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Vaginal progesterone for the prevention of preterm birth: who can benefit and who cannot? Evidence-based recommendations for clinical use

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Abstract: Vaginal progesterone (VP) has been recommended to prevent preterm birth (PTB) in women at high-risk. However, there is controversy as to whether VP is efficacious in some subsets of high-risk women. In this review, we examined the current best evidence on the efficacy of VP to prevent PTB in several subsets of high-risk women and provided recommendations for its clinical use. Compelling evidence indicates that VP reduces the risk of PTB and improves perinatal outcomes in singleton gestations with a short cervix (≤ 25 mm), both with and without a history of spontaneous PTB. VP appears promising to reduce the risk of PTB in twin gestations with a short cervix (≤ 25 mm) and in singleton gestations conceived by assisted reproductive technologies, but further research is needed. There is no convincing evidence that supports prescribing VP to prevent PTB in singleton gestations based solely on the history of spontaneous preterm birth. Persuasive evidence shows that VP does not prevent PTB nor does it improve perinatal outcomes in unselected twin gestations and in singleton

gestations with a history of spontaneous PTB and a cervical length > 25 mm. There is no evidence supporting the use of VP to prevent PTB in triplet or higher-order multifetal gestations, singleton gestations with a positive fetal fibronectin test and clinical risk factors for PTB, and gestations with congenital uterine anomalies or uterine leiomyoma. In conclusion, current evidence indicates that VP should only be recommended in singleton gestations with a short cervix, regardless of the history of spontaneous PTB.

Keywords: prematurity; preterm delivery; progestogens; recurrent preterm birth; short cervix.

Introduction

In 2021, the rate of preterm birth in the United States, which had declined from 2019 to 2020 (10.23 to 10.09%), increased to 10.49% [1]. This is the highest level reported in at least 14 years. An estimated 14.84 million infants (10.6% of all live births) are born preterm worldwide every year [2]. In 2019, complications relating to preterm birth were the leading cause of mortality in children under 5 years of age worldwide, accounting for 17.7% of all deaths, and for 36.1% of neonatal deaths [3]. Infants born prematurely are at increased risk for neonatal complications such as respiratory distress syndrome (RDS), bronchopulmonary dysplasia, necrotizing enterocolitis, and intraventricular hemorrhage, long-term neurodevelopmental behavioral and cognitive disorders, as well as chronic diseases in adulthood such as diabetes mellitus, hypertension, ischemic heart disease, cerebrovascular disease leading to stroke, and chronic kidney disease [4–10]. Moreover, preterm birth generates a significant economic burden to society and has a major impact on the quality of life of parents and families [4, 11, 12].

Preterm labor is a complex syndrome associated with multiple etiologic processes such as infection/inflammation, vascular disorders, decidual hemorrhage, uterine overdistention, decline in progesterone action, cervical disease, breakdown of maternal-fetal tolerance, immunologically mediated processes, and maternal stress, among others

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[13–15]. This is the reason why a single intervention does not prevent all, or even most, cases of preterm birth.

Several interventions have been proposed to prevent preterm birth: home uterine monitoring to detect preterm labor, risk scoring systems to predict preterm birth, psychosocial interventions, health system interventions (packages of antenatal care, specialized antenatal clinics, incentives for increasing prenatal care, midwifery led care), optimal birth spacing, bed rest, activity restriction, nutritional interventions (nutritional advice, macronutrient and micronutrient supplementation, vitamins, fish oil, zinc, calcium, iron and folic acid), prophylactic antibiotics during the second and third trimesters, screening and prevention/treatment of periodontal disease and infections, low-dose aspirin, prophylactic tocolysis, administration of progestogens, cervical cerclage, and cervical pessary. Unfortunately, most of these interventions have been shown to be ineffective in reducing the risk of preterm birth in singleton and twin gestations [16–18].

In 2012, both the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommended the administration of vaginal progesterone to women with a singleton gestation, no history of spontaneous preterm birth, and a transvaginal cervical length ≤ 20 mm at ≤ 24 weeks of gestation [19, 20]. A SMFM statement published in 2017 reaffirmed that “vaginal progesterone should not be considered a substitute for 17OHP-C [17 α -hydroxyprogesterone caproate]” in women with a singleton gestation and a history of spontaneous preterm birth [21]. In 2021, the ACOG updated its guidelines, which were endorsed by the SMFM, and recommended the administration of vaginal progesterone to women with a singleton gestation, no history of spontaneous preterm birth, and a transvaginal cervical length < 25 mm at 18–22 weeks of gestation [22]. In addition, for the first time, these guidelines recommended offering vaginal progesterone to women with a singleton gestation and a history of spontaneous preterm birth regardless of the cervical length measurement. The evidence base to make this last recommendation was the EPPPIC meta-analysis, an individual patient data (IPD) meta-analysis that included 9 trials comparing vaginal progesterone to placebo/no treatment in women with a singleton gestation considered at high risk for preterm birth due to a history of spontaneous preterm birth, short cervix, congenital uterine anomalies, uterine leiomyomas, pregnancy after assisted reproductive technologies, or a positive fetal fibronectin test combined with other clinical risk factors [23]. This study reported that vaginal progesterone significantly reduced the risk of preterm birth < 34 weeks of gestation in

