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

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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


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Preterm birth is the leading cause of perinatal morbidity and mortality worldwide and contributes to 70% of neonatal mortality and approximately half of long-term neurodevelopmental disabilities. 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. 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. 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.

Spontaneous preterm labor/delivery is considered to be one of the “great obstetrical syndromes,” a term that emphasizes that obstetrical disorders with a similar phenotype are caused by multiple pathologic processes, have a long subclinical phase, and may result from complex gene-environment interactions.

Progesterone is considered a key hormone for pregnancy maintenance, and a decline of progesterone action is implicated in the onset of parturition. 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.”

Progesterone actions are mediated by genomic and nongenomic effects which have been studied in the uterine cervix, myometrium, sperm, etc. A blockade of progesterone action can lead to the clinical, biochemical, and morphologic changes associated with cervical ripening. A short cervix detected with transvaginal ultrasound is a powerful predictor of preterm birth in women with singleton and twin gestations. The shorter the sonographic cervical length, the higher the risk of spontaneous preterm birth. Moreover, a short cervix is associated with intraamniotic infection and inflammation, and this may modify the response to interventions.

**EDITORS’ CHOICE**

An interest in the role of progestogens (natural and synthetic) for the prevention of preterm birth has existed for decades. 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 choioamniotic membranes. In 2007, Fonseca et al reported 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 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 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).

Since the publication of the trial of Hassan et al, several trials evaluating vaginal progesterone in women at high risk of spontaneous preterm birth, 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. 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. 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.

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 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 and suggested guidelines for IPD metaanalyses.

**Literature search**

We searched MEDLINE, EMBASE, CI-NAHL, 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); IS 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.nih.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. In addition, this cervical length is the most commonly used in studies evaluating the predictive accuracy of cervical length for preterm birth.

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.

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. 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) blindness 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. 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]). Heterogeneity of the results among studies was tested with the quantity I2, which describes the percentage of total variation across studies that can be attributed to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I2 values of ≥50% indicate a substantial level of heterogeneity. 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 reduc-
tion or increase in risk difference based on control event rates in the trials.\textsuperscript{147} Publication and related biases were assessed visually by examining the symmetry of funnel plots and statistically by using the Egger test.\textsuperscript{148} A $P$ value $< .05$ 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 $\geq 35$ years), race/ethnicity (Caucasian, Black, Asian, and other), and body mass index ($< 18.5$, $18.5-24.9$, $25.0-29.9$, $\geq 30$ 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.\textsuperscript{149,150} 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.\textsuperscript{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.\textsuperscript{137,152} 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.

