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VAGINAL PROGESTERONE FOR PREVENTING PRETERM BIRTH AND ADVERSE PERINATAL OUTCOMES IN SINGLETON GESTATIONS WITH A SHORT CERVIX: A META-ANALYSIS OF INDIVIDUAL PATIENT DATA

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Disclosure: RR, AC-A, EDF, EC, SSH, and KHN declare no conflict of interest. JMO'B 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 (USA Patent Number 7884093: progesterone for the treatment and prevention of spontaneous preterm birth). He has received no royalty payments. GWC was an Employee of Columbia Laboratories, Inc. when the previous meta-analysis of individual patient data was conducted in 2011. Professor Jane Norman has no conflict of interest in relation with our meta-analysis of individual patient data.

Abstract

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.

DATA SOURCES—MEDLINE, EMBASE, LILACS, and CINAHL (from their inception to September 2017), Cochrane databases, bibliographies, and conference proceedings.

STUDY ELIGIBILITY CRITERIA—Randomized controlled trials comparing vaginal progesterone with placebo/no treatment in women with a singleton gestation and a midtrimester sonographic cervical length ≤25 mm.

STUDY APPRAISAL AND SYNTHESIS METHODS—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 two-stage approach. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated. Quality of evidence was assessed using the GRADE methodology.

RESULTS—Data were available from 974 women (498 assigned to vaginal progesterone, 476 assigned to placebo) with a cervical length ≤25 mm participating in five high-quality trials. Vaginal progesterone was associated with a significant reduction in the risk of preterm birth <33 weeks of gestation (RR 0.62, 95% CI 0.47-0.81, *P*=0.0006; 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 (RRs from 0.47 to 0.82; high-quality evidence for all). There were seven (1.4%) neonatal deaths in the vaginal progesterone group and 15 (3.2%) in the placebo group (RR 0.44, 95% CI 0.18-1.07, *P*=0.07; low-quality evidence). Maternal adverse events, congenital anomalies, and adverse neurodevelopmental and health outcomes at 2 years of age did not differ between groups.

CONCLUSIONS—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.

Keywords

prematurity; preterm delivery; progestins; progestogens; transvaginal ultrasound; cervical length

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 over 2007-2014, 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] In addition, surviving preterm babies are at greater risk for short-term health complications including acute respiratory, gastrointestinal, infectious, central nervous system, hearing, and vision problems, and long-term neurodevelopmental disabilities such as cerebral palsy, 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 with 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 patients with a singleton gestation and a short cervix by the Society for Maternal-Fetal Medicine (SMFM),[50] the American College of Obstetricians and Gynecologists (ACOG),[51] the International Federation of Gynecology and Obstetrics (FIGO),[52] and the National Institute for Health and Care Excellence (NICE)[53], among others.

In 2016, the findings of the OPPTIMUM study were reported. This was a randomized controlled trial comparing vaginal progesterone versus placebo in women at risk of preterm birth because of previous spontaneous preterm birth <34 weeks of gestation, or a cervical length ≤25 mm, or because of 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 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 that 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).

MATERIAL AND METHODS

The study was prospectively registered with the PROSPERO database of systematic reviews (number 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 30 September 2017), and Google Scholar using the keywords “progesterone” and “preterm birth” to identify all randomized controlled trials comparing vaginal progesterone (any dose) versus placebo/no treatment for the prevention of preterm birth and/or adverse perinatal outcomes in women with singleton gestations. 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 short cervix but for whom outcomes were available in those with a pre-randomization cervical length ≤25 mm. Quasi-randomized 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 (RR and AC-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 supply 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 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 risk of bias for included trials were done independently by two investigators (RR and AC-A) according to the seven 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 bias).[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 the data on an intention-to-treat basis. IPD were analyzed using a two-stage approach. In the first stage, estimates of effect were derived from the IPD for each trial, and 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 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 ≤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. We calculated the number needed to treat (NNT) with 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 one 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 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 ten 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 only performed 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 (RevMan; version 5.3.5; The Nordic Cochrane Centre, Copenhagen, Denmark) and StatsDirect (version 3.0.198; StatsDirect Ltd, Cheshire, UK).

