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

Roberto Romero, MD; Kypros Nicolaides, MD; Agustin Conde-Agudelo, MD, MPH; Ann Tabor, MD; John M. O'Brien, MD; Elcin Cetingoz, MD; Eduardo Da Fonseca, MD; George W. Creasy, MD; Katharina Klein, MD; Line Rode, MD; Priya Soma-Pillay, MD; Shalini Fusey, MD; Cetin Cam, MD; Zarko Alfirevic, MD; Sonia S. Hassan, MD

From the Perinatology Research Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, and Detroit, MI (Drs Romero, Conde-Agudelo, and Hassan);

Department of Obstetrics and Gynecology, King's College Hospital, London, United Kingdom (Dr Nicolaides);

Department of Fetal Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark (Drs Tabor and Rode);

Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark (Dr Tabor);

Perinatal Diagnostic Center, Central Baptist Hospital and Department of Obstetrics and Gynecology, University of Kentucky, Lexington, KY (Dr O'Brien);

Department of Obstetrics and Gynecology, Zeynep Kamil Women and Children Diseases Education and Research Hospital, Uskudar, Istanbul, Turkey (Drs Cetingoz and Cam);

Departamento de Obstetrícia e Ginecologia, Hospital do Servidor Publico Estadual "Francisco Morato de Oliveira" and School of Medicine, University of São Paulo, São Paulo, Brazil (Dr Fonseca);

Columbia Laboratories Inc, Livingston, NJ (Dr Creasy);

Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria (Dr Klein);

Department of Obstetrics and Gynecology, Steve Biko Academic Hospital, and the University of Pretoria, Pretoria, South Africa (Dr Soma-Pillay);

Department of Obstetrics and Gynecology, Government Medical College and Hospital, Maharashtra, India (Dr Fusey);

Department for Women's and Children's Health, University of Liverpool, Liverpool, United Kingdom (Dr Alfirevic);

and Department of Obstetrics and Gynecology, Wayne State University/Hutzel Hospital, Detroit, MI (Dr Hassan).

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Objective

To determine whether the use of vaginal progesterone in asymptomatic women with a sonographic short cervix (≤25 mm) in the midtrimester reduces the risk of preterm birth and improves neonatal morbidity and mortality.

Study Design

Individual patient data metaanalysis of randomized controlled trials.

Results

Five trials of high quality were included with a total of 775 women and 827 infants. Treatment with vaginal progesterone was associated with a significant reduction in the rate of preterm birth <33 weeks (relative risk [RR], 0.58; 95% confidence interval [CI], 0.42–0.80), <35 weeks (RR, 0.69; 95% CI, 0.55–0.88), and <28 weeks (RR, 0.50; 95% CI, 0.30–0.81); respiratory distress syndrome (RR, 0.48; 95% CI, 0.30–0.76); composite neonatal morbidity and mortality (RR, 0.57; 95% CI, 0.40–0.81); birthweight <1500 g (RR, 0.55; 95% CI, 0.38–0.80); admission to neonatal intensive care unit (RR, 0.75; 95% CI, 0.59–0.94); and requirement for mechanical ventilation (RR, 0.66; 95% CI, 0.44–0.98). There were no significant differences between the vaginal progesterone and placebo groups in the rate of adverse maternal events or congenital anomalies.

Conclusion

Vaginal progesterone administration to asymptomatic women with a sonographic short cervix reduces the risk of preterm birth and neonatal morbidity and mortality.

Key words

admission to neonatal intensive care unit; birthweight <1500 g; mechanical ventilation; prematurity; preterm birth; progestin; respiratory distress syndrome; transvaginal ultrasound; uterine cervix; 17α-hydroxyprogesterone caproate

Preterm birth is the leading cause of perinatal morbidity and mortality worldwide[1] and contributes to 70% of neonatal mortality and approximately half of long-term neurodevelopmental disabilities.[2] A recent systematic review has estimated that 12.9 million births, or 9.6% of all births worldwide, were preterm, of which approximately 11.9 million (92.3%) were in Africa, Asia, Latin America, and the Caribbean.[3] During the last 25 years, the preterm birth rate in the United States increased 36%, from 9.4% in 1981 to 12.8% in 2006.[4] This increase has been attributed to a higher frequency of "indicated" preterm births in singleton gestations and preterm delivery in multiple gestations resulting, in part, from the use of assisted reproductive technologies.[5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15]

Spontaneous preterm labor/delivery is considered to be one of the "great obstetrical syndromes",[16 and 17] a term that emphasizes that obstetrical disorders with a similar phenotype are caused by multiple pathologic processes,[18] have a long subclinical phase, and may result from complex gene-environment interactions.[19, 20, 21 and 22]

Progesterone is considered a key hormone for pregnancy maintenance, and a decline of progesterone action is implicated in the onset of parturition.[23, 24, 25 and 26] If such a decline occurs in the midtrimester, cervical shortening may occur, and this would predispose to preterm delivery. Therefore, an untimely decline in progesterone action has been proposed as a mechanism of disease in the "preterm parturition syndrome".[27]

Progesterone actions are mediated by genomic and nongenomic effects which have been studied in the uterine cervix, myometrium, sperm, etc.[28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 and 101] A blockade of progesterone action can lead to the clinical, biochemical, and morphologic changes associated with cervical ripening.[28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 and 101] A short cervix detected with transvaginal ultrasound is a powerful predictor of preterm birth in women with singleton and twin gestations.[27, 102, 103, 104, 105, 106, 107, 108 and 109] The shorter the sonographic cervical length, the higher the risk of spontaneous preterm birth.[102, 103, 104, 105, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122 and 123] Moreover, a short cervix is associated with intraamniotic infection and inflammation, and this may modify the response to interventions.

An interest in the role of progestogens (natural and synthetic) for the prevention of preterm birth has existed for decades.[124, 125, 126, 127, 128, 129 and 130] Recently, the administration of vaginal progesterone was proposed for the prevention of preterm birth in women with a sonographic short cervix in the midtrimester based on its biologic effects on the cervix,

myometrium, and chorioamniotic membranes. In 2007, Fonseca et al,[131] on behalf of the Fetal Medicine Foundation of the United Kingdom, reported that the administration of vaginal progesterone in women with a cervical length ≤15 mm was associated with a significant 44% reduction in the rate of spontaneous preterm birth <34 weeks of gestation. Similar findings were reported by DeFranco et al[132] in a secondary analysis of a randomized clinical trial of vaginal progesterone in women with a history of preterm birth in which the cervix was measured. Hassan et al[133] reported the largest randomized clinical trial to date, indicating that vaginal progesterone, when administered to women with a cervical length of 10-20 mm, reduces the rate of preterm birth at <33, <28, and <35 weeks, and this was associated with a significant 61% reduction in the rate of respiratory distress syndrome (RDS).[133] Since the publication of the trial of Hassan et al,[133] several trials evaluating vaginal progesterone in women at high risk of spontaneous preterm birth,[134, 135 and 136] including a subset of women with a short cervix, have been published.

An individual patient data (IPD) metaanalysis is a specific type of systematic review in which the original research data for each participant in a study are sought directly from the investigators responsible for that trial.[137] Such an approach has been considered the gold standard for summarizing evidence across clinical studies since it offers several advantages, both statistically and clinically, over conventional metaanalyses, which are based on published aggregate data.[138] These advantages include standardizing and updating of data sets, the ability to verify the quality of the data and the appropriateness of the analyses, the improvement of consistency across trials (eg, definition of outcomes), the performance of subgroup analyses that could effectively identify groups of patients who might benefit from an intervention, the investigation of interaction between patient-level covariates and treatment effects, and the performance of time-to-event analyses.[139, 140 and 141]

Using IPD from randomized controlled trials, we performed a metaanalysis to evaluate the efficacy and safety of vaginal progesterone for the prevention of preterm birth and neonatal morbidity and mortality in asymptomatic women with a sonographic short cervix in the midtrimester. We also sought to determine whether there were clinical benefits associated with the administration of vaginal progesterone in singleton and twin pregnancies.

Materials and Methods

The study was conducted based on a prospectively prepared protocol, and is reported using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for metaanalyses of randomized controlled trials[142] and suggested guidelines for IPD metaanalyses.[141]

Literature search

We searched MEDLINE, EMBASE, CINAHL, and LILACS (all from inception through December 31, 2011); the Cochrane Central Register of Controlled Trials (www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html) (1960 through December 31, 2011); ISI Web of Science (www.isiknowledge.com) (1960 through December 31, 2011); Research Registers of ongoing trials (www.clinicaltrials.gov, www.controlled-trials.com, www.centerwatch.com, www.anzctr.org.au, www.nihr.ac.uk,

and www.umin.ac.jp/ctr); and Google Scholar using a combination of key words and text words related to *progesterone* ("progesterone," "progestins," "progestogen," "progestagen," "progestational agent") and *preterm birth* ("preterm," "premature"). Proceedings of the Society for Maternal-Fetal Medicine and international meetings on preterm birth, reference lists of identified studies, textbooks, previously published systematic reviews, and review articles were also searched. Experts in the field were contacted to identify further studies. No language restriction was used.

