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Vaginal progesterone for the prevention of preterm birth and adverse perinatal outcomes in twin gestations with a short cervix: an updated individual patient data meta-analysis

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In 2017, we reported the results of an individual patient data (IPD) meta-analysis on the efficacy of vaginal progesterone in asymptomatic women with a twin gestation and a sonographic cervical length (CL) ≤25 mm for the prevention of preterm birth and neonatal morbidity and mortality[1]. The primary outcome was preterm birth <33 weeks of gestation. This meta-analysis included data for 303 women and their 606 fetuses/infants from six randomized controlled trials[2–7] and showed that vaginal progesterone, compared to placebo/no treatment, was associated with a statistically significant reduction in the risk of preterm birth <33 weeks of gestation (relative risk [RR] 0.69, 95% confidence interval [CI] 0.51–0.93). Moreover, vaginal progesterone administration was associated with a significant decrease in the risk of preterm birth <35, <34, <32 and <30 weeks of gestation, neonatal death, respiratory distress syndrome (RDS), composite neonatal morbidity and mortality, use of mechanical ventilation, and birthweight <1500 g.

At present, we are performing a systematic review and meta-analysis on the efficacy and safety of vaginal progesterone for preventing preterm birth and perinatal morbidity and mortality in asymptomatic women with a twin gestation, which was registered with PROSPERO (number CRD42020205184). Recently, one[7] of the studies included in our previous IPD meta-analysis was retracted because, allegedly, "the authors did not obtain approval from a research ethics committee before conducting this interventional randomized control trial and therefore this study is in breach of the Declaration of Helsinki and the editorial policy of the Journal"[8]. Therefore, we have decided to update our IPD meta-analysis by excluding data from the retracted study and including those from eligible studies published since the last literature search date.

We followed the same methodology that was used in our previous IPD meta-analysis[1]. Briefly, a literature search was performed in MEDLINE, EMBASE, CINAHL, LILACS, and the Cochrane Central Register of Controlled Trials for randomized controlled trials published from January 1, 2017, to November 30, 2021, comparing vaginal progesterone (any dose) vs placebo/no treatment for the prevention of preterm birth and/or adverse perinatal outcomes in women with a twin gestation and a midtrimester sonographic CL ≤25 mm. Trials were eligible if the primary aim of the study was to prevent preterm birth in women with a twin gestation and a short cervix, or to prevent preterm birth in women with an unselected twin gestation but for whom outcomes were available in those with a pre-randomization CL ≤25 mm. The principal investigators of eligible trials were contacted and asked to share their data for this collaborative project. As in the previous IPD meta-analysis, the primary outcome was preterm birth <33 weeks of gestation. Secondary outcomes included preterm birth <37, <36, <35, <34, <32, <30, and <28 weeks of gestation, spontaneous preterm birth <33 and <34 weeks of gestation, and adverse perinatal outcomes. We assessed the risk of bias in each included study, using the tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions[9].

The IPD were combined in a two-stage approach in which outcomes were analyzed in the original trial, and summary statistics (pooled RR with 95% CI) were then generated, using standard summary data meta-analysis techniques[10]. Heterogeneity of treatment effect was assessed with the I^2 statistic, where I^2 ≥30% indicated substantial heterogeneity[11]. We used a fixed-effect model to calculate the pooled RR with 95% CI where it was reasonable to assume that studies were estimating the same underlying treatment effect. We planned to use the random-effects model if there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials or if we found substantial statistical heterogeneity. For perinatal outcomes, we estimated pooled RRs with 95% Cis, assuming independence between fetuses/neonates by using data reported in the studies at the fetal/neonatal level. We also used cluster analysis to estimate pooled adjusted RRs with 95% CIs to take into account non-independence of fetuses/neonates from twin gestations[12]. Adjusted RRs were considered as the main estimates of the vaginal progesterone's effect on perinatal outcomes. The number needed to treat (NNT) for benefit or harm with the 95% CI was calculated for outcomes for which there was a statistically significant reduction or increase in risk difference based on control event rates in the trials. Prespecified sensitivity analyses to explore the impact of risk of bias on results were not performed because all trials were judged to be at low risk of bias. We used the GRADE approach to assess the quality of evidence for the clinically relevant outcomes preterm birth <33 weeks of gestation and composite neonatal morbidity and mortality[13]. The GRADE approach categorizes the quality of the evidence into four levels: high, moderate, low, and very low.

For this update, the search strategy identified three additional studies for possible inclusion[14–16], of which we included one[16] and excluded two[14,15]. The trial by Crowther et al[14], which compared vaginal progesterone 100 mg/day versus placebo from 20 weeks until 34 weeks of gestation in women with a previous spontaneous preterm birth, included 12 women with a twin gestation (8 in the vaginal progesterone group and 4 in the placebo group). This study was excluded because data on cervical length were not collected before randomization. The study by Shabaan et al[15], which compared vaginal progesterone 400

mg/day versus no treatment in 140 women with a twin gestation, was excluded because vaginal progesterone administration was started in the third trimester (mean, 28.9 weeks of gestation). Moreover, this study did not report information about pre-randomization cervical length. The EVENTS trial by Rehal et al[16], which compared vaginal progesterone 600 mg/day to placebo from 11 to 14 weeks until 34 weeks of gestation in 1194 women with a twin gestation, met the inclusion criteria. In this study, all included women underwent cervical length measurement before randomization. A total of 16 women (9 in the vaginal progesterone group and 7 in the placebo group) had a cervical length ≤25 mm (mean gestational age at randomization, 13.2 weeks), and their IPD were provided for this updated meta-analysis.