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**FIGURE 1**

Flow of study identification

- Records identified through database searching (n = 2611)
- Additional records identified through other sources (n = 0)
- Records after duplicates removed (n = 1875)
- Records screened (n = 1875)
- Records excluded (n = 1865)
- Full-text articles assessed for eligibility (n = 10)
- Full-text articles excluded (n = 5)
  1. Cervical length was not measured or collected before randomization
  2. Vaginal progesterone was used as tocolytic therapy after threatened preterm labor
- Studies included in qualitative synthesis (n = 5)
- Studies included in metaanalysis (n = 5)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participating countries</th>
<th>Primary target population</th>
<th>Inclusion/exclusion criteria</th>
<th>No of women with CL ≤25 mm/fetuses or infants</th>
<th>Vaginal progesterone group</th>
<th>Placebo group</th>
<th>Intervention</th>
<th>Cointerventions</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fonseca et al, 2007</td>
<td>United Kingdom, Chile, Brazil, Greece</td>
<td>Women with a short cervix</td>
<td>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</td>
<td>125/136</td>
<td>125/138</td>
<td></td>
<td>Vaginal progesterone capsule (200 mg/d) or placebo from 24-33 6/7 wk of gestation</td>
<td>Cervical cerclage [1 (0.8%) in vaginal progesterone group and 0 (0.0%) in placebo group]</td>
<td>Spontaneous preterm birth ≤34 wk</td>
</tr>
<tr>
<td>O’Brien et al, 2007</td>
<td>United States, South Africa, India, Czech Republic, Chile, El Salvador</td>
<td>Women with a history of spontaneous preterm birth</td>
<td>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 &lt;350 cells/mm³ and requiring multiple antiretroviral agents, placenta previa, history or suspicion of breast or genital tract malignancy, history or suspicion of thromboembolic disease, Mullerian duct anomaly, major fetal anomaly or chromosomal disorder, or multifetal gestation</td>
<td>12/12</td>
<td>19/19</td>
<td></td>
<td>Vaginal progesterone gel (90 mg/d) or placebo from 18-22 to 37 0/7 wk of gestation</td>
<td>None</td>
<td>Preterm birth ≤32 wk</td>
</tr>
<tr>
<td>Cetingoz et al, 2011</td>
<td>Turkey</td>
<td>Women at high risk of preterm birth</td>
<td>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</td>
<td>9/14</td>
<td>6/8</td>
<td></td>
<td>Vaginal progesterone suppository (100 mg/d) or placebo from 24-34 wk of gestation</td>
<td>None</td>
<td>Preterm birth &lt;37 wk</td>
</tr>
<tr>
<td>Hassan et al, 2011</td>
<td>United States, Republic of Belarus, Chile, Czech Republic, India, Israel, Italy, Russia, South Africa, Ukraine</td>
<td>Women with a short cervix</td>
<td>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 prostaglandin treatment within previous 4 wk, chronic medical conditions that would interfere with study participation or evaluation of treatment, major fetal anomaly or known chromosomal abnormality, uterine anatomic malformation, vaginal bleeding, known or suspected clinical chorioamnionitis</td>
<td>235/235</td>
<td>223/223</td>
<td></td>
<td>Vaginal progesterone gel (90 mg/d) or placebo from 23-23 6/7 to 36 6/7 wk of gestation</td>
<td>Emergency cervical cerclage [10 (4.3%) in vaginal progesterone group and 6 (2.7%) in placebo group]</td>
<td>Preterm birth ≤33 wk</td>
</tr>
</tbody>
</table>

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.125,153-156 Three of these studies evaluated vaginal progesterone in women at high risk for preterm birth (previous preterm birth,125,154 uterine malformation,125 cervical insufficiency,125 and twins155) but none of them measured or collected data on cervical length. Two of these studies125,154 reported that prophylactic administration of vaginal progesterone reduced the risk of preterm birth in women with a previous preterm birth, whereas the study by Norman et al155 found that vaginal progesterone did not reduce the risk of the composite outcome death or fetal death before 34 weeks of gestation in women with a twin gestation. The remaining 2 studies evaluated vaginal progesterone as an adjunct to tocolytic therapy after threatened preterm labor.153,156 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.131,133,134,136,144

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,131,133 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 studies134,144 reported data of planned secondary analyses for women with a short cervix in additional reports.132,135 Data from the trials by O’Brien et al144 Cetinogoz et al.,136 and Rode et al134 relevant to
women with a cervical length of \( \leq 25 \) mm before randomization were provided by the authors for inclusion in this review. The 2 trials\(^{131,133}\) specifically designed to evaluate the use of vaginal pro-
gesterone 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 meta-
analysis). The other 3 studies provided data for 67 women and 95 infants.

Two studies used vaginal progesterone capsules or pessaries 200 mg/d\(^{131,134}\); 2 used vaginal progesterone gel 90 mg/d\(^{133,144}\) and the other used vaginal pro-
gesterone suppositories 100 mg/d\(^{136}\). The treatment was initiated at 24 weeks of gestation in 2 trials\(^{131,136}\) between 20-23 weeks of gestation in 2 trials\(^{133,134}\) and between 18-22 weeks of gestation in 1 trial\(^{144}\). Three studies\(^{131,134,136}\) reported that participating women received study medication from enrollment until 34 weeks of gestation, and 2 studies\(^{133,144}\) from enrollment until 36 6/7 weeks of gestation. In 3 stud-
ies\(^{131,133,134}\) 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\(^{133}\), \( \leq 32 \) 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 ade-
quate allocation concealment and used identical placebo to blind patients and clinical staff to treatment allocation. There was blinding of outcome assess-
ment and adequate handling of incom-
plete outcome data in all 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 meta-
analyses. 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; \( I^2 = 0\% \)); \( I^2 = 27\% \); RR, 0.61; 95% CI, 0.47–1.18; \( I^2 = 41\% \)). 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, 0.28–4.22; \( I^2 = 0\% \)).