Study selection

We included randomized controlled trials in which asymptomatic women with a sonographic short cervix (cervical length of ≤25 mm) in the midtrimester were randomly allocated to receive vaginal progesterone or placebo/no treatment for the prevention of preterm birth. Trials were included if the primary aim of the study was to prevent preterm birth in women with a sonographic short cervix, or if the primary aim was to prevent preterm birth in women with risk factors other than a short cervix, but outcomes were available for patients with a prerandomization cervical length of ≤25 mm. Trials were excluded if they: (1) were quasirandomized; (2) evaluated vaginal progesterone in women with threatened preterm labor, second trimester bleeding, or premature rupture of membranes; (3) evaluated the administration of vaginal progesterone in the first trimester only to prevent miscarriage; or (4) did not report clinical outcomes. Although there is no agreement on what is a sonographic short cervix, we chose 25 mm as the cutoff because this value corresponds approximately to the 10th percentile for cervical length in the midtrimester.[103 and 110] In addition, this cervical length is the most commonly used in studies evaluating the predictive accuracy of cervical length for preterm birth.[107 and 143]

Two investigators (R.R. and A.C.-A.) independently reviewed all potentially relevant articles for eligibility. Disagreements regarding trial eligibility were resolved by consensus.

Data collection

We contacted the corresponding authors to request access to the data. Authors were asked to supply anonymized data (without identifiers) about patient baseline characteristics, experimental intervention, control intervention, cointerventions, and prespecified outcome measures for every randomly assigned subject and were invited to become part of the collaborative group with joint authorship of the final publication. Data provided by the investigators were merged into a master database specifically constructed for the review. Data were checked for missing information, errors, and inconsistencies by cross-referencing the publications of the original trials. Quality and integrity of the randomization processes were assessed by reviewing the chronological randomization sequence and pattern of assignment, as well as the balance of baseline characteristics across treatment groups. Inconsistencies or missing data were discussed with the authors and corrections were made when deemed necessary.

Outcome measures

The prespecified primary outcome measure was preterm birth <33 weeks of gestation. Secondary outcome measures included preterm birth <37, <36, <35, <34, <30, and <28 weeks of gestation; spontaneous preterm birth <33 and <34 weeks of gestation; RDS; necrotizing enterocolitis; intraventricular hemorrhage (all grades); proven neonatal sepsis; retinopathy of prematurity; bronchopulmonary dysplasia; periventricular leukomalacia; fetal death; neonatal death; perinatal mortality, a composite neonatal morbidity and mortality outcome (defined as the occurrence of any of the following events: RDS, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis, or neonatal death); Apgar score <7 at 5 minutes; birthweight <1500 g and <2500 g; admission to the neonatal intensive care unit (NICU); use of mechanical ventilation; congenital anomaly; any maternal adverse event; vaginal discharge; vaginal pruritus; discontinuation of treatment because of adverse events; threatened preterm labor; and neurodevelopmental disability at 18-24 months of age. Neonatal morbidities were defined as in the original study.[131, 133, 134, 136 and 144]

Assessment of risk of bias

We assessed the risk of bias using the criteria recently outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[137] Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Review authors' judgments were categorized as “low”, “high”, or “unclear” risk of bias. The assessments considered the risk of *material* bias rather than *any* bias. “Material bias” is defined as a bias of sufficient magnitude to have a notable impact on the results or conclusions of the trial. [137] The risk of bias in each trial included was assessed individually by 2 reviewers (R.R. and A.C.-A.). In addition, methods of random sequence generation, allocation concealment, and blinding were confirmed with the authors of the trials. Any differences of opinion regarding assessment of risk of bias were resolved by discussion.

Statistical analysis

Statistical analyses were based on an intent-to-treat basis and included all randomized women and their fetuses/infants. For baseline data, maternal outcomes, and gestational age at birth-related outcomes, the unit of analysis was the pregnancy, whereas for neonatal outcomes, the unit of analysis was the neonate. To assess safety of vaginal progesterone, all patients exposed to progesterone were included. This included all studies and patients, even those in which the cervical length was not measured. IPD were combined in a 2-stage approach in which outcomes were analyzed in the original trial and then summary statistics were generated using standard summary data metaanalysis techniques to give an overall measure of effect (summary relative risk [RR] with 95% confidence interval [CI]).[145] Heterogeneity of the results among studies was tested with the quantity I^2, which describes the percentage of total variation across studies that can be attributed to heterogeneity rather than chance.[146] A value of 0% indicates no observed heterogeneity, whereas I^2 values of ≥50% indicate a substantial level of heterogeneity.[146] We planned to use a fixed effects

model if substantial statistical heterogeneity was not present. Random effects models were also used to test the robustness of results. The number needed to treat (NNT) for benefit or harm with the 95% CI was calculated for outcomes for which there was a statistically significant reduction or increase in risk difference based on control event rates in the trials.[147] Publication and related biases were assessed visually by examining the symmetry of funnel plots and statistically by using the Egger test.[148] A *P* value < .1 was considered to indicate significant asymmetry.

Access to data from individual patients also allowed the performance of subgroup analyses to examine whether the administration of vaginal progesterone was more effective in some subgroups than in others. Specifically, we assessed the effect of vaginal progesterone in singleton and twin gestations separately. Also, to explore treatment effects according to other patient characteristics, subgroup analyses were prespecified on the basis of sonographic cervical length (<10, 10-20, and 21-25 mm), obstetrical history (no previous spontaneous preterm birth and at least 1 previous spontaneous preterm birth <37 weeks), maternal age (<20, 20-34, and ≥35 years), race/ethnicity (Caucasian, Black, Asian, and other), and body mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2). To explore effects by trial characteristics, prespecified subgroup analyses were planned according to the daily dose of vaginal progesterone (90-100 vs 200 mg). Definitions and subgroup analyses were specified before any data were obtained or analyzed. Treatment effects in these subgroups were assessed by simple logistic regression models (which included a subgroup-allocated treatment interaction term), with adjustment for between-trial outcome differences. A test for interaction between treatment and subgroup is the standard method to examine whether treatment effects differ between subgroups.[149 and 150] This approach tests and estimates the difference between treatment effects across subgroups directly. It involves one statistical test regardless of the number of subgroups. An interaction *P* value > .05 was considered to indicate that the effect of treatment did not differ significantly between subgroups. Adjustment for predictive baseline characteristics, even when largely balanced, can lead to different estimates of treatment effects. [151] Therefore, multivariable logistic regression models were employed to estimate adjusted treatment effects. In the twin pregnancy subgroup, the lack of independence of twins may have influenced the outcome of the analysis. Thus, for adverse perinatal outcomes in twins, we used analytical methods assuming independence between neonates as well as methods recommended to take into account nonindependence of newborns from twin gestations. [137 and 152] We planned sensitivity analyses to test the robustness of the results by excluding trials with any risk of bias and including only studies for which the primary aim was to assess the effects of vaginal progesterone in women with a short cervix. Subgroup and sensitivity analyses were only performed for the primary outcome of preterm birth <33 weeks of gestation and for the secondary outcome of composite neonatal morbidity and mortality. Analyses were performed with the Review Manager (RevMan) version 5.1 (Nordic Cochrane Centre, Copenhagen, Denmark), and SAS version 9.2 (SAS Institute, Cary, NC) software.

Informed consent was provided by the patients upon enrollment in each of the original trials. In this study, the data were not used for any purposes other than those of the original trial, and no new data were collected. Therefore, informed consent specifically for this project was not considered necessary. No patient identifiers were provided by any

investigator. This study was exempted for review by the Human Investigations Committee of Wayne State University's Institutional Review Board, Detroit, MI.