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 four grades: (i) high: we are very confident that the true effect lies close to that of the estimate of the effect; (ii) moderate: we are moderately confident in the effect estimate, 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, 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, the true effect is likely to be substantially different from the estimate of effect. The evidence can be downgraded from 'high quality' by one level for serious (or by two 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 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, 77, 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 six trials.[54, 69-72, 74] Data from one trial, which compared vaginal progesterone versus 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 five 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 five studies included in the systematic review 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 and 20 mm[72]), one tested the effect of vaginal progesterone in women at risk for preterm birth because of previous spontaneous preterm birth, or 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] and the remaining trial examined the use of vaginal progesterone in women with a previous spontaneous preterm birth, uterine malformations, or twin gestations.[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 in >90% of patients participating in four trials. [69-72] In the trial by Norman et al,[54] only 66% of patients with a CL ≤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 two 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; $P = .0006$; $I^2 = 0\%$; NNT 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 to 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 to 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 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 less than 7 at 5 min, use of mechanical ventilation, congenital anomalies, and any maternal adverse event (low- to moderate-quality evidence). At two 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 (one 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 ≥ 0.18). 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 ($P = 0.22$), 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 = 0.74), as well as between US women and non-US women (P for interaction = 0.51). 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

(1) 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); (2) vaginal progesterone improved neonatal outcome. Indeed, neonates of mothers who received vaginal progesterone had a significantly lower risk of RDS. In addition, vaginal progesterone was also associated with a significant decrease in the risk of composite neonatal morbidity and mortality, low birthweight (<2500 grams), very low birthweight (<1500 grams), and NICU admission; (3) there was a non-significant trend towards reduction of neonatal mortality (by 66%, $P = 0.07$) and use of mechanical ventilation (by 35%, $P = 0.06$); (4) 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; and (5) there were no significant differences in the frequency of maternal adverse events and congenital 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 mid-trimester short cervix significantly reduces the risk of preterm birth <36 weeks and birthweight <2500 grams. 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 to 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 pre-specified 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 healthcare 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 pre-specified composite outcome measure did not restrict the endpoint of morbidity to complications which have a very low prevalence, such as severe intraventricular hemorrhage (grades III/IV), necrotizing enterocolitis (stages II/III), and retinopathy of prematurity (stages III to V). If the composite outcome measure had been restricted to only these severe complications, the risk for a type II error due to limited power could have missed an important clinical effect and mislead physicians and patients.[81]

In addition, 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, such as barotrauma, oxygen toxicity, systemic and local inflammation, neonatal sepsis, etc. Vaginal progesterone is aimed primarily at preventing preterm birth and may ameliorate some immediate neonatal complications (e.g. RDS); yet, it is unreasonable to expect that it will improve distal outcomes influenced by many other medical and non-medical factors.

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 lies 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 moderate to low quality.

Subgroup analyses according to 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 in patients with a singleton gestation, previous spontaneous preterm birth and a cervical length ≤25 mm.[82]

Subgroup analysis according to country of enrollment (USA vs. non-USA)

In 2012, the PREGNANT trial[72] was reviewed by the U.S. Food and Drug Administration (FDA) for a New Drug Application 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 USA.

Recently, Yusuf and Wittes 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.[83] The PREGNANT trial,[72] was one of the examples of variations in results among countries assessed by Yusuf and Wittes (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 U.S*". Consistent with this conclusion by Yusuf and Wittes, 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 U.S. (RR 0.73, 95% CI 0.42-1.27) and women enrolled outside the U.S. (RR 0.59, 95% CI 0.43-0.80), as the interaction test for subgroup differences was non-significant ($P = 0.51$).

Subgroup Analysis 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 per day of vaginal progesterone was used. 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 ($P = 0.22$), suggesting that vaginal progesterone has no differential efficacy in the pre-specified 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, 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 non-significant interaction *P* value of 0.75. 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 who have been 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 this trial, vaginal progesterone was associated with a non-significant 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 this 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 this 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 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, and 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 mid-trimester 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 four 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 three alternatives: cervical length screening for women at increased risk for preterm birth and treatment with vaginal progesterone; risk-based treatment with 17-OHPC 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 to 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 with 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 more than 36%.[99] In our IPD meta-analysis, vaginal progesterone decreased the risk of preterm birth <33 weeks of gestation by 38%. Finally, five 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 outlined by the World Health Organization of a good screening test. Combs[105] as well as Khalifeh and Berghella[106] have 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 in 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 with 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 in 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 non-significant reduction in the rate of preterm birth <34 weeks of gestation among screened women.

A smaller study that assessed a similar program in 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, this 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 US in the last seven 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 28-31 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 results of our IPD meta-analysis, we have 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%.[116]

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 the uterine cervix (i.e. 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 Elovitz et al.[140, 141], Mahendroo et al.[142, 143] Word et al.[144] Yellon et al.[145-147], 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 mid-trimester 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 NF-kB (nuclear factor-kappa B), a transcription factor which mediates the effect of certain pro-inflammatory cytokines such as interleukin-1β[165-168] and tumor necrosis factor-α.[169-171] This is potentially relevant because NF-kB can oppose progesterone action.[132, 167, 172-174] Thus, NFkB could provide a link between inflammation, a decline in progesterone action and cervical remodeling.

