for study language.

Outcome measures

The primary outcome was preterm birth <34 weeks of gestation. Secondary outcomes were preterm birth <37, <32, <30, and <28 weeks of gestation, spontaneous preterm birth <34 weeks of gestation, fetal death, neonatal death, perinatal death, birthweight <1500 g and <2500 g, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, neonatal sepsis, retinopathy of prematurity, any composite adverse neonatal/perinatal outcome, admission to the neonatal intensive care unit, and use of mechanical ventilation.

Data extraction

We used a standardized form to extract data on authors, title, publication date, language, duplicate publications, trial registration, funding sources, study characteristics (design, setting, follow-up period, attrition and exclusions from the analysis, and intention-to-treat analysis), participants (inclusion and exclusion criteria, number of women randomized, baseline characteristics, and country and date of recruitment), interventions (gestational age at trial entry, daily dose of vaginal progesterone, duration, compliance, use of cointerventions, and characteristics of interventions used in the control group), and outcomes (definition of outcomes, number of outcome events and/or mean±standard deviation for each outcome, and total number of participants in each group). Relevant additional data of included trials supplied to previous meta-analyses were included in the meta-analysis.

Assessment of risk of bias

Risk of bias assessments were carried out for each of the included studies for the primary and secondary outcomes using the Cochrane risk-of-bias tool (RoB 2) for randomized controlled trials.[62] This tool considers the following 5 domains: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in the selection of the reported result. Studies were classified as at overall "low risk of bias" if the study was judged to be at low risk of bias for all domains; "some concerns of bias" if the study was judged to raise some concerns in at least 1 domain but not to be at high risk of bias for any domain; and at "high risk of bias" if the study was judged to be at high risk of bias in at least 1 domain or to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Data synthesis

Data synthesis was performed by following the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[63] Data were analyzed according to the intention-to-treat principle. Analyses were undertaken separately for (1) all twin gestations, regardless of chorionicity, type of conception, obstetrical history, and midtrimester sonographic cervical length; (2) unselected twin gestations; (3) twin gestations with a transvaginal sonographic cervical length <30 mm; and (4) twin gestations with a

transvaginal sonographic cervical length ≤25 mm. The denominator for pregnancy outcomes was the number of women, whereas for perinatal outcomes, we used the number of fetuses/neonates.

Pooled relative risks (RR) with 95% confidence interval (CI) were calculated by using a random-effects model (DerSimonian and Laird inverse variance). This approach was chosen in anticipation of significant heterogeneity among the included studies. For perinatal outcomes, we estimated pooled RRs with 95% CIs assuming independence between fetuses/neonates by using data reported in the studies at the fetal/neonatal level. However, because of the potential of nonindependence of outcomes in fetuses/neonates from twin gestations, we also estimated pooled adjusted RRs with 95% CIs by using an estimate of the intracluster correlation coefficient (ICC) derived from the trial, or from similar trials, as recommended by the Cochrane Handbook.[64] Given that ICCs for perinatal outcomes were not reported in the included studies, we used those that had recently been estimated from randomized controlled trials in women with a twin gestation, which had similar aims and inclusion/exclusion criteria to those of trials included in our systematic review.[65] Adjusted RRs were considered as the main estimates of the vaginal progesterone's effect on perinatal outcomes in twin gestations. We calculated the number needed to treat (NNT) with 95% CI if a meta-analysis revealed a statistically significant beneficial or a harmful effect of vaginal progesterone.[66]

Heterogeneity of the results among studies was evaluated by visually inspecting forest plots and by estimating the I^2 statistical test, which describes the percentage of total variation across studies that can be attributed to heterogeneity rather than chance.[67] In the presence of statistical heterogeneity ($I^2 \geq 30\%$), we investigated the potential causes through subgroup analyses.[63] We also addressed heterogeneity by calculating 95% prediction intervals for meta-analyses that contained at least 5 studies.[68] The prediction interval is used to predict the possible underlying effect in a new study that is similar to the studies in the meta-analysis.[69] If there were at least 10 studies included in a meta-analysis, we constructed funnel plots to investigate small-study effects and publication biases.[70] Funnel plot asymmetry was assessed visually and with Egger[71] and Harbord[72] tests. A P value of <.10 suggested the presence of funnel plot asymmetry. In case of funnel plot asymmetry, a contour-enhanced funnel plot was constructed to differentiate asymmetry attributed to publication bias from that owing to other factors.[70,73,74] If studies appear to be missing in areas of statistical nonsignificance of the plot, then it is possible that the asymmetry is due to publication bias. Conversely, if studies appear to be missing in areas of high statistical significance, this reduces the plausibility that publication bias is the underlying cause of funnel plot asymmetry. If funnel plot asymmetry appeared to be due to publication bias, we planned to use the trim-and-fill method for adjusting treatment effect estimates as a sensitivity analysis.[75−77] The basic idea of this method is to first trim the studies that cause a funnel plot's asymmetry so that the overall effect estimate produced by the remaining studies can be considered minimally affected by publication bias, and then to fill imputed missing studies in the funnel plot on the basis of the bias-corrected overall estimate.

We carried out subgroup analyses according to chorionicity (monochorionic vs dichorionic), type of conception (natural vs by ovulation induction drugs vs by assisted reproductive technology), obstetric history (no previous spontaneous preterm birth vs at least 1 previous spontaneous preterm birth), daily dose of vaginal progesterone (90−200 vs 400 vs 600 mg), and gestational age at initiation of treatment (≤14 vs 16−24 vs 28 weeks). Subgroup differences were assessed by an interaction test in which a P value ≥.05 was considered to indicate that the effect of treatment did not differ significantly between subgroups.[78−80] To test the robustness of the meta-analyses, we performed sensitivity analyses by including only studies at overall low risk of bias. Subgroup and sensitivity analyses were restricted to the primary outcome of preterm birth <34 weeks of gestation.

Assessment of quality of evidence

We used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, which considers 5 domains (risk of bias, consistency of effect, imprecision, indirectness, and publication bias), to assess the quality of evidence for each individual outcome.[81,82] The GRADE approach classifies the quality of the evidence into 4 levels as follows: (1) high: we are very confident that the true effect lies close to the estimate of the effect; (2) moderate: we are moderately confident in the effect estimate, and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; (3) low: our confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect; and (4) very low: we have very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of effect.

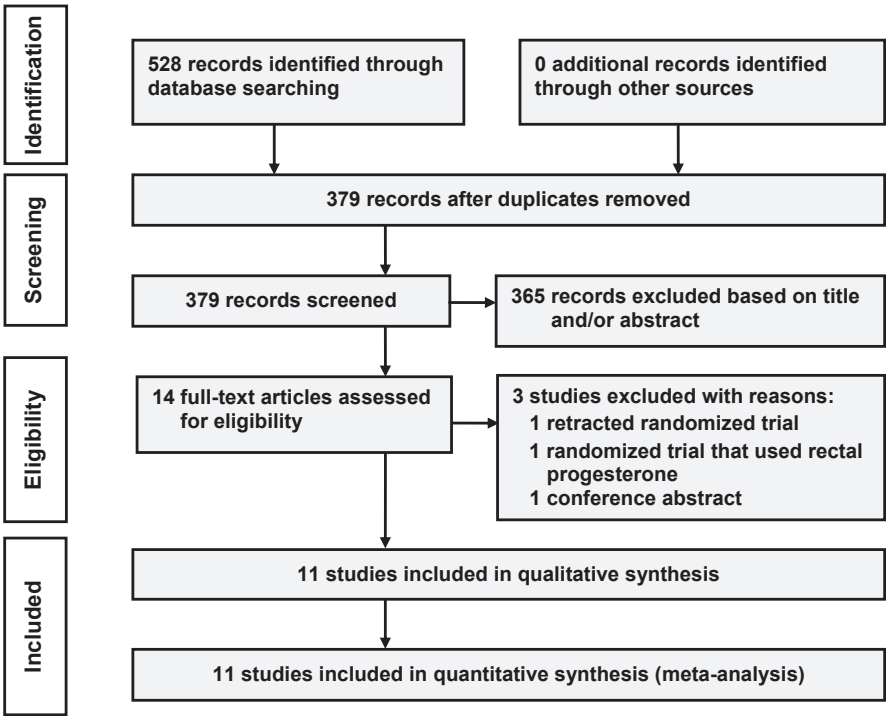
ReviewManager (RevMan [Computer program]. Version 5.4.1 The Cochrane Collaboration, 2020), StatsDirect (Version 3.3.5; StatsDirect Ltd, Wirral, United Kingdom), and Comprehensive Meta-Analysis (Version 3; Biostat Inc, Englewood, NJ) were used to perform all statistical analyses. The quality of evidence was assessed using the GRADEpro GDT (GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2021).

