Vaginal progesterone decreases preterm birth ≤34 weeks of gestation in women with a singleton gestation and a short cervix: an updated meta-analysis including data from the opptimum study

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Key words: prematurity, preterm delivery, progestins, progestogens, transvaginal

ultrasound, cervical length, neonatal morbidity, neonatal mortality

ABSTRACT

OBJECTIVE To evaluate the efficacy of vaginal progesterone administration in preventing preterm birth and perinatal morbidity and mortality in asymptomatic women with a singleton gestation and a midtrimester sonographic cervical length ≤25 mm.

METHODS Updated systematic review and meta-analysis of randomized controlled trials comparing vaginal progesterone with placebo/no treatment in women with a singleton gestation and a midtrimester sonographic cervical length ≤25 mm. Electronic databases from their inception to April 2016, bibliographies, and conference proceedings were searched. The primary outcome measure was preterm birth ≤34 weeks of gestation or fetal death. Two reviewers independently selected studies, assessed the risk of bias, and extracted the data. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated.

RESULTS Five trials involving a total of 974 women were included. A meta-analysis including data from the OPPTIMUM study showed that, compared with placebo, vaginal progesterone significantly decreased the risk of preterm birth ≤34

weeks of gestation or fetal death (18.1% vs 27.5%; RR 0.66, 95% CI 0.52– 0.83; *P* = 0.0005; five studies, 974 women). Moreover, meta-analyses of data from four trials (723 women) showed that vaginal progesterone administration was associated with a statistically significant reduction in the risk of preterm birth from <28 to <36 weeks of gestation (RRs from 0.51 to 0.79), respiratory distress syndrome (RR 0.47, 95% CI 0.27-0.81), composite neonatal morbidity and mortality (RR 0.59, 95% CI 0.38-0.91), birthweight <1500 g (RR 0.52, 95% CI 0.34-0.81), and admission to the neonatal intensive care unit (RR 0.67, 95% CI 0.50-0.91). There were no significant differences in neurodevelopmental outcomes at two years of age between the vaginal progesterone and placebo groups.

CONCLUSION This updated systematic review and meta-analysis reaffirms that vaginal progesterone reduces the risk of preterm birth and neonatal morbidity and mortality in women with a singleton gestation and a midtrimester cervical length ≤25 mm without any deleterious effects on child neurodevelopment. Clinicians should continue to perform universal transvaginal cervical length screening at 18-24 weeks of gestation in women with a singleton gestation and offer vaginal progesterone to those with a cervical length ≤25 mm.

INTRODUCTION

In 2013, preterm birth was the leading cause of both neonatal mortality (35% of 2.8 million deaths) and child mortality (17% of 6.3 million deaths) worldwide.[1,2] Neonates born preterm are at increased risk of both short-term complications attributed to immaturity of multiple organ systems[3,4] and long-term adverse health outcomes such as neurodevelopmental disabilities,[4,5] behavioral problems,[3,4] childhood asthma,[6] and cardiovascular disease,[7] diabetes,[8] and depression[9] in adult life. In addition, preterm birth is associated with a substantial economic cost and adverse psychosocial and emotional effects on families.[3,4]

Preterm birth is a syndrome attributable to multiple pathologic processes such as infection, vascular disorders, decidual senescence, uterine overdistension, a decline in progesterone action, cervical disease, breakdown of maternal-fetal

tolerance, and stress, among others.[10-12] A short cervix, traditionally defined as a transvaginal sonographic cervical length (CL) ≤25 mm in the midtrimester of pregnancy, is an important risk factor for preterm birth and has emerged as one of the strongest and most consistent predictors of preterm birth in asymptomatic women with singleton and twin gestations.[13-27]

In 2012, an individual patient data (IPD) meta-analysis evaluated the efficacy and safety of vaginal progesterone administration for the prevention of preterm birth and neonatal morbidity and mortality in asymptomatic women with a sonographic short cervix (CL ≤25 mm) in the midtrimester.[28] A total of 723 women with a singleton gestation from four randomized controlled trials (RCTs) were included in the study. Overall, the administration of vaginal progesterone significantly reduced the risk of preterm birth from <28 to <35 gestational weeks, as well as respiratory distress syndrome (RDS), composite neonatal morbidity and mortality, birthweight <1500 g, and admission to the neonatal intensive care unit (NICU). Since then, several authors and professional organizations around the world have recommended the use of vaginal progesterone in patients with a singleton gestation and a short cervix in the midtrimester.[29-42] In addition, it has been suggested that the use of vaginal progesterone in pregnant women with a short cervix is one of the interventions that has contributed to the reduction in the rate of preterm birth in the United States in the last seven years.[43]