The traditional understanding of the mechanisms of action of progesterone is that this hormone acts through nuclear receptors to induce genomic actions.[175-182] However, it is now clear that some of the actions of progesterone are induced through membrane receptors and non-genomic mechanisms.[183-187] The precise role of progesterone receptors, deoxyribonucleic acid-binding properties and/or transcriptional activity in determining progesterone action on the cervix remains 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 have provided evidence in support of a novel mechanism whereby a functional progesterone withdrawal could occur in the myometrium, independent of progesterone concentrations in the peripheral circulation[192-194]. Whether this specific mechanism is operational in the uterine cervix remains to be determined.

Recent studies[195] about the mechanisms of action of progestogens *in vivo* have shown that vaginal progesterone has local anti-inflammatory effects at the maternal fetal interface. Specifically, when vaginal progesterone is administered to pregnant mice, it fosters an anti-inflammatory microenvironment at the maternal-fetal interface by increasing CD4+ Tregs and reducing CD8+CD25+Foxp3+ T cells, macrophages, and Interferon γ+ neutrophils.[195] In addition, the administration of vaginal progesterone decreases the infiltration of active matrix metalloproteinase-9-positive neutrophils and monocytes in the cervix, reduces the plasma concentration of interleukin-1β, and reduces the frequency of endotoxin-induced preterm birth.[195]

In summary, progesterone has anti-inflammatory 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 individual patient data 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.

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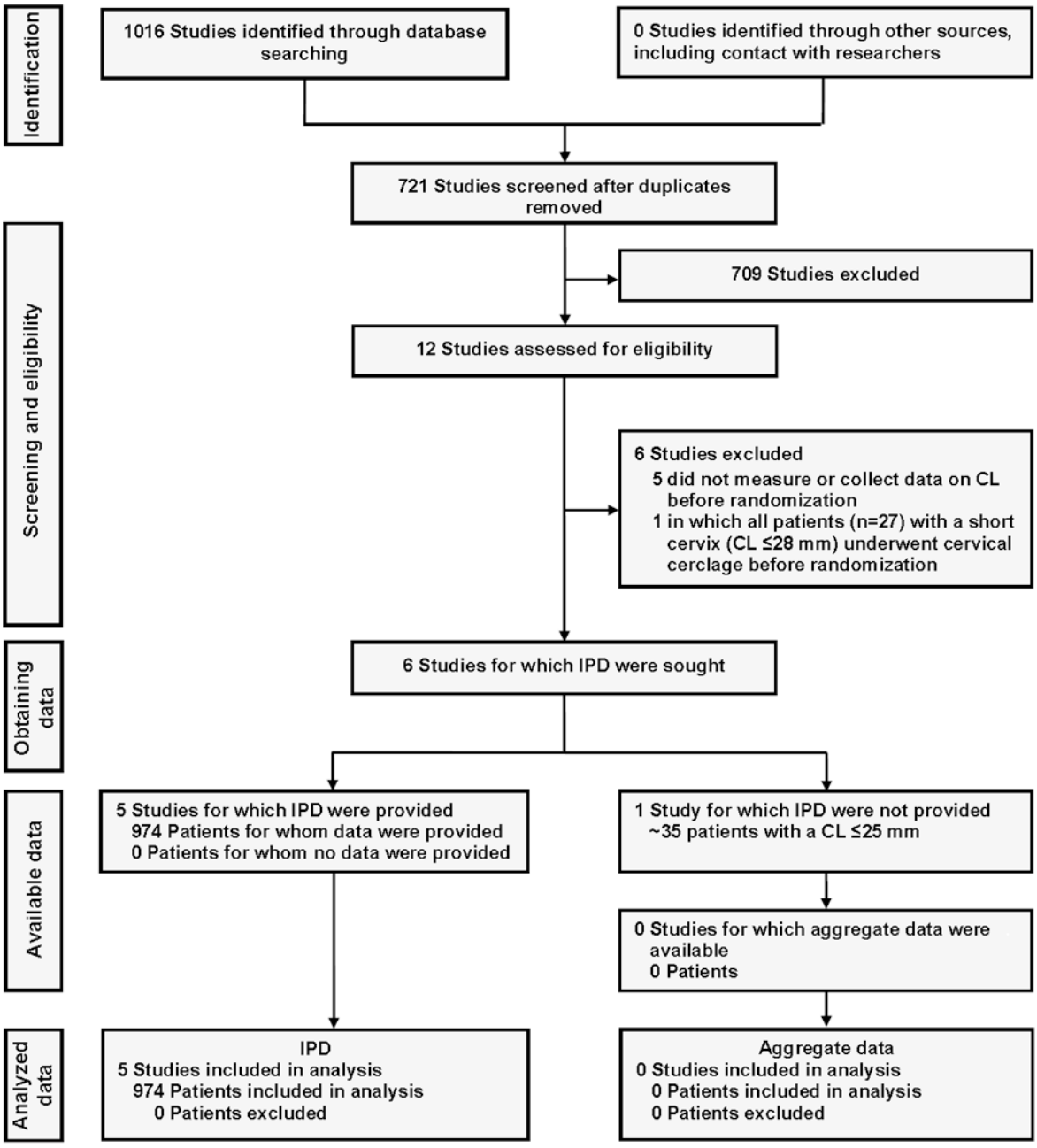

