# Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data

Roberto Romero, MD, DMedSci; Agustin Conde-Agudelo, MD, MPH, PhD; Eduardo Da Fonseca, MD; John M. O'Brien, MD; Elcin Cetingoz, MD; George W. Creasy, MD; Sonia S. Hassan, MD; Kypros H. Nicolaides, MD

**BACKGROUND:** The efficacy of vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix has been questioned after publication of the OPPTIMUM study.

**OBJECTIVE:** To determine whether vaginal progesterone prevents preterm birth and improves perinatal outcomes in asymptomatic women with a singleton gestation and a midtrimester sonographic short cervix.

**STUDY DESIGN:** We searched MEDLINE, EMBASE, LILACS, and CINAHL (from their inception to September 2017); Cochrane databases; bibliographies; and conference proceedings for randomized controlled trials comparing vaginal progesterone vs placebo/no treatment in women with a singleton gestation and a midtrimester sonographic cervical length ≤25 mm. This was a systematic review and meta-analysis of individual patient data. The primary outcome was preterm birth <33 weeks of gestation. Secondary outcomes included adverse perinatal outcomes and neurodevelopmental and health outcomes at 2 years of age. Individual patient data were analyzed using a 2-stage approach. Pooled relative risks with 95% confidence intervals were calculated. Quality of evidence was assessed using the GRADE methodology.

**RESULTS:** Data were available from 974 women (498 allocated to vaginal progesterone, 476 allocated to placebo) with a cervical length ≤25 mm participating in 5 high-quality trials. Vaginal progesterone was associated with a significant reduction in the risk of preterm birth <33 weeks of gestation (relative risk, 0.62; 95% confidence interval, 0.47–0.81; $P = .0006$; high-quality evidence). Moreover, vaginal progesterone significantly decreased the risk of preterm birth <36, <35, <34, <32, <30, and <28 weeks of gestation; spontaneous preterm birth <33 and <34 weeks of gestation; respiratory distress syndrome; composite neonatal morbidity and mortality; birthweight <1500 and <2500 g; and admission to the neonatal intensive care unit (relative risks from 0.47-0.82; high-quality evidence for all). There were 7 (1.4%) neonatal deaths in the vaginal progesterone group and 15 (3.2%) in the placebo group (relative risk, 0.44; 95% confidence interval, 0.18–1.07; $P = .07$; low-quality evidence). Maternal adverse events, congenital anomalies, and adverse neurodevelopmental and health outcomes at 2 years of age did not differ between groups.

**CONCLUSION:** Vaginal progesterone decreases the risk of preterm birth and improves perinatal outcomes in singleton gestations with a midtrimester sonographic short cervix, without any demonstrable deleterious effects on childhood neurodevelopment.

**Key words:** cervical length, prematurity, preterm delivery, progestins, progestogens, transvaginal ultrasound

## Introduction

Every year, an estimated 15 million babies are born preterm worldwide with rates ranging from 5% in several European countries to 18% in some African countries.[1] In 2015, the preterm birth rate in the United States, which had declined from 2007 through 2014, increased slightly to 9.63%.[2] Globally, preterm birth complications are the leading cause of child mortality, responsible for nearly 1 million deaths in 2013.[3] Additionally, surviving preterm babies are at greater risk for short-term health complications that may include acute respiratory, gastrointestinal, infectious, central nervous system, hearing, and vision problems, and for long-term neurodevelopmental disabilities such as cerebral palsy and impaired learning and visual disorders as well as chronic diseases in adulthood.[4-8]

Preterm parturition is a syndrome caused by multiple etiological factors such as intraamniotic infection, extrauterine infections, vascular disorders, decidual senescence, disruption of maternal-fetal tolerance, a decline in progesterone action, uterine overdistension, cervical disease, or maternal stress.[9-11] A short cervix, conventionally defined as a transvaginal sonographic cervical length ≤25 mm in the midtrimester of pregnancy, is a powerful risk factor for spontaneous preterm birth and has a high predictive accuracy for spontaneous preterm birth <34 weeks of gestation and a moderate to low predictive accuracy for spontaneous preterm birth <37 weeks of gestation in both singleton and twin gestations.[12-48]

In 2012, a systematic review and meta-analysis of individual patient data (IPD) from randomized controlled trials comparing vaginal progesterone vs placebo in women with a singleton gestation and a cervical length ≤25 mm in the midtrimester[49] reported that the administration of vaginal progesterone was associated with a significant reduction in the risk of preterm birth occurring from <28 weeks of gestation through <35 weeks of gestation. In addition, vaginal progesterone administration was associated with a reduction in the risk of admission to the neonatal intensive care unit (NICU), respiratory distress syndrome (RDS), composite neonatal morbidity and mortality, and birthweight <1500 g. Since the publication of that IPD meta-analysis, vaginal progesterone has been recommended for

0002-9378/$36.00
Published by Elsevier Inc.
https://doi.org/10.1016/j.ajog.2017.11.576

Related editorial, page 151.

Click Video under article title in Contents at **ajog.org**

patients with a singleton gestation and a short cervix by the Society for Maternal-Fetal Medicine,[50] the American Congress of Obstetricians and Gynecologists,[51] the International Federation of Gynecology and Obstetrics,[52] and the National Institute for Health and Care Excellence,[53] among others.

In 2016, the findings of the OPPTIMUM study were reported. This was a randomized controlled trial comparing vaginal progesterone vs placebo in women at risk of preterm birth because of previous spontaneous preterm birth <34 weeks of gestation, a cervical length ≤25 mm, or a positive fetal fibronectin test combined with other clinical risk factors for preterm birth.[54] The results of that trial showed that vaginal progesterone did not significantly reduce the risk of preterm birth or perinatal morbidity and mortality either in the entire population or in the subgroup of women with a cervical length ≤25 mm. That report created confusion among clinicians and professional/scientific organizations regarding the clinical efficacy of vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix.[55,56] Therefore, we performed a meta-analysis of aggregate data that assessed the effect of vaginal progesterone on the risk of preterm birth ≤34 weeks or fetal death in women with a singleton gestation and a cervical length ≤25 mm, the only outcome measure for which the publication of the OPPTIMUM study reported complete data in this subpopulation of women.[57] That meta-analysis showed that vaginal progesterone significantly reduced the risk of preterm birth ≤34 weeks or fetal death by 34%. Subsequently, the lead author of the OPPTIMUM study provided us the individual data for all women with a cervical length ≤25 mm who were included in that trial. Therefore, the objective of this systematic review and IPD meta-analysis was to assess the efficacy of vaginal progesterone in reducing the risk of preterm birth and adverse perinatal outcomes in asymptomatic women with a singleton gestation and a short cervix (cervical length ≤25 mm).

## Materials and Methods

The study was prospectively registered with the PROSPERO database of systematic reviews (no. CRD42017057155) and reported in accordance with the PRISMA-IPD statement.[58]

### Search strategy and selection criteria

We searched MEDLINE, EMBASE, LILACS, CINAHL, the Cochrane Central Register of Controlled Trials, and research registers of ongoing trials (all from inception to Sept. 30, 2017), and Google Scholar using the key words "progesterone" and "preterm birth" to identify all randomized controlled trials comparing vaginal progesterone (any dose) vs placebo/no treatment for the prevention of preterm birth and/or adverse perinatal outcomes in women with a singleton gestation. No language restrictions were imposed. We also searched in proceedings of congresses/meetings on maternal-fetal medicine and bibliographies of the retrieved articles, and contacted investigators in the field to locate unpublished studies. Trials were eligible if the primary aim of the study was to prevent preterm birth in women with a "short cervix," or to prevent preterm birth in women with risk factors other than a short cervix but for whom outcomes were available in those with a prerandomization cervical length ≤25 mm. Quasirandomized trials, trials that assessed vaginal progesterone in women with threatened or arrested preterm labor, and trials in which vaginal progesterone was administered in the first trimester to prevent miscarriage were excluded from the review. Two authors (R.R. and A.C-A.) independently assessed all the potential studies identified in the literature search for eligibility. Disagreements about inclusion were resolved through discussion.

### Data collection

The principal investigators of eligible trials were contacted and asked to share their data for this collaborative project. Authors were supplied with a data extraction sheet and requested to provide anonymized data about baseline characteristics, interventions, and outcomes for each randomized patient in the trial. Data provided by the investigators were systematically checked for completeness, duplication, consistency, feasibility, and integrity of randomization. In addition, the results from the review's analysis were cross-checked against the published reports of the trials. Authors were contacted for clarification where discrepancies existed and asked to supply missing data when necessary. Once queries had been resolved, clean data were uploaded to the main study database.

### Outcome measures

As in the previous IPD meta-analysis,[49] the primary outcome was preterm birth <33 weeks of gestation. Secondary outcomes were preterm birth <37, <36, <35, <34, <32, <30, and <28 weeks of gestation; spontaneous preterm birth <33 and <34 weeks of gestation; mean gestational age at delivery; RDS; necrotizing enterocolitis; intraventricular hemorrhage; proven neonatal sepsis; bronchopulmonary dysplasia; retinopathy of prematurity; fetal death; neonatal death; perinatal death; composite neonatal morbidity and mortality (RDS, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis, or neonatal death); Apgar score <7 at 5 minutes; birthweight <1500 and <2500 g; admission to the NICU; use of mechanical ventilation; congenital anomaly; any adverse maternal event; and the Bayley-III cognitive composite score, moderate or severe neurodevelopmental impairment, visual or hearing impairment, and disability in renal, gastrointestinal, or respiratory function at 2 years of age.

### Risk of bias assessment

Assessments of the risk of bias for the included trials were done independently by 2 investigators (R.R. and A.C-A.) according to the 7 domains outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (random sequence generation, allocation concealment, blinding of participants and personnel,

blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases).[59] This tool categorizes studies by low, unclear, or high risk of bias in each domain. When the information was not available in the published paper, the trial's principal investigator was contacted to request clarification or additional information. We resolved any disagreement regarding the risk of bias assessment by consensus.

### Data analysis

We analyzed all data on an intention-to-treat basis. IPD were analyzed using a 2-stage approach. In the first stage, estimates of effect were derived from the IPD for each trial; in the second stage, these were combined using standard methods for meta-analyses of aggregate data.[60] We calculated the pooled relative risk (RR) for dichotomous data and mean difference for continuous data with an associated 95% confidence interval (CI). Heterogeneity of treatment effect was assessed with the $I^2$ statistic.[61] Results from individual studies were pooled using a fixed-effects model if substantial statistical heterogeneity was not present ($I^2 \leq 30\%$). If $I^2$ values were >30%, a random-effects model was used to pool data across studies, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*.[59] We calculated the number needed to treat with a 95% CI where meta-analysis of dichotomous outcomes revealed a statistically significant beneficial or harmful effect of vaginal progesterone.[62]

Prespecified subgroup analyses were carried out according to obstetrical history (no previous spontaneous preterm birth and at least 1 previous spontaneous preterm birth), cervical length (<10, 10-20, and 21-25 mm), maternal age (<20, 20-34, and ≥35 years), race/ethnicity (White, Black, Asian, and Other), body mass index (<18.5, 18.5-24.9, 25.0-29.9, and ≥30 kg/m$^2$), gestational age at treatment initiation (18-21 and 22-25 weeks), and daily dose of vaginal progesterone (90-100 and 200 mg). Moreover, we performed a post-hoc subgroup analysis according to the country in which women were enrolled (United States vs other countries). A test for interaction between intervention and patient or trial characteristics was calculated to examine whether intervention effects differ between subgroups.[63-65] An interaction $P$ value ≥.05 was considered to indicate that the effect of intervention did not differ significantly between subgroups. We also planned to explore potential sources of heterogeneity and to assess publication and related biases if at least 10 studies were included in a meta-analysis, but these analyses were not undertaken due to the limited number of trials included in the review. Subgroup analyses were performed only for the primary outcome of preterm birth <33 weeks of gestation. Prespecified sensitivity analyses to explore the impact of selection, performance, and detection biases on results were not carried out because all trials were considered at low risk for these biases. Statistical analyses were performed using Review Manager (Version 5.3.5; Nordic Cochrane Center, Copenhagen, Denmark) and StatsDirect (Version 3.0.198; StatsDirect Ltd, Cheshire, United Kingdom).

### Quality of evidence

The quality of the body of evidence relating to primary and secondary outcomes was assessed using the GRADE approach.[66] We used the GRADEpro guideline development tool[67] to import data from Review Manager in order to create "Summary of Findings" tables. The GRADE approach results in an assessment of the quality of evidence in 4 grades: (i) high: we are very confident that the true effect is close to that of the estimate of the effect; (ii) moderate: we are moderately confident in the effect estimate, and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; (iii) low: our confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect; and (iv) very low: we have very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of effect. The evidence can be downgraded from high quality by 1 level for serious (or by 2 levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias.

This study was exempted from review by the Human Investigation Committee Administration Office of Wayne State University because all included studies were published previously and had each previously received local Institutional Review Board approvals and written consent from participants.