Results

Selection, characteristics, and risk of bias of studies

The literature search identified 528 citations. After removing duplicates and clearly ineligible records, we assessed 14 potentially eligible trials (Figure 1), of which 3 were excluded (1 retracted trial,[83] 1 trial that used rectal progesterone,[84] and 1 study published only in abstract form with insufficient information[85]). A total of 11 studies, including 3401 women with a twin gestation (6802 fetuses/infants), met the

FIGURE 1
Flow diagram of the study selection process



Conde-Agudelo. Vaginal progesterone to prevent preterm birth in twin gestations. Am J Obstet Gynecol 2023.

inclusion criteria.[86–96] The study by Wood et al[91] included 3 women with a triplet gestation (2 in the vaginal progesterone group and 1 in the placebo group) whose outcome data were not reported separately. For the purpose of this meta-analysis, these 3 triplet gestations were considered as twin gestations. We obtained individual patient data (IPD) from 5 trials[86,88,92,93,96] and additional unpublished data from 1 trial.[95]

The characteristics of each included trial are summarized in Table 1. All but 1 study[95] were double-blind, placebo-controlled trials. Six studies were conducted in high-income countries,[87,89,91,92,94,96] 4 in low/middle-income countries,[88,90,93,95] and 1 in both high-income and low/middle-income countries.[86] Eight studies were multicenter trials[86,87,89,91,92,94–96] and 3 were conducted in single centers.[88,90,93] The sample size ranged from 12[94] to 1169[96] women (median, 118 women), and all but 1 trial[88] were registered in a clinical trials registry. The daily dose of vaginal progesterone used in the trials was 90 to 100 mg in 4 studies,[87,88,91,94] 200 mg in 3 studies,[86,89,93] 400 mg in 2 studies,[90,95] and 600 mg in 1 study.[96] One trial used 2 different daily doses of vaginal progesterone (200 and 400 mg).[92] Treatment was started between 11 and 14 weeks of gestation in 1 trial,[96] between 16 and 24 weeks of gestation in 9 trials,[86–94] and at 28 weeks of gestation in the remaining trial.[95] Most studies reported that participants received vaginal progesterone until 34 weeks of gestation. Compliance ≥80% was reported in 8 studies.[86,88,89,91–94,96] Compliance was not reported in 3 trials.[87,90,95]

The risk of bias in each included study is shown in Figure 2. All but 1 trial[95] were judged to have an overall low risk of bias for the primary outcome and most secondary outcomes. The study by Shabaan et al[95] was judged as having some concerns of bias because participants, personnel, and outcome assessors were not blinded to intervention status and 22 of 140 (16%) randomized women were lost to follow-up.

Vaginal progesterone vs placebo or no treatment in all twin gestations

The frequency of preterm birth <34 weeks of gestation among women with a twin gestation allocated to receive vaginal progesterone was very similar to that observed in women in the placebo or no treatment group (17.8% vs 17.9%; RR, 0.99; 95% CI, 0.84−1.17; P=.95; I^2=12%; 95% prediction interval of the RR, 0.75−1.32; high-quality evidence) (Figure 3). There were no significant differences between the vaginal progesterone and placebo or no treatment groups in the risk of preterm birth <37 weeks of gestation (RR, 0.99; 95% CI, 0.92−1.06; high-quality evidence), <32 weeks of gestation (RR, 0.85; 95% CI, 0.67−1.08; moderate-quality evidence), <30 weeks of gestation (RR, 0.78; 95% CI, 0.55−1.10; moderate-quality evidence), and <28 weeks of gestation (RR, 1.00; 95% CI, 0.64−1.55; moderate-quality evidence), and spontaneous preterm birth <34 weeks of gestation (RR, 0.97; 95% CI, 0.80−1.18; high-quality evidence) (Table 2). Vaginal progesterone had no significant effect on any of the perinatal outcomes evaluated. The quality of evidence was judged as moderate for most perinatal outcomes.

Prespecified subgroup analyses (Table 3) showed that the effect of vaginal progesterone on preterm birth <34 weeks of gestation did not significantly differ between women with a dichorionic pregnancy and those with a monochorionic pregnancy (P for interaction=.37), between women with a naturally conceived pregnancy and those with a pregnancy conceived after use of ovulation induction drugs or assisted reproductive technology (P for interaction=.60), and between women with a history of spontaneous preterm birth and those without such history (P for interaction=.46). There was no evidence of a different effect related to daily dose of vaginal progesterone (P for interaction=.32). Treatment effect estimates did not significantly differ between studies for which vaginal progesterone administration was initiated at 11 to 14 weeks of gestation and those for which it was initiated at 16 to

TABLE 1
Main characteristics of studies included in the systematic review

First author, y	Trial enrollment	Main inclusion/exclusion criteria	Interventions (number of women with a twin gestation)	Compliance	Trial registration	Primary outcome
Fonseca,[86] 2007	5 centers in United Kingdom, 1 in Chile, 1 in Brazil, and 1 in Greece	• Inclusion: singleton or twin gestation and a sonographic cervical length ≤15 mm at 20−25 weeks of gestation • Exclusion: major fetal abnormalities, painful regular uterine contractions, history of ruptured membranes, or cervical cerclage	• Vaginal progesterone capsule 200 mg/d from 24−33^{+6} weeks of gestation (n=11) • Placebo (n=13)	99.4% for vaginal progesterone group and 83.3% for placebo group|	NCT00422526	Spontaneous preterm birth <34 wk
Norman,[87] 2009	9 centers in United Kingdom	• Inclusion: twin gestation • Exclusion: structural or chromosomal fetal abnormality, contraindications to progesterone, planned cervical suture, planned elective delivery before 34 weeks of gestation, or planned intervention for twin-to-twin transfusion before 22 weeks of gestation	• Vaginal progesterone gel 90 mg/d from 24-34^{+0} weeks of gestation (n=247) • Placebo (n=247)	Unclearly reported	ISRCTN35782581	Preterm birth <34 wk
Cetingoz,[88] 2011	Single center in Turkey	• Inclusion: singleton gestation with a history of spontaneous preterm birth or uterine malformation, or twin gestation • Exclusion: in-place or planned cervical cerclage, or serious fetal anomalies	• Vaginal progesterone suppository 100 mg/d from 24−34 weeks of gestation (n=39) • Placebo (n=28)	100% for both study groups	Not registered	Preterm birth <37 wk
Rode,[89] 2011	13 centers in Denmark and 4 in Austria	• Inclusion: diamniotic twin gestation • Exclusion: known allergy to progesterone or peanuts (because the active treatment contained peanut oil), history of hormone-associated thromboembolic disorders, rupture of membranes, pregnancies treated for or with 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, or known liver disease	• Vaginal progesterone pessary 200 mg/d from 20−23 to 33^{+6} weeks of gestation (n=334) • Placebo (n=341)	82.6% for vaginal progesterone group and 83.0% for placebo group	NCT00329914	Preterm birth <34 wk
Aboulghar,[90] 2012	Single center in Egypt	• Inclusion: singleton or dichorionic twin gestation conceived after IVF/ICSI and first pregnancy • Exclusion: previous pregnancy, serious fetal anomalies, fetal growth restriction, monochorionic and monoamniotic twin gestations, uterine anomalies, triplet gestations, or cervical cerclage	• Vaginal progesterone suppository 400 mg/d from 18−24 to 37^{+0} weeks of gestation (n=49) • Placebo (n=42)	Unreported	ISRCTN06959967	Preterm birth <37 and <34 wk

Conde-Agudelo. Vaginal progesterone to prevent preterm birth in twin gestations. Am J Obstet Gynecol 2023.