Figure 1. Summary of evidence search and selection

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

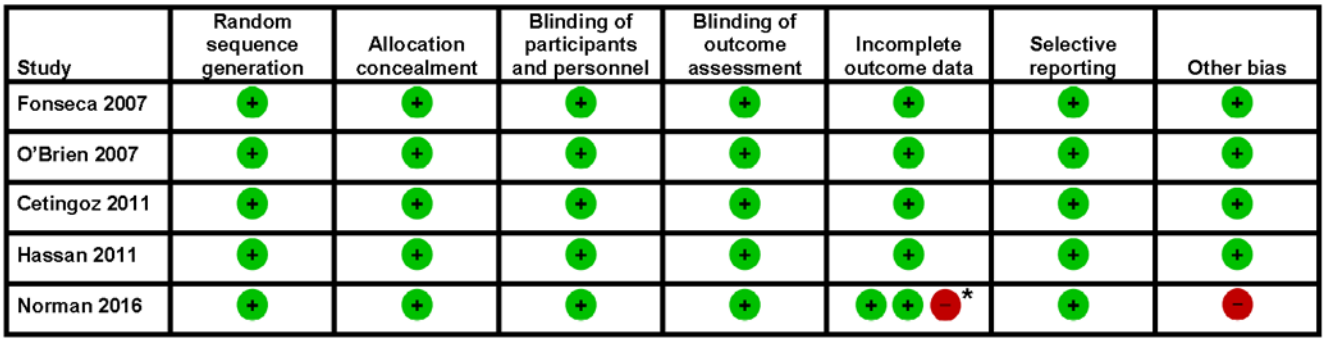

Figure 2. Risk of bias in each included study

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

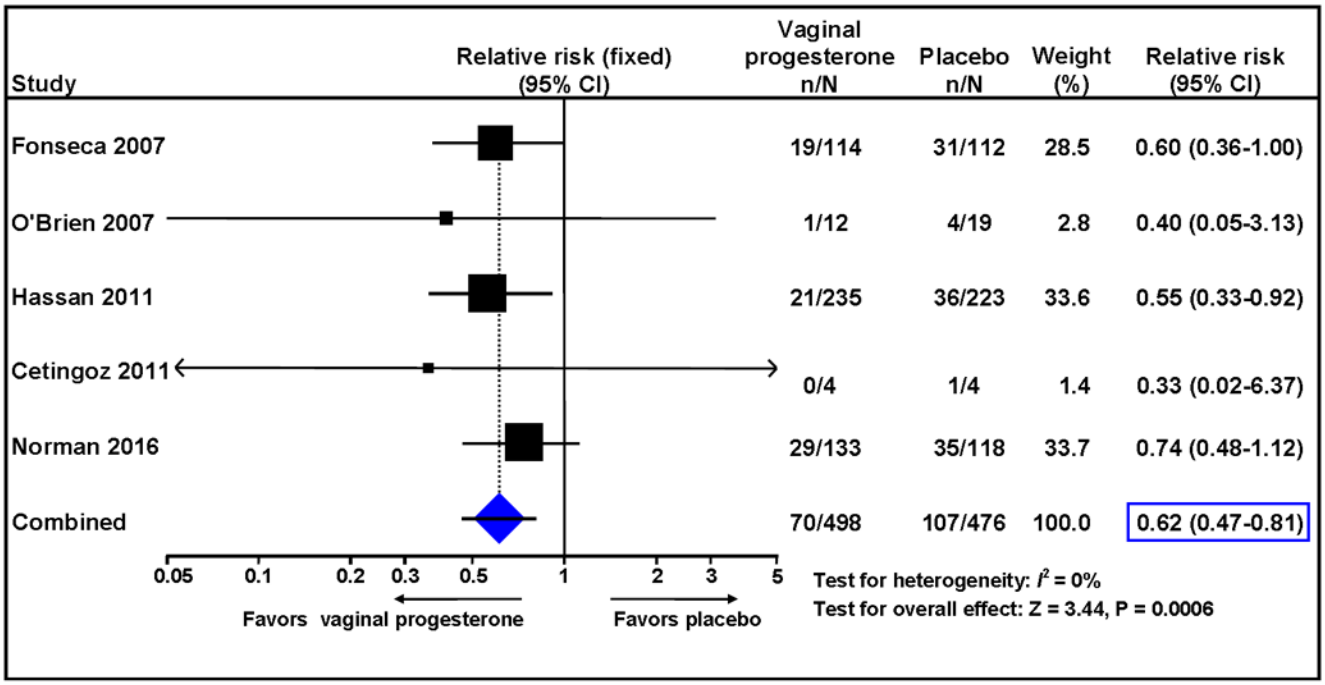

Figure 3. Effect of vaginal progesterone on preterm birth <33 weeks of gestation

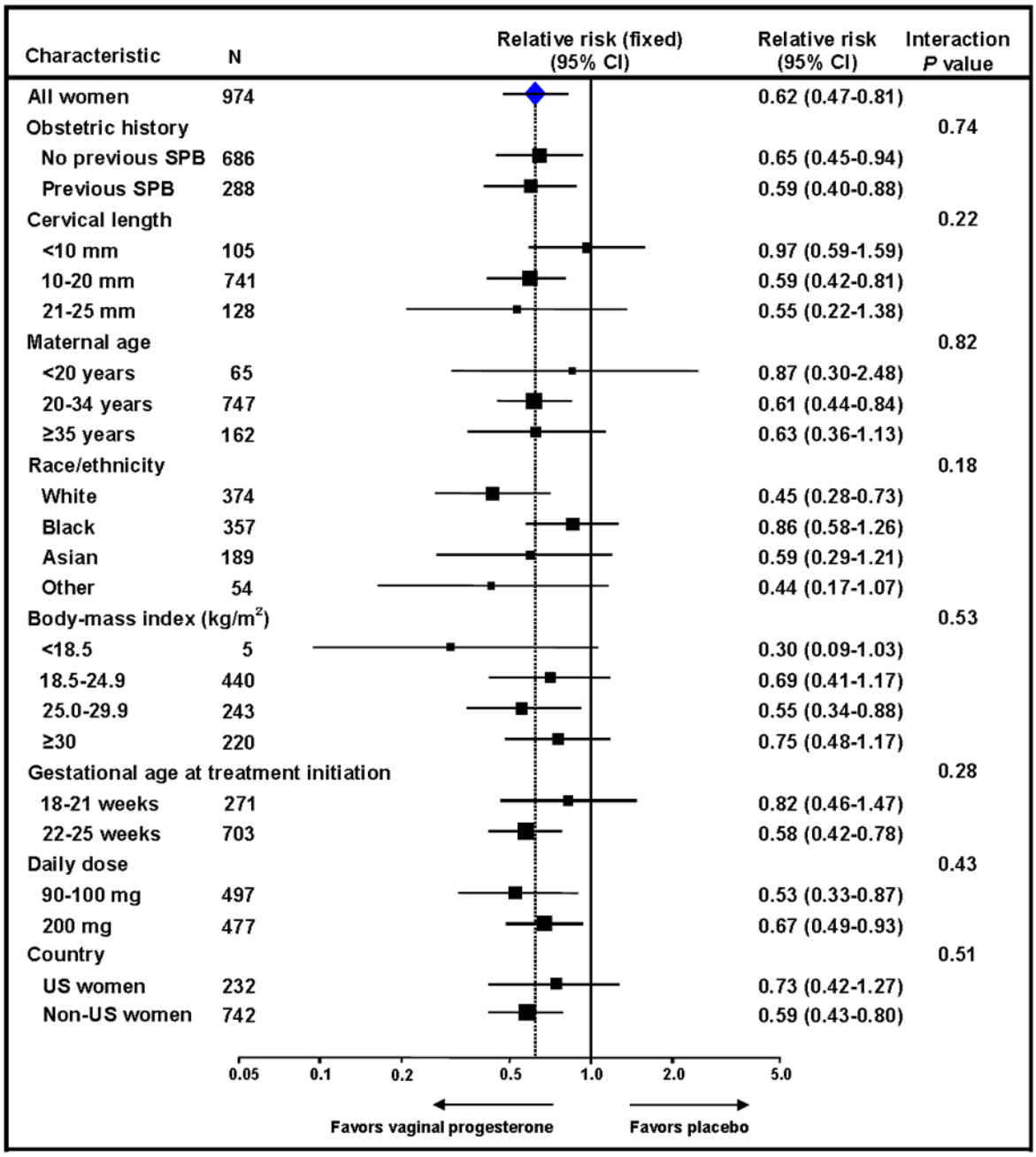

Figure 4. Subgroup analyses of the effect of vaginal progesterone on preterm birth <33 weeks of gestation

SPB, spontaneous preterm birth

Table 1

Baseline characteristics of pooled women

	Vaginal progesterone (n=498)	Placebo (n=476)
Maternal age (years)	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 enrolment		
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 (weeks)	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