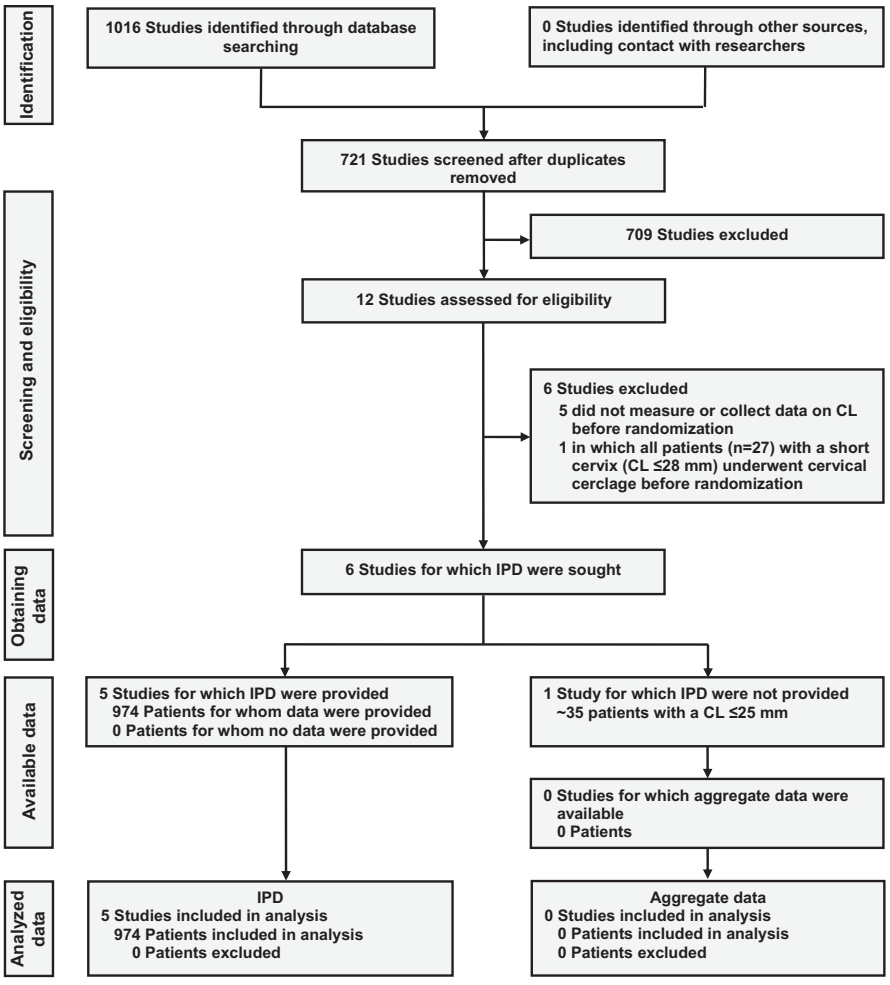
## Results

### Selection, characteristics, and risk of bias of studies

Literature searches identified 12 randomized controlled trials that compared vaginal progesterone vs placebo[54,68-76] or no treatment[77,78] in singleton gestations with the aim of preventing preterm birth and/or adverse perinatal outcomes (Figure 1). Six studies that assessed vaginal progesterone in women at high risk for preterm birth were excluded for the following reasons: cervical length was not measured or data on cervical length were not collected before randomization,[68,73,76-78] and inclusion of 27 women with a short cervix (defined as a cervical length ≤28 mm) who underwent cervical cerclage before randomization.[75] We requested IPD for women with a cervical length ≤25 mm before randomization from the principal investigators of the remaining 6 trials.[54,69-72,74] Data from 1 trial, which compared vaginal progesterone vs placebo in women with a singleton gestation without previous spontaneous preterm birth and a cervical length ≤30 mm (n = 80), could not be obtained.[74] We estimated that this trial included approximately 35 patients with a cervical length ≤25 mm. IPD were obtained for 974 women with a cervical length ≤25 mm from 5 double-blind, placebo-controlled trials;[54,69-72] 498 women were assigned to vaginal progesterone and 476 to placebo. Baseline characteristics were largely balanced between the vaginal progesterone and placebo groups (Table 1).

The main characteristics of the 5 studies included in the systematic review

**FIGURE 1**
**Summary of evidence and search selection**




*CL*, cervical length; *IPD*, individual patient data.

*Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018.*

are depicted in Table 2. Two trials were specifically designed to evaluate the use of vaginal progesterone in women with a short cervix (cervical length ≤15 mm[69] and cervical length between 10-20 mm[72]). One tested the effect of vaginal progesterone in women at risk for preterm birth because of previous spontaneous preterm birth, a sonographic cervical length ≤25 mm, or a positive fetal fibronectin test combined with other clinical risk factors for preterm birth.[54] Another evaluated the use of vaginal progesterone in women with a history of spontaneous preterm birth.[70] The remaining trial examined the use of vaginal progesterone in women with a previous spontaneous preterm birth, uterine malformations, or a twin gestation.[71] Three studies[54,69,72] provided 96% of the total sample size of the IPD meta-analysis. The daily dose of vaginal progesterone used in the trials varied from 90-200 mg and the treatment was administered from 18-25 to 34-36 weeks of gestation. An adequate compliance or adherence to treatment (≥80% of prescribed medication) was reported for >90% of patients participating in 4 trials.[69-72] In the trial by Norman et al,[54] only 66% of patients with a cervical length ≤25 mm had a compliance ≥80%. Four studies[69-72] were considered to be at low risk of selection, performance, detection, attrition, and reporting biases (Figure 2). One study[54] was considered to be at high risk of attrition bias for the childhood primary outcome because information on the Bayley-III cognitive composite score at 2 years of age was available for ~70% of surviving children. Moreover, this study was at high risk of compliance bias, which can affect the trial's statistical power to detect the effects of the intervention.[79]

## Effect of vaginal progesterone on preterm birth

Vaginal progesterone significantly reduced the risk of preterm birth <33 weeks of gestation (14% vs 22%; RR, 0.62; 95% CI, 0.47−0.81; $P = .0006$; $I^2 = 0\%$; number needed to treat, 12; 95% CI, 8−23; high-quality evidence) (Figure 3). The frequencies of preterm birth <36, <35, <34, <32, <30, and <28 weeks of gestation and spontaneous preterm birth <33 and <34 weeks of gestation were significantly lower in the vaginal progesterone group (RRs from 0.64-0.80; $I^2 = 0$ for all; high-quality evidence for all) (Table 3). Additionally, the mean gestational age at delivery was significantly greater in the vaginal progesterone group than in the placebo group (mean difference, 0.74 weeks; 95% CI, 0.18−1.30). There was no evidence of an effect of vaginal progesterone on preterm birth <37 weeks of gestation (high-quality evidence).

## Effect of vaginal progesterone on adverse perinatal and neurodevelopmental outcomes

Treatment with vaginal progesterone was also associated with a significant reduction in the risk of RDS, composite neonatal morbidity and mortality, birthweight <1500 and <2500 g, and admission to the NICU (RRs from 0.47-0.82; $I^2 = 0$ for all; high-quality evidence for all). The frequency of neonatal death was 1.4% (7/498) in the vaginal progesterone group and 3.2% (15/476) in the placebo group (RR, 0.44; 95% CI, 0.18−1.07; $P = .07$; $I^2 = 0\%$; low-quality evidence). There were no significant

**TABLE 1**
**Baseline characteristics of the pooled women**

| | Vaginal progesterone n = 498 | Placebo n = 476 |
|---|---|---|
| Maternal age, y | 28.0 (23.6–33.0) | 27.5 (23.5–32.8) |
| Body mass index, kg/m$^2$ | 24.8 (21.6–29.2)[a] | 24.8 (21.5–29.4)[b] |
| Race/ethnicity | | |
| White | 185 (37.2) | 189 (39.7) |
| Black | 181 (36.3) | 176 (37.0) |
| Asian | 100 (20.1) | 89 (18.7) |
| Other | 32 (6.4) | 22 (4.6) |
| Region of enrollment | | |
| Europe | 275 (55.2) | 252 (52.9) |
| North America | 115 (23.1) | 117 (24.6) |
| Asia | 80 (16.1) | 77 (16.2) |
| South America | 15 (3.0) | 17 (3.6) |
| Africa | 13 (2.6) | 13 (2.7) |
| Obstetrical history | | |
| Nulliparous | 225 (45.2) | 215 (45.2) |
| Parous with no previous spontaneous preterm birth | 126 (25.3) | 120 (25.2) |
| Parous with ≥1 previous spontaneous preterm birth | 147 (29.5) | 141 (29.6) |
| Cervical length at randomization | | |
| <10 mm | 48 (9.6) | 57 (12.0) |
| 10–20 mm | 379 (76.1) | 362 (76.0) |
| 21–25 mm | 71 (14.3) | 57 (12.0) |
| Gestational age at randomization, wk | 22.6 (21.4–23.6) | 22.6 (21.4–23.4) |

Data are median (interquartile range) or n (%).

[a] n = 491; [b] n = 470.

*Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018.*

differences between the study groups in the risk of necrotizing enterocolitis, intraventricular hemorrhage, proven neonatal sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, fetal death, perinatal death, Apgar score <7 at 5 minutes, use of mechanical ventilation, congenital anomalies, and any maternal adverse event (low- to moderate-quality evidence). At 2 years of age, the Bayley-III cognitive composite scores and the frequencies of moderate/severe neurodevelopmental impairment, visual or hearing impairment, and disability in renal, gastrointestinal, or respiratory function did not differ significantly between the vaginal progesterone and placebo groups (1 study,[54] low-quality evidence for all).

### Subgroup analyses

Subgroup analyses of the primary outcome according to maternal and trial characteristics are shown in Figure 4. There was no evidence of heterogeneity of treatment effect across any of the prespecified variables (all *P* for interaction ≥.18). The direction of effect favored vaginal progesterone across all strata, although it appeared that the intervention had no effect in women with a cervical length <10 mm. However, the test of interaction among the cervical length groups was not significant ($P = .22$), suggesting that the response to treatment in the cervical length groups was not significantly different. The beneficial effect of vaginal progesterone did not differ significantly between patients with previous spontaneous preterm birth and those with no previous spontaneous preterm birth (*P* for interaction = .74), as well as between US women and non-US women (*P* for interaction = .51). Effects favoring the intervention were statistically significant in several subgroups of particular clinical interest, including patients with no previous spontaneous preterm birth, patients with a history of spontaneous preterm birth, and those receiving either 90-100 or 200 mg/d of vaginal progesterone.

## Comment

### Principal findings of the study

First, women with a singleton gestation and a midtrimester short cervix who received vaginal progesterone had a significant reduction in the risk of preterm birth (<28, <30, <32, <33, <34, <35, and <36 weeks of gestation). Second, vaginal progesterone improved neonatal outcome. Indeed, neonates of mothers who received vaginal progesterone had a significantly lower risk of RDS. Additionally, vaginal progesterone was also associated with a significant decrease in the risk of composite neonatal morbidity and mortality, low birthweight (<2500 g), very low birthweight (<1500 g), and NICU admission. Third, there was a nonsignificant trend toward reduction of neonatal mortality (by 66%, $P = .07$) and use of mechanical ventilation (by 35%, $P = .06$). Fourth, evidence from one trial[54] showed that, at 2 years of age, there were no significant differences in cognitive scores or the frequency of neurodevelopmental impairment or renal, gastrointestinal, and respiratory morbidity between children exposed prenatally to vaginal progesterone vs placebo. Finally, there were no significant differences in the frequency of maternal adverse events and congenital

**TABLE 2**
**Studies included in the meta-analysis of individual patient data**

| Study | Trial enrollment | Participants randomly assigned in original trial | Participants eligible for IPDMA | Treatment groups | Compliance ≥80% |
|---|---|---|---|---|---|
| Fonseca et al,[69] 2007 | 8 Centers in United Kingdom, Chile, Brazil, and Greece | 250 with singleton or twin gestation and cervical length ≤15 mm | 226 | Vaginal progesterone 200 mg/d or placebo from 24–33 6/7 wk of gestation | 92% for vaginal progesterone group and 94% for placebo group |
| O'Brien et al,[70] 2007 | 53 Centers in United States, South Africa, India, Czech Republic, Chile, and El Salvador | 659 with singleton gestation and previous spontaneous preterm birth | 31 | Vaginal progesterone 90 mg/d or placebo from 18–22 to 37 0/7 wk of gestation, rupture of membranes or preterm delivery, whichever occurred first | 100% for vaginal progesterone group and 95% for placebo group |
| Cetingoz et al,[71] 2011 | Single Center in Turkey | 160 with twin gestation, or singleton gestation with previous spontaneous preterm birth, or uterine malformation | 8 | Vaginal progesterone suppository 100 mg/d or placebo from 24–34 wk of gestation | 100% for both study groups |
| Hassan et al,[72] 2011 | 44 Centers in United States, Belarus, Chile, Czech Republic, India, Israel, Italy, Russia, South Africa, and Ukraine | 465 with singleton gestation and cervical length between 10–20 mm | 458 | Vaginal progesterone 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 | 89% for vaginal progesterone group and 93% for placebo group |
| Norman et al,[54] 2016 | 66 Centers in United Kingdom and Sweden | 1228 with singleton gestation and previous spontaneous preterm birth, or cervical length ≤25 mm, or positive fetal fibronectin test combined with other clinical risk factors for preterm birth | 251 | Vaginal progesterone 200 mg/d or placebo from 22–24 to 34 wk of gestation or preterm delivery, whichever occurred first | 63% for vaginal progesterone group and 69% for placebo group |

*IPDMA*, individual patient data meta-analysis.

*Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018.*

anomalies between the vaginal progesterone and placebo groups.