Recently, the OPPTIMUM study[44] tested the effect of vaginal progesterone in 1228 women at risk for preterm birth due to three major risk factors: (1) history of spontaneous preterm birth; (2) positive cervico-vaginal fetal fibronectin test combined with other clinical risk factors for preterm birth; or (3) a sonographic short cervix (CL ≤25 mm). This double-blind, placebo-controlled trial reported that vaginal progesterone did not reduce the risk of preterm birth or neonatal morbidity and mortality in the entire population, or in the subgroup of women with a CL ≤25 mm. The report has created confusion as to the efficacy of vaginal progesterone to reduce the rate of preterm birth in women with a short cervix.[45]

To address this issue, we updated the previous systematic review and meta-analysis to quantify the efficacy of vaginal progesterone administration in preventing preterm birth and perinatal morbidity and mortality in asymptomatic women with a singleton gestation and a sonographic CL ≤25 mm at midtrimester.

METHODS

This study followed a prospective protocol and is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[46]

Data sources and searches

A literature search was undertaken in MEDLINE, EMBASE, POPLINE, CINAHL, and LILACS (all from inception to April 19, 2016), the Cochrane Central Register of Controlled Trials, and Research Registers of ongoing trials using a combination of

keywords and text words related to *progesterone* ("progesterone", "progestins", "progestogen", "progestagen", "progestational agent"), *preterm birth* ("preterm", "premature"), and *randomized controlled trial* ("randomized controlled trial", "controlled clinical trial"). Google scholar, proceedings of congresses on obstetrics, maternal-fetal medicine, and ultrasound in obstetrics, reference lists of identified studies, previously published systematic reviews, and review articles were also searched. In addition, we contacted investigators involved in the field to locate unpublished studies. There were no language restrictions.

Study selection

We included RCTs in which asymptomatic women with a singleton gestation and a sonographic short cervix (CL ≤25 mm) in the midtrimester were randomly allocated to receive vaginal progesterone or placebo/no treatment for the prevention of preterm birth and/or adverse perinatal outcomes. Trials were included 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 short cervix but outcomes were available for women with a pre-randomization CL ≤25 mm. Exclusion criteria included quasi-randomized trials, trials that evaluated vaginal progesterone in women with multiple gestations, preterm labor, arrested preterm labor (as maintenance tocolysis), premature rupture of membranes, or second trimester bleeding, trials that assessed vaginal progesterone in the first trimester only to prevent miscarriage, and studies that did not report clinical outcomes.

Published abstracts alone were excluded if additional information on methodological issues and results could not be obtained. When a study included women with singleton and multiple gestations, it was not considered for inclusion in the review unless data for women with singleton gestations were extractable separately.

All published studies deemed suitable were retrieved and reviewed independently by two authors to determine inclusion. Disagreements about inclusion were resolved through discussion.

Outcome measures

The primary outcome measure of interest was preterm birth ≤34 weeks of gestation or fetal death. Prespecified secondary outcome measures included preterm birth <37, <36, <35, <34, <33, <32, <30 and <28 weeks of gestation; spontaneous preterm birth <34 weeks of gestation; RDS; necrotizing enterocolitis; intraventricular hemorrhage; proven neonatal sepsis; retinopathy of prematurity; fetal death; neonatal death; perinatal death; a composite outcome of neonatal morbidity and mortality (defined as the occurrence of any of the following events: RDS, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis, or neonatal death); birthweight <1500 and <2500 g; admission to the NICU; use of mechanical ventilation; and long-term neurodevelopmental outcomes.

Assessment of risk of bias

Two authors evaluated the risk of bias in each study included in the meta-analysis using the Cochrane Collaboration tool for assessing risk of bias.[47] This tool assesses seven domains related to risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias) and categorizes studies by low, unclear, or high risk of bias in each domain. Discrepancies in risk of bias assessment were resolved by consensus.