Table 2

Studies included in the individual patient data meta-analysis

Study, year	Trial enrolment	Participants randomly assigned in original trial	Participants eligible for IPDMA	Treatment groups	Compliance ≥80%
Fonseca,[69] 2007	8 centers in the UK, Chile, Brazil, and Greece	250 with a singleton or twin gestation and a cervical length ≤15 mm	226	Vaginal progesterone 200 mg/day or placebo from 24-33 6/7 weeks of gestation	92% for the vaginal progesterone group and 94% for the placebo group
O'Brien,[70] 2007	53 centers in US, South Africa, India, Czech Republic, Chile, and El Salvador	659 with a singleton gestation and previous spontaneous preterm birth	31	Vaginal progesterone 90 mg/day or placebo from 18-22 to 37 0/7 weeks of gestation, rupture of membranes or preterm delivery, whichever occurred first	100% for the vaginal progesterone group and 95% for the placebo group
Cetingoz,[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/day or placebo from 24-34 weeks of gestation	100% for both study groups
Hassan,[72] 2011	44 centers in US, Belarus, Chile, Czech Republic, India, Israel, Italy, Russia, South Africa, and Ukraine	465 with a singleton gestation and a cervical length between 10-20 mm	458	Vaginal progesterone 90 mg/day or placebo from 20-23 6/7 to 36 6/7 weeks of gestation, rupture of membranes or preterm delivery, whichever occurred first	89% for the vaginal progesterone group and 93% for the placebo group
Norman,[54] 2016	66 centers in the UK and Sweden	1228 with a singleton gestation and previous spontaneous preterm birth, or cervical length ≤25 mm, or a positive fetal fibronectin test combined with other clinical risk factors for preterm birth	251	Vaginal progesterone 200 mg/day or placebo from 22-24 to 34 weeks of gestation or preterm delivery, whichever occurred first	63% for the vaginal progesterone group and 69% for the placebo group

IPDMA, individual patient data meta-analysis

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 weeks	5[54,69-72]	187/498 (38%)	199/476 (42%)	0.90 (0.77-1.05)	0.19	0	—
Preterm birth <36 weeks	5[54,69-72]	139/498 (28%)	166/476 (35%)	0.80 (0.67-0.97)	0.02	0	14 (9-96)
Preterm birth <35 weeks	5[54,69-72]	106/498 (21%)	141/476 (30%)	0.72 (0.58-0.89)	0.003	0	12 (8-31)
Preterm birth <34 weeks	5[54,69-72]	86/498 (17%)	126/476 (26%)	0.65 (0.51-0.83)	0.0006	0	11 (8-22)
Preterm birth <32 weeks	5[54,69-72]	62/498 (12%)	92/476 (19%)	0.64 (0.48-0.86)	0.003	0	14 (10-37)
Preterm birth <30 weeks	5[54,69-72]	49/498 (10%)	67/476 (14%)	0.70 (0.49-0.98)	0.04	0	24 (14-355)
Preterm birth <28 weeks	5[54,69-72]	38/498 (8%)	54/476 (11%)	0.67 (0.45-0.99)	0.04	0	27(16-881)
Spontaneous preterm birth <33 weeks	5[54,69-72]	60/498 (12%)	82/476 (17%)	0.70 (0.51-0.95)	0.02	0	19 (12-116)
Spontaneous preterm birth <34 weeks	5[54,69-72]	73/498 (15%)	97/476 (20%)	0.72 (0.55-0.95)	0.02	0	18 (11-98)
Gestational age at delivery (weeks)	5[54,69-72]	498[a]	476[a]	0.74 (0.18-1.30)	0.01	0	NA
Any maternal adverse event	5[54,69-72]	51/424 (12%)	47/422 (11%)	1.21 (0.87-1.69)	0.26	5	—
Perinatal outcome							
Respiratory distress syndrome	4[69-72]	17/365 (5%)	37/358 (10%)	0.47 (0.27-0.81)	0.007	0	18 (13-51)
Necrotizing enterocolitis	5[54,69-72]	11/495 (2%)	12/475 (3%)	0.89 (0.41-1.93)	0.77	0	—
Intraventricular hemorrhage	5[54,69-72]	5/494 (1%)	10/475 (2%)	0.50 (0.18-1.38)	0.18	0	—
Proven neonatal sepsis	5[54,69-72]	18/494 (4%)	28/470 (6%)	0.61 (0.34-1.08)	0.09	0	—
Bronchopulmonary dysplasia	3[54,71,72]	11/367 (3%)	13/340 (4%)	0.77 (0.35-1.68)	0.51	0	—
Retinopathy of prematurity	4[69-72]	6/365 (2%)	3/358 (1%)	1.78 (0.49-6.47)	0.38	29	—
Fetal death	5[54,69-72]	9/498 (2%)	8/476 (2%)	1.06 (0.41-2.72)	0.91	0	—
Neonatal death	5[54,69-72]	7/498 (1%)	15/476 (3%)	0.44 (0.18-1.07)	0.07	0	—
Perinatal death	5[54,69-72]	16/498 (3%)	23/476 (5%)	0.66 (0.35-1.22)	0.19	0	—
Composite neonatal morbidity/mortality[b]	4[69-72]	29/365 (8%)	49/358 (14%)	0.59 (0.38-0.91)	0.02	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)	0.39	0	—