## Clinical meaning of the findings

A new finding is that vaginal progesterone administered to women with a midtrimester short cervix significantly reduces the risk of preterm birth <36 weeks and birthweight <2500 g. In a previous IPD meta-analysis, vaginal progesterone reduced the rate of preterm birth from <28 to <35 weeks.[49] The extended efficacy in reducing the rate of preterm birth to <36 weeks is probably attributable to the larger sample size of the current meta-analysis. This has important implications as late preterm birth (34-36 6/7 weeks) represents approximately 72% of all preterm births.[80]

Vaginal progesterone is expected to reduce neonatal complications by preventing preterm birth. The current IPD meta-analysis shows that vaginal progesterone is significantly associated with a 41% reduction in the frequency of a prespecified composite outcome of neonatal death combined with the most common neonatal complications affecting preterm neonates, such as RDS, intraventricular hemorrhage, necrotizing enterocolitis, and proven neonatal sepsis, which are important to patients, families, and health care providers. This finding is strengthened by the fact that the magnitude of the beneficial effect of vaginal progesterone on the individual components of the composite outcome was consistent with a reduction of about 40-50% for neonatal death, RDS, intraventricular hemorrhage, and proven neonatal sepsis.

The prespecified composite outcome measure did not restrict the endpoint of morbidity to complications that have a very low prevalence, such as severe intraventricular hemorrhage (grades III/IV), necrotizing enterocolitis (stages II/III), and retinopathy of prematurity (stages III-V). If the composite outcome measure had been restricted to only

FIGURE 2
**Risk of bias in each included study**

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| Fonseca 2007 | + | + | + | + | + | + | + |
| O'Brien 2007 | + | + | + | + | + | + | + |
| Cetingoz 2011 | + | + | + | + | + | + | + |
| Hassan 2011 | + | + | + | + | + | + | + |
| Norman 2016 | + | + | + | + | + + − * | + | − |

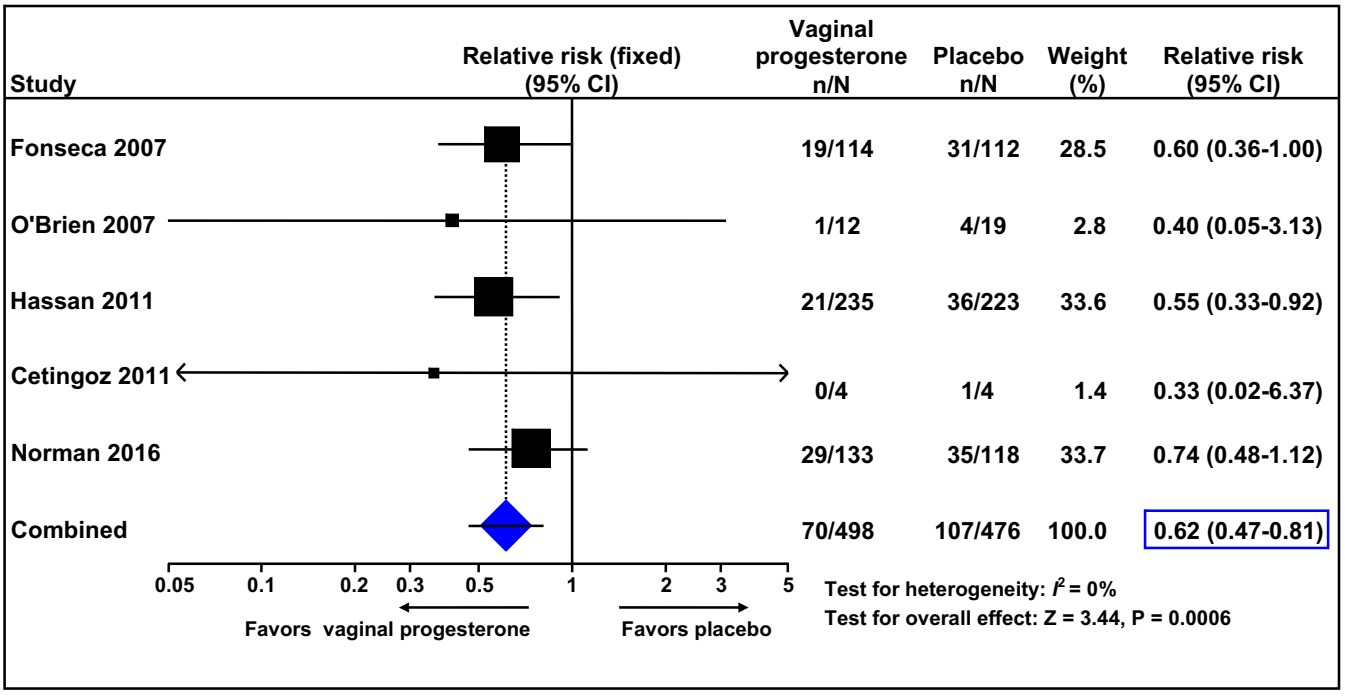
*Low risk of bias for obstetric and neonatal primary outcomes; high risk of bias for childhood primary outcome

*Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018.*

these severe complications, the risk for a type II error due to limited power could have missed an important clinical effect and misled physicians and patients.[81]

Additionally, the expectation that vaginal progesterone administered to patients with a short cervix would reduce the frequency of all severe complications of preterm neonates is not realistic, since many morbid events are influenced by postnatal factors, e.g., barotrauma, oxygen toxicity, systemic and local inflammation, and neonatal sepsis, among others. Vaginal progesterone is aimed primarily at preventing preterm birth and may ameliorate some immediate neonatal complications (eg, RDS). It is unreasonable to expect that it will improve distal outcomes influenced by many other medical and nonmedical factors.

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




*CI*, confidence interval.

*Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018*

**TABLE 3**
**Secondary outcomes by intervention group**

| Outcome | No of trials | Vaginal progesterone group | Placebo group | RR or mean difference (95% CI) | *P* value | $I^2$, % | NNT (95% CI) |
|---|---|---|---|---|---|---|---|
| Pregnancy outcome | | | | | | | |
| Preterm birth <37 wk | 5[54,69-72] | 187/498 (38%) | 199/476 (42%) | 0.90 (0.77–1.05) | .19 | 0 | - |
| Preterm birth <36 wk | 5[54,69-72] | 139/498 (28%) | 166/476 (35%) | 0.80 (0.67–0.97) | .02 | 0 | 14 (9–96) |
| Preterm birth <35 wk | 5[54,69-72] | 106/498 (21%) | 141/476 (30%) | 0.72 (0.58–0.89) | .003 | 0 | 12 (8–31) |
| Preterm birth <34 wk | 5[54,69-72] | 86/498 (17%) | 126/476 (26%) | 0.65 (0.51–0.83) | .0006 | 0 | 11 (8–22) |
| Preterm birth <32 wk | 5[54,69-72] | 62/498 (12%) | 92/476 (19%) | 0.64 (0.48–0.86) | .003 | 0 | 14 (10–37) |
| Preterm birth <30 wk | 5[54,69-72] | 49/498 (10%) | 67/476 (14%) | 0.70 (0.49–0.98) | .04 | 0 | 24 (14–355) |
| Preterm birth <28 wk | 5[54,69-72] | 38/498 (8%) | 54/476 (11%) | 0.67 (0.45–0.99) | .04 | 0 | 27 (16–881) |
| Spontaneous preterm birth <33 wk | 5[54,69-72] | 60/498 (12%) | 82/476 (17%) | 0.70 (0.51–0.95) | .02 | 0 | 19 (12–116) |
| Spontaneous preterm birth <34 wk | 5[54,69-72] | 73/498 (15%) | 97/476 (20%) | 0.72 (0.55–0.95) | .02 | 0 | 18 (11–98) |
| Gestational age at delivery, wk | 5[54,69-72] | 498[a] | 476[a] | 0.74 (0.18–1.30) | .01 | 0 | NA |
| Any maternal adverse event | 5[54,69-72] | 51/424 (12%) | 47/422 (11%) | 1.21 (0.87–1.69) | .26 | 5 | - |
| Perinatal outcome | | | | | | | |
| Respiratory distress syndrome | 4[69-72] | 17/365 (5%) | 37/358 (10%) | 0.47 (0.27–0.81) | .007 | 0 | 18 (13–51) |
| Necrotizing enterocolitis | 5[54,69-72] | 11/495 (2%) | 12/475 (3%) | 0.89 (0.41–1.93) | .77 | 0 | - |
| Intraventricular hemorrhage | 5[54,69-72] | 5/494 (1%) | 10/475 (2%) | 0.50 (0.18–1.38) | .18 | 0 | - |
| Proven neonatal sepsis | 5[54,69-72] | 18/494 (4%) | 28/470 (6%) | 0.61 (0.34–1.08) | .09 | 0 | - |
| Bronchopulmonary dysplasia | 3[54,71,72] | 11/367 (3%) | 13/340 (4%) | 0.77 (0.35–1.68) | .51 | 0 | - |
| Retinopathy of prematurity | 4[69-72] | 6/365 (2%) | 3/358 (1%) | 1.78 (0.49–6.47) | .38 | 29 | - |
| Fetal death | 5[54,69-72] | 9/498 (2%) | 8/476 (2%) | 1.06 (0.41–2.72) | .91 | 0 | - |
| Neonatal death | 5[54,69-72] | 7/498 (1%) | 15/476 (3%) | 0.44 (0.18–1.07) | .07 | 0 | - |
| Perinatal death | 5[54,69-72] | 16/498 (3%) | 23/476 (5%) | 0.66 (0.35–1.22) | .19 | 0 | - |
| Composite neonatal morbidity/mortality[b] | 4[69-72] | 29/365 (8%) | 49/358 (14%) | 0.59 (0.38–0.91) | .02 | 0 | 18 (12–81) |
| Apgar score <7 at 5 min | 5[54,69-72] | 38/491 (8%) | 43/469 (9%) | 0.83 (0.55–1.26) | .39 | 0 | - |
| Birthweight <1500 g | 5[54,69-72] | 50/497 (10%) | 77/473 (16%) | 0.62 (0.44–0.86) | .004 | 0 | 16 (11–44) |
| Birthweight <2500 g | 5[54,69-72] | 144/497 (29%) | 168/473 (36%) | 0.82 (0.68–0.98) | .03 | 0 | 16 (9–141) |
| Admission to NICU | 5[54,69-72] | 83/496 (17%) | 117/474 (25%) | 0.68 (0.53–0.88) | .003 | 0 | 13 (9–34) |
| Mechanical ventilation | 4[69-72] | 28/365 (8%) | 43/358 (12%) | 0.65 (0.41–1.01) | .06 | 0 | - |
| Congenital anomaly | 5[54,69-72] | 4/491 (1%) | 6/469 (1%) | 0.72 (0.23–2.26) | .57 | 0 | - |
| Childhood [age 2 y] outcome | | | | | | | |
| Bayley-III cognitive composite score | 1[54] | 95.5 (16.1) 88 | 97.7 (16.9) 80 | −2.17 (−7.16 to 2.83) | .40 | NA | NA |

*Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018.*

(continued)

**TABLE 3**
**Secondary outcomes by intervention group** *(continued)*

| Outcome | No of trials | Vaginal progesterone group | Placebo group | RR or mean difference (95% CI) | *P* value | $I^2$, % | NNT (95% CI) |
|---|---|---|---|---|---|---|---|
| Moderate/severe neurodevelopmental impairment | 1[54] | 10/81 (12%) | 7/77 (9%) | 1.36 (0.54–3.39) | .51 | NA | - |
| Visual or hearing impairment | 1[54] | 0/100 (0%) | 2/87 (2%) | 0.17 (0.01–3.58) | .26 | NA | - |
| Disability in renal, gastrointestinal, or respiratory function | 1[54] | 1/91 (1%) | 1/84 (1%) | 0.92 (0.06–14.52) | .95 | NA | - |

Data are n/N or mean (SD) N unless otherwise indicated.

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

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

*Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018.*

## Quality of evidence based on GRADE

We assessed primary and secondary outcomes with GRADE methodology, as shown in Table 4. Evidence was graded as "high quality" for all outcomes for which vaginal progesterone significantly reduced their risk. A determination of "high quality" signifies that we are very confident that the true effect is close to that of the estimate of the effect, and that further research is very unlikely to change this level of confidence.[66] Evidence for the remaining outcomes was considered to be of moderate to low quality.

## Subgroup analysis according to a history of spontaneous preterm birth

This meta-analysis also shows a beneficial effect of vaginal progesterone across a range of subgroups, including patients with or without a previous spontaneous preterm birth.

The results of an indirect comparison meta-analysis concluded that vaginal progesterone and cerclage have a similar efficacy to prevent preterm birth and perinatal morbidity and mortality in patients with a short cervix and a history of preterm birth.[82] The findings reported herein reaffirm that vaginal progesterone should be offered as an alternative to cerclage for patients with a singleton gestation, previous spontaneous preterm birth, and a cervical length ≤25 mm.[82]

## Subgroup analysis according to country of enrollment (United States vs other countries)

In 2012, the US Food and Drug Administration (FDA) reviewed the PREGNANT trial[72] as it considered a New Drug Application (NDA) proposing a pharmaceutical for the treatment of women with a singleton gestation and a midtrimester sonographic short cervix with vaginal progesterone. The application filed by a pharmaceutical company was not approved by the FDA. One of the reasons posited by the FDA was an alleged lack of statistically significant efficacy of vaginal progesterone in women enrolled in the United States.