(continued)

TABLE 1
Main characteristics of studies included in the systematic review *(continued)*

First author, y	Trial enrollment	Main inclusion/exclusion criteria	Interventions (number of women with a twin gestation)	Compliance	Trial registration	Primary outcome
Wood,[91] 2012	2 centers in Canada	• Inclusion: multiple gestation • Exclusion: placenta previa, preexisting hypertension, known major fetal anomaly, monoamniotic monozygotic multiple pregnancies, maternal seizure disorder, active or history of thromboembolic disease, maternal liver disease, known or suspected breast malignancy or pathology, known or suspected progesterone-dependent neoplasia, or known sensitivity to progesterone	• Vaginal progesterone gel 90 mg/d from 16−20 to 35^{+6} weeks of gestation (n=40) • Placebo (n=41)	97.8% for both study groups	NCT00343265	Gestational age at delivery
Serra,[92] 2013	5 centers in Spain	• Inclusion: dichorionic-diamniotic twin gestation • Exclusion: monochorionic twin gestations, triplets or higher-order multiple gestations, elective cervical cerclage before 14 weeks of gestation, history of hepatic problems or gestational cholestasis, abnormal liver enzymes, abnormal kidney function, local allergy to micronized natural progesterone, allergy to peanuts, recurrent vaginal bleeding, recurrent vaginal infections, fetal anomalies, alcohol or illicit drug consumption, or smoking ≥10 cigarettes/d	• Vaginal progesterone pessary 400 mg/d (n=97) or 200 mg/d (n=97) from 20−34 weeks of gestation • Placebo (n=96)	77.5% in the 400 mg/d progesterone group, 81.9% in the 200 mg/d progesterone group, and 85.1% in the placebo group .	EudraCT 2004-004136-31 and NCT00480402	Preterm birth <37 wk
Brizot,[93] 2015	Single center in Brazil	• Inclusion: naturally conceived diamniotic twin gestations without history of preterm birth • Exclusion: major fetal abnormality, allergy to progesterone or peanuts, hepatic dysfunction, porphyria, otosclerosis, malignant disease, severe depressive state, current or previous thromboembolic disease, uterine malformation, prophylactic cerclage, or ovular infection	• Vaginal progesterone ovule 200 mg/d from 18−21 to 34^{+6} weeks of gestation (n=189) • Placebo (n=191)	95.3% for vaginal progesterone group and 96.4% for placebo group	NCT01031017	Gestational age at delivery

Conde-Agudelo. Vaginal progesterone to prevent preterm birth in twin gestations. Am J Obstet Gynecol 2023. *(continued)*

TABLE 1
Main characteristics of studies included in the systematic review *(continued)*

First author, y	Trial enrollment	Main inclusion/exclusion criteria	Interventions (number of women with a twin gestation)	Compliance	Trial registration	Primary outcome
Crowther,[94] 2017	32 centers in Australia, 5 in New Zealand, and 2 in Canada	• Inclusion: singleton or twin gestation and history of spontaneous preterm birth in the preceding pregnancy • Exclusion: active vaginal bleeding requiring hospital admission at ≥18 weeks of gestation, preterm prelabor rupture of membranes, active labor, known lethal fetal anomaly or fetal demise, progesterone treatment after 16 weeks' gestation, or any contraindication to continuation of the pregnancy or progesterone therapy	• Vaginal progesterone pessary 100 mg/d from 20−24 to 34^{+0} weeks of gestation or delivery, whichever occurred first (n=8) • Placebo (n=4)	91.6% for vaginal progesterone group and 90.8% for placebo group	ISRCTN20269066	Respiratory distress syndrome and severity of respiratory disease
Shabaan,[95] 2018	3 centers in Egypt	• Inclusion: naturally conceived dichorionic-diamniotic twin gestation • Exclusion: major fetal anomalies, contraindication to progesterone treatment, single fetal demise or fetal growth restriction of cotwin, polyhydramnios, threatened preterm labor, premature rupture of membranes, cervical cerclage from a previous or a current pregnancy, or chronic medical diseases	• Vaginal progesterone pessary 400 mg/d from 28 weeks of gestation to delivery (n=59) • Standard care (n=59)	Unreported	NCT02350231	Preterm birth <37 wk
Rehal,[96] 2021	22 centers in England, Spain, Bulgaria, Italy, Belgium, and France	• Inclusion: dichorionic or monochorionic-diamniotic twin gestation • Exclusion: monoamniotic gestations, monochorionic-diamniotic gestations with early signs of twin-to-twin transfusion syndrome, major fetal abnormality or nuchal translucency thickness of >3.5 mm at 11−13 weeks of gestation, maternal severe illness, hypersensitivity to progesterone, regular treatment with progesterone within the previous 7 days, severe hepatic dysfunction, mammary or genital tract carcinoma, thrombophlebitis, or thromboembolic disorders, porphyria, cerebral hemorrhage, or allergy to sunflower oil, soya lecithin, gelatin, glycerol, or titanium dioxide.	• Vaginal progesterone capsule 600 mg/d from 11−14 to 34^{+0} weeks of gestation or delivery, whichever occurred first (n=582) • Placebo (n=587)	87.2% for vaginal progesterone group and 87.3% for placebo group	EudraCT 2015-005180-16 and ISRCTN66445401	Spontaneous birth between 24^{+0} and 33^{+6} weeks of gestation

ICSI, intracytoplasmic sperm injection; *IVF*, in vitro fertilization.

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FIGURE 2
Risk of bias for each included study

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24 weeks of gestation or at 28 weeks of gestation (*P* for interaction=.58). A sensitivity analysis restricted to the 10 trials at overall low risk of bias confirmed that vaginal progesterone did not reduce the risk of preterm birth <34 weeks of gestation (RR, 1.01; 95% CI, 0.85−1.20; I^2=13%).

Visual inspection of the funnel plot for the outcome of preterm birth <34 weeks of gestation suggested some degree of asymmetry (Supplemental Figure 1), with a *P* value of .07 for both Egger and Harbord tests. A contour-enhanced funnel plot (not shown) indicated that missing studies would be in areas of statistical nonsignificance of the plot, which suggests that the asymmetry could be due to publication bias. After applying the trim-and-fill method to adjust for publication bias, the overall effect of vaginal progesterone on preterm birth <34 weeks of gestation remained unchanged (RR, 1.04; 95% CI, 0.88−1.22).