Results

Study selection, details, and quality

The searches yielded 2611 citations, of which 10 were considered for potential inclusion (Figure 1). Five studies were excluded.[125, 153, 154, 155 and 156] Three of these studies evaluated vaginal progesterone in women at high risk for preterm birth (previous preterm birth,[125 and 154] uterine malformation,[125] cervical insufficiency,[125] and twins[155]) but none of them measured or collected data on cervical length. Two of these studies[125 and 154] reported that prophylactic administration of vaginal progesterone reduced the risk of preterm birth in

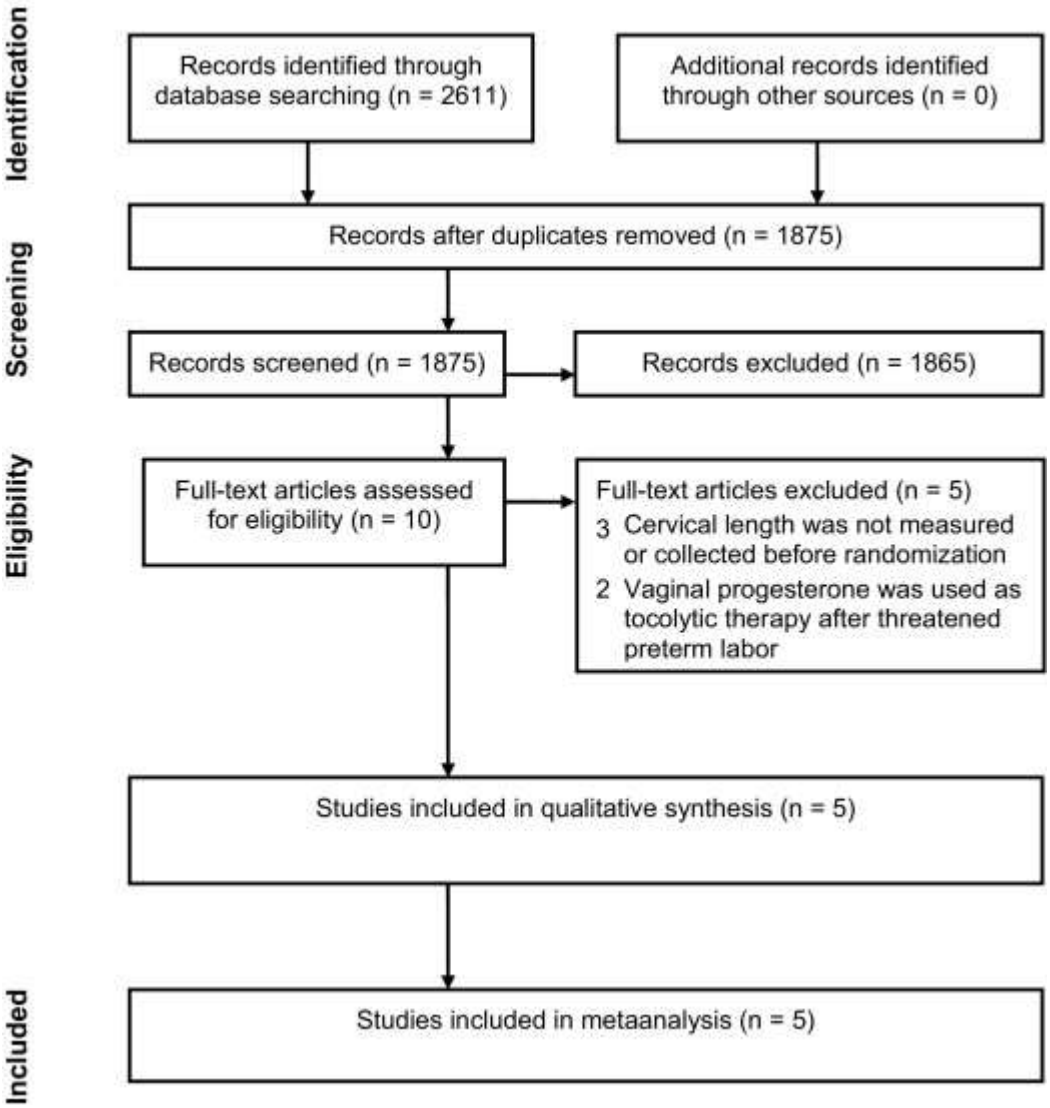

FIGURE 1. Flow of study identification

Romero. Vaginal progesterone to prevent preterm birth in women with a short cervix: an IPD metaanalysis. Am J Obstet Gynecol 2012.

women with a previous preterm birth, whereas the study by Norman et al[155] found that vaginal progesterone did not reduce the risk of the composite outcome delivery or fetal death <34 weeks of gestation in women with a twin gestation. The 2 remaining studies evaluated vaginal progesterone as an adjunct to tocolytic therapy after threatened preterm labor.[153 and 156] Five studies, which provided data for 775 women (723 [93.3%] with singleton pregnancies and 52 [6.7%] with twin pregnancies) and 827 fetuses/infants (723 [87.4%] from singleton pregnancies and 104 [12.6%] from twin pregnancies), met the inclusion criteria.[131, 133, 134, 136 and 144]

The main characteristics of studies included in this IPD metaanalysis are shown in Table 1. All studies were double-blind, placebo-controlled trials, of which 4 were multicenter, conducted in sites from both developed and developing countries. Two trials were specifically designed to evaluate the administration of vaginal progesterone in women with a sonographic short cervix,[131 and 133] one evaluated the use of vaginal progesterone in women with a history of spontaneous preterm birth,[144] another assessed vaginal progesterone in women with a twin gestation,[134] and the remaining trial examined the use of progesterone in women with a prior spontaneous preterm birth, uterine malformations, or twin gestations.[136] Two of these studies[134 and 144] reported data of planned secondary analyses for women with a short cervix in additional reports.[132 and 135] Data from the trials by O'Brien et al,[144] Cetingoz et al,[136] and Rode et al[134] relevant to women with a cervical length of ≤25 mm before randomization were provided by the authors for inclusion in this review. The 2 trials[131 and 133] specifically designed to evaluate the use of vaginal progesterone in women with a short cervix screened a total of 56,711 women, of which 1146 (2.0%) had a sonographic short cervix as defined by the authors for the purposes of each study. Of these women, 715 (62.4%) were randomized; 708 mothers with their 732 infants provided data for the metaanalysis (~90% of total sample size of the IPD metaanalysis). The other 3 studies provided data for 67 women and 95 infants.

Two studies used vaginal progesterone capsules or pessaries 200 mg/d,[131 and 134] 2 used vaginal progesterone gel 90 mg/d,[133 and 144] and the other used vaginal progesterone suppositories 100 mg/d.[136] The treatment was initiated at 24 weeks of gestation in 2 trials,[131 and 136] between 20-23 weeks of gestation in 2 trials,[133 and 134] and between 18-22 weeks of gestation in 1 trial.[144] Three studies[131, 134 and 136] reported that participating women received study medication from enrollment until 34 weeks of gestation, and 2 studies[133 and 144] from enrollment until 36 6/7 weeks of gestation. In 3 studies,[131, 133 and 134] cervical cerclage was allowed after randomization. In the study by Cetingoz et al,[136] cervical cerclage was not performed in any women. The primary outcome was preterm birth <33 weeks of gestation for 1 trial,[133] ≤32 weeks of gestation for 1 trial,[144] <34 weeks for 1 trial,[134] <37 weeks for 1 trial,[136] and spontaneous preterm birth <34 weeks for the remaining study.[131]

All of the 5 studies included in this IPD metaanalysis had high methodological quality and were considered to be at low risk of bias (Figure 2). One study did not report the method of random sequence generation in the article but reported, upon request, having used a table of random numbers.[131] All 5 studies had adequate allocation concealment and used identical placebo to blind patients and clinical staff to treatment allocation. There was blinding of outcome assessment and adequate handling of incomplete outcome data in all

TABLE 1. Characteristics of studies included

Study	Participating countries	Primary target population	Inclusion/exclusion criteria	No of women with CL ≤25 mm/fetuses or infants		Intervention	Cointerventions	Primary outcome
				Vaginal progesterone group	Placebo group			
Fonseca et al,[131] 2007	United Kingdom, Chile, Brazil, Greece	Women with a short cervix	Inclusion: women with a singleton or twin pregnancy and sonographic CL ≤15 mm Exclusion: major fetal abnormalities, painful regular uterine contractions, history of ruptured membranes, and cervical cerclage	125/136	125/138	Vaginal progesterone capsule (200 mg/d) or placebo from 24-33 6/7 wk of gestation	Cervical cerclage (1 [0.8%] in vaginal progesterone group and 0 [0.0%] in placebo group)	Spontaneous preterm birth <34 wk
O'Brien et al,[144] 2007	United States, South Africa, India, Czech Republic, Chile, El Salvador	Women with a history of spontaneous preterm birth	Inclusion: women with a singleton pregnancy, gestational age between 16 0/7-22 6/7 wk, and a history of spontaneous singleton preterm birth at 20-35 wk of gestation in the immediately preceding pregnancy Exclusion: planned cervical cerclage, history of adverse reaction to progesterone, treatment with progesterone within 4 wk before enrollment, treatment for seizure disorder, psychiatric illness or chronic hypertension at time of enrollment, history of acute or chronic congestive heart failure, renal failure, uncontrolled diabetes mellitus, active liver disorder, HIV infection with CD4 count of <350 cells/mm^3 and requiring multiple antiviral agents, placenta previa, history or suspicion of breast or genital tract malignancy, history or suspicion of thromboembolic disease, müllerian duct anomaly, major fetal anomaly or chromosomal disorder, or multifetal gestation	12/12	19/19	Vaginal progesterone gel (90 mg/d) or placebo from 18-22 to 37 0/7 wk of gestation, rupture of membranes or preterm delivery, whichever occurred first	None	Preterm birth ≤32 wk
Cetingoz et al,[136] 2011	Turkey	Women at high risk of preterm birth	Inclusion: women with at least 1 previous spontaneous preterm birth, uterine malformation, or twin pregnancy Exclusion: in-place or planned cervical cerclage, serious fetal anomalies	9/14	6/8	Vaginal progesterone suppository (100 mg/d) or placebo from 24-34 wk of gestation	None	Preterm birth <37 wk
Hassan et al,[133] 2011	United States, Republic of Belarus, Chile, Czech Republic, India, Israel, Italy, Russia, South Africa, Ukraine	Women with a short cervix	Inclusion: women with a singleton pregnancy, gestational age between 19 0/7-23 6/7 wk, transvaginal sonographic CL between 10-20 mm, and without signs or symptoms of preterm labor Exclusion: planned cerclage, acute cervical dilation, allergic reaction to progesterone, current or recent progestogen treatment within previous 4 wk, chronic medical conditions that would interfere with study participation or evaluation of treatment, major fetal	235/235	223/223	Vaginal progesterone gel (90 mg/d) or placebo from 20-23 6/7 to 36 6/7 wk of gestation, rupture of membranes or preterm delivery, whichever occurred first	Emergency cervical cerclage (10 [4.3%] in vaginal progesterone group and 6 [2.7%] in placebo group)	Preterm birth <33 wk