Data extraction

One investigator extracted the relevant data from eligible studies, which were then independently checked by another investigator. Information was extracted on study characteristics (randomization procedure, concealment allocation method, blinding of clinicians, women and outcome assessors, follow-up period, completeness of outcome data for each outcome, including attrition and exclusions from the analysis, and intention-to-treat analysis), participants (inclusion and exclusion criteria, number of women in randomized groups, baseline characteristics, and country and date of recruitment), details of intervention (aim, gestational age at trial entry, daily dose of vaginal progesterone, duration, compliance, and use of co-interventions), and outcomes (prespecified outcome measures, definition of outcome measures, and the number of events and total number of participants in each group to calculate effect sizes).

We included additional data from four studies[48-51] included in our previous IPD meta-analysis.[28] Corresponding authors of three RCTs identified in the new literature search were contacted by email to obtain additional data.[44,52,53] No author supplied additional data. Disagreements regarding data extraction were resolved by discussion among the authors.

Data synthesis

The data synthesis was performed according to the guidelines of the Cochrane Collaboration.[54] Outcomes were analyzed on an intention-to-treat basis. Results from different trials were combined to calculate pooled relative risk (RR) with 95% confidence interval (CI) for dichotomous outcomes. Heterogeneity of the results among studies was tested with the quantity I^2.[55] A substantial level of heterogeneity was defined as an I^2 ≥50%.[54,55] We pooled results from individual studies using a fixed-effect model if substantial statistical heterogeneity was not present. If I^2 values were ≥50%, a random effects model was used to pool data across studies. The number needed to treat (NNT) for benefit or harm with 95% CI was calculated for outcomes for which there was a statistically significant reduction or increase in risk difference based on control event rates in the trials.[56]

Subgroup analyses were planned to assess primary and secondary outcome measures according to several characteristics such as CL, obstetrical history, maternal age, race/ethnicity, body mass index and daily dose of vaginal progesterone. However, the limited data reported in the OPPTIMUM study[44]

allowed only the performance of one subgroup analysis for the primary outcome measure according to daily dose of vaginal progesterone. A test for interaction between treatment and subgroup was calculated to examine whether treatment effects differ between subgroups.[57,58] An interaction *P* value >0.05 was considered to indicate that the effect of treatment 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 small number of trials included in the review.

All statistical analyses were performed by using the Review Manager (RevMan; version 5.3.5; The Nordic Cochrane Centre, Copenhagen, Denmark) and StatsDirect (version 3.0.167; StatsDirect Ltd, Cheshire, UK) statistical packages.

RESULTS

Selection, characteristics, and risk of bias of studies

Figure 1 summarizes the process of identification and selection of studies. The searches produced 707 records, of which 11 were considered relevant. Six studies were excluded.[52,53,59-62] Five of these studies assessed vaginal progesterone in women at high risk for preterm birth (previous preterm birth,[52,59-61] uterine malformation,[52,59,61] cervical insufficiency or history of prophylactic cervical cerclage,[59,61] uterine leiomyoma,[52] "short cervix",[52] and pregnancies conceived by

in vitro fertilization or intracytoplasmic sperm injection[62] but none of them reported results according to CL at randomization. The remaining study evaluated vaginal progesterone in 80 Dutch women with a singleton gestation, no previous spontaneous preterm birth at <34 weeks of gestation, and a CL ≤30 mm at 18-22 weeks, but did not report results for women with a CL ≤25 mm.[53] That study, which was stopped early due to low enrollment, reported that vaginal progesterone was associated with a non-significant reduction in the risk of preterm birth <34 weeks of gestation (RR, 0.81; 95% CI, 0.27-2.44), preterm birth <32 weeks of gestation (RR 0.58, 95% CI 0.14-2.30), and composite neonatal morbidity and mortality (RR 0.47, 95% CI 0.09-2.40). Five studies, including 974 women with a CL ≤25 mm, fulfilled inclusion criteria.[44,48-51]

The main characteristics of the studies included in the systematic review are summarized in Table 1. All studies were double-blind, placebo-controlled trials, of which four were multicenter, conducted in hospitals from both developed and developing countries. Two trials were specifically designed to evaluate the use of vaginal progesterone in women with a sonographic short cervix,[48,51] one evaluated the use of vaginal progesterone in women with a history of spontaneous preterm birth,[49] another examined the use of vaginal progesterone in women with a prior spontaneous preterm birth, uterine malformations, or twin gestations,[50] and the remaining trial tested the effect of vaginal progesterone in women at risk for preterm birth because of previous spontaneous preterm birth at ≤34 weeks of

gestation, or a sonographic CL ≤25 mm at 18-24 weeks, or a positive cervico-vaginal fetal fibronectin test combined with other clinical risk factors for preterm birth.[44] The two studies[48,51] specifically designed to assess the administration of vaginal progesterone in women with a short cervix provided 70% of the total sample size of the meta-analysis.