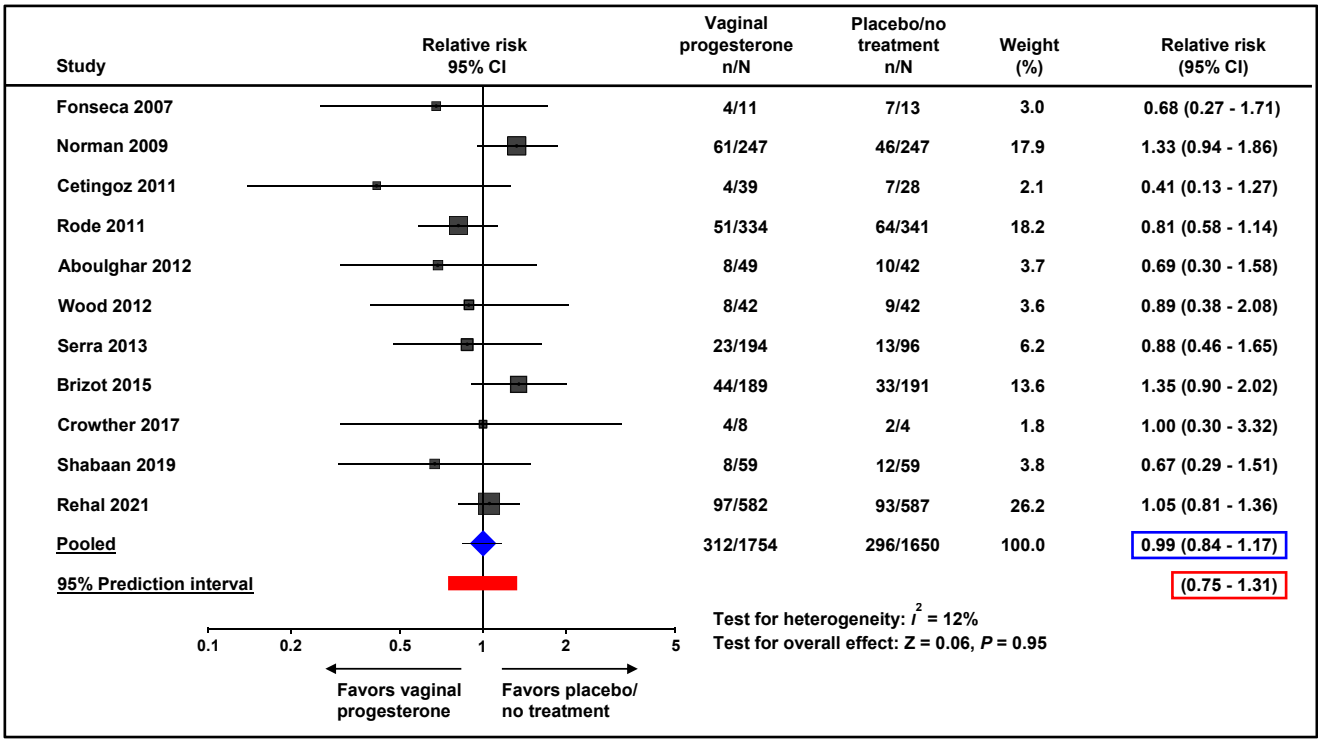
Vaginal progesterone vs placebo or no treatment in unselected twin gestations

Eight studies (3274 women and 6548 fetuses/infants) evaluated vaginal progesterone vs placebo or no treatment in unselected twin gestations.[87−89,91−93,95,96] The proportion of infants born before 34 weeks of gestation was similar in the vaginal progesterone and placebo or no treatment groups (17.6% vs 17.4%; RR, 1.01; 95% CI, 0.83−1.23; *P*=0.90; I^2=28%; 95% prediction interval of the RR, 0.69−1.49; high-quality evidence) (Supplemental Figure 2). A sensitivity analysis restricted to the trials at overall low risk of bias showed a similar estimate of treatment effect (RR, 1.03; 95% CI, 0.85−1.26). The frequencies of preterm birth <37, <32, <30, and <28 weeks of gestation and spontaneous preterm birth <34 weeks of gestation did not significantly differ between the study groups. No significant differences were observed between the vaginal progesterone and placebo or no treatment groups for adverse perinatal outcomes (moderate- and high-quality evidence for most outcomes) (Table 4).

Vaginal progesterone vs placebo in twin gestations with a transvaginal sonographic cervical length <30 mm

Six double-blind, placebo-controlled trials (306 women; 612 fetuses/infants) provided data for this comparison.[86,88,89,92,93,96] The study by Rehal et al[96] contributed 50% of the total sample size of this meta-analysis. There was no significant difference between the vaginal progesterone and placebo groups in the risk of preterm birth <34 weeks of gestation (28.8% vs 36.3%; RR, 0.80; 95% CI, 0.58−1.12; *P*=.20; I^2=0%; moderate-quality evidence) (Supplemental Figure 3). Vaginal progesterone significantly decreased the risk of preterm birth <32 weeks (RR, 0.65; 95% CI, 0.43−0.99; NNT for benefit, 11; 95% CI, 7−375; high-quality evidence),

FIGURE 3
Effect of vaginal progesterone on preterm birth <34 weeks of gestation in twin gestations (all)



CI, confidence interval.

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<30 weeks (RR, 0.48; 95% CI, 0.26−0.86; NNT for benefit, 10; 95% CI, 7−35; moderate-quality evidence), and <28 weeks (RR, 0.48; 95% CI, 0.24−0.99; NNT for benefit, 13; 95% CI, 9−682; moderate-quality evidence) (Table 5). Moreover, vaginal progesterone was associated with a significant decrease in the risk of neonatal death (adjusted RR, 0.32; 95% CI, 0.11−0.92; NNT for benefit, 24; 95% CI, 18−203; moderate-quality evidence) and birthweight <1500 g (adjusted RR, 0.60; 95% CI, 0.39−0.88; NNT for benefit, 10; 95% CI, 6−31; high-quality evidence). There were no significant differences between the vaginal progesterone and placebo groups in the risk of preterm birth <37 weeks of gestation, spontaneous preterm birth <34 weeks of gestation, as well as in other adverse perinatal outcomes (low- and moderate-quality evidence for most outcomes).

Vaginal progesterone vs placebo in twin gestations with a transvaginal sonographic cervical length ≤25 mm

The results for this comparison were recently published in a separate report.[97] Six double-blind, placebo-controlled trials assessed vaginal progesterone in 95 women (190 fetuses/infants) with a twin gestation and a sonographic cervical length ≤25 mm.[86,88,89,92,93,96] Vaginal progesterone was associated with a significant reduction in the risk of preterm birth <34 weeks of gestation (46.2% vs 65.1%; RR, 0.68; 95% CI, 0.46−0.99; P=.047; I^2=7%; 95% prediction interval of the RR, 0.40−1.15; NNT for benefit, 5; 95% CI, 3−154; moderate-quality evidence) (Supplemental Figure 4). In addition, vaginal progesterone significantly decreased the risk of preterm birth <32 weeks (RR, 0.56; 95% CI, 0.33−0.93), <30 weeks (RR, 0.45; 95% CI, 0.23−0.89), and <28 weeks (RR, 0.41; 95% CI, 0.19−0.91) of gestation, spontaneous preterm birth <34 weeks of gestation (RR, 0.58; 95% CI, 0.38−0.89), composite neonatal morbidity and mortality (RR, 0.59; 95% CI, 0.33−0.98), and birthweight <1500 g (RR, 0.55; 95% CI, 0.33−0.94) (all NNTs for benefit were between 4 and 7). The quality of evidence was moderate for all of these outcomes. There was no evidence of an effect of vaginal progesterone on preterm birth <37 and <35 weeks of gestation or on other adverse perinatal outcomes.