high-risk singleton gestations (pooled relative risk [RR], 0.78; 95% confidence interval [CI], 0.68–0.90). There were no significant differences between the vaginal progesterone and placebo/no treatment groups in the risk of the remaining primary outcomes (preterm birth < 37 and < 28 weeks of gestation, perinatal death, serious neonatal complications, and maternal complications). This IPD meta-analysis has been criticized by the U.S. Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER) because it grouped together trials of patients with differences in their risk profiles, including combining women with a history of spontaneous preterm birth and those without a history of spontaneous preterm birth, and women with and without a short cervix [24]. Because of this grouping, this IPD meta-analysis does not provide relevant information regarding the efficacy of vaginal progesterone in different subsets of patients at high risk for preterm birth. Hence, an assessment of the efficacy of vaginal progesterone for preventing preterm birth in such subsets of patients is justified.

The objectives of this review were (1) to examine the current best evidence regarding the efficacy of vaginal progesterone to prevent preterm birth and improve perinatal outcomes in several subsets of women at high risk for this entity; and (2) to provide evidence-based recommendations for the clinical use of vaginal progesterone in women at high risk for preterm birth. We prioritized data from randomized controlled trials and systematic reviews and meta-analyses of randomized controlled trials.

Efficacy of vaginal progesterone to prevent preterm birth in high-risk women

Women with a singleton gestation and a midtrimester transvaginal sonographic short cervix

In 2018, a meta-analysis of IPD was published that assessed 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 midtrimester (18–24 weeks of gestation) transvaginal sonographic short cervix (cervical length ≤ 25 mm) [25]. The primary outcome was preterm birth < 33 weeks of gestation. IPD were obtained

for 974 women with a cervical length ≤ 25 mm from 5 double-blind, placebo-controlled, high-quality trials [26–30]. The daily dose of vaginal progesterone used in the trials was 200 mg in 2 studies [27, 30], 100 mg in 1 study [28], and 90 mg in 2 studies [26, 29], and the treatment was administered from 18^{+0} – 24^{+6} to 34^{+0} – 37^{+0} weeks of gestation. A total of 498 women were assigned to receive vaginal progesterone and 476 to receive placebo. Vaginal progesterone significantly reduced the risk of preterm birth <36 weeks (RR, 0.80; 95% CI, 0.67–0.97), <35 weeks (RR, 0.72; 95% CI, 0.58–0.89), <34 weeks (RR, 0.65; 95% CI, 0.51–0.83), <33 weeks (RR, 0.62; 95% CI, 0.47–0.81), <32 weeks (RR, 0.64; 95% CI, 0.48–0.86), <30 weeks (RR, 0.70; 95% CI, 0.49–0.98), and <28 weeks (RR, 0.67; 95% CI, 0.45–0.99). Importantly, vaginal progesterone was also associated with a significant decrease in the risk of RDS (RR, 0.47; 95% CI, 0.27–0.81), composite neonatal morbidity and mortality (RR, 0.59; 95% CI, 0.38–0.91), birthweight $<1,500$ g (RR, 0.62; 95% CI, 0.44–0.86) and $<2,500$ g (RR, 0.82; 95% CI, 0.68–0.98), and admission to the neonatal intensive care unit (NICU) (RR, 0.68; 95% CI, 0.53–0.88) (Table 1). Moreover, there was a nonsignificant trend toward reduction of neonatal death (RR, 0.44; 95% CI, 0.18–1.07), neonatal sepsis (RR, 0.61; 95% CI, 0.34–1.08), and use of mechanical ventilation (RR, 0.65; 95% CI, 0.41–1.01). Maternal adverse events, congenital anomalies, and adverse neurodevelopmental and health outcomes at 2 years of age did not significantly differ between the vaginal progesterone and placebo groups. According to the GRADE approach [31], evidence was graded as high-quality for all outcomes for

which vaginal progesterone significantly reduced their risk. It 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 our confidence in the estimate of effect. The mechanisms by which vaginal progesterone prevents preterm birth in women with a singleton gestation and a sonographic short cervix are not clear but may involve alterations of molecular pathways involved in premature cervical ripening and/or the anti-inflammatory effects of vaginal progesterone [32–34].

Prespecified subgroup analyses showed that the beneficial effect of vaginal progesterone on preterm birth <33 weeks of gestation did not differ significantly between patients with a history of spontaneous preterm birth (RR, 0.59; 95% CI, 0.40–0.88) and those without a history of spontaneous preterm birth (RR, 0.65; 95% CI, 0.45–0.94; p for interaction=0.74), as well as between US women (RR, 0.73; 95% CI, 0.42–1.27) and non-US women (RR, 0.59; 95% CI, 0.43–0.80; p for interaction=0.51). There was no difference in efficacy in the prevention of preterm birth <33 weeks of gestation when either 90–100 mg/d (RR, 0.53; 95% CI, 0.33–0.87) or 200 mg/d (RR, 0.67; 95% CI, 0.49–0.93) of vaginal progesterone was administered. Therefore, either regimen can be used in practice. However, it is recommended to use a daily dose of 90–100 mg of vaginal progesterone because it is the lowest dose that reduced the risk of preterm birth <33 weeks of gestation.