Study	Participating countries	Primary target population	Inclusion/exclusion criteria	No of women with CL ≤25 mm/fetuses or infants		Intervention	Cointerventions	Primary outcome
				Vaginal progesterone group	Placebo group			
			anomaly or known chromosomal abnormality, uterine anatomic malformation, vaginal bleeding, known or suspected clinical chorioamnionitis					
Rode et al,[134] 2011	Denmark, Austria	Women with a twin pregnancy	Inclusion: women with a diamniotic twin pregnancy and chorionicity assessed by ultrasound <16 wk of gestation Exclusion: higher order multiple pregnancies, known allergy to progesterone or peanuts as 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, known liver disease	7/14	14/28	Vaginal progesterone pessary (200 mg/d) or placebo from 20-23 6/7 to 33 6/7 wk of gestation	Cervical cerclage (2 [28.6%] in vaginal progesterone group and 2 [14.3%] in placebo group)	Preterm birth <34 wk

CL, cervical length; *HIV*, human immunodeficiency virus.Romero.

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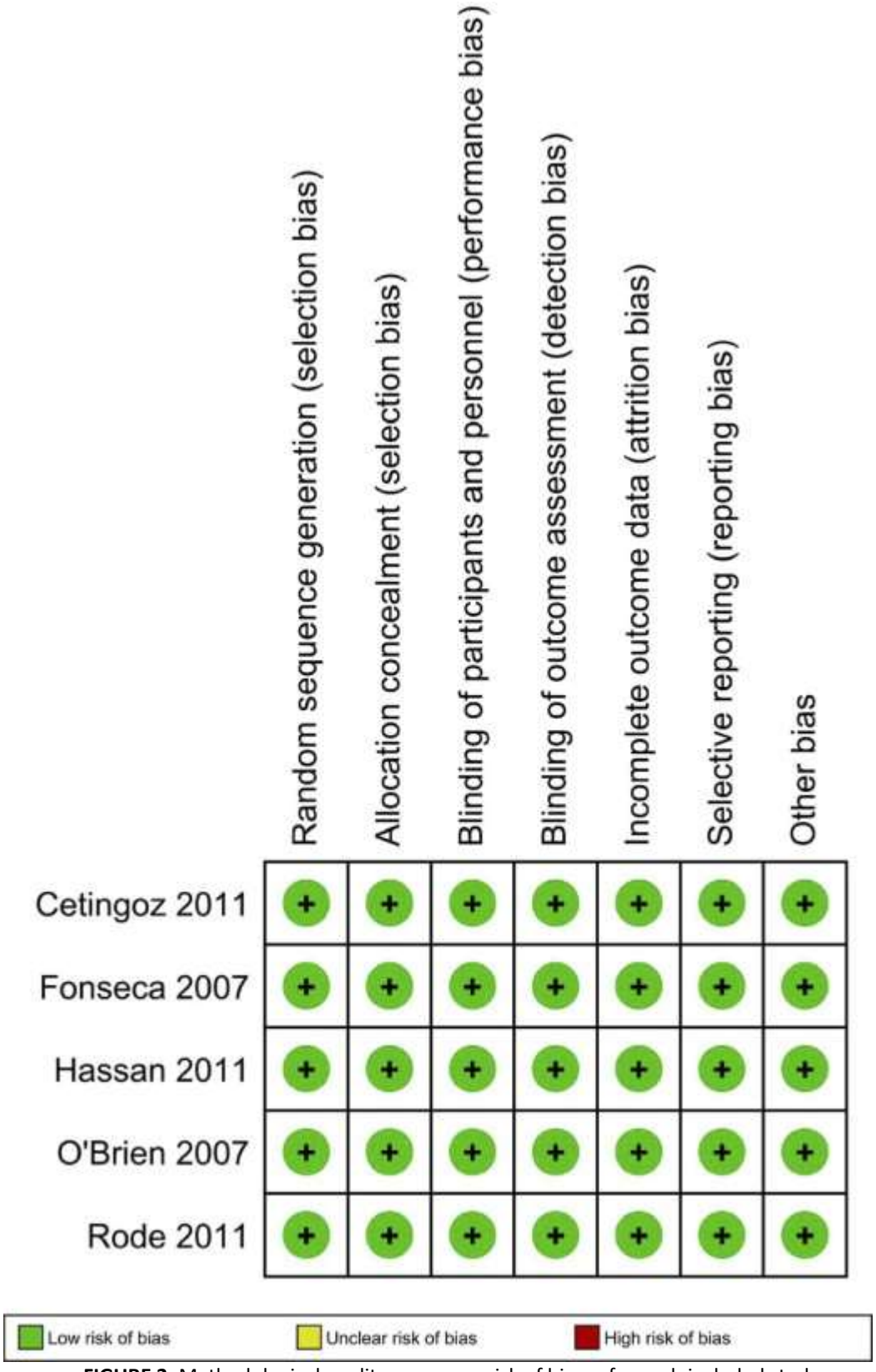

FIGURE 2. Methodological quality summary: risk of biases for each included study

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studies. One study[136] did not report several secondary neonatal outcomes of interest to the present study, but they were provided to the investigators (R.R. and A.C.-A.) with the database and included into the metaanalyses. Overall, there was no obvious risk of other biases for the 5 trials.

Primary outcome

Treatment with vaginal progesterone in patients with a sonographic short cervix was associated with a significant reduction in the risk of preterm birth <33 weeks of gestation (12.4% vs 22.0%; RR, 0.58; 95% CI, 0.42–0.80; I^2 = 0%; 775 women) (Figure 3). The number of patients with a short cervix who needed to be treated with vaginal progesterone rather than with placebo to prevent 1 case of preterm birth <33 weeks of gestation was 11 (95% CI, 8–23).