Comment

Principal findings

The main findings of this systematic review and meta-analysis are as follows: (1) overall, vaginal progesterone does not

TABLE 2
Effect of vaginal progesterone on preterm birth and adverse perinatal outcomes in twin gestations (all)

Outcome	Number of trials	Vaginal progesterone		Placebo/no treatment		Relative risk (95% CI)	*P* value	I^2, %	Adjusted relative risk[a] (95% CI)	Quality of evidence
Preterm birth <37 wk	11[86–96]	955/1754	(54.4%)	906/1650	(54.9%)	0.99 (0.92–1.06)	.82	16	NA	High
Preterm birth <32 wk	7[86,88,89,92,93,95,96]	120/1408	(8.5%)	136/1315	(10.3%)	0.85 (0.67–1.08)	.18	0	NA	Moderate
Preterm birth <30 wk	6[86,88,92,93,95,96]	54/1074	(5.0%)	68/974	(7.0%)	0.78 (0.55–1.10)	.16	0	NA	Moderate
Preterm birth <28 wk	10[86–94,96]	64/1695	(3.8%)	64/1591	(4.0%)	1.00 (0.64–1.55)	.98	18	NA	Moderate
Spontaneous preterm birth <34 wk	6[86,88,89,92,93,96]	213/1349	(15.8%)	191/1256	(15.2%)	0.97 (0.80–1.18)	.78	8	NA	High
Fetal death	11[86–96]	37/3510	(1.1%)	34/3301	(1.0%)	1.01 (0.63–1.61)	.98	0	1.00 (0.59–1.72)	Moderate
Neonatal death	11[86–96]	45/3510	(1.3%)	35/3301	(1.1%)	1.14 (0.73–1.80)	.56	0	1.09 (0.67–1.89)	Moderate
Perinatal death	11[86–96]	82/3510	(2.3%)	69/3301	(2.1%)	1.09 (0.79–1.49)	.60	0	1.06 (0.77–1.50)	Moderate
Birthweight <1500 g	11[86–96]	260/3421	(7.6%)	295/3226	(9.1%)	0.85 (0.72–1.00)	.05	0	0.87 (0.68–1.04)	Moderate
Birthweight <2500 g	11[86–96]	1889/3421	(55.2%)	1834/3226	(56.9%)	0.97 (0.91–1.04)	.41	56	0.97 (0.89–1.06)	Moderate
Respiratory distress syndrome	9[86,88,89,91–96]	271/2785	(9.7%)	270/2591	(10.4%)	0.90 (0.77–1.06)	.20	0	0.91 (0.74–1.15)	High
Necrotizing enterocolitis	8[86–89,91–93,96]	11/3132	(0.4%)	13/2948	(0.4%)	0.80 (0.36–1.81)	.59	0	0.83 (0.33–1.92)	Low
Intraventricular hemorrhage	8[86–89,91,93,95,96]	35/2864	(1.2%)	32/2876	(1.1%)	1.08 (0.67–1.76)	.74	0	1.04 (0.65–1.82)	Moderate
Neonatal sepsis	8[86–89,92–94,96]	78/3060	(2.5%)	66/2871	(2.3%)	1.14 (0.74–1.76)	.56	28	1.10 (0.73–1.79)	Moderate
Retinopathy of prematurity	7[86–89,92,93,96]	27/3045	(0.9%)	34/2863	(1.2%)	0.83 (0.45–1.50)	.53	17	0.85 (0.41–1.58)	Moderate
Any composite adverse neonatal/ perinatal outcome	9[86–89,91–94,96]	255/3151	(8.1%)	245/2959	(8.3%)	0.92 (0.75–1.13)	.43	21	0.92 (0.73–1.16)	Moderate
Admission to NICU	10[86–90,92–96]	911/3340	(27.3%)	951/3129	(30.4%)	0.87 (0.75–1.01)	.07	61	0.89 (0.73–1.03)	Moderate
Mechanical ventilation	10[86–89,91–96]	343/3176	(10.8%)	342/2999	(11.4%)	0.96 (0.83–1.10)	.52	0	0.97 (0.82–1.12)	High

Data are number/total number.

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit.

[a] Taking into account the nonindependence of perinatal outcomes between twins.

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TABLE 3
Subgroup analyses of effect of vaginal progesterone on preterm birth <34 weeks in twin gestations (all)

Subgroup	Number of trials	Vaginal progesterone		Placebo/no treatment		Relative risk (95% CI)	I^2, %	Interaction *P* value
Chorionicity								.37
Monochorionic gestations	5[86,87,89,93,96]	64/271	(23.6%)	73/276	(26.4%)	0.89 (0.67–1.18)	0	
Dichorionic gestations	8[86,87,89,90,92,93,95,96]	231/1391	(16.6%)	206/1296	(15.9%)	1.04 (0.84–1.30)	28	
Type of conception								.60
Natural	4[92,93,95,96]	121/634	(19.1%)	109/634	(17.2%)	1.11 (0.88–1.41)	0	
By ovulation induction drugs	2[92,96]	12/112	(10.7%)	9/76	(11.8%)	0.86 (0.36–2.02)	0	
By assisted reproductive technology	3[90,92,96]	47/327	(14.4%)	43/265	(16.2%)	0.90 (0.62–1.32)	0	
History of spontaneous preterm birth								.46
No	7[86,88,89,91–93,96]	217/1344	(16.1%)	205/1239	(16.5%)	0.97 (0.79–1.20)	19	
Yes	5[89,91,92,94,96]	18/55	(32.7%)	23/63	(36.5%)	0.79 (0.47–1.33)	0	
Daily dose of vaginal progesterone								.32
90–200 mg	8[86–89,91–94]	189/967	(19.5%)	180/962	(18.7%)	1.02 (0.81–1.28)	22	
400 mg	3[90,92,95]	26/205	(12.7%)	35/197	(17.8%)	0.71 (0.44–1.12)	0	
600 mg	1[96]	97/582	(16.7%)	93/587	(15.8%)	1.05 (0.81–1.36)	NA	
Gestational age at initiation of treatment								.58
11–14 wk	1[96]	97/582	(16.7%)	93/587	(15.8%)	1.05 (0.81–1.36)	NA	
16–24 wk	9[86–94]	207/1113	(18.6%)	190/1004	(18.9%)	0.99 (0.79–1.22)	20	
28 wk	1[95]	8/59	(13.6%)	12/59	(20.3%)	0.67 (0.29–1.51)	NA	

Data are number/total number.

CI, confidence interval; *NA*, not applicable.

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TABLE 4
Effect of vaginal progesterone on preterm birth and adverse perinatal outcomes in unselected twin gestations

