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Letters to the Editor

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

In 2017, we reported the results of an individual patient data (IPD) meta-analysis on the efficacy of vaginal progesterone for the prevention of preterm birth and neonatal morbidity and mortality in asymptomatic women with a twin gestation and a sonographic cervical length (CL) ≤ 25 mm[1]. The primary outcome was preterm birth < 33 weeks' 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' gestation (relative risk (RR), 0.69 (95% 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 birth weight < 1500 g[1].

Recently, the study of El-Refaie *et al.*[7] that was included in our previous IPD meta-analysis[1] was retracted because, allegedly, '.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' in which it was published[8,9]. Therefore, we have decided to update our IPD meta-analysis by excluding the 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 1 January 2017 to 30 November 2021, comparing vaginal progesterone (any dose) *vs* placebo/no treatment for the prevention of preterm birth and/or adverse perinatal outcome in women with a twin gestation and a mid-trimester sonographic CL ≤ 25 mm. Trials were eligible if the primary aim of the study was to evaluate prevention of preterm birth in women with a twin gestation and a short cervix, or to evaluate prevention of preterm birth in women with an unselected twin gestation but for whom outcomes were available in those with a prerandomization 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[1], the primary outcome was preterm birth < 33 weeks of gestation. Secondary outcomes included preterm birth < 37, < 36, < 35, < 34, < 32, < 30 and < 28 weeks' gestation, spontaneous preterm birth < 33 and < 34 weeks' gestation and adverse perinatal outcomes (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 at least one of: RDS, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis or neonatal death), birth weight < 1500 g or < 2500 g, admission to the neonatal intensive care unit and use of mechanical ventilation). The risk of bias in each included study was assessed using the criteria recommended by the Cochrane Handbook for Systematic Reviews of Interventions[10].

IPD were combined in a two-stage approach in which outcomes were analyzed in the original trial and then summary statistics (pooled RR with 95% CI) were generated using standard summary data meta-analysis techniques[11]. Heterogeneity of treatment effect was assessed using the I^2 statistic, with $I^2 \geq 30\%$ indicating substantial heterogeneity[12]. We used a fixed-effect model to calculate pooled RR with 95% CI when 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, pooled RRs with 95% CIs were estimated, 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[13]. Adjusted RRs were considered as the main estimates of the effect of vaginal progesterone on perinatal outcome. 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 based on control event rates in the trials. Prespecified sensitivity analyses to explore the impact of risk of bias on the results were not performed because all trials were judged to be at low risk of bias. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[14] to assess the quality of evidence for the clinically relevant outcomes of preterm birth < 33 weeks' gestation and composite neonatal morbidity and mortality. The GRADE approach categorizes the quality of the evidence into four levels: high, moderate, low and very low.

In this updated IPD meta-analysis, the search strategy identified three additional potentially eligible studies[15–17], of which two[15,16] were excluded and one[17] was included. The trial by Crowther *et al.*[15] compared vaginal progesterone 100 mg/day *vs* placebo from 20 weeks until 34 weeks of gestation in women with a previous spontaneous preterm birth, and included 12 women with a twin gestation (eight in the vaginal progesterone group and four in the placebo group). This study was excluded because data on CL were not collected before randomization. The study by Shabaan *et al.*[16], which compared vaginal progesterone 400 mg/day *vs* 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). Moreover, the study did not report information about prerandomization CL. The EVENTS trial by Rehal *et al.*[17], which compared vaginal progesterone 600 mg/day to placebo from 11–14 weeks until 34 weeks of gestation in 1194 women with a twin gestation, met the inclusion criteria. In that study, all included women underwent CL measurement before randomization. A total of 16 women (nine in the vaginal progesterone group and seven in the placebo group) had CL ≤ 25 mm (mean gestational age at randomization, 13.2 weeks), and their IPD were provided for this updated meta-analysis.

Therefore, six double-blind, placebo-controlled trials[2–6,17], which provided IPD for 95 women and their 190 fetuses/infants, met the inclusion criteria for this updated meta-analysis (Figure S1). All studies were deemed to be at low risk of bias for all domains of the Cochrane Handbook for Systematic Reviews of Interventions tool (Figure S2). Vaginal progesterone reduced significantly the risk of preterm birth < 33 weeks' 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 and spontaneous preterm birth < 33 and < 34 weeks of gestation were significantly lower in the vaginal progesterone group compared with the placebo group (RRs ranging from 0.41 to 0.68) (Table 1). There was no evidence of an effect of vaginal progesterone on preterm birth < 37, < 36 and < 35 weeks' 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 birth weight < 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 of preterm birth < 33 weeks' gestation and composite neonatal morbidity and mortality (Table S1). We downgraded the quality of evidence by one level for imprecision due to failure to meet the optimal information size (small total sample size). According to GRADE, '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 of El-Refaie *et al.*[7] and included information from the recently published EVENTS trial by Rehal *et al.*[17], shows that vaginal progesterone decreases significantly the risk of preterm birth < 33 weeks' gestation among women with a twin gestation and a mid-trimester CL ≤ 25 mm. In addition,