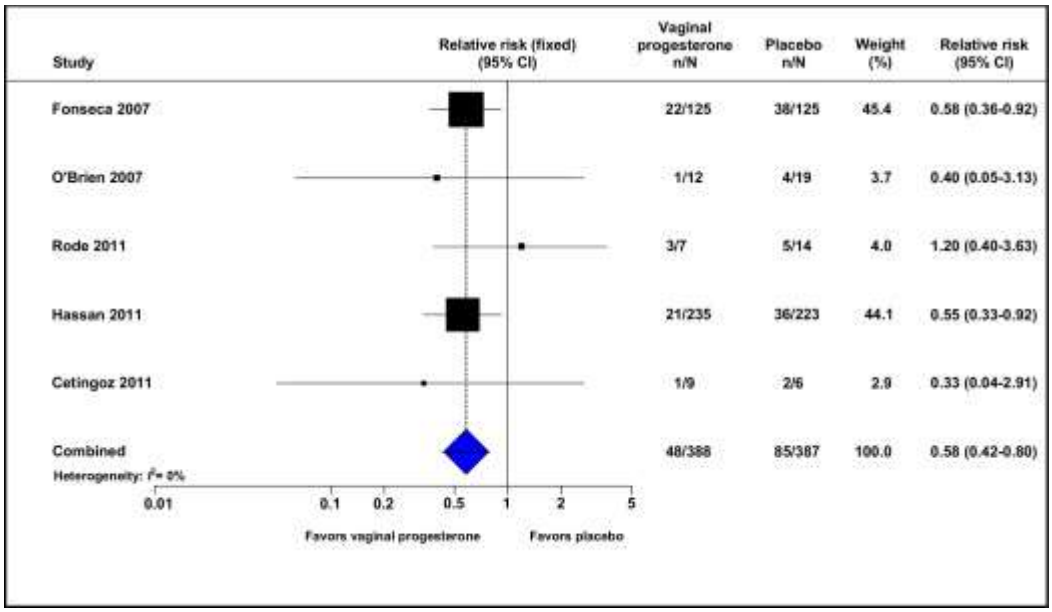

FIGURE 3. Effect of vaginal progesterone on preterm birth <33 weeks of gestation

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Secondary outcomes

Patients allocated to receive vaginal progesterone had a significantly lower risk of preterm birth <35 weeks of gestation (20.4% vs 30.5%; RR, 0.69; 95% CI, 0.55–0.88; I^2 = 0%; NNT for benefit 11; 95% CI, 7–27), <34 weeks (16.0% vs 27.1%; RR, 0.61; 95% CI, 0.47–0.81; I^2 = 0%; NNT for benefit 9; 95% CI, 7–19), <30 weeks (7.5% vs 13.2%; RR, 0.58; 95% CI, 0.38–0.89; I^2 = 0%; NNT for benefit 18; 95% CI, 12–69), and <28 weeks (5.4% vs 11.1%; RR, 0.50; 95% CI, 0.30–0.81; I^2 = 0%; NNT for benefit 18; 95% CI, 13–47) compared to those allocated to placebo (Table 2). Moreover, vaginal progesterone administration was associated with a significantly reduced risk of spontaneous preterm birth <33 and <34 weeks of gestation. The reduction in the risk of preterm birth <36 weeks of gestation was marginally significant (RR, 0.82; 95% CI, 0.67–1.00). Treatment with vaginal progesterone was associated with an overall nonsignificant reduction in the risk of perinatal mortality (3.4% vs 5.3%; RR, 0.63;

TABLE 2. Effect of vaginal progesterone on secondary outcome measures[a]

Outcome	No. of trials	No. of events/total no.		Pooled RR (95% CI)	I^2 (%)	NNT (95% CI)
		Vaginal progesterone	Placebo			
Preterm birth <37 wk	5	144/388	165/387	0.89 (0.75–1.06)	0	–
Preterm birth <36 wk	5	108/388	136/387	0.82 (0.67–1.00)	0	–
Preterm birth <35 wk	5	79/388	118/387	0.69 (0.55–0.88)	0	11 (7–27)
Preterm birth <34 wk	5	62/388	105/387	0.61 (0.47–0.81)	0	9 (7–19)
Preterm birth <30 wk	5	29/388	51/387	0.58 (0.38–0.89)	0	18 (12–69)
Preterm birth <28 wk	5	21/388	43/387	0.50 (0.30–0.81)	0	18 (13–47)
Spontaneous preterm birth <33 wk	5	39/388	71/387	0.57 (0.40–0.81)	0	13 (9–29)
Spontaneous preterm birth <34 wk	5	51/388	87/387	0.62 (0.46–0.84)	0	12 (8–28)
Respiratory distress syndrome	5	25/411	52/416	0.48 (0.30–0.76)	0	15 (11–33)
Necrotizing enterocolitis	5	5/411	6/416	0.88 (0.30–2.64)	0	–
Intraventricular hemorrhage	5	6/411	9/416	0.74 (0.27–2.05)	0	–
Proven neonatal sepsis	5	12/411	20/416	0.64 (0.32–1.29)	13	–
Retinopathy of prematurity	5	6/411	3/416	1.56 (0.46–5.28)	0	–
Bronchopulmonary dysplasia	2	4/249	5/231	0.76 (0.21–2.79)	NA	–
Periventricular leukomalacia	2	0/249	0/231	Not estimable	NA	–
Fetal death	5	6/411	7/416	0.82 (0.28–2.42)	0	–
Neonatal death	5	8/411	15/416	0.55 (0.26–1.19)	43	–
Perinatal death	5	14/411	22/416	0.63 (0.34–1.18)	41	–
Composite neonatal morbidity/mortality[a]	5	40/411	72/416	0.57 (0.40–0.81)	0	13 (10–30)
Apgar score <7 at 5 min	5	15/408	27/412	0.57 (0.32–1.02)	16	–
Birthweight <1500 g	5	36/410	68/413	0.55 (0.38–0.80)	6	13 (10–30)

Outcome	No. of trials	No. of events/total no.		Pooled RR (95% CI)	I^2 (%)	NNT (95% CI)
		Vaginal progesterone	Placebo			
Birthweight <2500 g	5	140/410	162/413	0.91 (0.76–1.08)	0	–
Admission to NICU	5	85/411	121/416	0.75 (0.59–0.94)	0	14 (8–57)
Mechanical ventilation	5	35/411	51/416	0.66 (0.44–0.98)	0	24 (15–408)
Congenital anomaly	7	30/1967	34/1954	0.89 (0.55–1.44)	0	–
Any maternal adverse event	3	86/624	80/595	1.04 (0.79–1.38)	0	–
Vaginal discharge	4	244/1065	248/1057	1.00 (0.87–1.15)	33	–
Vaginal pruritus	4	54/1065	50/1057	1.08 (0.74–1.57)	0	–
Discontinuation of treatment because of adverse events	5	28/1083	28/1061	1.01 (0.61–1.69)	0	–
Threatened preterm labor	5	115/384	139/383	0.83 (0.68–1.02)	16	–
Low ASQ developmental and socioemotional score at 18 mo of age[b]	1	19/503	18/488	1.02 (0.54–1.93)	NA	–

ASQ, Ages and Stages Questionnaire; *CI,* confidence interval; *NA,* not applicable; *NICU,* neonatal intensive care unit; *NNT,* number needed to treat; *RR,* relative risk.

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[a]Occurrence of any of the following events: respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis, or neonatal death;
[b] ASQ score <115 points.

95% CI, 0.34–1.18; I^2 = 41%). This reduction appeared to be attributable to a reduction in neonatal death (1.9% vs 3.6%; RR, 0.55; 95% CI, 0.26–1.19; I^2 = 43%) rather than fetal death (1.5% vs 1.7%; RR, 0.82; 95% CI, 0.28–2.42; I^2 = 0%).

Infants whose mothers received vaginal progesterone also had a significantly lower risk of RDS (6.1% vs 12.5%; RR, 0.48; 95% CI, 0.30–0.76; I^2 = 0%; NNT for benefit 15; 95% CI, 11–33), composite neonatal morbidity and mortality (9.7% vs 17.3%; RR, 0.57; 95% CI, 0.40–0.81; I^2 = 0%; NNT for benefit 13; 95% CI, 10–30), birthweight <1500 g (8.8% vs 16.5%; RR, 0.55; 95% CI, 0.38–0.80; I^2 = 6%; NNT for benefit 13; 95% CI, 10–30), admission to NICU (20.7% vs 29.1%; RR, 0.75; 95% CI, 0.59–0.94; I^2 = 0%; NNT for benefit 14; 95% CI, 8–57), and mechanical ventilation (8.5% vs 12.3%; RR, 0.66; 95% CI, 0.44–0.98; I^2 = 0%; NNT for benefit 24; 95% CI, 15–408) than infants whose mothers had received placebo.

There was no evidence of an effect of vaginal progesterone on necrotizing enterocolitis, intraventricular hemorrhage, proven neonatal sepsis, retinopathy of prematurity, bronchopulmonary dysplasia, periventricular leukomalacia, Apgar score <7 at 5 minutes, birthweight <2500 g, or threatened preterm labor.

In addition, the rates of maternal adverse effects, discontinuation of treatment because of adverse effects, and congenital anomalies did not differ significantly between the vaginal progesterone and placebo groups. One study[134] reported that the mean Ages and Stages Questionnaire scores (a tool that measures neurodevelopmental disability) at 18 months of age were 193 ± 42.6 for infants in the progesterone group and 194 ± 40.6 for infants in the placebo group (P = .89).

Effect of vaginal progesterone in singleton and twin gestations

Table 3 shows the effect of vaginal progesterone on the risk of preterm birth and perinatal outcomes in singleton and twin gestations separately. According to the interaction P values (all > .10), there was no evidence that women with singleton pregnancies benefit more or less from the use of vaginal progesterone than women with twin pregnancies.

Among singleton gestations, the administration of vaginal progesterone was associated with a statistically significant reduction in the risk of preterm birth <33, <35, and <28 weeks of gestation; RDS; composite neonatal morbidity and mortality; Apgar score <7 at 5 minutes; birthweight <1500 g; and admission to the NICU.