Outcome	Number of trials	Vaginal progesterone		Placebo/no treatment		Relative risk (95% CI)	*P* value	I^2, %	Adjusted relative risk[a] (95% CI)	Quality of evidence
Preterm birth <34 wk	8[87–89,91–93,95,96]	296/1686	(17.6%)	277/1591	(17.4%)	1.01 (0.83–1.23)	0.90	28	NA	High
Preterm birth <37 wk	8[87–89,91–93,95,96]	908/1686	(53.9%)	864/1591	(54.3%)	0.98 (0.90–1.08)	.72	40	NA	High
Preterm birth <32 wk	6[88,89,92,93,95,96]	117/1397	(8.4%)	131/1302	(10.1%)	0.86 (0.68–1.09)	.21	0	NA	Moderate
Preterm birth <30 wk	5[88,92,93,95,96]	53/1063	(5.0%)	66/961	(6.9%)	0.78 (0.55–1.12)	.18	0	NA	Moderate
Preterm birth <28 wk	7[87–89,91–93,96]	62/1627	(3.8%)	58/1532	(3.8%)	1.14 (0.71–1.84)	.58	24	NA	Moderate
Spontaneous preterm birth <34 wk	5[88,89,92,93,96]	209/1338	(15.6%)	184/1243	(14.8%)	0.99 (0.80–1.21)	.90	17	NA	Moderate
Fetal death	8[87–89,91–93,95,96]	33/3374	(1.0%)	29/3183	(0.9%)	1.07 (0.64–1.78)	.80	0	1.07 (0.60–1.89)	Moderate
Neonatal death	8[87–89,91–93,95,96]	41/3374	(1.2%)	28/3183	(0.9%)	1.29 (0.79–2.10)	.31	0	1.26 (0.73–2.20)	Moderate
Perinatal death	8[87–89,91–93,95,96]	74/3374	(2.2%)	57/3183	(1.8%)	1.19 (0.84–1.68)	.32	0	1.16 (0.81–1.70)	Moderate
Birthweight <1500 g	8[87–89,91–93,95,96]	247/3294	(7.5%)	276/3118	(8.9%)	0.87 (0.74–1.03)	.10	0	0.89 (0.72–1.05)	High
Birthweight <2500 g	8[87–89,91–93,95,96]	1815/3294	(55.1%)	1762/3118	(56.5%)	0.97 (0.91–1.03)	.35	38	0.98 (0.90–1.04)	High
Respiratory distress syndrome	7[88,89,91–93,95,96]	264/2747	(9.6%)	262/2557	(10.2%)	0.91 (0.78–1.07)	.27	0	0.91 (0.75–1.16)	High
Necrotizing enterocolitis	7[87–89,91–93,96]	11/3110	(0.4%)	13/2922	(0.4%)	0.80 (0.36–1.81)	.59	0	0.83 (0.31–1.92)	Low
Intraventricular hemorrhage	7[87–89,91,93,95,96]	35/2842	(1.2%)	32/2850	(1.1%)	1.08 (0.67–1.76)	.74	0	1.06 (0.64–1.85)	Moderate
Neonatal sepsis	6[87–89,92,93,96]	77/3022	(2.5%)	59/2837	(2.1%)	1.28 (0.91–1.80)	.15	0	1.23 (0.85–1.92)	Moderate
Retinopathy of prematurity	6[87–89,92,93,96]	27/3023	(0.9%)	34/2837	(1.2%)	0.83 (0.45–1.50)	.53	17	0.83 (0.40–1.54)	Moderate
Any composite adverse neonatal/perinatal outcome	7[87–89,91–93,96]	251/3113	(8.1%)	232/2925	(7.9%)	0.97 (0.82–1.15)	.71	0	0.99 (0.81–1.17)	High
Admission to NICU	7[87–89,92,93,95,96]	887/3208	(27.6%)	922/3013	(30.6%)	0.90 (0.78–1.04)	.16	62	0.90 (0.76–1.07)	Moderate
Mechanical ventilation	8[87–89,91–93,95,96]	330/3138	(10.5%)	332/2965	(11.2%)	0.96 (0.83–1.10)	.56	0	0.97 (0.81–1.12)	High

Data are number/total number.

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit.

[a] Taking into account the nonindependence of perinatal outcomes between twins.

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TABLE 5

Effect of vaginal progesterone on preterm birth and adverse perinatal outcomes in twin gestations with a transvaginal sonographic cervical length <30 mm

Outcome	Number of trials	Vaginal progesterone		Placebo		Relative risk (95% CI)	*P* value	I^2, %	Adjusted relative risk[a] (95% CI)	Quality of evidence
Preterm birth <34 wk	6[86,88,89,92,93,96]	46/160	(28.8%)	53/146	(36.3%)	0.80 (0.58–1.12)	.20	0	NA	Moderate
Preterm birth <37 wk	5[86,88,92,93,96]	94/143	(65.7%)	78/116	(67.2%)	0.99 (0.73–1.33)	.92	54	NA	Low
Preterm birth <32 wk	6[86,88,89,92,93,96]	28/160	(17.5%)	39/146	(26.7%)	0.65 (0.43–0.99)	.048	0	NA	High
Preterm birth <30 wk	5[86,88,89,92,93,96]	14/143	(9.8%)	24/116	(20.7%)	0.48 (0.26–0.86)	.01	0	NA	Moderate
Preterm birth <28 wk	5[86,88,92,93,96]	10/143	(7.0%)	17/116	(14.7%)	0.48 (0.24–0.99)	.049	0	NA	Moderate
Spontaneous preterm birth <34 wk	5[86,88,92,93,96]	31/143	(21.7%)	37/116	(31.9%)	0.71 (0.43–1.17)	.18	26	NA	Low
Fetal death	6[86,88,89,92,93,96]	12/320	(3.8%)	8/292	(2.7%)	1.15 (0.52–2.58)	.73	0	1.13 (0.49–2.73)	Low
Neonatal death	6[86,88,89,92,93,96]	4/320	(1.3%)	13/292	(4.5%)	0.32 (0.12–0.86)	.02	0	0.32 (0.11–0.92)	Moderate
Perinatal death	6[86,88,89,92,93,96]	16/320	(5.0%)	21/292	(7.2%)	0.64 (0.34–1.21)	.17	0	0.66 (0.31–1.25)	Moderate
Birthweight <1500 g	6[86,88,89,92,93,96]	39/320	(12.2%)	66/292	(22.6%)	0.57(0.40–0.82)	.002	0	0.60 (0.39–0.88)	High
Birthweight <2500 g	6[86,88,89,92,93,96]	210/320	(65.6%)	192/292	(65.8%)	1.03 (0.92–1.15)	.61	0	1.01 (0.90–1.17)	High
Respiratory distress syndrome	6[86,88,89,92,93,96]	39/320	(12.2%)	41/292	(14.0%)	0.84 (0.56–1.27)	.42	0	0.85 (0.53–1.31)	Moderate
Necrotizing enterocolitis	6[86,88,89,92,93,96]	1/320	(0.3%)	2/292	(0.7%)	0.52 (0.06–4.15)	.54	0	0.63 (0.04–5.21)	Low
Intraventricular hemorrhage	5[86,88,89,93,96]	3/304	(1.0%)	4/286	(1.4%)	0.79 (0.17–3.55)	.76	0	0.81 (0.12–4.08)	Low
Neonatal sepsis	6[86,88,89,92,93,96]	11/320	(3.4%)	14/292	(4.8%)	0.84 (0.37–1.92)	.69	0	0.84 (0.33–2.01)	Low
Retinopathy of prematurity	6[86,88,89,92,93,96]	3/320	(0.9%)	14/292	(4.8%)	0.33 (0.06–1.92)	.22	44	0.45 (0.04–2.13)	Low
Any composite adverse neonatal/perinatal outcome	5[86,88,92,93,96]	38/286	(13.3%)	45/232	(19.4%)	0.67 (0.45–1.00)	.05	0	0.67 (0.40–1.12)	Moderate
Admission to NICU	6[86,88,89,92,93,96]	99/320	(30.9%)	110/292	(37.7%)	0.91 (0.74–1.12)	.39	0	0.90 (0.72–1.15)	Moderate
Mechanical ventilation	5[86,88,92,93,96]	40/228	(17.5%)	45/184	(24.5%)	0.74 (0.51–1.08)	.12	0	0.77 (0.48–1.12)	Moderate

Data are number/total number.

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit.

[a] Taking into account the nonindependence of perinatal outcomes between twins.