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 (17.5% vs 19.5%; RR, 0.86; 95% CI, 0.62–1.20; \( I^2 = 0\% \); NNT for benefit 13; 95% CI, 7–30), birthweight <1500 g (8.8% vs 19.5%; RR, 0.43; 95% CI, 0.26–0.73; \( I^2 = 0\% \); NNT for benefit 10; 95% CI, 6–24), and mechanical ventilation (15.5% vs 26.5%; RR, 0.60; 95% CI, 0.41–0.89; \( I^2 = 0\% \); NNT for benefit 10; 95% CI, 6–24) compared to those who did not receive vaginal progesterone administration.

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 who did not receive 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; 95% CI, 0.34–1.18; \( I^2 = 0\% \)). 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, 0.28–4.22; \( I^2 = 0\% \)).

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; and a statistically significant reduction in morbidity and mortality in twins (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 separately. According to the interaction analysis, there was no evidence that women with singleton pregnancies benefit more or less from the use of vaginal progesterone than women with twin pregnancies.

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. Among singleton gestations, the administration of vaginal progesterone was associated with a statistically significant reduction in 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 an 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 morbidity and mortality in twins remained statistically significant (RR, 0.56; 95% CI, 0.30–0.97).
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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of trials</th>
<th>Vaginal progesterone</th>
<th>Placebo</th>
<th>Pooled RR (95% CI)</th>
<th>I² (%)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth &lt;37 wk</td>
<td>5</td>
<td>144/388</td>
<td>165/387</td>
<td>0.89 (0.75–1.06)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Preterm birth &lt;36 wk</td>
<td>5</td>
<td>108/388</td>
<td>136/387</td>
<td>0.82 (0.67–1.00)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Preterm birth &lt;35 wk</td>
<td>5</td>
<td>79/388</td>
<td>118/387</td>
<td>0.69 (0.55–0.88)</td>
<td>0</td>
<td>11 (7–27)</td>
</tr>
<tr>
<td>Preterm birth &lt;34 wk</td>
<td>5</td>
<td>62/388</td>
<td>105/387</td>
<td>0.61 (0.47–0.81)</td>
<td>0</td>
<td>9 (7–19)</td>
</tr>
<tr>
<td>Preterm birth &lt;30 wk</td>
<td>5</td>
<td>29/388</td>
<td>51/387</td>
<td>0.58 (0.38–0.89)</td>
<td>0</td>
<td>18 (12–69)</td>
</tr>
<tr>
<td>Preterm birth &lt;28 wk</td>
<td>5</td>
<td>21/388</td>
<td>43/387</td>
<td>0.50 (0.30–0.81)</td>
<td>0</td>
<td>18 (13–47)</td>
</tr>
<tr>
<td>Spontaneous preterm birth &lt;33 wk</td>
<td>5</td>
<td>39/388</td>
<td>71/387</td>
<td>0.57 (0.40–0.81)</td>
<td>0</td>
<td>13 (9–29)</td>
</tr>
<tr>
<td>Spontaneous preterm birth &lt;34 wk</td>
<td>5</td>
<td>51/388</td>
<td>87/387</td>
<td>0.62 (0.46–0.84)</td>
<td>0</td>
<td>12 (8–28)</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>5</td>
<td>25/411</td>
<td>52/416</td>
<td>0.48 (0.30–0.76)</td>
<td>0</td>
<td>15 (11–33)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>5</td>
<td>5/411</td>
<td>6/416</td>
<td>0.88 (0.30–2.64)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>5</td>
<td>6/411</td>
<td>9/416</td>
<td>0.74 (0.27–2.05)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Proven neonatal sepsis</td>
<td>5</td>
<td>12/411</td>
<td>20/416</td>
<td>0.64 (0.32–1.29)</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>5</td>
<td>6/411</td>
<td>3/416</td>
<td>1.56 (0.46–5.28)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>2</td>
<td>4/249</td>
<td>5/231</td>
<td>0.76 (0.21–2.79)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>2</td>
<td>0/249</td>
<td>0/231</td>
<td>Not estimable</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Fetal death</td>
<td>5</td>
<td>6/411</td>
<td>7/416</td>