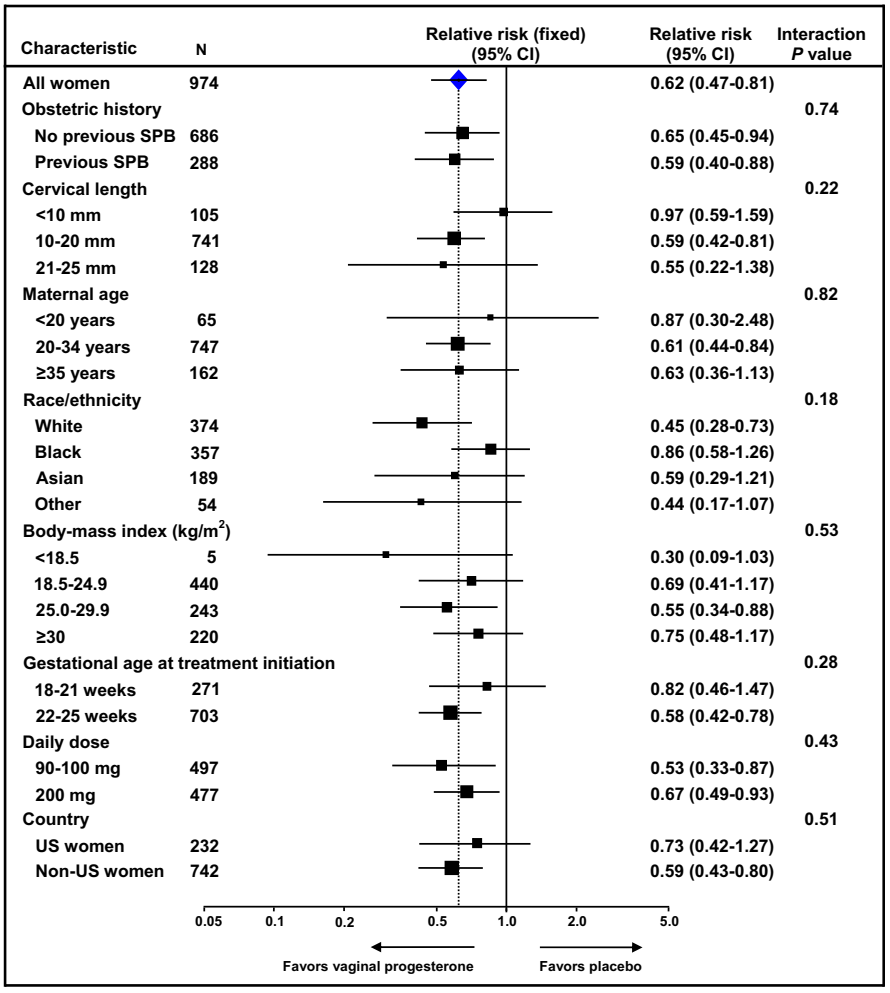
Recently, Yusuf and Wittes[83] analyzed several examples of regional differences in the results of randomized clinical trials in medicine and provided their assessment as to whether or not such differences are likely to be due to chance. The PREGNANT trial[72] was one of the examples of variations in results among countries assessed by Yusuf and Wittes[83] (who also examined the post-hoc analysis of the FDA). These investigators concluded that "geography does not trump biology in this case, and we would have applied the overall results of the trial to the US."[83] Consistent with this conclusion by Yusuf and Wittes,[83] a subgroup analysis in the current IPD meta-analysis showed that the beneficial effects of vaginal progesterone on preterm birth <33 weeks of gestation did not differ significantly between women enrolled in the United States (RR, 0.73; 95% CI, 0.42–1.27) and women enrolled outside the United States (RR, 0.59; 95% CI, 0.43–0.80), as the interaction test for subgroup differences was nonsignificant ($P = .51$).

## Subgroup analyses according to vaginal progesterone dose and cervical length

There was no difference in efficacy in the prevention of preterm birth when either 90-100 or 200 mg/d of vaginal progesterone was administered. Therefore, either regimen can be used in practice.

Insofar as cervical length, vaginal progesterone appeared to have no effect on the risk of preterm birth <33 weeks in patients with a cervical length <10 mm. Whether this lack of efficacy has a biological basis, or is a chance finding, is unclear. Although the interaction test for subgroup differences was not significant ($P = .22$), suggesting that vaginal progesterone has no differential efficacy in the prespecified cervical length groups, it is possible that women with a very short cervix are more likely to have intra-amniotic inflammation and may be less responsive to vaginal progesterone.[84-87] However, we performed a post-hoc subgroup analysis examining the effect of vaginal progesterone on the risk of composite neonatal morbidity and mortality according to cervical length,

FIGURE 4
**Subgroup analyses of the effect of vaginal progesterone on preterm birth <33 weeks of gestation**




*CI*, confidence interval; *SPB*, spontaneous preterm birth.

*Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018.*

which showed that the beneficial effect of vaginal progesterone did not differ significantly between women with a cervical length <10 mm (RR, 0.68; 95% CI, 0.33−1.41) and those with a cervical length between 10-25 mm (RR, 0.59; 95% CI, 0.35−0.99) with a nonsignificant interaction *P* value of .75. Further trials assessing the efficacy of vaginal progesterone in women with a cervical length <10 mm are warranted.

## Long-term effects of prenatal exposure to vaginal progesterone

Current evidence suggests that in utero exposure to vaginal progesterone does not have an effect on neurodevelopmental outcomes at least until 2 years of age and, possibly, until 6 years of age. Overall, the OPPTIMUM study[54] found that there were no significant differences in neurodevelopmental outcomes at 2 years of age between children exposed in utero to vaginal progesterone and those exposed to placebo. O'Brien et al[88] assessed neurodevelopmental outcomes at 6, 12, and 24 months of age in children born to women enrolled in their trial[70] and found similar frequencies of suspected developmental delay in the vaginal progesterone and placebo groups. Similar findings have been reported in children born to mothers participating in trials that compared vaginal progesterone and placebo in unselected twin gestations,[89,90] at a mean age of ~56 months.[91,92] Therefore, there is no evidence that vaginal progesterone has adverse effects on childhood neurodevelopmental outcomes.

## Strengths and limitations

A major strength of this study was the inclusion of individual data for most patients (97%) with a singleton gestation and a short cervix randomized to receive vaginal progesterone or placebo in trials that assessed this intervention with the aim of preventing preterm birth. Individual data for approximately 35 patients with a cervical length ≤25 mm who participated in a trial stopped early due to low enrollment could not be obtained from the investigators.[74] In that trial, vaginal progesterone was associated with a nonsignificant reduction in the risk of composite neonatal morbidity and mortality and preterm birth <32 and <34 weeks of gestation. We performed several simulated meta-analyses by including the results for women with a cervical length ≤30 mm reported in that study. After assuming the worst-case scenario (all adverse outcomes among patients with a cervical length ≤25 mm receiving vaginal progesterone and none among patients with a cervical length ≤25 mm receiving placebo), we found that the inclusion of data from that study in the meta-analyses resulted in minimal changes in the overall estimates of effect size, whereas the beneficial effects of vaginal progesterone on the risk of preterm birth and neonatal morbidity and mortality remained statistically significant. Other strengths of the present study are the absence of clinical and statistical heterogeneity in almost all meta-analyses and the balance in prognostic factors between the vaginal progesterone and placebo groups at baseline, which reduces the possibility of introducing biases in the estimates of intervention effects.

The main limitation of our study was the lack of data on the outcome measure RDS and the use of

**TABLE 4**
**Summary of findings on the quality of evidence for each outcome measure**

| Outcomes | Anticipated absolute effects[a] (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of evidence (GRADE)[b] |
|---|---|---|---|---|---|
| | Risk with placebo | Risk with vaginal progesterone | | | |
| Preterm birth <33 wk | Study population | | RR 0.62 (0.47–0.81) | 974 (5 studies) | ⊕⊕⊕⊕ High |
| | 225 per 1000 | 139 per 1000 (106–182) | | | |
| Preterm birth <37 wk | Study population | | RR 0.90 (0.77–1.05) | 974 (5 studies) | ⊕⊕⊕⊕ High |
| | 418 per 1000 | 376 per 1000 (322–439) | | | |
| Preterm birth <36 wk | Study population | | RR 0.80 (0.67–0.97) | 974 (5 studies) | ⊕⊕⊕⊕ High |
| | 349 per 1000 | 279 per 1000 (234–338) | | | |
| Preterm birth <35 wk | Study population | | RR 0.72 (0.58–0.89) | 974 (5 studies) | ⊕⊕⊕⊕ High |
| | 296 per 1000 | 213 per 1000 (172–264) | | | |
| Preterm birth <34 wk | Study population | | RR 0.65 (0.51–0.83) | 974 (5 studies) | ⊕⊕⊕⊕ High |
| | 265 per 1000 | 172 per 1000 (135–220) | | | |
| Preterm birth <32 wk | Study population | | RR 0.64 (0.48–0.86) | 974 (5 studies) | ⊕⊕⊕⊕ High |
| | 193 per 1000 | 124 per 1000 (93–166) | | | |
| Preterm birth <30 wk | Study population | | RR 0.70 (0.49–0.98) | 974 (5 studies) | ⊕⊕⊕⊕ High |
| | 141 per 1000 | 99 per 1000 (69–138) | | | |
| Preterm birth <28 wk | Study population | | RR 0.67 (0.45–0.99) | 974 (5 studies) | ⊕⊕⊕⊕ High |
| | 113 per 1000 | 76 per 1000 (51–112) | | | |
| Spontaneous preterm birth <33 wk | Study population | | RR 0.70 (0.51–0.95) | 974 (5 studies) | ⊕⊕⊕⊕ High |
| | 172 per 1000 | 121 per 1000 (88–164) | | | |
| Spontaneous preterm birth <34 wk | Study population | | RR 0.72 (0.55–0.95) | 974 (5 studies) | ⊕⊕⊕⊕ High |
| | 204 per 1000 | 147 per 1000 (112–194) | | | |
| Gestational age at delivery, wk | Mean gestational age at delivery [wk] in intervention groups was 0.74 higher (0.18–1.3 higher) | | | 974 (5 studies) | ⊕⊕⊕⊕ High |
| Respiratory distress syndrome | Study population | | RR 0.47 (0.27–0.81) | 723 (4 studies) | ⊕⊕⊕⊕ High |
| | 103 per 1000 | 49 per 1000 (28–84) | | | |
| Necrotizing enterocolitis | Study population | | RR 0.89 (0.41–1.93) | 970 (5 studies) | ⊕⊕⊖⊖ Low[c] |
| | 25 per 1000 | 22 per 1000 (10–49) | | | |
| Intraventricular hemorrhage | Study population | | RR 0.50 (0.18–1.38) | 969 (5 studies) | ⊕⊕⊖⊖ Low[c] |
| | 21 per 1000 | 11 per 1000 (4–29) | | | |
| Proven neonatal sepsis | Study population | | RR 0.61 (0.34–1.08) | 964 (5 studies) | ⊕⊕⊕⊖ Moderate[d] |
| | 60 per 1000 | 36 per 1000 (20–64) | | | |
| Bronchopulmonary dysplasia | Study population | | RR 0.77 (0.35–1.68) | 707 (3 studies) | ⊕⊕⊖⊖ Low[c] |
| | 38 per 1000 | 29 per 1000 (13–64) | | | |
| Retinopathy of prematurity | Study population | | RR 1.78 (0.49–6.47) | 723 (4 studies) | ⊕⊕⊖⊖ Low[c] |
| | 8 per 1000 | 15 per 1000 (4–54) | | | |
| Fetal death | Study population | | RR 1.06 (0.41–2.72) | 974 (5 studies) | ⊕⊕⊖⊖ Low[c] |
| | 17 per 1000 | 18 per 1000 (7–46) | | | |

*Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018.* *(continued)*

**TABLE 4**
**Summary of findings on the quality of evidence for each outcome measure** *(continued)*

| Outcomes | Anticipated absolute effects[a] (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of evidence (GRADE)[b] |
|---|---|---|---|---|---|
| | Risk with placebo | Risk with vaginal progesterone | | | |
| Neonatal death | Study population | | RR 0.44 (0.18–1.07) | 974 (5 studies) | ⊕⊕⊖⊖ Low[e] |
| | 32 per 1000 | 14 per 1000 (6–34) | | | |
| Perinatal death | Study population | | RR 0.66 (0.35–1.22) | 974 (5 studies) | ⊕⊕⊕⊖ Moderate[d] |
| | 48 per 1000 | 32 per 1000 (17–59) | | | |
| Composite neonatal morbidity/mortality | Study population | | RR 0.59 (0.38–0.91) | 723 (4 studies) | ⊕⊕⊕⊕ High |
| | 137 per 1000 | 81 per 1000 (52–125) | | | |
| Apgar score <7 at 5 min | Study population | | RR 0.83 (0.55–1.26) | 960 (5 studies) | ⊕⊕⊕⊖ Moderate[f] |
| | 92 per 1000 | 76 per 1000 (50–116) | | | |
| Birthweight <1500 g | Study population | | RR 0.62 (0.44–0.86) | 970 (5 studies) | ⊕⊕⊕⊕ High |
| | 163 per 1000 | 101 per 1000 (72–140) | | | |
| Birthweight <2500 g | Study population | | RR 0.82 (0.68–0.98) | 970 (5 studies) | ⊕⊕⊕⊕ High |
| | 355 per 1000 | 291 per 1000 (242–348) | | | |
| Admission to NICU | Study population | | RR 0.68 (0.53–0.88) | 970 (5 studies) | ⊕⊕⊕⊕ High |
| | 247 per 1000 | 168 per 1000 (131–217) | | | |
| Mechanical ventilation | Study population | | RR 0.65 (0.41–1.01) | 723 (4 studies) | ⊕⊕⊕⊖ Moderate[d] |
| | 120 per 1000 | 78 per 1000 (49–121) | | | |
| Congenital anomaly | Study population | | RR 0.72 (0.23–2.26) | 960 (5 studies) | ⊕⊕⊖⊖ Low[c] |
| | 13 per 1000 | 9 per 1000 (3–29) | | | |
| Bayley-III cognitive composite score at age 2 y | Mean Bayley-III cognitive composite score at age 2 y in intervention groups was 2.17 lower (7.16 lower to 2.83 higher) | | | 168 (1 study) | ⊕⊕⊖⊖ Low[g] |
| Moderate/severe neurodevelopmental impairment at age 2 y | Study population | | RR 1.36 (0.54–3.39) | 158 (1 study) | ⊕⊕⊖⊖ Low[h] |
| | 91 per 1000 | 124 per 1000 (49–308) | | | |
| Visual or hearing Impairment at age 2 y | Study population | | RR 0.17 (0.01–3.58) | 187 (1 study) | ⊕⊕⊖⊖ low[h] |
| | 23 per 1000 | 4 per 1000 (0–82) | | | |
| Disability in renal, gastrointestinal, or respiratory function at age 2 y | Study population | | RR 0.92 (0.06–14.52) | 175 (1 study) | ⊕⊕⊖⊖ Low[h] |
| | 12 per 1000 | 11 per 1000 (1–173) | | | |
| Any maternal adverse event | Study population | | RR 1.21 (0.87–1.69) | 846 (5 studies) | ⊕⊕⊕⊖ Moderate[i] |
| | 111 per 1000 | 135 per 1000 (97–188) | | | |