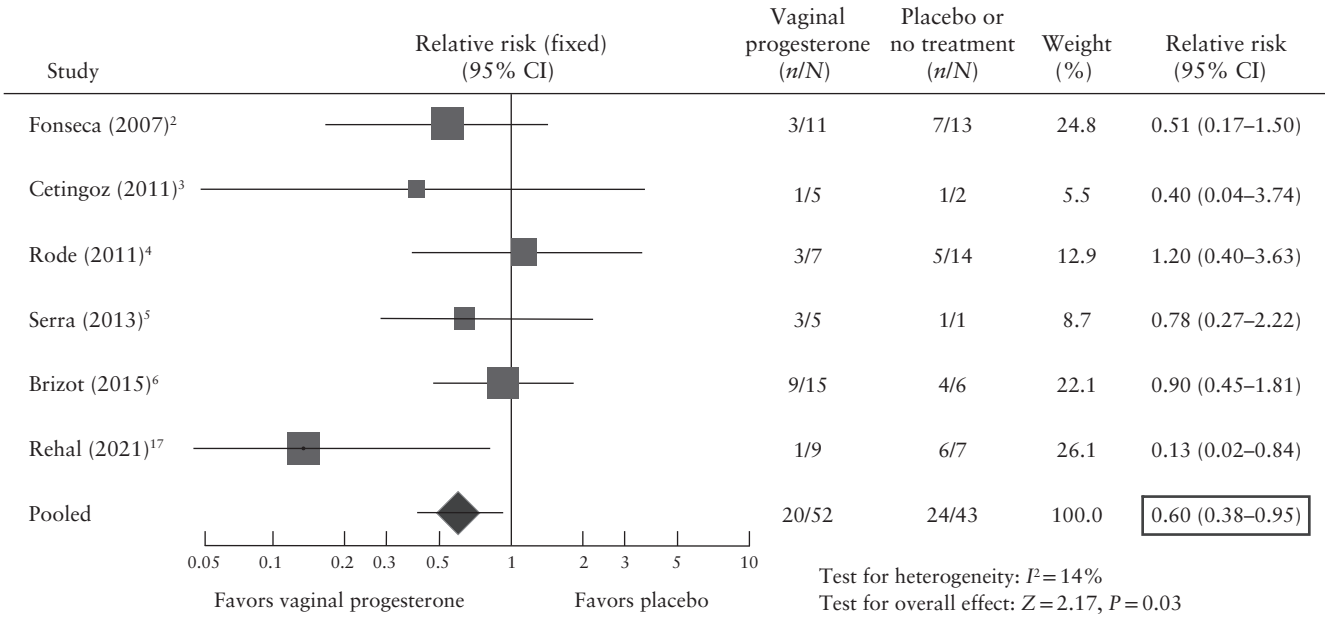

Figure 1 Forest plot showing effect of vaginal progesterone on the risk of preterm birth < 33 weeks' gestation in women with a twin gestation and a mid-trimester sonographic cervical length ≤ 25 mm. Only first author is given for each study.

Table 1 Effect of vaginal progesterone on the risk of preterm birth (PTB) in women with a twin gestation and a mid-trimester sonographic cervical length ≤ 25 mm

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

NNT, number needed to treat; refs, reference numbers; RR, relative risk.

Table 2 Effect of vaginal progesterone on the risk of adverse perinatal outcomes in women with a twin gestation and a mid-trimester sonographic cervical length ≤ 25 mm

Outcome	*Trials* (n[*refs*])	*Events* (n)/*Total* (N)		*Pooled RR (95% CI)*		I^2 *(%)*	*NNT (95% CI)*
		Vaginal progesterone	*Placebo or no treatment*	*Assuming independence between twins*	*Adjustment for non-independence between twins*		
Respiratory distress syndrome	6[2–6,17]	21/100	21/84	0.63 (0.36–1.10)	0.74 (0.41–1.33)	0	—
Necrotizing enterocolitis	6[2–6,17]	1/100	0/82	1.00 (0.04–22.43)	1.07 (0.05–22.25)	N/A	—
Intraventricular hemorrhage	6[2–6,17]	2/98	2/82	0.93 (0.15–5.75)	1.47 (0.22–9.63)	0	—
Proven neonatal sepsis	6[2–6,17]	5/98	7/82	0.56 (0.19–1.65)	0.74 (0.25–2.16)	0	—
Retinopathy of prematurity	6[2–6,17]	1/98	2/82	0.36 (0.07–1.75)	0.38 (0.08–1.76)	0	—
Fetal death	6[2–6,17]	6/104	4/86	0.59 (0.19–1.80)	0.54 (0.17–1.77)	0	—
Neonatal death	6[2–6,17]	4/104	9/86	0.41 (0.18–0.95)	0.51 (0.20–1.28)	0	—
Perinatal death	6[2–6,17]	10/104	13/86	0.46 (0.24–0.88)	0.59 (0.27–1.26)	0	—
Composite neonatal morbidity and mortality*	6[2–6,17]	24/102	31/84	0.54 (0.34–0.86)	0.59 (0.33–0.98)	0	6 (4–117)
Birth weight < 1500 g	6[2–6,17]	26/104	35/84	0.49 (0.33–0.74)	0.55 (0.33–0.94)	0	5 (4–37)
Birth weight < 2500 g	6[2–6,17]	88/104	69/84	1.05 (0.92–1.19)	1.04 (0.89–1.21)	0	—
Admission to NICU	6[2–6,17]	53/104	48/86	0.96 (0.74–1.26)	0.99 (0.70–1.41)	0	—
Mechanical ventilation	6[2–6,17]	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. N/A, not applicable; NICU, neonatal intensive care unit; NNT, number needed to treat; refs, reference numbers; RR, relative risk.