Six double-blind, placebo-controlled trials[2–6,16], which provided IPD for 95 women and their 190 fetuses/infants, met the inclusion criteria for the updated meta-analysis (Supplementary Figure 1). All studies were deemed to be at low risk of bias for all domains of the Cochrane Handbook for Systematic Reviews of Interventions' tool (Supplementary Figure 2). Vaginal progesterone significantly reduced the risk of preterm birth <33 weeks of gestation (38.5% vs 55.8%; RR 0.60; 95% CI 0.38–0.95; P=0.03; I^2 =14%; NNT for benefit 5, 95% CI 3–36) (Figure 1). The frequencies of preterm birth <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 than in the placebo group (RRs from 0.41–0.68) (Table 1). There was no evidence of an effect of vaginal progesterone on preterm birth <37, <36, and <35 weeks of gestation. Treatment with vaginal progesterone was also associated with a significant decrease in the risk of composite neonatal morbidity and mortality (RR 0.59; 95% CI 0.33–0.98) and birthweight <1500 g (RR 0.55; 95% CI 0.33–0.94) (Table 2). There were no significant differences between the study groups in the risk of the remaining adverse perinatal outcomes assessed. After applying the GRADE approach, the evidence was judged to be of "moderate quality" for the outcomes preterm birth <33 weeks of gestation and composite neonatal morbidity and mortality (Supplementary Table). We downgraded one level for imprecision due to failure to meet the optimal information size (small total sample size). An assignment of "moderate quality" signifies that we are moderately confident in the effect estimate, and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

In conclusion, this updated meta-analysis, which excluded data from the retracted study and included information from the EVENTS trial, shows that vaginal progesterone significantly decreases the risk of preterm birth <33 weeks of gestation among women with a twin gestation and a midtrimester CL ≤25 mm. In addition, despite the limited sample size of the meta-analysis, vaginal progesterone was associated with a significant reduction in the risk of preterm birth <34, <32, <30, and <28 weeks of gestation, spontaneous preterm birth <33 and <34 weeks of gestation, composite neonatal morbidity and mortality, and birthweight <1500 g. Nevertheless, it should be emphasized that evidence from an ongoing randomized controlled trial (PROSPECT study) is needed to establish whether this promising intervention can be recommended to women with a twin gestation and a short cervix. The PROSPECT study (NCT02518594) is a randomized controlled trial of 630 women evaluating the use of vaginal progesterone 200 mg/day or cervical pessary versus control (placebo) to prevent early preterm birth in women carrying twins and with a CL <30

mm between 16 and 23 weeks of gestation[17]. This study began in November 2015, and the estimated completion date is February 2025.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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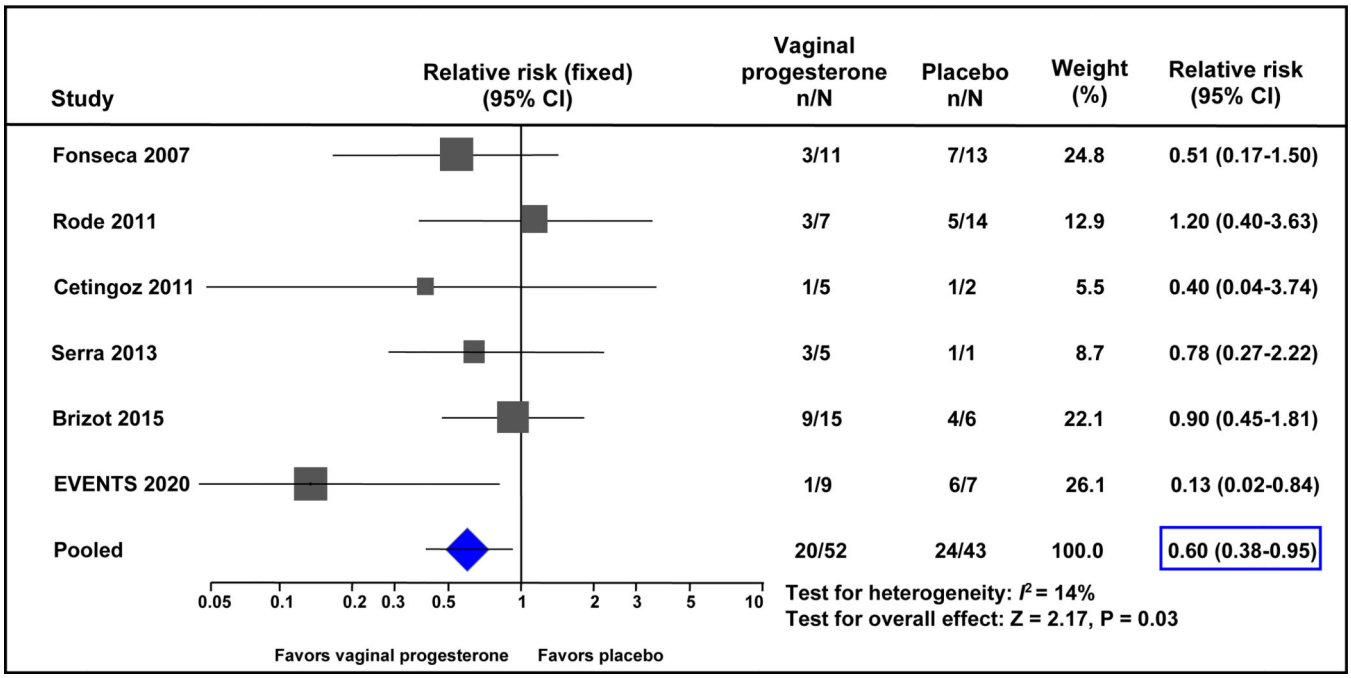