<td>0.82 (0.28–2.42)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>5</td>
<td>8/411</td>
<td>15/416</td>
<td>0.55 (0.26–1.19)</td>
<td>43</td>
<td>–</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>5</td>
<td>14/411</td>
<td>22/416</td>
<td>0.63 (0.34–1.18)</td>
<td>41</td>
<td>–</td>
</tr>
<tr>
<td>Composite neonatal morbidity/mortalitya</td>
<td>5</td>
<td>40/411</td>
<td>72/416</td>
<td>0.57 (0.40–0.81)</td>
<td>0</td>
<td>13 (10–30)</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 5 min</td>
<td>5</td>
<td>15/408</td>
<td>27/412</td>
<td>0.57 (0.32–1.02)</td>
<td>16</td>
<td>–</td>
</tr>
<tr>
<td>Birthweight &lt;1500 g</td>
<td>5</td>
<td>36/410</td>
<td>68/413</td>
<td>0.55 (0.38–0.80)</td>
<td>6</td>
<td>13 (10–30)</td>
</tr>
<tr>
<td>Birthweight &lt;2500 g</td>
<td>5</td>
<td>140/410</td>
<td>162/413</td>
<td>0.91 (0.76–1.08)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>5</td>
<td>85/411</td>
<td>121/416</td>
<td>0.75 (0.59–0.94)</td>
<td>0</td>
<td>14 (8–57)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>5</td>
<td>35/411</td>
<td>51/416</td>
<td>0.66 (0.44–0.98)</td>
<td>0</td>
<td>24 (15–408)</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>7</td>
<td>30/1967</td>
<td>34/1954</td>
<td>0.89 (0.55–1.44)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Any maternal adverse event</td>
<td>3</td>
<td>86/624</td>
<td>80/595</td>
<td>1.04 (0.79–1.38)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>4</td>
<td>244/1065</td>
<td>248/1057</td>
<td>1.00 (0.87–1.15)</td>
<td>33</td>
<td>–</td>
</tr>
<tr>
<td>Vaginal pruritus</td>
<td>4</td>
<td>54/1065</td>
<td>50/1057</td>
<td>1.08 (0.74–1.57)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Discontinuation of treatment because of adverse events</td>
<td>5</td>
<td>28/1083</td>
<td>28/1061</td>
<td>1.01 (0.61–1.69)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Threatened preterm labor</td>
<td>5</td>
<td>115/384</td>
<td>139/383</td>
<td>0.83 (0.68–1.02)</td>
<td>16</td>
<td>–</td>
</tr>
<tr>
<td>Low ASQ developmental and socioemotional score at 18 mo of ageb</td>
<td>1</td>
<td>19/503</td>
<td>18/488</td>
<td>1.02 (0.54–1.93)</td>
<td>NA</td>
<td>–</td>
</tr>
</tbody>
</table>

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

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.

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 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.

Table 3: Effect of vaginal progesterone on preterm birth and perinatal outcomes in singleton and twin gestations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Singleton pregnancy</th>
<th>Twin pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of trials</td>
<td>Vaginal progesterone</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth &lt;33 wk</td>
<td>4</td>
<td>41/365</td>
</tr>
<tr>
<td>Preterm birth &lt;37 wk</td>
<td>4</td>
<td>127/365</td>
</tr>
<tr>
<td>Preterm birth &lt;35 wk</td>
<td>4</td>
<td>67/365</td>
</tr>
<tr>
<td>Preterm birth &lt;28 wk</td>
<td>4</td>
<td>20/365</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>4</td>
<td>17/365</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>4</td>
<td>5/365</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>4</td>
<td>5/365</td>
</tr>
<tr>
<td>Fetal death</td>
<td>4</td>
<td>6/365</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>4</td>
<td>6/365</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>4</td>
<td>12/365</td>
</tr>
<tr>
<td>Composite neonatal morbidity/mortality</td>
<td>4</td>
<td>29/365</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 5 min</td>
<td>4</td>
<td>11/362</td>
</tr>
<tr>
<td>Birthweight &lt;1500 g</td>
<td>4</td>
<td>28/364</td>
</tr>
<tr>
<td>Birthweight &lt;2500 g</td>
<td>4</td>
<td>102/364</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>4</td>
<td>59/365</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4</td>
<td>28/365</td>
</tr>
</tbody>
</table>