Two studies used vaginal progesterone capsules 200 mg/day,[44,48] two used vaginal progesterone gel 90 mg/day,[49,51] and the other used vaginal progesterone suppositories 100 mg/day.[50] The treatment was started at 24 weeks of gestation in two trials,[48,50] between 18-22 weeks of gestation in one trial,[49] between 20-23 weeks of gestation in another,[51] and between 22-24 weeks of gestation in the remaining one.[44] Three studies reported that participants received study medication from enrollment until 34 weeks of gestation,[44,48,50] and two from enrollment until 37 weeks of gestation.[49,51] The primary outcome measure differed among studies: spontaneous preterm birth <34 weeks,[48] preterm birth ≤32 0/7 weeks,[49] preterm birth <37 weeks,[50] and preterm birth <33 weeks.[51] The remaining study[44] had three primary outcome measures: preterm birth ≤34 0/7 weeks or fetal death, a composite outcome of neonatal death, bronchopulmonary dysplasia or brain injury assessed by neurosonography, and the Bayley-III cognitive composite score at two years of age.

Figure 2 shows the risk of bias in each included study. All studies were judged to be at low risk for selection (random sequence generation and allocation

concealment), performance (blinding of patients and clinical staff) and detection (blinding of outcome assessment) biases. All but the OPPTIMUM study[44] had low risk of attrition (incomplete outcome data), reporting (selective reporting) and other biases. The OPPTIMUM study[44] was considered to be at high risk of "attrition bias" because information on the Bayley-III cognitive composite score at two years of age, one of the primary outcome measures, was available for only ~70% of children (869/1228 in the entire population and 179/256 in the subgroup of women with a CL≤25 mm). High attrition rates may bias an observed effect, mainly if the rate of the outcome measure is relatively low as was "moderate-to-severe neurodevelopment impairment" in the entire population (10.5%). Information on the two other primary outcome measures was available for >95% of participants (97% for the obstetric outcome and 96% for the neonatal outcome) and thus, there was no evidence of attrition bias for these outcome measures. Moreover, this study was judged to be at high risk of "reporting bias" because the publication did not include results for key outcomes such as preterm birth <37, <32, and <28 weeks of gestation, RDS, retinopathy of prematurity, and birthweight <1500 and <2500 g, among others. In addition, most primary and secondary outcome measures were reported incompletely for the three subgroups of women at risk of preterm birth so they cannot be entered in meta-analyses. Finally, the OPPTIMUM study[44] is at high risk of "compliance bias" because only 68.6% of women (66.3% in the vaginal progesterone group) used at least 80% of study medication in comparison with

93.6% in the study by Fonseca et al[48] and 88.5% in the study by Hassan et al.[51] In RCTs, non-compliance or non-adherence can be one of the major barriers to achieving statistical power to detect intervention effects.[63]

Primary outcome

Vaginal progesterone administration to patients with a transvaginal sonographic short cervix was associated with a significant reduction in the risk of preterm birth ≤34 weeks of gestation or fetal death (18.1% vs 27.5%; RR 0.66, 95% CI 0.52–0.83; P = 0.0005; I^2 = 0%; five studies, 974 women) (Figure 3). The number of patients needed to treat with vaginal progesterone to prevent one case of preterm birth ≤34 weeks of gestation or fetal death was 11 (95% CI, 8 –21).

A significant decrease in the risk of preterm birth ≤34 weeks of gestation or fetal death was found in women who received either 90-100 mg/d (RR 0.62, 95% CI 0.42-0.91; I^2 = 0%; three studies, 497 women) or 200 mg/d (RR 0.69, 95% CI 0.51-0.92; I^2 = 0%; two studies, 477 women) of vaginal progesterone. The P value for the interaction effect of vaginal progesterone based on daily dose was non-significant (0.65).