Figure 1:
Forest plot of the effect of vaginal progesterone on the risk of preterm birth <33 weeks of gestation. CI, confidence interval.

Table 1.

Effect of vaginal progesterone on the risk of preterm birth

Outcome	No of trials	Events (n)/Total (N)		Pooled RR (95% CI)	I^2 (%)	NNT (95% CI)
		Vaginal progesterone	Placebo			
Preterm birth <37 weeks	6	43/52	38/43	0.91 (0.75–1.10)	0	---
Preterm birth <36 weeks	6	35/52	32/43	0.89 (0.69–1.15)	0	---
Preterm birth <35 weeks	6	31/52	31/43	0.81 (0.61–1.09)	0	---
Preterm birth <34 weeks	6	24/52	28/43	0.68 (0.46–0.99)	7	5 (3–154)
Preterm birth <32 weeks	6	16/52	20/43	0.56 (0.33–0.93)	6	5 (3–31)
Preterm birth <30 weeks	6	10/52	14/43	0.45 (0.23–0.89)	0	6 (4–28)
Preterm birth <28 weeks	6	7/52	11/43	0.41 (0.19–0.91)	0	7 (5–44)
Spontaneous preterm birth <33 weeks	6	17/52	24/43	0.53 (0.33–0.87)	12	4 (3–14)
Spontaneous preterm birth <34 weeks	6	20/52	28/43	0.58 (0.38–0.89)	24	4 (3–14)

CI, confidence interval; NNT, number needed to treat; RR, relative risk.

Table 2.

Effect of vaginal progesterone on the risk of adverse perinatal outcomes

Outcome	No of trials	Events (n)/Total (N)		Pooled RR (95% CI)		I^2 (%)	NNT (95% CI)
		Vaginal progesterone	Placebo/no treatment	Assuming independence between twins	Adjustment for the non-independence between twins		
Respiratory distress syndrome	6	21/100	21/84	0.63 (0.36–1.10)	0.74 (0.41–1.33)	0	---
Necrotizing enterocolitis	6	1/100	0/82	1.00 (0.04–22.43)	1.07 (0.05–22.25)	NA	---
Intraventricular hemorrhage	6	2/98	2/82	0.93 (0.15–5.75)	1.47 (0.22–9.63)	0	---
Proven neonatal sepsis	6	5/98	7/82	0.56 (0.19–1.65)	0.74 (0.25–2.16)	0	---
Retinopathy of prematurity	6	1/98	2/82	0.36 (0.07–1.75)	0.38 (0.08–1.76)	0	---
Fetal death	6	6/104	4/86	0.59 (0.19–1.80)	0.54 (0.17–1.77)	0	---
Neonatal death	6	4/104	9/86	0.41 (0.18–0.95)	0.51 (0.20–1.28)	0	---
Perinatal death	6	10/104	13/86	0.46 (0.24–0.88)	0.59 (0.27–1.26)	0	---
Composite neonatal morbidity/ mortality *	6	24/102	31/84	0.54 (0.34–0.86)	0.59 (0.33–0.98)	0	6 (4–117)
Birthweight <1500 g	6	26/104	35/84	0.49 (0.33–0.74)	0.55 (0.33–0.94)	0	5 (4–37)
Birthweight <2500 g	6	88/104	69/84	1.05 (0.92–1.19)	1.04 (0.89–1.21)	0	---
Admission to NICU	6	53/104	48/86	0.96 (0.74–1.26)	0.99 (0.70–1.41)	0	---
Mechanical ventilation	6	22/100	18/84	0.73 (0.44–1.23)	0.60 (0.33–1.09)	0	---

* Occurrence of any of the following events: respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis, or neonatal death. CI, confidence interval; NICU, neonatal intensive care unit; NA, not applicable; NNT, number needed to treat; RR, relative risk.