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

[a] Risk in intervention group (and its 95% CI) is based on assumed risk in comparison group and relative effect of intervention (and its 95% CI); [b] GRADE Working Group grades of evidence: High quality = further research is very unlikely to change our confidence in estimate of effect; Moderate quality = further research is likely to have important impact on our confidence in estimate of effect and may change estimate; Low quality = further research is very likely to have important impact on our confidence in estimate of effect and is likely to change estimate; and Very low quality = we are very uncertain about estimate; [c] Few events—95% CI does not include effect and is imprecise (lower and upper bounds <0.75 and >1.25, respectively); [d] 95% CI does not include effect and is imprecise (lower bound <0.75); [e] Few events—95% CI does not include effect and is imprecise (lower bound <0.75); [f] 95% CI does not include effect and is imprecise (lower and upper bounds <0.75 and >1.25, respectively); [g] Small sample size—95% CI does not include effect and is imprecise; [h] Small sample size and few events—95% CI does not include effect and is imprecise (lower and upper bounds <0.75 and >1.25, respectively); [i] 95% CI does not include effect and is imprecise (upper bound >1.25).

*Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix. Am J Obstet Gynecol 2018.*

mechanical ventilation, because this information was not collected in the OPPTIMUM study.[54] The net effect was a reduction in the sample size of meta-analyses for these outcomes and for the composite outcome of neonatal morbidity and mortality. A second limitation was that some subgroup analyses included a small number of patients, which limits the statistical power to estimate the effects within these subgroups.

RDS is the most common complication of preterm birth; therefore, it is an appropriate endpoint when assessing neonatal morbidity. Similarly, the requirement for mechanical ventilation is an important endpoint, given that it reflects the severity of RDS, and complications may arise during or after mechanical ventilation. Most trials designed to study the effects of interventions in the prevention of preterm birth have also included RDS as a main endpoint. Indeed, even the PROGRESS trial, aimed at determining the effect of vaginal progesterone in patients with a history of preterm birth, used RDS as a primary endpoint.[76]

## Cost-effectiveness of midtrimester sonographic cervical length and vaginal progesterone in women with a short cervix

Several cost-effectiveness studies have shown that the combination of universal transvaginal cervical length screening and vaginal progesterone administration to women with a short cervix is a cost-effective intervention that reduces preterm birth and associated perinatal morbidity and mortality, regardless of the cutoff used to define a short cervix in the decision and economic analyses. Cahill et al[93] compared 4 strategies and found that universal cervical length screening to identify women with a cervical length ≤15 mm and subsequent treatment with vaginal progesterone was the most cost-effective strategy and the dominant choice over the other 3 alternatives: cervical length screening for women at increased risk for preterm birth and treatment with vaginal progesterone; risk-based treatment with 17-alpha hydroxyprogesterone caproate without screening; and no screening or treatment.[93]

Werner et al[94] found that universal cervical length screening followed by treatment with vaginal progesterone if cervical length <15 mm could prevent 22 cases of neonatal death or long-term neurologic deficits and save approximately $19.6 million for every 100,000 women screened. In 2015, Werner et al[95] reevaluated the cost-effectiveness of universal transvaginal cervical length screening and vaginal progesterone administration to women with a singleton gestation, no previous spontaneous preterm birth, and a cervical length ≤20 mm. Despite using a low prevalence of cervical length ≤20 mm in the model (0.83%), this intervention continued to be cost-effective when compared to routine care.

In 2016, Einerson et al[96] reported that universal transvaginal cervical length screening of women with no previous spontaneous preterm birth and treatment with vaginal progesterone to those with a cervical length ≤20 mm was more cost-effective in comparison to both risk-based screening and no screening of transvaginal cervical length. Crosby et al[97] reported that universal cervical length screening and treatment with vaginal progesterone to women with a cervical length ≤15 mm in a population at low risk of preterm birth in Ireland would reduce the rate of preterm birth <34 weeks of gestation by 28% and would be cost-effective. Pizzi et al[98] performed an economic analysis of the PREGNANT trial[72] and found that vaginal progesterone was both cost-saving and cost-effective as compared to placebo. A cost-effectiveness analysis of universal cervical length screening in women without a previous spontaneous preterm birth and treatment with vaginal progesterone to those with a short cervix (cervical length ≤20 mm) reported that this intervention would be cost-effective if vaginal progesterone reduces the risk of preterm birth <33 weeks of gestation by >36%.[99] In our IPD meta-analysis, vaginal progesterone decreased the risk of preterm birth <33 weeks of gestation by 38%. Finally, 5 cost-effectiveness and decision analyses published only in abstract form also reported that vaginal progesterone administration was a cost-effective strategy for preventing preterm birth in women with a short cervix.[100-104]

## Implementation of universal cervical length screening and vaginal progesterone administration to patients with a sonographic short cervix

Several authors have critically assessed if cervical length screening meets the criteria of a good screening test outlined by the World Health Organization. Combs[105] as well as Khalifeh and Berghella[106] concluded that universal midtrimester transvaginal cervical length screening for women with a singleton gestation, followed by treatment with vaginal progesterone for those with a short cervix, meets all 10 criteria outlined by the World Health Organization for endorsing the implementation of a screening test in clinical medicine.[107] Based on the totality of evidence, we and others have recommended universal transvaginal cervical length screening at 18-24 weeks of gestation in women with a singleton gestation and the administration of vaginal progesterone for those with a sonographic short cervix.[52,57,105,106,108-118]

In 2016, Son et al[119] reported on the results of introducing a universal transvaginal cervical length screening program for women with a singleton gestation without a previous preterm birth and treatment with vaginal progesterone to those with a cervical length ≤20 mm at Northwestern Memorial Hospital in Chicago, IL (46,598 women in the prescreening group and 17,609 in the screened group). The implementation of this program was associated with a significant reduction in the rates of preterm birth <37, <34, and <32 weeks of gestation when compared to preterm birth rates before implementation of the program. These significant differences were driven by a reduction in spontaneous preterm births. Furthermore, these reductions were similar in both nulliparous and parous women.

Similarly, Temming et al[120] evaluated the implementation of a universal

transvaginal cervical length screening program for women with a singleton gestation followed by treatment with vaginal progesterone to those with a cervical length ≤20 mm in St Louis, MO. The rates of preterm birth <24 and <28 weeks of gestation were significantly lower among women who underwent cervical length screening (N = 9731) than those patients who did not participate in the screening program (N = 1661). There was also a nonsignificant reduction in the rate of preterm birth <34 weeks of gestation among screened women.

A smaller study that assessed a similar program for women with a singleton gestation without a history of spontaneous preterm birth at a single institution in Philadelphia, PA, reported that the rate of spontaneous preterm birth was similar between women undergoing transvaginal cervical length screening (N = 1569) and those not screened (N = 602).[121] However, that study was underpowered to detect differences in spontaneous preterm birth rates between the study groups. Schoen et al[122] assessed the reasons behind the decrease in preterm birth rates in the United States during the last 7 years and suggested that the use of vaginal progesterone in pregnant women with a short cervix is one of the interventions that contributed to this reduction.

Recently, Newnham et al[123] reported the results of a prospective population-based cohort study that evaluated the effects of implementation of a statewide multifaceted program on the preterm birth rates in Western Australia before and after the first full year of operation. One of the key interventions of the program was the universal cervical length measurement at 18-20 weeks of gestation in women with a singleton gestation and treatment with vaginal progesterone to those with a cervical length ≤25 mm. The implementation of the program in 2014 was followed by a statistically significant 7.6% reduction in the rate of preterm birth in 2015, which was lower than in any of the preceding 6 years. The effect extended from the 28- to 31-week gestational age group onward. Further studies are required to elucidate the precise contribution of the different elements of the program to the reduction in preterm birth.

Based on current national vital statistics[2] and the results of our IPD meta-analysis, we estimated that the implementation of universal transvaginal cervical length screening in women with a singleton gestation in the United States and treatment with vaginal progesterone to those with a short cervix (cervical length ≤25 mm) would result in an annual reduction of approximately 31,800 preterm births <34 weeks of gestation and of 19,800 cases of major neonatal morbidity or neonatal mortality if the overall prevalence of a short cervix is 9%,[13] and of approximately 7000 preterm births <34 weeks of gestation and of 4400 cases of major neonatal morbidity or neonatal mortality if the overall prevalence of a short cervix is 2%.[120]

## The effects of progesterone on the uterine cervix

Progesterone is critical for pregnancy maintenance, and a withdrawal of progesterone action is believed to be central to the initiation of parturition in most mammalian species, including primates.[124-131] Progesterone exerts biological effects in the myometrium,[132-136] chorioamniotic membranes,[137] and uterine cervix (ie, control of cervical remodeling).[138,139] Progesterone withdrawal (in rats, rabbits, and sheep) or a decline in progesterone action (in guinea pigs and primates)[129] has been proposed as a key control mechanism for cervical ripening by Xu et al,[140] Nold et al,[141] Mahendroo et al,[142,143] Word et al,[144] Kirby et al,[145] Yellon et al,[146,147] and Chwalisz et al.[148-150] Thus, a large body of evidence supports a role for progesterone in cervical remodeling.[151-158] For example: (1) administration of antiprogestins to women in the midtrimester and at term induces cervical ripening;[151-158] and (2) administration of progesterone-receptor antagonists such as mifepristone (RU486) or onapristone to pregnant guinea pigs,[159] old-world monkeys,[160] and Tupaja belangeri induces cervical ripening.[144] It is interesting that cervical responsiveness to antiprogestins increases with advancing gestational age[144] and that their effects on the cervix are not always accompanied by changes in myometrial activity.[144] Indeed, Stys et al[161] demonstrated a functional dissociation between the effects of progesterone in the myometrium and those in the cervix. Collectively, the evidence indicates that a major site of progesterone action is the uterine cervix.

A decline in progesterone action probably causes cervical changes by inducing changes in extracellular matrix metabolism, and perhaps inflammation (leukocyte infiltration and production of chemokines[162] such as interleukin-8,[139] nitric oxide,[150,157] prostaglandins,[139] and matrix-degrading enzymes).[163,164] It is also possible that cervical remodeling is influenced by nuclear factor (NF)-κB, a transcription factor that mediates the effect of certain proinflammatory cytokines such as interleukin-1β[165-168] and tumor necrosis factor-α.[169-171] This is potentially relevant because NF-κB can oppose progesterone action.[132,167,172-174] Thus, NF-κB could provide a link among inflammation, a decline in progesterone action and cervical remodeling.

The traditional understanding of the mechanisms of progesterone action is that this hormone functions through nuclear receptors to prompt genomic processes.[175-182] However, it is now clear that some progesterone actions in pregnancy are induced through membrane receptors and nongenomic mechanisms.[183-187] The precise roles of progesterone receptors, deoxyribonucleic acid-binding properties, and/or transcriptional activity in determining the mechanisms of progesterone action on the cervix remain to be elucidated.

Another unresolved issue is why progesterone administration to pregnant women, who already have a very high concentration of circulating progesterone,[144] would result in a therapeutic effect. In fact, it has been argued that the circulating concentration of progesterone in pregnant women is in excess of that required to saturate progesterone receptors.[144] However, these biochemical considerations were developed before the realization that some actions

of progesterone are independent of its nuclear receptors.[188,189] It is possible that the change in progesterone concentrations at the time of spontaneous parturition in the human occurs locally and not in the systemic circulation.[190,191] Recently, the laboratories of Lye and Mesiano[192-194] have provided evidence in support of a novel mechanism whereby a functional progesterone withdrawal could occur in the myometrium, independent of a progesterone concentration in the peripheral circulation. Whether this specific mechanism is operational in the uterine cervix remains to be determined.

A recent study[195] about the mechanisms of action of progestogens in vivo has shown that vaginal progesterone has local antiinflammatory effects at the maternal-fetal interface. Specifically, when vaginal progesterone is administered to pregnant mice, it fosters an antiinflammatory microenvironment at the maternal-fetal interface by increasing $CD4^+$ Tregs and reducing $CD8^+CD25^+Foxp3^+$ T cells, macrophages, and interferon $\gamma^+$ neutrophils.[195] In addition, the administration of vaginal progesterone decreases the infiltration of active matrix metalloproteinase-$9^+$ neutrophils and monocytes in the cervix, reduces the plasma concentration of interleukin-1$\beta$, and reduces the frequency of endotoxin-induced preterm birth.[195]

In summary, progesterone has antiinflammatory effects and also modulates other biological processes implicated in cervical ripening.