Outcome	No of trials	Vaginal progesterone group	Placebo group	RR or mean difference (95% CI)	*P* value	I^2 (%)	NNT (95% CI)
Birthweight <1500 g	5[54,69-72]	50/497 (10%)	77/473 (16%)	0.62 (0.44-0.86)	0.004	0	16 (11-44)
Birthweight <2500 g	5[54,69-72]	144/497 (29%)	168/473 (36%)	0.82 (0.68-0.98)	0.03	0	16 (9-141)
Admission to NICU	5[54,69-72]	83/496 (17%)	117/474 (25%)	0.68 (0.53-0.88)	0.003	0	13 (9-34)
Mechanical ventilation	4[69-72]	28/365 (8%)	43/358 (12%)	0.65 (0.41-1.01)	0.06	0	—
Congenital anomaly	5[54,69-72]	4/491 (1%)	6/469 (1%)	0.72 (0.23-2.26)	0.57	0	—
Childhood (2 years of age) 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)	0.40	NA	NA
Moderate/severe neurodevelopmental impairment	1[54]	10/81 (12%)	7/77 (9%)	1.36 (0.54-3.39)	0.51	NA	—
Visual or hearing impairment	1[54]	0/100 (0%)	2/87 (2%)	0.17 (0.01-3.58)	0.26	NA	—
Disability in renal, gastrointestinal, or respiratory function	1[54]	1/91 (1%)	1/84 (1%)	0.92 (0.06-14.52)	0.95	NA	—