Secondary outcomes

All pooled estimates of the effects of vaginal progesterone on secondary outcome measures were obtained by the meta-analysis of data from four trials[48-51] (Table 2). Treatment with vaginal progesterone was associated with a significantly lower risk of preterm birth <36 weeks of gestation (RR 0.79, 95% CI 0.63-0.99), <35 weeks of

gestation (RR 0.67, 95% CI 0.51-0.87), <34 weeks of gestation (RR 0.60, 95% CI 0.44-0.82), <33 weeks of gestation (RR 0.56, 95% CI 0.40-0.80), <32 weeks of gestation (RR 0.56, 95% CI 0.38-0.82), <30 weeks of gestation (RR 0.59, 95% CI 0.37-0.92), and <28 weeks of gestation (RR 0.51, 95% CI 0.31-0.85), spontaneous preterm birth <34 weeks of gestation (RR 0.63, 95% CI 0.44-0.88), RDS (RR 0.47, 95% CI 0.27-0.81), composite neonatal morbidity and mortality (RR 0.59, 95% CI 0.38-0.91), birthweight <1500 g (RR 0.52, 95% CI 0.34-0.81), and admission to the NICU (RR 0.67, 95% CI 0.50-0.91). The NNT to prevent one case of preterm birth from <28 to <36 weeks of gestation or adverse neonatal outcomes varies from 10-19. There were no significant differences between the two groups in the risk of preterm birth <37 weeks of gestation, necrotizing enterocolitis, intraventricular hemorrhage, proven neonatal sepsis, retinopathy of prematurity, fetal death, neonatal death, perinatal death, birthweight <2500 g, and use of mechanical ventilation.

The OPPTIMUM study[44] reported that infants whose mothers received vaginal progesterone had a non-significantly decreased risk of a composite outcome of neonatal death, bronchopulmonary dysplasia or brain injury (odds ratio 0.54, 95% CI 0.25-1.16; *P* = 0.113; 246 infants). The Bayley-III cognitive composite scores at two years of age did not differ significantly between the vaginal progesterone and placebo groups (mean difference -2.15, 95% CI -7.23 to 2.93; *P* = 0.408; 179 children).

DISCUSSION

Principal findings

This updated systematic review and meta-analysis, which includes data reported by the OPPTIMUM study,[44] shows that vaginal progesterone significantly decreases the risk of preterm birth ≤34 weeks of gestation or fetal death by 34% among women with a singleton gestation and a midtrimester CL ≤25 mm. Clearly, the reduction in this composite outcome is attributable to a decrease in preterm birth ≤34 weeks of gestation rather than fetal death because vaginal progesterone had no effect on the risk of this adverse outcome in either the meta-analysis of data from four studies (RR 0.82, 95% CI 0.28-2.40) or in the OPPTIMUM study[44] (RR 1.14, 95% CI 0.41-3.12 for the entire population). In addition, pooled estimates obtained by combining data from four trials indicate that vaginal progesterone administration was associated with a statistically significant reduction in the risk of preterm birth from <28 to <36 weeks of gestation, RDS, composite neonatal morbidity and mortality, birthweight <1500 g, and admission to NICU.

Unfortunately, it was not possible to update most endpoints assessed in our previous meta-analysis,[28] because the OPPTIMUM study publication[44] did not report data for most adverse pregnancy and neonatal outcomes. It is noteworthy that the OPPTIMUM trial[44] was underpowered to detect a meaningful difference between vaginal progesterone and placebo in the subgroup of women with a CL ≤25 mm. Indeed, the OPPTIMUM study[44] had a post-hoc statistical power of only

26% to detect a 23% reduction in the risk of preterm birth ≤34 weeks of gestation or fetal death (from 32.2% in the placebo group to 24.8% in the vaginal progesterone group) and 33% to detect a 42% reduction in the risk of the composite outcome of neonatal morbidity and mortality (from ~14% in the placebo group to ~8% in the vaginal progesterone group) at an α level (two-sided) of 0.05. Nonetheless, in this subpopulation, the OPPTIMUM study[44] reported a non-significant ~42% reduction in the risk of neonatal death or serious neonatal morbidity, which is very similar to the 41% significant reduction in the risk of composite neonatal morbidity and mortality found in the meta-analysis of data from the other four trials.[48-51]