Among twin gestations, the administration of progesterone did not significantly reduce the risk of preterm birth <33 weeks of gestation (RR, 0.70; 95% CI, 0.34–1.44). However, it significantly decreased the risk of composite neonatal morbidity and mortality (RR, 0.52; 95% CI, 0.29–0.93). There were no significant differences in other outcome measures among the vaginal progesterone and placebo groups. The effects of vaginal progesterone on adverse perinatal outcome in twins were tested with 2 methods: one that assumed independence of the twins, and another that did not make such assumption. The results of both analyses were similar, with a slightly wider CI when the method which assumed nonindependence was employed (Table 4). The beneficial effects on composite neonatal

TABLE 3. Effect of vaginal progesterone on preterm birth and perinatal outcomes in singleton and twin gestations

Outcome	Singleton pregnancy				Twin pregnancy				
		No. of events/total No.				No. of events/total No.			
	No. of trials	Vaginal progesterone	Placebo	Pooled RR (95% CI)	No. of trials	Vaginal progesterone	Placebo	Pooled RR (95% CI)	Interaction *P* value
Primary outcome									
Preterm birth <33 wk	4	41/365	72/358	0.56 (0.40–0.80)	3	7/23	13/29	0.70 (0.34–1.44)	.55
Secondary outcomes									
Preterm birth <37 wk	4	127/365	141/358	0.91 (0.75–1.10)	3	17/23	24/29	0.91 (0.68–1.23)	.88
Preterm birth <35 wk	4	67/365	100/358	0.67 (0.51–0.87)	3	12/23	18/29	0.91 (0.57–1.46)	.24
Preterm birth <28 wk	4	20/365	39/358	0.51 (0.31–0.85)	3	1/23	4/29	0.44 (0.11–1.85)	.83
Respiratory distress syndrome	4	17/365	37/358	0.47 (0.27–0.81)	3	8/46	15/58	0.48 (0.21–1.09)	.68
Necrotizing enterocolitis	4	5/365	6/358	0.88 (0.29–2.62)	3	0/46	0/58	Not estimable	NA
Intraventricular hemorrhage	4	5/365	7/358	0.68 (0.22–2.13)	3	1/46	2/58	1.00 (0.10–10.11)	.74
Proven neonatal sepsis	4	11/365	14/358	0.80 (0.37–1.74)	3	1/46	6/58	0.33 (0.06–1.67)	.30
Retinopathy of prematurity	4	5/365	3/358	1.51 (0.40–5.69)	3	1/46	0/58	1.42 (0.05–42.22)	.91
Fetal death	4	6/365	7/358	0.82 (0.28–2.40)	3	0/46	0/58	Not estimable	NA
Neonatal death	4	6/365	11/358	0.53 (0.20–1.39)	3	2/46	4/58	0.68 (0.23–2.02)	.69
Perinatal death	4	12/365	18/358	0.64 (0.31–	3	2/46	4/58	0.68 (0.23–	.90

Outcome	Singleton pregnancy				Twin pregnancy				
	No. of trials	No. of events/total No.		Pooled RR (95% CI)	No. of trials	No. of events/total No.		Pooled RR (95% CI)	Interaction *P* value
		Vaginal progesterone	Placebo			Vaginal progesterone	Placebo		
				1.31)				2.02)	
Composite neonatal morbidity/mortality[a]	4	29/365	49/358	0.59 (0.38–0.91)	3	11/46	23/58	0.52(0.29–0.93)	.69
Apgar score <7 at 5 min	4	11/362	23/354	0.48 (0.24–0.95)	3	4/46	4/58	1.03 (0.38–2.81)	.20
Birthweight <1500 g	4	28/364	53/355	0.52 (0.34–0.81)	3	8/46	15/58	0.69 (0.34–1.39)	.47
Birthweight <2500 g	4	102/364	117/355	0.86 (0.69–1.07)	3	38/46	45/58	1.11 (0.92–1.35)	.11
Admission to NICU	4	59/365	87/358	0.67 (0.50–0.91)	3	26/46	34/58	0.98 (0.70–1.35)	.12
Mechanical ventilation	4	28/365	43/358	0.65 (0.41–1.01)	3	7/46	8/58	0.68 (0.30–1.56)	.88

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

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[a] Occurrence of any of the following events: respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis, or neonatal death.

morbidity and mortality in twins remained statistically significant (RR, 0.56; 95% CI, 0.30–0.97).

TABLE 4. Effect of vaginal progesterone on adverse perinatal outcomes in twins according to analytical method used

Outcome	Pooled RR (95% CI)	
	Assuming independence of newborns	Adjustment for the lack of independence of newborns
Respiratory distress syndrome	0.48 (0.21–1.09)	0.58 (0.25–1.39)
Necrotizing enterocolitis	Not estimable	Not estimable
Intraventricular hemorrhage	1.00 (0.10–10.11)	1.00 (0.05–18.19)
Proven neonatal sepsis	0.33 (0.06–1.67)	0.44 (0.04–4.67)
Retinopathy of prematurity	1.42 (0.05–42.22)	1.36 (0.03–58.74)
Fetal death	Not estimable	Not estimable
Neonatal death	0.68 (0.23–2.02)	0.48 (0.06–3.74)
Perinatal death	0.68 (0.23–2.02)	0.48 (0.06–3.74)
Composite neonatal morbidity/mortality[a]	0.52 (0.29–0.93)	0.56 (0.30–0.97)
Apgar score <7 at 5 min	1.03 (0.38–2.81)	0.88 (0.16–4.75)
Birthweight <1500 g	0.69 (0.34–1.39)	0.73 (0.29–1.83)
Birthweight <2500 g	1.11 (0.92–1.35)	1.13 (0.91–1.40)
Admission to NICU	0.98 (0.70–1.35)	0.89 (0.60–1.31)
Mechanical ventilation	0.68 (0.30–1.56)	0.60 (0.22–1.65)

CI, confidence interval; *NICU*, neonatal intensive care unit; *RR*, relative risk.

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a Occurrence of any of the following events: respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis, or neonatal death.

Importantly, vaginal progesterone was associated with a significant reduction in the risk of preterm birth <33 weeks of gestation in both women with a singleton gestation with no previous preterm birth (RR, 0.60; 95% CI, 0.39–0.92) as well as in women with a singleton gestation and at least 1 previous spontaneous preterm birth <37 weeks of gestation (RR, 0.54; 95% CI, 0.30–0.98). Moreover, vaginal progesterone significantly decreased the risk of composite neonatal morbidity and mortality in women with a singleton gestation and at least 1 previous spontaneous preterm birth <37 weeks of gestation (RR, 0.41; 95% CI, 0.17–0.98), and in women with a twin gestation and no previous preterm birth (RR, 0.52; 95% CI, 0.29–0.93).

Subgroup and sensitivity analyses

Subgroup analyses of the effect of vaginal progesterone on primary outcomes are presented in Table 5. There was no evidence that women in any one of the prespecified subgroups

TABLE 5. Subgroup analyses of effect of vaginal progesterone on preterm birth <33 weeks of gestation and composite neonatal morbidity/mortality[a]

	Preterm birth <33 wk of gestation			Composite neonatal morbidity/mortality[a]		
Subgroup	**n**	**RR (95% CI)**	**Interaction *P* value**	**n**	**RR (95% CI)**	**Interaction *P* value**
Patient characteristics						
Cervical length, mm			.32			.93
<10	79	0.83 (0.49–1.41)		90	0.62 (0.28–1.38)	
10-20	653	0.52 (0.35–0.76)		680	0.54 (0.35–0.84)	
21-25	43	0.50 (0.10–2.41)	.68	57	0.55 (0.26–1.19)	.40
Obstetric history						
With no previous preterm birth	606	0.61 (0.42–0.89)		658	0.62 (0.43–0.91)	
With ≥1 previous preterm birth	169	0.54 (0.30–0.98)		169	0.41 (0.17–0.96)	
Maternal age, y			.85			.31
<20	63	0.66 (0.21–2.14)		66	1.05 (0.25–4.37)	
20-34	620	0.58 (0.41–0.84)		659	0.48 (0.31–0.73)	
≥35	92	0.49 (0.20–1.15)		102	0.89 (0.33–2.36)	
Race/ethnicity			.44			.68
Caucasian	269	0.39 (0.22–0.69)		291	0.57 (0.35–0.93)	
Black	287	0.74 (0.46–1.19)		293	0.60 (0.32–1.12)	
Asian	157	0.53 (0.21–1.34)		159	0.87 (0.20–3.78)	
Other	41	0.60 (0.19–1.92)		42	0.20 (0.03–1.57)	
Body mass index, kg/m^2			.70			.58
<18.5	58	0.35 (0.10–1.20)		62	0.26 (0.05–1.34)	
18.5-24.9	359	0.63 (0.36–1.10)		390	0.62 (0.37–1.03)	
25.0-29.9	187	0.68 (0.39–1.19)		200	0.76 (0.39–1.47)	
≥30	159	0.49 (0.26–0.92)		163	0.46 (0.21–1.03)	
Trial characteristics						
Daily dose of vaginal progesterone, mg			.57			.92
90-100	504	0.53 (0.33–0.85)		511	0.58 (0.35–0.95)	

	Preterm birth <33 wk of gestation			Composite neonatal morbidity/mortality[a]		
Subgroup	**n**	**RR (95% CI)**	**Interaction *P* value**	**n**	**RR (95% CI)**	**Interaction *P* value**
200	271	0.63 (0.41–0.96)		316	0.56 (0.34–0.94)	

CI, confidence interval; *RR*, relative risk.