## Conclusions

There is persuasive evidence that vaginal progesterone reduces the risk of preterm birth and adverse perinatal outcomes in patients with a singleton gestation and a midtrimester short cervix, regardless of the history of spontaneous preterm birth, without any demonstrable deleterious effects on childhood neurodevelopment or maternal health. The findings of our meta-analysis of IPD should reassure clinicians and professional/scientific organizations that vaginal progesterone is efficacious and safe for reducing preterm birth and neonatal morbidity and mortality in these women. In addition, recent evidence assessing the implementation of universal cervical length screening in women with a singleton gestation and treatment with vaginal progesterone to those with a short cervix suggests that this intervention could contribute to a reduction in the rate of preterm birth and associated neonatal morbidity and mortality in the United States. ■

## Acknowledgment

We are grateful to Professor Jane E. Norman and the investigators of the OPPTIMUM trial for providing the individual data for the 251 patients with a cervical length of ≤25 mm. Professor Jane Norman is Principal Investigator at the Tommy's Centre for Maternal and Fetal Health, Medical Research Council (MRC) Center for Reproductive Health, University of Edinburgh, Edinburgh, United Kingdom. The OPPTIMUM study was funded by the Efficacy and Mechanism Evaluation (EME) program, a MRC and National Institute for Health Research (NIHR) partnership, award number G0700452, revised to 09/800/27. The EME program is funded by the MRC and NIHR, with contributions from the Chief Scientist Office in Scotland and the National Institute for Social Care and Research in Wales. Professor Jane Norman has no conflict of interest in relation to our meta-analysis of individual patient data.

## References

1. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162-72.
2. Martin JA, Hamilton BE, Osterman MJ, Driscoll AK, Mathews TJ. Births: final data for 2015. Natl Vital Stat Rep 2017;66:1.
3. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015;385:430-40.
4. Institute of Medicine Committee on Understanding Premature Birth and Assuring Healthy Outcomes. The National Academies Collection: reports funded by National Institutes of Health. In: Behrman RE, Butler AS, eds. Preterm birth: causes, consequences, and prevention. Washington (DC): National Academies Press (US), National Academy of Sciences; 2007.
5. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008;371:261-9.
6. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet 2012;379:445-52.
7. Parkinson JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. Pediatrics 2013;131:e1240-63.
8. Li S, Zhang M, Tian H, Liu Z, Yin X, Xi B. Preterm birth and risk of type 1 and type 2 diabetes: systematic review and meta-analysis. Obes Rev 2014;15:804-11.
9. Romero R, Mazor M, Munoz H, Gomez R, Galasso M, Sherer DM. The preterm labor syndrome. Ann N Y Acad Sci 1994;734:414-29.
10. Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. BJOG 2006;113(Suppl):17-42.
11. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science 2014;345:760-5.
12. Andersen HF, Nugent CE, Wanty SD, Hayashi RH. Prediction of risk for preterm delivery by ultrasonographic measurement of cervical length. Am J Obstet Gynecol 1990;163:859-67.
13. Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. N Engl J Med 1996;334:567-72.
14. Goldenberg RL, Iams JD, Miodovnik M, et al. The preterm prediction study: risk factors in twin gestations. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1996;175:1047-53.
15. Imseis HM, Albert TA, Iams JD. Identifying twin gestations at low risk for preterm birth with a transvaginal ultrasonographic cervical measurement at 24 to 26 weeks' gestation. Am J Obstet Gynecol 1997;177:1149-55.
16. Wennerholm UB, Holm B, Mattsby-Baltzer I, et al. Fetal fibronectin, endotoxin, bacterial vaginosis and cervical length as predictors of preterm birth and neonatal morbidity in twin pregnancies. Br J Obstet Gynaecol 1997;104:1398-404.
17. Berghella V, Tolosa JE, Kuhlman K, Weiner S, Bolognese RJ, Wapner RJ. Cervical ultrasonography compared with manual examination as a predictor of preterm delivery. Am J Obstet Gynecol 1997;177:723-30.
18. Grisaru-Granovsky S, Farine D, Barrett J, et al. Is a single ultrasound measurement of cervical length a predictor of the risk of preterm delivery in multifetal pregnancy? Am J Obstet Gynecol 1998;178:191S.
19. Hassan SS, Romero R, Berry SM, et al. Patients with an ultrasonographic cervical length < or =15 mm have nearly a 50% risk of early spontaneous preterm delivery. Am J Obstet Gynecol 2000;182:1458-67.
20. Yang JH, Kuhlman K, Daly S, Berghella V. Prediction of preterm birth by second trimester cervical sonography in twin pregnancies. Ultrasound Obstet Gynecol 2000;15:288-91.
21. Guzman ER, Walters C, O'Reilly-Green C, et al. Use of cervical ultrasonography in

prediction of spontaneous preterm birth in twin gestations. Am J Obstet Gynecol 2000;183:1103-7.
**22.** Soriano D, Weisz B, Seidman DS, et al. The role of sonographic assessment of cervical length in the prediction of preterm birth in primigravidae with twin gestation conceived after infertility treatment. Acta Obstet Gynecol Scand 2002;81:39-43.
**23.** Vayssiere C, Favre R, Audibert F, et al. Cervical length and funneling at 22 and 27 weeks to predict spontaneous birth before 32 weeks in twin pregnancies: a French prospective multicenter study. Am J Obstet Gynecol 2002;187:1596-604.
**24.** Honest H, Bachmann LM, Coomarasamy A, Gupta JK, Kleijnen J, Khan KS. Accuracy of cervical transvaginal sonography in predicting preterm birth: a systematic review. Ultrasound Obstet Gynecol 2003;22:305-22.
**25.** Owen J, Yost N, Berghella V, et al. Can shortened midtrimester cervical length predict very early spontaneous preterm birth? Am J Obstet Gynecol 2004;191:298-303.
**26.** Gibson JL, Macara LM, Owen P, Young D, Macauley J, Mackenzie F. Prediction of preterm delivery in twin pregnancy: a prospective, observational study of cervical length and fetal fibronectin testing. Ultrasound Obstet Gynecol 2004;23:561-6.
**27.** Sperling L, Kiil C, Larsen LU, et al. How to identify twins at low risk of spontaneous preterm delivery. Ultrasound Obstet Gynecol 2005;26:138-44.
**28.** Fait G, Har-Toov J, Gull I, Lessing JB, Jaffa A, Wolman I. Cervical length, multifetal pregnancy reduction, and prediction of preterm birth. J Clin Ultrasound 2005;33:329-32.
**29.** Arabin B, Roos C, Kollen B, van Eyck J. Comparison of transvaginal sonography in recumbent and standing maternal positions to predict spontaneous preterm birth in singleton and twin pregnancies. Ultrasound Obstet Gynecol 2006;27:377-86.
**30.** To MS, Skentou CA, Royston P, Yu CK, Nicolaides KH. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of cervical length: a population-based prospective study. Ultrasound Obstet Gynecol 2006;27:362-7.
**31.** To MS, Fonseca EB, Molina FS, Cacho AM, Nicolaides KH. Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins. Am J Obstet Gynecol 2006;194:1360-5.
**32.** Crane JM, Hutchens D. Transvaginal sonographic measurement of cervical length to predict preterm birth in asymptomatic women at increased risk: a systematic review. Ultrasound Obstet Gynecol 2008;31:579-87.
**33.** Klein K, Gregor H, Hirtenlehner-Ferber K, et al. Prediction of spontaneous preterm delivery in twin pregnancies by cervical length at mid-gestation. Twin Res Hum Genet 2008;11:552-7.
**34.** Fox NS, Saltzman DH, Klauser CK, Peress D, Gutierrez CV, Rebarber A. Prediction of spontaneous preterm birth in asymptomatic twin pregnancies with the use of combined fetal fibronectin and cervical length. Am J Obstet Gynecol 2009;201:313.e1-5.
**35.** Honest H, Forbes CA, Duree KH, et al. Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling. Health Technol Assess 2009;13:1-627.
**36.** Domin CM, Smith EJ, Terplan M. Transvaginal ultrasonographic measurement of cervical length as a predictor of preterm birth: a systematic review with meta-analysis. Ultrasound Q 2010;26:241-8.
**37.** Conde-Agudelo A, Romero R, Hassan SS, Yeo L. Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and metaanalysis. Am J Obstet Gynecol 2010;203:128.e1-12.
**38.** Lim AC, Hegeman MA, Huis In TVMA, Opmeer BC, Bruinse HW, Mol BW. Cervical length measurement for the prediction of preterm birth in multiple pregnancies: a systematic review and bivariate meta-analysis. Ultrasound Obstet Gynecol 2011;38:10-7.
**39.** Barros-Silva J, Pedrosa AC, Matias A. Sonographic measurement of cervical length as a predictor of preterm delivery: a systematic review. J Perinat Med 2014;42:281-93.
**40.** Conde-Agudelo A, Romero R. Prediction of preterm birth in twin gestations using biophysical and biochemical tests. Am J Obstet Gynecol 2014;211:583-95.
**41.** Li Q, Reeves M, Owen J, Keith LG. Precocious cervical ripening as a screening target to predict spontaneous preterm delivery among asymptomatic singleton pregnancies: a systematic review. Am J Obstet Gynecol 2015;212:145-56.
**42.** Conde-Agudelo A, Romero R. Predictive accuracy of changes in transvaginal sonographic cervical length over time for preterm birth: a systematic review and metaanalysis. Am J Obstet Gynecol 2015;213:789-801.
**43.** Kindinger LM, Poon LC, Cacciatore S, et al. The effect of gestational age and cervical length measurements in the prediction of spontaneous preterm birth in twin pregnancies: an individual patient level meta-analysis. BJOG 2016;123:877-84.
**44.** Melamed N, Pittini A, Hiersch L, et al. Serial cervical length determination in twin pregnancies reveals 4 distinct patterns with prognostic significance for preterm birth. Am J Obstet Gynecol 2016;215:476.e1-11.
**45.** Vandermolen BI, Hezelgrave NL, Smout EM, Abbott DS, Seed PT, Shennan AH. Quantitative fetal fibronectin and cervical length to predict preterm birth in asymptomatic women with previous cervical surgery. Am J Obstet Gynecol 2016;215:480.e1-10.
**46.** Melamed N, Pittini A, Hiersch L, et al. Do serial measurements of cervical length improve the prediction of preterm birth in asymptomatic women with twin gestations? Am J Obstet Gynecol 2016;215:616.e1-14.
**47.** Moroz LA, Brock CO, Govindappagari S, Johnson DL, Leopold BH, Gyamfi-Bannerman C. Association between change in cervical length and spontaneous preterm birth in twin pregnancies. Am J Obstet Gynecol 2017;216:159.e1-7.
**48.** Esplin MS, Elovitz MA, Iams JD, et al. Predictive accuracy of serial transvaginal cervical lengths and quantitative vaginal fetal fibronectin levels for spontaneous preterm birth among nulliparous women. JAMA 2017;317:1047-56.
**49.** Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol 2012;206:124.e1-19.
**50.** Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol 2012;206:376-86.
**51.** Committee on Practice Bulletins—Obstetrics, American College of Obstetricians and Gynecologists. Prediction and prevention of preterm birth. Practice bulletin no. 130. Obstet Gynecol 2012;120:964-73.
**52.** FIGO Working Group on Best Practice in Maternal-Fetal Medicine; International Federation of Gynecology and Obstetrics. Best practice in maternal-fetal medicine. Int J Gynaecol Obstet 2015;128:80-2.
**53.** National Institute for Health and Care Excellence. Preterm labor and birth. Available at: guideline.2015. https://www.nice.org.uk/guidance/ng25/evidence/resources/full-guideline-2176838029. Accessed Nov. 12, 2017.
**54.** Norman JE, Marlow N, Messow CM, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicenter, randomized, double-blind trial. Lancet 2016;387:2106-16.
**55.** National Institute for Health and Care Excellence. Surveillance report (exceptional review) 2017—preterm labor and birth (2015) NICE guidelines NG25. Available at: http://www.nice.org.uk/guidance/ng25/resources/surveillance-report-exceptional-%20review-2017-preterm-labour-and-birth-2015-nice-guideline-ng25-5642777402053. Accessed July 3, 2017.
**56.** Society for Maternal-Fetal Medicine (SMFM) Publications Committee. The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth. Am J Obstet Gynecol 2017;216:B11-3.
**57.** Romero R, Nicolaides KH, Conde-Agudelo A, et al. Vaginal progesterone decreases preterm birth </= 34 weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study. Ultrasound Obstet Gynecol 2016;48:308-17.