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prevent preterm birth, nor does it improve perinatal outcomes, in women with a twin gestation; (2) there is no substantial evidence that vaginal progesterone is effective for any identified subset of twin gestations based on chorionicity, type of conception, and history of spontaneous preterm birth; (3) vaginal progesterone is ineffective in reducing the risk of preterm birth and adverse perinatal outcomes in women with an unselected twin gestation; (4) to date, vaginal progesterone is associated with a significant reduction in the risk of preterm birth occurring at <28 to <34 gestational weeks, composite neonatal morbidity and mortality, and birthweight <1500 g among women with a twin gestation and a transvaginal sonographic cervical length ≤25 mm; and (5) vaginal progesterone also significantly reduces the risk of preterm birth occurring at <28 to <32 gestational weeks, neonatal death, and birthweight <1500 g among women with a twin gestation and a transvaginal sonographic cervical length <30 mm.

Subgroup analyses

Although subgroup analyses for inference of efficacy are not recommended when the primary analysis result does not demonstrate efficacy, we performed the subgroup analyses that were prespecified in the protocol, aiming to determine whether vaginal progesterone is effective among a subgroup of patients with a twin gestation. We found that the effect of vaginal progesterone on the risk of preterm birth <34 weeks of gestation in twin gestations did not differ significantly between women with a dichorionic gestation and those with a monochorionic gestation, between patients with a history of spontaneous preterm birth and those without such history, and between women whose pregnancies were naturally conceived and those whose pregnancies were conceived after the use of ovulation induction drugs or assisted reproductive technologies. Therefore, although baseline risk factors based on chorionicity, type of conception, and obstetric history can affect the overall probability of preterm birth <34 weeks of gestation among women with a twin gestation, there is no evidence that they are effect modifiers to the treatment effect of vaginal progesterone.

Some have argued that the apparent lack of efficacy of vaginal progesterone in preventing preterm birth among twin gestations could be due to inadequate dosage or to treatment initiated too late in pregnancy. Our subgroup analyses revealed that the effect of vaginal progesterone on the risk of preterm birth <34 weeks of gestation did not significantly differ between women receiving 90 to 200 mg/d of vaginal progesterone and those receiving a daily dose of 400 or 600 mg, as well as between women in whom vaginal progesterone was initiated at 11 to 14 weeks and those in whom vaginal progesterone was initiated at 16 to 24 or at 28 weeks of gestation.

Comparison to existing literature

In 2021, the EPPPIC (Evaluating Progestogens for Preventing Preterm birth International Collaborative) group published the results of an IPD meta-analysis[39] that evaluated the efficacy of progestogens in preventing preterm birth in asymptomatic high-risk women, reporting that vaginal progesterone did not decrease the risk of preterm birth <37, <34, and <28 weeks of gestation, serious neonatal complications, or perinatal death among women with a twin gestation. In addition, this study reported that there was no evidence of any consistent variation in the relative treatment effect with cervical length or previous preterm birth status. Overall, the findings of our study are in concordance with those from the EPPPIC meta-analysis for all twin gestations. However, this IPD meta-analysis did not include data from the largest randomized controlled trial evaluating vaginal progesterone in twin gestations by Rehal et al[96] (N=1169), as well as from 2 other smaller trials[88,95] (N=185), which were included in our meta-analysis. Moreover, the EPPPIC meta-analysis did not assess the efficacy of vaginal progesterone in preventing preterm birth in subgroups of twin gestations based on chorionicity and type of conception, and it did not report detailed results for unselected twin gestations and those with a transvaginal sonographic cervical length ≤25 and <30 mm.

Strengths and limitations

The major strengths of our meta-analysis include: (1) the use of the most rigorous and up-to-date methodology for performing a systematic review and meta-analysis of randomized controlled trials; (2) the inclusion of a large number of twin gestations (>3400 women and >6800 fetuses/infants); (3) the access to data from individual patients who participated in 5 trials that enabled a more rigorous analysis than what is possible from only published data; (4) the performance of subgroup analyses according to clinically relevant characteristics of twin gestations and vaginal progesterone's daily dose and time of initiation; (5) the high methodological quality of most trials included in the systematic review; (6) consistency with the overall results in the sensitivity analyses restricted to studies at overall low risk of bias; and (7) most studies provided data for perinatal outcomes.

Some limitations of our study should be noted: (1) some subgroup analyses were based on a small number of women. As a result, these analyses were limited in their power to detect differences, if any existed; (2) the relatively small number of patients with a transvaginal sonographic cervical length ≤25 and <30 mm. Therefore, our analyses on these subsets of patients may have been underpowered for several outcomes; (3) the presence of funnel plot asymmetry in the meta-analysis of preterm birth <34 weeks of gestation suggested nonreporting biases. However, the pooled RR obtained after adjusting for publication bias (1.04; 95% CI, 0.88−1.22) was similar to that obtained in the primary meta-analysis (0.99; 95% CI, 0.84−1.17); and (4) quality of evidence was judged to be moderate or low for most outcomes in the subsets of patients with a transvaginal sonographic cervical length ≤25 and <30 mm, which means that subsequent trials may change the results of our meta-analysis.

Conclusions and implications

There is convincing evidence that vaginal progesterone, regardless of the daily dose used and the gestational age at which it is initiated, is ineffective in reducing preterm birth and adverse perinatal outcomes in unselected twin gestations. Therefore, vaginal progesterone should not be offered to women with an unselected twin gestation aiming to prevent preterm birth regardless of whether the pregnancy is dichorionic or monochorionic, naturally conceived or conceived after the use of ovulation induction drugs or assisted reproductive technologies, or whether the woman has a history of spontaneous preterm birth.

Vaginal progesterone appears promising for reducing the risk of preterm birth occurring at <28 to <32 or <34 gestational weeks and of neonatal morbidity and mortality in twin gestations with a transvaginal sonographic short cervix (cervical length ≤25 or <30 mm). However, given the limited sample sizes of these meta-analyses and that 50% of the total sample size of twin gestations with a transvaginal sonographic cervical length <30 mm was provided by 1 study,[96] in which vaginal progesterone was initiated at 11 to 14 weeks of gestation at a dose of 600 mg per day, we consider that further evidence is required before recommending the use of this intervention among women with a twin gestation and a short cervix. We identified 4 ongoing (N=1) or presumably completed but not yet reported (N=3) randomized controlled trials comparing vaginal progesterone vs placebo or no treatment in twin gestations with a sonographic short cervix: (1) the PROSPECT study (ClinicalTrials.gov identifier NCT02518594), a US multicenter trial (N=630) with an estimated completion date in February 2025; (2) the PRECEPET study (ClinicalTrials.gov identifier NCT03058536), a Brazilian single-center trial (N=312) with an estimated completion date in March 2019; and (3) 2 Egyptian single-center trials (ClinicalTrials.gov identifiers NCT02697331 [N=144] and NCT03781674 [N=200]) with estimated completion dates in December 2019 and March 2022, respectively. The results of these studies will help to establish whether vaginal progesterone can be recommended to women with a twin gestation and a short cervix, and to determine the optimal dosage and timing for initiation of treatment in the event that this intervention is effective. ■