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a Occurrence of any of the following events: respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis, or neonatal death.

benefit more or less from the use of vaginal progesterone than those in any other subgroup (all *P* for interaction > .30). However, the use of vaginal progesterone was associated with a statistically significant reduction in the risk of preterm birth <33 weeks and composite neonatal morbidity and mortality in both women with no previous spontaneous preterm birth and women with at least 1 previous spontaneous preterm birth <37 weeks of gestation, women with a sonographic cervical length between 10-20 mm, women aged 20-34 years, and Caucasian women.

No significant differences were noted for preterm birth <33 weeks of gestation and composite neonatal morbidity and mortality between subgroups based on the daily dose of progesterone. A significant decrease in the risk of preterm birth <33 weeks of gestation and composite neonatal morbidity and mortality was found in women who received either 90-100 or 200 mg/d of vaginal progesterone.

The effect of vaginal progesterone on the risk of preterm birth <33 weeks of gestation and composite neonatal morbidity/mortality did not change when sensitivity analysis was limited to the 2 trials[131] and [133] in which the primary aim was to evaluate the effect of vaginal progesterone in women with a short cervix (pooled RR, 0.57; 95% CI, 0.40–0.80 for preterm birth <33 weeks and pooled RR, 0.54; 95% CI, 0.35–0.82 for composite neonatal morbidity/mortality). In addition, the results of the metaanalyses did not change significantly when random effects models were used for preterm birth <33 weeks (RR, 0.59; 95% CI, 0.43–0.81) or for composite neonatal morbidity/mortality (RR, 0.59; 95% CI, 0.41–0.83). Sensitivity analyses based on trial quality were not performed because all trials were considered at low risk for biases. No funnel plots showed asymmetry, either visually or in terms of statistical significance (*P* > .10 for all, by Egger test).

Comment

Principal findings of this study

Vaginal progesterone administration to asymptomatic women with a sonographic short cervix in the midtrimester was associated with: (1) a significant 42% reduction in the rate of preterm birth <33 weeks (primary outcome); (2) a significant reduction in the risk of preterm birth <35, <34, <30, and <28 weeks and a trend for a reduction in the rate of preterm birth <36 weeks; (3) a significant reduction in the risk of spontaneous preterm birth <33 and <34 weeks; (4) a significantly lower rate of RDS (6.1% vs 12.5% in the placebo group); (5) a significant 43% decrease in composite neonatal morbidity and mortality; (6) a significantly lower rate of admission to NICU (20.7% vs 29.1%) and use of mechanical ventilation (8.5% vs 12.3%); (7) a significantly lower rate of neonates with a birthweight <1500 g (8.8% vs 16.5%); and (8) a nonsignificant difference in the rate of maternal adverse events (13.8% vs 13.4%), discontinuation of therapy because of adverse events (2.6% vs 2.6%), congenital anomalies (1.5% vs 1.7%), and neurodevelopmental disability at 18 months of age (3.8% vs 3.7%). Furthermore, most results remained significant when the analyses were restricted to patients with a singleton gestation. In patients with a twin gestation, there was a nonsignificant trend toward reduction of the rate of preterm birth <33 weeks of gestation. However, there was a significant reduction in the risk of composite neonatal morbidity/mortality (pooled RR, 0.52; 95% CI, 0.29–0.93). Importantly, the

reduction in the rates of preterm birth <33 weeks of gestation and composite neonatal morbidity and mortality was observed in both women with no previous spontaneous preterm birth and women with a history of spontaneous preterm birth. Finally, there was no difference in efficacy when a dose of either 90-100 or 200 mg/d of vaginal progesterone was used.

The major effect of vaginal progesterone was to reduce the rate of early preterm birth; however, our results indicate that a fraction of late preterm births (34-36 6/7 weeks) can also be prevented with the administration of vaginal progesterone. Further studies are required to explore the reasons for the differential effect in early vs late preterm births. One possibility is that vaginal progesterone was stopped at 36 6/7 weeks of gestation in the largest trial, but at 34 weeks of gestation in the trial of Fonseca et al.[131] Nonetheless, the importance of preventing early preterm birth stems from their disproportionate contribution to serious perinatal morbidity and long-term neurodevelopmental disability.

A decrease in the rate of preterm birth has been considered a surrogate endpoint for neonatal morbidity and mortality, and indeed, in some trials, a reduction in the rate of preterm birth has not been accompanied by a demonstrable reduction in the frequency of neonatal morbid events. It has been argued that a preventive strategy for preterm birth should accomplish both a reduction in preterm birth and neonatal morbidity. Hassan et al[133] demonstrated that the significant reduction in the rate of preterm birth at <33 weeks was associated with a significant reduction in the rate of RDS by 61%, whereas Fonseca et al[131] reported a nonsignificant reduction in the risk of RDS by 41%. However, in this IPD metaanalysis, we found that vaginal progesterone significantly decreased the risk of RDS by 52%.

There was no significant difference in the risk of adverse maternal events, discontinuation of treatment because of adverse events, and congenital anomalies between vaginal progesterone and placebo groups. Only 1 study of twin gestations[134] examined developmental and socioemotional scores at 18 months of age, and found that there was no difference between infants exposed to vaginal progesterone and those exposed to placebo. These results are consistent with those of an unpublished observation in a trial of singleton gestations exposed to vaginal progesterone.[157]

Subgroup analyses

Subgroup analyses did not indicate that vaginal progesterone has differential efficacy in the main clinical subgroups of interest. For example, patients with a sonographic short cervix with or without a history of preterm birth seem to benefit from vaginal progesterone for the reduction of preterm birth. On the other hand, there was some suggestion that patients with a singleton gestation, sonographic cervical length between 10-20 mm, history of preterm birth, age 20-34 years, Caucasian, and body mass index ≥30 kg/m^2 might derive a larger benefit from the use of vaginal progesterone than those with other characteristics. Although such analysis was prespecified, subgroup analyses should, of course, be interpreted cautiously because of the risk for false-positive and false-negative results.[149 and 150]

An important question is the range of cervical length in which vaginal progesterone is effective. Fonseca et al[131] noted that vaginal progesterone reduced the rate of spontaneous preterm delivery at <34 weeks of gestation by only 15% in women with a cervical length of 1-5 mm and 25% in patients with a cervical length of 6-10 mm, but the effect size was 75% in patients with a cervical length between 11-15 mm. One possible explanation for this observation is that women with a very short cervix are more likely to have intraamniotic inflammation and may be less responsive to progesterone.[158] and [159] These observations are in keeping with the rationale for excluding patients with a cervical length of <10 mm in the study reported by Hassan et al.[133] A subgroup analysis of this IPD metaanalysis suggests that progesterone might be less effective in patients with a cervical length of <10 mm. However, there was no statistically significant differential effect according to cervical length (interaction *P* value of .32 for preterm birth <33 weeks of gestation and .93 for composite neonatal morbidity/mortality). Therefore, this result is subject to all limitations of analysis of subgroups. [149] and [150]

Fonseca et al[131] and Hassan et al[133] reported that vaginal progesterone was associated with a nonstatistically significant reduction in the rate of preterm birth <34 weeks and preterm birth <33 weeks, respectively, in patients with a short cervix and history of spontaneous preterm birth. Some have interpreted such findings as suggesting that vaginal progesterone does not reduce the rate of preterm birth in these women. This is not a correct interpretation of the results of the trials, because the number of patients with a prior preterm birth in each individual trial was small. Indeed, patients with a history of preterm birth <37 weeks of gestation represented only 15% and 21% of those enrolled in the trials of Fonseca et al[131] and Hassan et al,[133] respectively. Moreover, the primary objective of both trials was to test whether vaginal progesterone would reduce the rate of preterm birth in women with a sonographic short cervix, and not in a particular subgroup. Although the inclusion of patients with a history of spontaneous preterm birth was not a central focus in the design of these trials, this IPD metaanalysis sheds light on this question, because with the increased statistical power afforded by the larger sample size, we were able to show that patients with a short cervix and a history of preterm birth benefitted to the same extent as patients with a short cervix without a history of preterm birth. There is no biological explanation as to why patients with a history of spontaneous preterm birth would not benefit from progesterone administration if they have a short cervix.