**58.** Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD statement. JAMA 2015;313:1657-65.
**59.** Higgins J, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0 (updated March 2011). The Cochrane Collaboration; 2011.
**60.** Tierney JF, Vale C, Riley R, et al. Individual participant data (IPD) meta-analyses of randomized controlled trials: guidance on their use. PLoS Med 2015;12:e1001855.
**61.** Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
**62.** Altman DG. Confidence intervals for the number needed to treat. BMJ 1998;317:1309-12.
**63.** Klebanoff MA. Subgroup analysis in obstetrics clinical trials. Am J Obstet Gynecol 2007;197:119-22.
**64.** Sun X, Ioannidis JP, Agoritsas T, Alba AC, Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. JAMA 2014;311:405-11.
**65.** Klebanoff MA. 17 alpha-Hydroxyprogesterone caproate for preterm prevention: issues in subgroup analysis. Am J Obstet Gynecol 2016;214:306-7.
**66.** Schünemann H, Brozek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendation. The GRADE Working Group; 2013.
**67.** GRADEpro G. GRADEpro guideline development tool [software]. Hamilton, Ontario, (Canada): McMaster University; 2015.
**68.** da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419-24.
**69.** Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462-9.
**70.** O'Brien JM, Adair CD, Lewis DF, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2007;30:687-96.
**71.** Cetingoz E, Cam C, Sakalli M, Karateke A, Celik C, Sancak A. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. Arch Gynecol Obstet 2011;283:423-9.
**72.** Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2011;38:18-31.
**73.** Aboulghar MM, Aboulghar MA, Amin YM, Al-Inany HG, Mansour RT, Serour GI. The use of vaginal natural progesterone for prevention of preterm birth in IVF/ICSI pregnancies. Reprod Biomed Online 2012;25:133-8.
**74.** van Os MA, van der Ven AJ, Kleinrouweler CE, et al. Preventing preterm birth with progesterone in women with a short cervical length from a low-risk population: a multicenter double-blind placebo-controlled randomized trial. Am J Perinatol 2015;32:993-1000.
**75.** Azargoon A, Ghorbani R, Aslebahar F. Vaginal progesterone on the prevention of preterm birth and neonatal complications in high risk women: a randomized placebo-controlled double-blind study. Int J Reprod Biomed (Yazd) 2016;14:309-16.
**76.** Crowther CA, Ashwood P, McPhee AJ, et al. Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS study): a multicenter, randomized, placebo-controlled trial. PLoS Med 2017;14:e1002390.
**77.** Majhi P, Bagga R, Kalra J, Sharma M. Intravaginal use of natural micronized progesterone to prevent pre-term birth: a randomized trial in India. J Obstet Gynaecol 2009;29:493-8.
**78.** Akbari S, Birjandi M, Mohtasham N. Evaluation of the effect of progesterone on prevention of preterm delivery and its complications. Sci J Kurdistan Univ Med Sci 2009;14:11-9.
**79.** Jo B. Statistical power in randomized intervention studies with noncompliance. Psychol Methods 2002;7:178-93.
**80.** Shapiro-Mendoza CK, Lackritz EM. Epidemiology of late and moderate preterm birth. Semin Fetal Neonatal Med 2012;17:120-5.
**81.** Raju TN, Langenberg P, Sen A, Aldana O. How much 'better' is good enough? The magnitude of treatment effect in clinical trials. Am J Dis Child 1992;146:407-11.
**82.** Conde-Agudelo A, Romero R, Nicolaides K, et al. Vaginal progesterone vs cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis. Am J Obstet Gynecol 2013;208:42.e1-18.
**83.** Yusuf S, Wittes J. Interpreting geographic variations in results of randomized, controlled trials. N Engl J Med 2016;375:2263-71.
**84.** Kiefer DG, Keeler SM, Rust OA, Wayock CP, Vintzileos AM, Hanna N. Is midtrimester short cervix a sign of intraamniotic inflammation? Am J Obstet Gynecol 2009;200:374.e1-5.
**85.** Vaisbuch E, Hassan SS, Mazaki-Tovi S, et al. Patients with an asymptomatic short cervix (<or=15 mm) have a high rate of subclinical intraamniotic inflammation: implications for patient counseling. Am J Obstet Gynecol 2010;202:433.e1-8.
**86.** Romero R, Miranda J, Chaiworapongsa T, et al. Sterile intra-amniotic inflammation in asymptomatic patients with a sonographic short cervix: prevalence and clinical significance. J Matern Fetal Neonatal Med 2014:1-17.
**87.** Tarca AL, Fitzgerald W, Chaemsaithong P, et al. The cytokine network in women with an asymptomatic short cervix and the risk of preterm delivery. Am J Reprod Immunol 2017;78.
**88.** O'Brien JM, Steichen JJ, Phillips JA, Creasy GW. Two year infant outcomes for children exposed to supplemental intravaginal progesterone gel in utero: secondary analysis of a multicenter, randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol 2012;206:S223.
**89.** Norman JE, Mackenzie F, Owen P, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomized, double-blind, placebo-controlled study and meta-analysis. Lancet 2009;373:2034-40.
**90.** Rode L, Klein K, Nicolaides KH, Krampl-Bettelheim E, Tabor A. Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. Ultrasound Obstet Gynecol 2011;38:272-80.
**91.** McNamara HC, Wood R, Chalmers J, et al. STOPPIT Baby Follow-up Study: the effect of prophylactic progesterone in twin pregnancy on childhood outcome. PLoS One 2015;10:e0122341.
**92.** Vedel C, Larsen H, Holmskov A, et al. Long-term effects of prenatal progesterone exposure: neurophysiological development and hospital admissions in twins up to 8 years of age. Ultrasound Obstet Gynecol 2016;48:382-9.
**93.** Cahill AG, Odibo AO, Caughey AB, et al. Universal cervical length screening and treatment with vaginal progesterone to prevent preterm birth: a decision and economic analysis. Am J Obstet Gynecol 2010;202:548.e1-8.
**94.** Werner EF, Han CS, Pettker CM, et al. Universal cervical-length screening to prevent preterm birth: a cost-effectiveness analysis. Ultrasound Obstet Gynecol 2011;38:32-7.
**95.** Werner EF, Hamel MS, Orzechowski K, Berghella V, Thung SF. Cost-effectiveness of transvaginal ultrasound cervical length screening in singletons without a prior preterm birth: an update. Am J Obstet Gynecol 2015;213:554.e1-6.
**96.** Einerson BD, Grobman WA, Miller ES. Cost-effectiveness of risk-based screening for cervical length to prevent preterm birth. Am J Obstet Gynecol 2016;215:100.e1-7.
**97.** Crosby DA, Miletin J, Semberova J, Daly S. Is routine transvaginal cervical length measurement cost-effective in a population where the risk of spontaneous preterm birth is low? Acta Obstet Gynecol Scand 2016;95:1391-5.
**98.** Pizzi LT, Seligman NS, Baxter JK, Jutkowitz E, Berghella V. Cost and cost effectiveness of vaginal progesterone gel in reducing preterm birth: an economic analysis of the PREGNANT trial. Pharmacoeconomics 2014;32:467-78.
**99.** Jain S, Kilgore M, Edwards RK, Owen J. Revisiting the cost-effectiveness of universal cervical length screening: importance of progesterone efficacy. Am J Obstet Gynecol 2016;215:101.e1-7.

**100.** Page J, Emerson J, Cahill A, et al. The impact of cervical length on the cost-effectiveness of vaginal progesterone as a preterm birth intervention. Am J Obstet Gynecol 2013;208:S66.
**101.** Brown S, Mozurkewich E. Cost analysis of universal cervical length screening and progesterone therapy in remote populations. Am J Obstet Gynecol 2014;210:S201.
**102.** Fonseca EB, Nishikawa AM, Paladini L, Clark OA. Cervical assessment with progesterone in the prevention of preterm birth: a strategy based on cost-effectiveness. Value Health 2014;17:A510.
**103.** Eke A, Buras A, Drnec S, Woo J. Vaginal progesterone versus cervical cerclage for the prevention of preterm births in women with a sonographically short cervix—a cost effectiveness and decision analysis. Am J Obstet Gynecol 2015;212:S367-8.
**104.** Green PM, Argyelan A, Mutual F, Nynas J, Williams J, Keeton K. Implementation of universal cervical length screening is associated with a reduction in the rate of spontaneous preterm delivery in a low-risk cohort. Am J Obstet Gynecol 2017;216:S10.
**105.** Combs CA. Vaginal progesterone for asymptomatic cervical shortening and the case for universal screening of cervical length. Am J Obstet Gynecol 2012;206:101-3.
**106.** Khalifeh A, Berghella V. Universal cervical length screening in singleton gestations without a previous preterm birth: ten reasons why it should be implemented. Am J Obstet Gynecol 2016;214:603.e1-5.
**107.** Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization; 1968.
**108.** Romero R, Yeo L, Miranda J, Hassan SS, Conde-Agudelo A, Chaiworapongsa T. A blueprint for the prevention of preterm birth: vaginal progesterone in women with a short cervix. J Perinat Med 2013;41:27-44.
**109.** Romero R, Yeo L, Chaemsaithong P, Chaiworapongsa T, Hassan SS. Progesterone to prevent spontaneous preterm birth. Semin Fetal Neonatal Med 2014;19:15-26.
**110.** Campbell S. Universal cervical-length screening and vaginal progesterone prevents early preterm births, reduces neonatal morbidity and is cost saving: doing nothing is no longer an option. Ultrasound Obstet Gynecol 2011;38:1-9.
**111.** Iams JD. Clinical practice. Prevention of preterm parturition. N Engl J Med 2014;370:254-61.
**112.** Kuon RJ, Abele H, Berger R, et al. Progesterone for prevention of preterm birth—evidence-based indications [in German]. Z Geburtshilfe Neonatol 2015;219:125-35.
**113.** Conde-Agudelo A, Romero R. Vaginal progesterone to prevent preterm birth in pregnant women with a sonographic short cervix: clinical and public health implications. Am J Obstet Gynecol 2016;214:235-42.
**114.** Goodnight W. Clinical application of progesterone for the prevention of preterm birth, 2016. Am J Perinatol 2016;33:253-7.
**115.** O'Brien JM, Lewis DF. Prevention of preterm birth with vaginal progesterone or 17-alpha-hydroxyprogesterone caproate: a critical examination of efficacy and safety. Am J Obstet Gynecol 2016;214:45-56.
**116.** Vintzileos AM, Visser GH. Interventions for women with mid-trimester short cervix: which ones work? Ultrasound Obstet Gynecol 2017;49:295-300.
**117.** Pedretti MK, Kazemier BM, Dickinson JE, Mol BW. Implementing universal cervical length screening in asymptomatic women with singleton pregnancies: challenges and opportunities. Aust N Z J Obstet Gynaecol 2017;57:221-7.
**118.** Newnham JP, Kemp MW, White SW, Arrese CA, Hart RJ, Keelan JA. Applying precision public health to prevent preterm birth. Front Public Health 2017;5:66.
**119.** Son M, Grobman WA, Ayala NK, Miller ES. A universal mid-trimester transvaginal cervical length screening program and its associated reduced preterm birth rate. Am J Obstet Gynecol 2016;214:365.e1-5.
**120.** Temming LA, Durst JK, Tuuli MG, et al. Universal cervical length screening: implementation and outcomes. Am J Obstet Gynecol 2016;214:523.e1-8.
**121.** Orzechowski KM, Boelig RC, Baxter JK, Berghella V. A universal transvaginal cervical length screening program for preterm birth prevention. Obstet Gynecol 2014;124:520-5.
**122.** Schoen CN, Tabbah S, Iams JD, Caughey AB, Berghella V. Why the United States preterm birth rate is declining. Am J Obstet Gynecol 2015;213:175-80.
**123.** Newnham JP, White SW, Meharry S, et al. Reducing preterm birth by a statewide multifaceted program: an implementation study. Am J Obstet Gynecol 2017;216:434-42.
**124.** Stites DP, Siiteri PK. Steroids as immunosuppressants in pregnancy. Immunol Rev 1983;75:117-38.
**125.** Chwalisz K. The use of progesterone antagonists for cervical ripening and as an adjunct to labor and delivery. Hum Reprod 1994;9(Suppl):131-61.
**126.** Pepe GJ, Albrecht ED. Actions of placental and fetal adrenal steroid hormones in primate pregnancy. Endocr Rev 1995;16:608-48.
**127.** Fidel PI Jr, Romero R, Maymon E, Hertelendy F. Bacteria-induced or bacterial product-induced preterm parturition in mice and rabbits is preceded by a significant fall in serum progesterone concentrations. J Matern Fetal Med 1998;7:222-6.
**128.** Henson MC. Pregnancy maintenance and the regulation of placental progesterone biosynthesis in the baboon. Hum Reprod Update 1998;4:389-405.
**129.** Bernal AL. Overview of current research in parturition. Exp Physiol 2001;86:213-22.
**130.** Mesiano S. Roles of estrogen and progesterone in human parturition. Front Horm Res 2001;27:86-104.
**131.** Mesiano S. Myometrial progesterone responsiveness and the control of human parturition. J Soc Gynecol Investig 2004;11:193-202.
**132.** Mendelson CR, Condon JC. New insights into the molecular endocrinology of parturition. J Steroid Biochem Mol Biol 2005;93:113-9.
**133.** Merlino AA, Welsh TN, Tan H, et al. Nuclear progesterone receptors in the human pregnancy myometrium: evidence that parturition involves functional progesterone withdrawal mediated by increased expression of progesterone receptor-A. J Clin Endocrinol Metab 2007;92:1927-33.
**134.** Blanks AM, Brosens JJ. Progesterone action in the myometrium and decidua in preterm birth. Facts Views Vis Obgyn 2012;4:33-43.
**135.** Tan H, Yi L, Rote NS, Hurd WW, Mesiano S. Progesterone receptor-A and -B have opposite effects on proinflammatory gene expression in human myometrial cells: implications for progesterone actions in human pregnancy and parturition. J Clin Endocrinol Metab 2012;97:E719-30.
**136.** Williams KC, Renthal NE, Gerard RD, Mendelson CR. The microRNA (miR)-199a/214 cluster mediates opposing effects of progesterone and estrogen on uterine contractility during pregnancy and labor. Mol Endocrinol 2012;26:1857-67.
**137.** Merlino A, Welsh T, Erdonmez T, et al. Nuclear progesterone receptor expression in the human fetal membranes and decidua at term before and after labor. Reprod Sci 2009;16:357-63.
**138.** Rajabi M, Solomon S, Poole AR. Hormonal regulation of interstitial collagenase in the uterine cervix of the pregnant guinea pig. Endocrinology 1991;128:863-71.
**139.** Denison FC, Calder AA, Kelly RW. The action of prostaglandin E2 on the human cervix: stimulation of interleukin 8 and inhibition of secretory leukocyte protease inhibitor. Am J Obstet Gynecol 1999;180:614-20.
**140.** Xu H, Gonzalez JM, Ofori E, Elovitz MA. Preventing cervical ripening: the primary mechanism by which progestational agents prevent preterm birth? Am J Obstet Gynecol 2008;198:314.e1-8.
**141.** Nold C, Maubert M, Anton L, Yellon S, Elovitz MA. Prevention of preterm birth by progestational agents: what are the molecular mechanisms? Am J Obstet Gynecol 2013;208:223.e1-7.
**142.** Mahendroo MS, Cala KM, Russell DW. 5 alpha-Reduced androgens play a key role in murine parturition. Mol Endocrinol 1996;10:380-92.
**143.** Mahendroo MS, Porter A, Russell DW, Word RA. The parturition defect in steroid 5alpha-reductase type 1 knockout mice is due to impaired cervical ripening. Mol Endocrinol 1999;13:981-92.
**144.** Word RA, Li XH, Hnat M, Carrick K. Dynamics of cervical remodeling during pregnancy and parturition: mechanisms and current concepts. Semin Reprod Med 2007;25:69-79.
**145.** Kirby MA, Heuerman AC, Custer M, et al. Progesterone receptor-mediated actions regulate remodeling of the cervix in preparation for