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

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

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 morbidity 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 gestations134 examined developmental and socioemotional scores at 18 months of age, and found that there was no difference between infants ex-

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**TABLE 4**

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

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

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

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

posed 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/m² 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.149,150

An important question is the range of cervical length in which vaginal progesterone is effective. Fonseca et al131 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

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### TABLE 5

**Subgroup analyses of effect of vaginal progesterone on preterm birth <33 weeks of gestation and composite neonatal morbidity/mortality**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Preterm birth &lt;33 wk of gestation</th>
<th>Composite neonatal morbidity/mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical length, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>79</td>
<td>0.83 (0.49–1.41)</td>
</tr>
<tr>
<td>10-20</td>
<td>653</td>
<td>0.52 (0.35–0.76)</td>
</tr>
<tr>
<td>21-25</td>
<td>43</td>
<td>0.50 (0.10–2.41)</td>
</tr>
<tr>
<td><strong>Obstetric history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With no previous preterm birth</td>
<td>606</td>
<td>0.61 (0.42–0.89)</td>
</tr>
<tr>
<td>With ≥1 previous preterm birth</td>
<td>169</td>
<td>0.54 (0.30–0.98)</td>
</tr>
<tr>
<td>Maternal age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>63</td>
<td>0.66 (0.21–2.14)</td>
</tr>
<tr>
<td>20-34</td>
<td>620</td>
<td>0.58 (0.41–0.84)</td>
</tr>
<tr>
<td>≥35</td>
<td>92</td>
<td>0.49 (0.20–1.15)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>269</td>
<td>0.39 (0.22–0.69)</td>
</tr>
<tr>
<td>Black</td>
<td>287</td>
<td>0.74 (0.46–1.19)</td>
</tr>
<tr>
<td>Asian</td>
<td>157</td>
<td>0.53 (0.21–1.34)</td>
</tr>
<tr>
<td>Other</td>
<td>41</td>
<td>0.60 (0.19–1.92)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>58</td>
<td>0.35 (0.10–1.20)</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>359</td>
<td>0.63 (0.36–1.10)</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>187</td>
<td>0.68 (0.39–1.19)</td>
</tr>
<tr>
<td>≥30</td>
<td>159</td>
<td>0.49 (0.26–0.92)</td>
</tr>
<tr>
<td><strong>Trial characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily dose of vaginal progesterone, mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-100</td>
<td>504</td>
<td>0.53 (0.33–0.85)</td>
</tr>
<tr>
<td>200</td>
<td>271</td>
<td>0.63 (0.41–0.96)</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.

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

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.158,159 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.149,150

Fonseca et al131 and Hassan et al133 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 al131 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—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).162-171

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.126,172-174 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% non-significant 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.
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 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. 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 collected information about bronchopulmonary dysplasia, but the study of Fonseca et al did not. Similarly, some studies did not collect information about the intraventricular hemorrhage grade.

**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 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 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 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 pro-
gesterone 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\textsuperscript{179} or those with elevated concentrations of cervical proinflammatory cytokines\textsuperscript{180} or other biomarkers for intraamniotic infection/inflammation\textsuperscript{138,159}). Antibiotic and antiinflammatory agents may have a role under these circumstances. Indeed, intraamniotic infection can be eradicated in patients with a short cervix,\textsuperscript{118} such observations is consistent with experimental infection in nonhuman primates.\textsuperscript{181} The complexities of addressing this important clinical question should not be underestimated.

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