The results reported herein have clinical implications because they extend the indication of vaginal progesterone to women with a history of spontaneous preterm birth with a short cervix. Some have claimed that 17α-hydroxyprogesterone caproate is the only therapeutic intervention effective in reducing the rate of preterm birth in women with a history of preterm birth[160]–such conclusion is contradicted by the results of this IPD metaanalysis. In addition, a recent metaanalysis reported that cervical cerclage (compared with no cervical cerclage) significantly reduces the risk of preterm birth <35 weeks of gestation by 30% (RR, 0.70; 95% CI, 0.55–0.89) and composite perinatal morbidity and mortality by 36% (RR, 0.64; 95% CI, 0.45–0.91) in women with a singleton gestation, previous spontaneous preterm birth, and cervical length <25 mm.[161] In the present IPD metaanalysis, vaginal progesterone significantly decreased the risk of preterm birth <33 weeks of gestation by 46% (RR, 0.54; 95% CI, 0.30–0.98) in patients with a singleton gestation, prior preterm birth, and sonographic short cervix. Therefore, it appears that administration of vaginal progesterone

could be an alternative treatment to cervical cerclage in patients with a singleton pregnancy, short cervix, and history of spontaneous preterm birth for preventing preterm birth and neonatal morbidity and mortality. Vaginal progesterone administration does not carry the risks of anesthesia, the surgical procedure per se, or some of the complications attributed to cerclage (ie, rupture of membranes).[162, 163, 164, 165, 166, 167, 168, 169, 170 and 171]

The role of progestins in women with a twin gestation has been of interest to several investigators. Several randomized clinical trials have evaluated the effects of 17α-hydroxyprogesterone caproate or vaginal progesterone for the prevention of preterm birth in twin gestations, and the results have been uniformly negative.[126, 172, 173 and 174] However, the excess rate of preterm birth of twin gestations is due to multiple causes. In both singleton and multiple gestations, preterm labor is syndromic; therefore, it is unrealistic to expect that one treatment will reduce the rate of preterm birth in all cases.[175] Thus, we explored the hypothesis that vaginal progesterone may benefit women with twin gestations and a short cervix. This IPD metaanalysis revealed a 30% nonsignificant reduction in the rate of preterm birth <33 weeks of gestation (30.4% vs 44.8%; RR, 0.70; 95% CI, 0.34–1.44). Importantly, vaginal progesterone was associated with a significant reduction in composite neonatal morbidity and mortality (23.9% vs 39.7%; RR, 0.52; 95% CI, 0.29–0.93). We believe that a randomized controlled trial is urgently needed to explore whether women with dichorionic twin gestations and a short cervix may benefit from vaginal progesterone.

Randomized controlled trials included in this IPD metaanalysis have used 3 different doses and formulations of vaginal progesterone: progesterone gel with 90 mg, progesterone suppositories with 100 mg, and progesterone suppositories with 200 mg. To explore whether the dose altered the effectiveness of treatment, we conducted a subgroup analysis comparing patients allocated to receive 90-100 mg/d vs those who received 200 mg/d. Both doses were associated with a statistically significant reduction in the rate of preterm birth <33 weeks and composite neonatal morbidity and mortality. Yet, the only primary trial that showed a reduction in preterm birth, RDS, and composite morbidity was that of Hassan et al,[133] which used 90 mg daily. This represents level-1 evidence of efficacy. The findings of this IPD metaanalysis favor the use of a daily vaginal administration of 90 mg of progesterone because it is the lowest dose that reduced the risk of preterm birth <33 weeks and neonatal morbidity and mortality. Patients who used 90 mg/d of vaginal progesterone received it in a gel, whereas patients who used either 100 or 200 mg/d of vaginal progesterone received it in a suppository. It is known that these suppositories melt in the vagina and there is often loss of the product over the course of a day. The gel is administered as a bioadhesive preparation applied against the vaginal wall; therefore, it is less likely to lead to loss of the active compound.

Strengths and limitations

The reliability and robustness of the results reported herein are supported by several considerations. First, the access to data from individual patients enabled a more rigorous analysis than what is possible from published data. The collection of data from individual patients allowed the use of previously unreported data, improved assessment of the study quality, standardization of outcome measures, undertaking an intent-to-treat analysis, and use of optimal analytical methods. Subgroup and multivariable analyses would not have

been possible without the availability of individual patient data. Second, a rigorous methodology for performing a systematic review and IPD metaanalysis of randomized controlled trials was employed. Third, we retrieved data for most patients with a sonographic short cervix included in randomized controlled trials of vaginal progesterone. We obtained data for 775 patients with a sonographic cervical length ≤25 mm from 5 studies. Data for approximately 30 women with a cervical length ≤25 mm from 3 studies that did not measure or collect data on cervical length were not available for our metaanalysis. Thus, we were able to retrieve individual data from at least 96% of patients with a sonographic short cervix who were randomized to receive vaginal progesterone or placebo. Since a large proportion of data were obtained, the results are likely to be representative. Fourth, the methodological quality of all trials included in the review was high. Fifth, there was evidence of clinical and statistical homogeneity for the primary outcome and for most of the secondary outcomes evaluated. Sixth, subgroup analyses were performed according to patient characteristics at trial entry and trial characteristics. Finally, the sensitivity analyses were consistent with the primary results.

The study has limitations. First, some subgroup analyses were based on a small number of patients. As a result, the analyses were limited in their power to detect differences, if any existed. Second, 3 trials evaluated the effect of vaginal progesterone in women at high risk for preterm delivery, but the investigators did not measure the cervix or the data were not collected. However, it is unlikely that the overall estimate of effect size in our study would change with the inclusion of approximately 30 patients with a short cervix from such studies. Third, to date, only 1 study[134] has reported on the neurodevelopmental outcomes of children at 18 months of age. Another report in abstract form suggests that there is no evidence of adverse outcome at 24 months of age.[157] Collectively, these observations would be consistent with the long-standing view that the administration of progesterone during pregnancy is safe. Such a view is derived from studies in which vaginal progesterone is used in the first trimester of pregnancy of patients undergoing assisted reproductive technologies.

Another limitation is that neonatal morbidity was not collected consistently across the studies. For example, the study of Hassan et al[133] collected information about bronchopulmonary dysplasia, but the study of Fonseca et al[131] did not. Similarly, some studies did not collect information about the intraventricular hemorrhage grade.[134] and [136]

Cost-effectiveness of the intervention

Thus far, 2 studies have evaluated the cost-effectiveness of routine transvaginal cervical length measurement and treatment with vaginal progesterone to prevent preterm birth and resultant neonatal morbidity and mortality. In 2010, Cahill et al[176] reported that a strategy of universal cervical length screening at the time of the routine fetal anatomy sonogram to identify women with a cervical length of ≤15 mm and subsequent treatment with vaginal progesterone was the most cost-effective strategy and the dominant choice over the following 3 alternatives: cervical length screening for women at increased risk for preterm birth and treatment with vaginal progesterone, risk-based treatment with 17α-hydroxyprogesterone caproate without screening, and no screening or treatment. These investigators concluded that universal screening of cervical length and treatment with

vaginal progesterone would be the most effective of the different approaches considered. Recently, Werner et al[177] compared the cost-effectiveness of 2 strategies, no routine cervical length screening and single routine transvaginal cervical length measurement at 18-24 weeks of gestation followed by treatment with vaginal progesterone if cervical length <15 mm. This study showed that routine cervical length screening/use of vaginal progesterone was the dominant strategy when compared to routine care. For every 100,000 women screened, 22 cases of neonatal death or long-term neurologic deficits could be prevented, and approximately $19 million could potentially be saved. Therefore, it appears that universal cervical length screening and treatment with vaginal progesterone is a cost-effective strategy to prevent preterm birth and resultant neonatal morbidity and mortality. Similarly, Campbell[178] has concluded that, in light of the available evidence, doing nothing to prevent preterm birth is no longer an option.

Implications for practice

The present IPD metaanalysis provides compelling evidence of the benefit of vaginal progesterone to prevent preterm birth and neonatal morbidity/mortality in women with a sonographic short cervix. Importantly, there was no evidence of demonstrable risk. This IPD metaanalysis indicates that vaginal progesterone is effective in women with and without a history of preterm birth and a short cervix. Therefore, we recommend that transvaginal sonographic measurement of cervical length be performed at 19-24 weeks of gestation. Vaginal progesterone at a dose of 90 mg/d should be considered for use in patients with a short cervix, mainly those with a cervical length between 10-20 mm, from 20-36 6/7 weeks of gestation.

Implications for research

A properly-designed randomized controlled trial in twin gestations is needed to determine the efficacy of vaginal progesterone to prevent preterm birth and neonatal morbidity and mortality in women with a short cervix. The results of this metaanalysis suggest that this subset of twin gestations is likely to benefit from progesterone.

Another issue that deserves further investigation is the optimal management of women who have an extremely short cervix with some evidence of subclinical intraamniotic infection/inflammation (eg, patients with a short cervix and amniotic fluid sludge[179] or those with elevated concentrations of cervical proinflammatory cytokines[180] or other biomarkers for intraamniotic infection/inflammation[158 and 159]). Antibiotic and antiinflammatory agents may have a role under these circumstances. Indeed, intraamniotic infection can be eradicated in patients with a short cervix[118]–such observations are consistent with experimental infection in nonhuman primates.[181] The complexities of addressing this important clinical question should not be underestimated.

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