preterm parturition. Reprod Sci 2016;23:1473-83.
**146.** Yellon SM, Dobyns AE, Beck HL, Kurtzman JT, Garfield RE, Kirby MA. Loss of progesterone receptor-mediated actions induce preterm cellular and structural remodeling of the cervix and premature birth. PLoS One 2013;8:e81340.
**147.** Yellon SM. Contributions to the dynamics of cervix remodeling prior to term and preterm birth. Biol Reprod 2017;96:13-23.
**148.** Chwalisz K, Garfield RE. Regulation of the uterus and cervix during pregnancy and labor. Role of progesterone and nitric oxide. Ann N Y Acad Sci 1997;828:238-53.
**149.** Chwalisz K, Shao-Qing S, Garfield RE, Beier HM. Cervical ripening in guinea-pigs after a local application of nitric oxide. Hum Reprod 1997;12:2093-101.
**150.** Chwalisz K, Garfield RE. Nitric oxide as the final metabolic mediator of cervical ripening. Hum Reprod 1998;13:245-8.
**151.** Saito Y, Takahashi S, Maki M. Effects of some drugs on ripening of uterine cervix in nonpregnant castrated and pregnant rats. Tohoku J Exp Med 1981;133:205-20.
**152.** Garfield RE, Puri CP, Csapo AI. Endocrine, structural, and functional changes in the uterus during premature labor. Am J Obstet Gynecol 1982;142:21-7.
**153.** Zuidema LJ, Khan-Dawood F, Dawood MY, Work BA Jr. Hormones and cervical ripening: dehydroepiandrosterone sulfate, estradiol, estriol, and progesterone. Am J Obstet Gynecol 1986;155:1252-4.
**154.** Stiemer B, Elger W. Cervical ripening of the rat in dependence on endocrine milieu; effects of antigestagens. J Perinat Med 1990;18:419-29.
**155.** Ito A, Imada K, Sato T, Kubo T, Matsushima K, Mori Y. Suppression of interleukin 8 production by progesterone in rabbit uterine cervix. Biochem J 1994;301:183-6.
**156.** Elovitz M, Wang Z. Medroxyprogesterone acetate, but not progesterone, protects against inflammation-induced parturition and intrauterine fetal demise. Am J Obstet Gynecol 2004;190:693-701.
**157.** Marx SG, Wentz MJ, Mackay LB, et al. Effects of progesterone on iNOS, COX-2, and collagen expression in the cervix. J Histochem Cytochem 2006;54:623-39.
**158.** Facchinetti F, Paganelli S, Comitini G, Dante G, Volpe A. Cervical length changes during preterm cervical ripening: effects of 17-alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol 2007;196:453.e1-4.
**159.** Hegele-Hartung C, Chwalisz K, Beier HM, Elger W. Ripening of the uterine cervix of the guinea-pig after treatment with the progesterone antagonist onapristone (ZK 98.299): an electron microscopic study. Hum Reprod 1989;4:369-77.
**160.** Wolf JP, Sinosich M, Anderson TL, Ulmann A, Baulieu EE, Hodgen GD. Progesterone antagonist (RU 486) for cervical dilation, labor induction, and delivery in monkeys: effectiveness in combination with oxytocin. Am J Obstet Gynecol 1989;160:45-7.
**161.** Stys SJ, Clewell WH, Meschia G. Changes in cervical compliance at parturition independent of uterine activity. Am J Obstet Gynecol 1978;130:414-8.
**162.** Elovitz MA, Mrinalini C. The use of progestational agents for preterm birth: lessons from a mouse model. Am J Obstet Gynecol 2006;195:1004-10.
**163.** Sato T, Ito A, Mori Y, Yamashita K, Hayakawa T, Nagase H. Hormonal regulation of collagenolysis in uterine cervical fibroblasts. Modulation of synthesis of procollagenase, prostromelysin and tissue inhibitor of metalloproteinases (TIMP) by progesterone and oestradiol-17 beta. Biochem J 1991;275:645-50.
**164.** Imada K, Ito A, Sato T, Namiki M, Nagase H, Mori Y. Hormonal regulation of matrix metalloproteinase 9/gelatinase B gene expression in rabbit uterine cervical fibroblasts. Biol Reprod 1997;56:575-80.
**165.** Choi SJ, Oh S, Kim JH, Roh CR. Changes of nuclear factor kappa B (NF-kappaB), cyclooxygenase-2 (COX-2) and matrix metalloproteinase-9 (MMP-9) in human myometrium before and during term labor. Eur J Obstet Gynecol Reprod Biol 2007;132:182-8.
**166.** Duggan SV, Lindstrom T, Iglesias T, Bennett PR, Mann GE, Bartlett SR. Role of atypical protein kinase C isozymes and NF-kappaB in IL-1beta-induced expression of cyclooxygenase-2 in human myometrial smooth muscle cells. J Cell Physiol 2007;210:637-43.
**167.** Vidaeff AC, Ramin SM, Gilstrap LC III, Bishop KD, Alcorn JL. Impact of progesterone on cytokine-stimulated nuclear factor-kappaB signaling in HeLa cells. J Matern Fetal Neonatal Med 2007;20:23-8.
**168.** Zaragoza DB, Wilson RR, Mitchell BF, Olson DM. The interleukin 1beta-induced expression of human prostaglandin F2alpha receptor messenger RNA in human myometrial-derived ULTR cells requires the transcription factor, NFkappaB. Biol Reprod 2006;75:697-704.
**169.** Bukowski R, Hankins GD, Saade GR, Anderson GD, Thornton S. Labor-associated gene expression in the human uterine fundus, lower segment, and cervix. PLoS Med 2006;3:e169.
**170.** Lappas M, Yee K, Permezel M, Rice GE. Lipopolysaccharide and TNF-alpha activate the nuclear factor kappa B pathway in the human placental JEG-3 cells. Placenta 2006;27:568-75.
**171.** Schmitz T, Souil E, Herve R, et al. PDE4 inhibition prevents preterm delivery induced by an intrauterine inflammation. J Immunol 2007;178:1115-21.
**172.** Bennett P, Allport V, Loudon J, Elliott C. Prostaglandins, the fetal membranes and the cervix. Front Horm Res 2001;27:147-64.
**173.** Condon JC, Hardy DB, Kovaric K, Mendelson CR. Up-regulation of the progesterone receptor (PR)-C isoform in laboring myometrium by activation of nuclear factor-kappaB may contribute to the onset of labor through inhibition of PR function. Mol Endocrinol 2006;20:764-75.
**174.** Hardy DB, Janowski BA, Corey DR, Mendelson CR. Progesterone receptor plays a major antiinflammatory role in human myometrial cells by antagonism of nuclear factor-kappaB activation of cyclooxygenase 2 expression. Mol Endocrinol 2006;20:2724-33.
**175.** Beato M. Gene regulation by steroid hormones. Cell 1989;56:335-44.
**176.** Rodriguez R, Carson MA, Weigel NL, O'Malley BW, Schrader WT. Hormone-induced changes in the in vitro DNA-binding activity of the chicken progesterone receptor. Mol Endocrinol 1989;3:356-62.
**177.** Denner LA, Weigel NL, Maxwell BL, Schrader WT, O'Malley BW. Regulation of progesterone receptor-mediated transcription by phosphorylation. Science 1990;250:1740-3.
**178.** Allan GF, Tsai SY, Tsai MJ, O'Malley BW. Ligand-dependent conformational changes in the progesterone receptor are necessary for events that follow DNA binding. Proc Natl Acad Sci U S A 1992;89:11750-4.
**179.** Power RF, Conneely OM, O'Malley BW. New insights into activation of the steroid hormone receptor superfamily. Trends Pharmacol Sci 1992;13:318-23.
**180.** Vegeto E, Shahbaz MM, Wen DX, Goldman ME, O'Malley BW, McDonnell DP. Human progesterone receptor A form is a cell- and promoter-specific repressor of human progesterone receptor B function. Mol Endocrinol 1993;7:1244-55.
**181.** Henderson D, Wilson T. Reduced binding of progesterone receptor to its nuclear response element after human labor onset. Am J Obstet Gynecol 2001;185:579-85.
**182.** Brosens JJ, Tullet J, Varshochi R, Lam EW. Steroid receptor action. Best Pract Res Clin Obstet Gynaecol 2004;18:265-83.
**183.** Meizel S, Turner KO. Progesterone acts at the plasma membrane of human sperm. Mol Cell Endocrinol 1991;77:R1-5.
**184.** Grazzini E, Guillon G, Mouillac B, Zingg HH. Inhibition of oxytocin receptor function by direct binding of progesterone. Nature 1998;392:509-12.
**185.** Luconi M, Bonaccorsi L, Maggi M, et al. Identification and characterization of functional nongenomic progesterone receptors on human sperm membrane. J Clin Endocrinol Metab 1998;83:877-85.
**186.** Losel R, Wehling M. Nongenomic actions of steroid hormones. Nat Rev Mol Cell Biol 2003;4:46-56.
**187.** Losel RM, Falkenstein E, Feuring M, et al. Nongenomic steroid action: controversies, questions, and answers. Physiol Rev 2003;83:965-1016.
**188.** Sfakianaki AK, Norwitz ER. Mechanisms of progesterone action in inhibiting prematurity. J Matern Fetal Neonatal Med 2006;19:763-72.
**189.** Mesiano S. Myometrial progesterone responsiveness. Semin Reprod Med 2007;25:5-13.
**190.** Romero R, Scoccia B, Mazor M, Wu YK, Benveniste R. Evidence for a local change in the progesterone/estrogen ratio in human parturition at term. Am J Obstet Gynecol 1988;159:657-60.

**191.** Cicinelli E, de Ziegler D. Transvaginal progesterone: evidence for a new functional 'portal system' flowing from the vagina to the uterus. Hum Reprod Update 1999;5:365-72.
**192.** Amini P, Michniuk D, Kuo K, et al. Human parturition involves phosphorylation of progesterone receptor-A at serine-345 in myometrial cells. Endocrinology 2016;157:4434-45.
**193.** Nadeem L, Shynlova O, Matysiak-Zablocki E, Mesiano S, Dong X, Lye S. Molecular evidence of functional progesterone withdrawal in human myometrium. Nat Commun 2016;7:11565.
**194.** Peters GA, Yi L, Skomorovska-Prokvolit Y, et al. Inflammatory stimuli increase progesterone receptor-A stability and transrepressive activity in myometrial cells. Endocrinology 2017;158:158-69.
**195.** Furcron AE, Romero R, Plazyo O, et al. Vaginal progesterone, but not 17alpha-hydroxyprogesterone caproate, has antiinflammatory effects at the murine maternal-fetal interface. Am J Obstet Gynecol 2015;213:846.e1-19.

## Author and article information

From the Perinatology Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, *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, University of Michigan, Ann Arbor, MI (Dr Romero); Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI (Dr Romero); Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI (Dr Romero); Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI (Drs Conde-Agudelo and Hassan); 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 Da Fonseca); Department of Obstetrics and Gynecology, University of Kentucky, Lexington, KY (Dr O'Brien); Department of Obstetrics and Gynecology, Turkish Red Crescent Altintepe Medical Center, Maltepe, Istanbul, Turkey (Dr Cetingoz); Center for Biomedical Research, Population Council, New York, NY (Dr Creasy); and Harris Birthright Research Center for Fetal Medicine, King's College Hospital, London, United Kingdom (Dr Nicolaides).

Received Aug. 30, 2017; revised Nov. 13, 2017; accepted Nov. 13, 2017.

This research was supported, in part, by the Perinatology Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services. The funder had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Disclosure: Dr O'Brien was involved in studies of progesterone gel treatment for preterm birth prevention sponsored by a maker of progesterone gel. He served on advisory boards and as a consultant for Watson Pharmaceuticals, a company with a financial interest in marketing vaginal progesterone gel for preterm birth prevention; he and others are listed in a patent on the use of progesterone compounds to prevent preterm birth (US patent 7884093: progesterone for the treatment and prevention of spontaneous preterm birth). He has received no royalty payments. Dr Creasy was an employee of Columbia Laboratories Inc when the previous meta-analysis of individual patient data was conducted in 2011. No other authors declare a conflict of interest.

Corresponding author: Roberto Romero, MD, DMedSci. prbchiefstaff@med.wayne.edu