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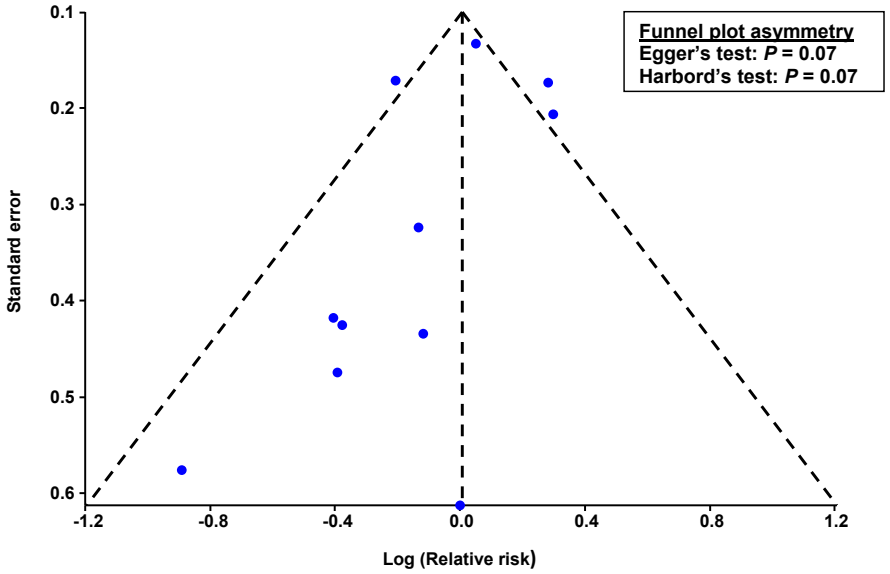
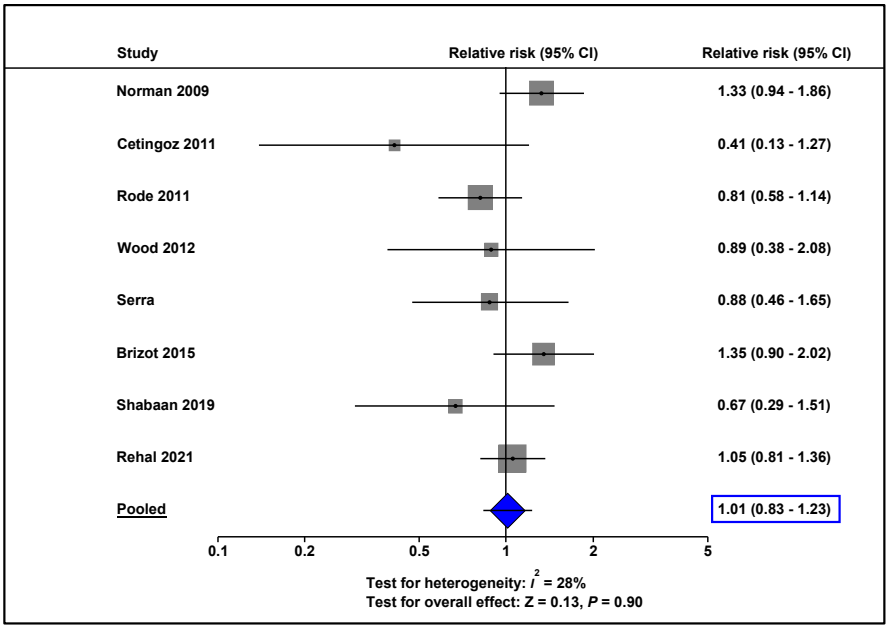
SUPPLEMENTAL FIGURE 1
Funnel plot for the outcome of preterm birth <34 weeks of gestation



Conde-Agudelo. Vaginal progesterone to prevent preterm birth in twin gestations. Am J Obstet Gynecol 2023.

SUPPLEMENTAL FIGURE 2
Effect of vaginal progesterone on preterm birth <34 weeks of gestation in unselected twin gestations

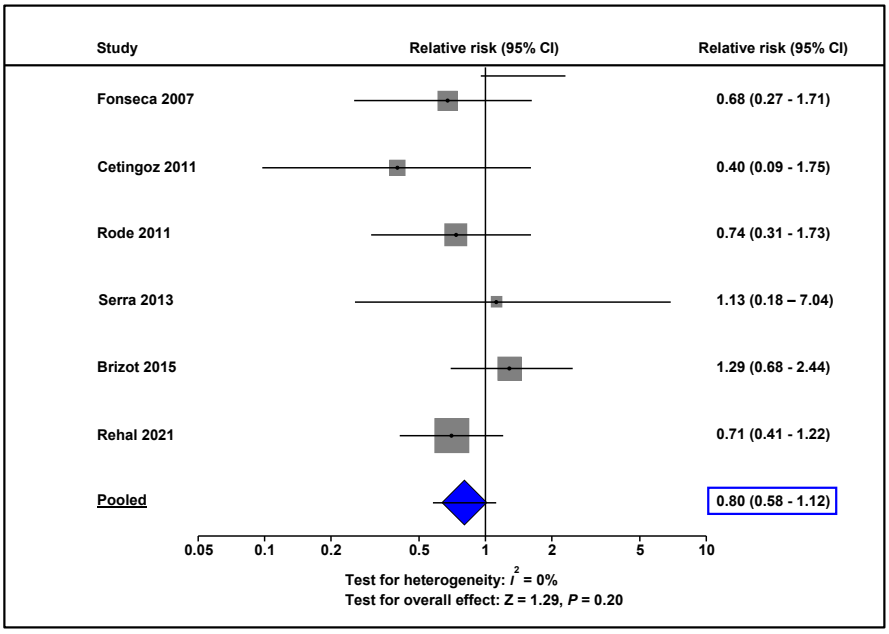


CI, confidence interval.

Conde-Agudelo. Vaginal progesterone to prevent preterm birth in twin gestations. Am J Obstet Gynecol 2023.

SUPPLEMENTAL FIGURE 3

Effect of vaginal progesterone on preterm birth <34 weeks of gestation in twin gestations with a transvaginal cervical length <30 mm

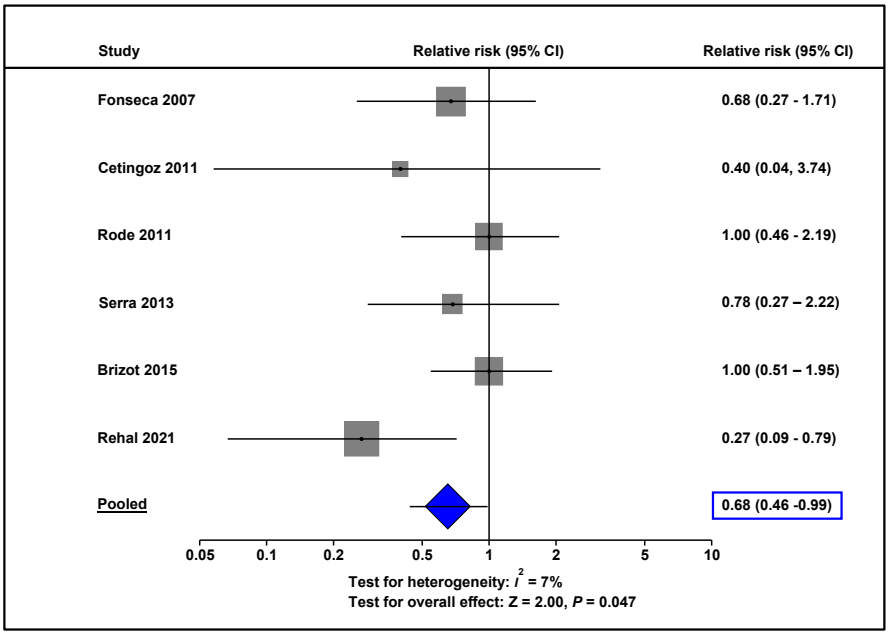


CI, confidence interval.

Conde-Agudelo. Vaginal progesterone to prevent preterm birth in twin gestations. Am J Obstet Gynecol 2023.

SUPPLEMENTAL FIGURE 4

Effect of vaginal progesterone on preterm birth <34 weeks of gestation in twin gestations with a transvaginal cervical length ≤25 mm



CI, confidence interval.

Conde-Agudelo. Vaginal progesterone to prevent preterm birth in twin gestations. Am J Obstet Gynecol 2023.