To explore the consequences of the lack of data of the OPPTIMUM study publication,[44] we performed several simulated meta-analyses by using denominators of vaginal progesterone and placebo groups in the subgroup of women with a CL ≤25 mm reported in this study. In summary, we found that the statistically significant beneficial effects of vaginal progesterone administration on the risk of preterm birth <35, <33, <32, <30, and <28 weeks of gestation, RDS, composite neonatal morbidity and mortality, birthweight <1500 g, and admission to NICU obtained in the meta-analyses of data from four trials, could only become non-statistically significant if the rates of these adverse outcomes in the OPPTIMUM study[44] were higher in the vaginal progesterone group than in the placebo group and the RRs were >1.12 for most of these outcomes. This

hypothetical scenario is unlikely, given that the OPPTIMUM study[44] showed a clear trend towards reduction in the risk of preterm birth ≤34 weeks of gestation (23%) and neonatal death or serious neonatal morbidity (~42%) associated with the use of vaginal progesterone.

With regard to the effect of vaginal progesterone on the risk of adverse neurodevelopmental outcomes, the OPPTIMUM study[44] found that there were no significant differences in the mean Bayley-III cognitive composite scores or rates of neurodevelopmental impairment at two years of age between children exposed *in utero* to vaginal progesterone and those exposed to placebo. Similar findings were reported by O'Brien et al,[64] who assessed neurodevelopmental outcomes among children born to women enrolled in their trial[49] using the Denver II Developmental Screening Test at 6 months of age (445 children), 12 months of age (389 children), and 24 months of age (293 children). There were no significant differences in the rate of suspected developmental delay at any time during the 24-month follow-up between the vaginal progesterone and the placebo groups. These findings are in accordance with those reported in children whose mothers participated in RCTs of vaginal progesterone versus placebo for the prevention of preterm birth in twin gestations.[65,66] Rode et al[65] reported that the mean Ages and Stages Questionnaire scores (a tool that measures neurodevelopmental disability) at 6 months (1050 children) and 18 months (991 children) of age were not significantly different between the two groups, whereas McNamara et al[66] reported that there

were no significant differences in neurodevelopmental outcomes (assessed by using the Child Development Inventory tool) between twins in the vaginal progesterone and placebo groups at 3 to 6 years of age (759 children). In conclusion, the current available evidence suggests that *in utero* exposure to vaginal progesterone has no impact on neurodevelopmental outcomes at least until 2 years of age and, possibly, until 6 years of age.

Strengths and limitations

The reliability and robustness of the results obtained in this updated review are supported by: (1) the use of the most rigorous methodology for performing a systematic review and meta-analysis of RCTs; (2) the extensive literature searches without language restrictions; (3) the strict assessment of methodological quality of included trials that was based on widely recommended criteria; (4) the quantitative way of summarizing the evidence; (5) the evidence of clinical and statistical homogeneity in the meta-analyses of all outcome measures evaluated; (6) the relatively narrow CIs obtained that made our estimates of effect size more precise; and (7) the subgroup analysis that did not show any significant influence of daily dose of vaginal progesterone on effect size. The main limitation of our study was the lack of data on several secondary outcome measures which were not reported in the OPPTIMUM study publication.[44] However, as previously mentioned, it is very unlikely that the significant beneficial effects of vaginal progesterone on the risk of

preterm birth and neonatal morbidity and mortality are turned into non-significant after the inclusion of data from this study in the meta-analyses.

Implications for practice and research

Evidence from this updated meta-analysis reaffirms that vaginal progesterone reduces the risk of preterm birth ≤34 weeks of gestation in women with a singleton gestation and a midtrimester CL ≤25 mm. Therefore, clinicians should continue performing universal transvaginal CL screening at 18-24 weeks of gestation in women with a singleton gestation and to offer vaginal progesterone to those with a CL ≤25 mm, regardless of the history of spontaneous preterm birth, with the goal of preventing preterm birth and reducing neonatal morbidity and mortality. This recommendation is buttressed by the safety margin of vaginal progesterone[44,64-66] and the cost-effectiveness of the intervention.[67-74] We believe that an IPD meta-analysis including data from the OPPTIMUM trial[44] and the Dutch study[53] is warranted to enable a more rigorous analysis and the performance of several subgroup analyses. We have invited to the investigators of these trials to participate in such a study.

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FIGURE LEGENDS

Legend for Figure 1: Study selection process

Legend for Figure 2: Methodological quality of studies included in the systematic review

Legend for Figure 3: Forest plot of the effect of vaginal progesterone on the risk of preterm birth ≤34 weeks of gestation or fetal death