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, spontaneous preterm birth < 33 and < 34 weeks, composite neonatal morbidity and mortality, and birth weight < 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 *vs* control (placebo) to prevent early preterm birth in women carrying twins and with a CL < 30 mm between 16 and 23 weeks of gestation. This study began in November 2015 and the estimated completion date is February 2025.

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References

1. Romero R, Conde-Agudelo A, El-Refaie W, Rode L, Brizot ML, Cetingoz E, Serra V, Da Fonseca E, Abdelhafez MS, Tabor A, Perales A, Hassan SS, Nicolaides KH. Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. *Ultrasound Obstet Gynecol* 2017; **49**: 303–314.
2. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med* 2007; **357**: 462–469.
3. Cetingoz E, Cam C, Sakalli M, Karateke A, Celik C, Sancak A. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. *Arch Gynecol Obstet* 2011; **283**: 423–429.
4. Rode L, Klein K, Nicolaides KH, Krampl-Bettelheim E, Tabor A; PREDICT Group. Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. *Ultrasound Obstet Gynecol* 2011; **38**: 272–280.
5. Serra V, Perales A, Meseguer J, Parrilla JJ, Lara C, Bellver J, Grifol R, Alcover I, Sala M, Martínez-Escoriza JC, Pellicer A. Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. *BJOG* 2013; **120**: 50–57.
6. Brizot ML, Hernandez W, Liao AW, Bittar RE, Francisco RP, Krebs VL, Zugaib M. Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* 2015; **213**: 82.e1–9.
7. El-Refaie W, Abdelhafez MS, Badawy A. Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety. *Arch Gynecol Obstet* 2016; **293**: 61–67.
8. El-Refaie W, Abdelhafez MS, Badawy A. Retraction Note: Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety. *Arch Gynecol Obstet* 2021; **304**: 1113.
9. Romero R, Conde-Agudelo A, Rode L, Brizot ML, Cetingoz E, Serra V, Da Fonseca E, Tabor A, Perales A, Hassan SS, Nicolaides KH. Vaginal progesterone in twin gestation with a short cervix: revisiting an individual patient data systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2021; **58**: 943–945.
10. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In *Cochrane Handbook for Systematic Reviews of Interventions version 6.2* (updated February 2021), Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds). Cochrane, 2021. Available from www.training.cochrane.org/handbook.
11. Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, Rovers M. Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. *PLoS Med* 2015; **12**: e1001855.
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
13. Gates S, Brocklehurst P. How should randomised trials including multiple pregnancies be analysed? *BJOG* 2004; **111**: 213–219.
14. Schünemann H, Brozek J, Guyatt G, Oxman A. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations*. Updated October 2013. The GRADE Working Group, 2013.
15. Crowther CA, Ashwood P, McPhee AJ, Flenady V, Tran T, Dodd JM, Robinson JS; PROGRESS Study Group. Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS Study): A multicentre, randomised, placebo-controlled trial. *PLoS Med* 2017; **14**: e1002390.
16. Shabaan OM, Hassanin IM, Makhlouf AM, Salem MN, Hussein M, Mohamed M, Abbas AM. Vaginal progesterone for prevention of preterm delivery in women with twin pregnancy: a randomized controlled trial. *Facts Views Vis ObGyn* 2018; **10**: 93–98.
17. Rehal A, Benkő Z, De Paco Matallana C, Syngelaki A, Janga D, Cicero S, Akolekar R, Singh M, Chaveeva P, Burgos J, Molina FS, Savvidou M, De La Calle M, Persico N, Quezada Rojas MS, Sau A, Greco E, O'Gorman N, Plasencia W, Pereira S, Jani JC, Valino N, Del Mar Gil M, Maclagan K, Wright A, Wright D, Nicolaides KH. Early vaginal progesterone versus placebo in twin pregnancies for the prevention of spontaneous preterm birth: a randomized, double-blind trial. *Am J Obstet Gynecol* 2021; **224**: 86.e1–19.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Flowchart showing selection of studies included in the updated systematic review and meta-analysis.

Figure S2 Risk of bias of studies included in the systematic review.

Table S1 Quality of evidence (according to GRADE criteria) for the effect of vaginal progesterone on preterm birth < 33 weeks' gestation and composite neonatal morbidity and mortality