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

Table 4

Summary of Findings table on the quality of evidence for each outcome measure

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with vaginal progesterone			
Preterm birth <33 weeks	Study population		RR 0.62 (0.47 to 0.81)	974 (5 studies)	⊕⊕⊕⊕ High
	225 per 1000	139 per 1000 (106 to 182)			
Preterm birth <37 weeks	Study population		RR 0.90 (0.77 to 1.05)	974 (5 studies)	⊕⊕⊕⊕ High
	418 per 1000	376 per 1000 (322 to 439)			
Preterm birth <36 weeks	Study population		RR 0.80 (0.67 to 0.97)	974 (5 studies)	⊕⊕⊕⊕ High
	349 per 1000	279 per 1000 (234 to 338)			
Preterm birth <35 weeks	Study population		RR 0.72 (0.58 to 0.89)	974 (5 studies)	⊕⊕⊕⊕ High
	296 per 1000	213 per 1000 (172 to 264)			
Preterm birth <34 weeks	Study population		RR 0.65 (0.51 to 0.83)	974 (5 studies)	⊕⊕⊕⊕ High
	265 per 1000	172 per 1000 (135 to 220)			
Preterm birth <32 weeks	Study population		RR 0.64 (0.48 to 0.86)	974 (5 studies)	⊕⊕⊕⊕ High
	193 per 1000	124 per 1000 (93 to 166)			
Preterm birth <30 weeks	Study population		RR 0.70 (0.49 to 0.98)	974 (5 studies)	⊕⊕⊕⊕ High
	141 per 1000	99 per 1000 (69 to 138)			
Preterm birth <28 weeks	Study population		RR 0.67 (0.45 to 0.99)	974 (5 studies)	⊕⊕⊕⊕ High
	113 per 1000	76 per 1000 (51 to 112)			
Spontaneous preterm birth <33 weeks	Study population		RR 0.70 (0.51 to 0.95)	974 (5 studies)	⊕⊕⊕⊕ High
	172 per 1000	121 per 1000 (88 to 164)			
Spontaneous preterm birth <34 weeks	Study population		RR 0.72 (0.55 to 0.95)	974 (5 studies)	⊕⊕⊕⊕ High
	204 per 1000	147 per 1000 (112 to 194)			
Gestational age at delivery (weeks)	The mean gestational age at delivery (weeks) in the intervention groups was 0.74 higher (0.18 to 1.3 higher)			974 (5 studies)	⊕⊕⊕⊕ High
Respiratory distress syndrome	Study population		RR 0.47 (0.27 to 0.81)	723 (4 studies)	⊕⊕⊕⊕ High
	103 per 1000	49 per 1000 (28 to 84)			
Necrotizing enterocolitis	Study population		RR 0.89 (0.41 to 1.93)	970 (5 studies)	⊕⊕⊖⊖ low[1]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with vaginal progesterone			
	25 per 1000	22 per 1000 (10 to 49)			
Intraventricular hemorrhage	Study population		RR 0.50 (0.18 to 1.38)	969 (5 studies)	⊕⊕⊖⊖ low[1]
	21 per 1000	11 per 1000 (4 to 29)			
Proven neonatal sepsis	Study population		RR 0.61 (0.34 to 1.08)	964 (5 studies)	⊕⊕⊕⊖ Moderate[2]
	60 per 1000	36 per 1000 (20 to 64)			
Bronchopulmonary dysplasia	Study population		RR 0.77 (0.35 to 1.68)	707 (3 studies)	⊕⊕⊖⊖ low[1]
	38 per 1000	29 per 1000 (13 to 64)			
Retinopathy of prematurity	Study population		RR 1.78 (0.49 to 6.47)	723 (4 studies)	⊕⊕⊖⊖ low[1]
	8 per 1000	15 per 1000 (4 to 54)			
Fetal death	Study population		RR 1.06 (0.41 to 2.72)	974 (5 studies)	⊕⊕⊖⊖ low[1]
	17 per 1000	18 per 1000 (7 to 46)			
Neonatal death	Study population		RR 0.44 (0.18 to 1.07)	974 (5 studies)	⊕⊕⊖⊖ low[3]
	32 per 1000	14 per 1000 (6 to 34)			
Perinatal death	Study population		RR 0.66 (0.35 to 1.22)	974 (5 studies)	⊕⊕⊕⊖ Moderate[2]
	48 per 1000	32 per 1000 (17 to 59)			
Composite neonatal morbidity/mortality	Study population		RR 0.59 (0.38 to 0.91)	723 (4 studies)	⊕⊕⊕⊕ High
	137 per 1000	81 per 1000 (52 to 125)			
Apgar score <7 at 5 min	Study population		RR 0.83 (0.55 to 1.26)	960 (5 studies)	⊕⊕⊕⊖ Moderate[4]
	92 per 1000	76 per 1000 (50 to 116)			
Birthweight <1500 g	Study population		RR 0.62 (0.44 to 0.86)	970 (5 studies)	⊕⊕⊕⊕ High
	163 per 1000	101 per 1000 (72 to 140)			
Birthweight <2500 g	Study population		RR 0.82 (0.68 to 0.98)	970 (5 studies)	⊕⊕⊕⊕ High
	355 per 1000	291 per 1000 (242 to 348)			
Admission to NICU	Study population		RR 0.68 (0.53 to 0.88)	970 (5 studies)	⊕⊕⊕⊕ High
	247 per 1000	168 per 1000 (131 to 217)			
Mechanical ventilation	Study population		RR 0.65 (0.41 to 1.01)	723 (4 studies)	⊕⊕⊕⊖ Moderate[2]
	120 per 1000	78 per 1000 (49 to 121)			
Congenital anomaly	Study population		RR 0.72 (0.23 to 2.26)	960 (5 studies)	⊕⊕⊖⊖ low[1]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with vaginal progesterone			
	13 per 1000	9 per 1000 (3 to 29)			
Bayley-III cognitive composite score at 2 years of age	The mean Bayley-III cognitive composite score at 2 years of age in the intervention groups was 2.17 lower (7.16 lower to 2.83 higher)			168 (1 study)	⊕⊕⊖⊖ low[5]
Moderate/severe neurodevelopmental impairment at 2 years of age	Study population		RR 1.36 (0.54 to 3.39)	158 (1 study)	⊕⊕⊖⊖ low[6]
	91 per 1000	124 per 1000 (49 to 308)			
Visual or hearing Impairment at 2 years of age	Study population		RR 0.17 (0.01 to 3.58)	187 (1 study)	⊕⊕⊖⊖ low[6]
	23 per 1000	4 per 1000 (0 to 82)			
Disability in renal, gastrointestinal, or respiratory function at 2 years of age	Study population		RR 0.92 (0.06 to 14.52)	175 (1 study)	⊕⊕⊖⊖ Low[6]
	12 per 1000	11 per 1000 (1 to 173)			
Any maternal adverse event	Study population		RR 1.21 (0.87 to 1.69)	846 (5 studies)	⊕⊕⊕⊖ Moderate[7]
	111 per 1000	135 per 1000 (97 to 188)			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95%CI).

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Few events; 95% CI does not include effect and is imprecise (lower and upper bounds <0.75 and >1.25, respectively)

[2] 95% CI does not include effect and is imprecise (lower bound <0.75)

[3] Few events; 95% CI does not include effect and is imprecise (lower bound <0.75)

[4] 95% CI does not include effect and is imprecise (lower and upper bounds <0.75 and >1.25, respectively)

[5] Small sample size; 95% CI does not include effect and is imprecise

[6] 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

[7] 95% CI does not include effect and is imprecise (upper bound >1.25)