In conclusion, there is compelling evidence that vaginal progesterone decreases the risk of preterm birth

Table 1: Statistically significant beneficial effects of vaginal progesterone in women with a singleton gestation and a midtrimester transvaginal sonographic short cervix.

Outcome	No of trials	Vaginal progesterone		Placebo		Relative risk (95% CI)	p-Value
Preterm birth <36 weeks	5	139/498	(28%)	166/476	(35%)	0.80 (0.67–0.97)	0.02
Preterm birth <35 weeks	5	106/498	(21%)	141/476	(30%)	0.72 (0.58–0.89)	0.003
Preterm birth <34 weeks	5	86/498	(17%)	126/476	(26%)	0.65 (0.51–0.83)	0.0006
Preterm birth <33 weeks	5	70/498	(14%)	107/476	(22%)	0.62 (0.47–0.81)	0.0006
Preterm birth <32 weeks	5	62/498	(12%)	92/476	(19%)	0.64 (0.48–0.86)	0.003
Preterm birth <30 weeks	5	49/498	(10%)	67/476	(14%)	0.70 (0.49–0.98)	0.04
Preterm birth <28 weeks	5	38/498	(8%)	54/476	(11%)	0.67 (0.45–0.99)	0.04
Spontaneous preterm birth <33 weeks	5	60/498	(12%)	82/476	(17%)	0.70 (0.51–0.95)	0.02
Spontaneous preterm birth <34 weeks	5	73/498	(15%)	97/476	(20%)	0.72 (0.55–0.95)	0.02
Respiratory distress syndrome	4	17/365	(5%)	37/358	(10%)	0.47 (0.27–0.81)	0.007
Composite neonatal morbidity and mortality	4	29/365	(8%)	49/358	(14%)	0.59 (0.38–0.91)	0.02
Birthweight $<1,500$ g	5	50/497	(10%)	77/473	(16%)	0.62 (0.44–0.86)	0.004
Birthweight $<2,500$ g	5	144/497	(29%)	168/473	(36%)	0.82 (0.68–0.98)	0.03
Admission to NICU	5	83/496	(17%)	117/474	(25%)	0.68 (0.53–0.88)	0.003

Data are presented as number/total number. CI, confidence interval; NICU, neonatal intensive care unit.

and improves perinatal outcomes in women with a singleton gestation and a midtrimester transvaginal sonographic short cervix, both with and without a history of spontaneous preterm birth, without any demonstrable deleterious effects on childhood neurodevelopment.

Women with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester transvaginal sonographic short cervix

In 2011, an IPD meta-analysis assessed the efficacy of cerclage for the prevention of preterm birth and perinatal morbidity and mortality in asymptomatic women with a singleton gestation, a history of spontaneous preterm birth, and a cervical length <25 mm before 24 weeks of gestation [35]. Cerclage was associated with a significant reduction in the risk of preterm birth <37, <35, <32, and <28 weeks of gestation, composite perinatal morbidity and mortality, and birthweight <1,500 g when compared to no cerclage. Given that our 2018 IPD meta-analysis [25] showed that vaginal progesterone significantly reduced the risk of preterm birth <33 weeks among women with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester transvaginal sonographic short cervix (cervical length ≤25 mm), we compared the efficacy of vaginal progesterone and cerclage in preventing preterm birth and adverse perinatal outcomes in this subset of patients by using adjusted indirect comparison meta-analytic techniques [36]. Vaginal progesterone, compared to placebo, significantly reduced the risk of preterm birth <35 weeks (RR, 0.68; 95% CI, 0.50–0.93) and <32 weeks (RR, 0.60; 95% CI, 0.39–0.92), composite perinatal morbidity and mortality (RR, 0.43; 95% CI, 0.20–0.94), neonatal sepsis (RR, 0.38; 95% CI, 0.15–0.96), composite neonatal morbidity (RR, 0.29; 95% CI, 0.11–0.81), and admission to the NICU (RR, 0.46; 95% CI, 0.30–0.70).

Adjusted indirect comparison meta-analyses did not show statistically significant differences between vaginal progesterone and cerclage in the reduction of preterm birth or adverse perinatal outcomes. These results indicate that vaginal progesterone and cerclage are equally efficacious in preventing preterm birth in women with a singleton gestation, a history of spontaneous preterm birth, and a sonographic short cervix.

In conclusion, vaginal progesterone should be offered as an alternative to cerclage in patients with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester transvaginal short cervix (cervical length ≤25 mm).

Women with a twin gestation and a midtrimester transvaginal sonographic short cervix

In February 2022, we published the results of an updated IPD meta-analysis that assessed 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 midtrimester transvaginal sonographic cervical length ≤25 mm [37]. The primary outcome was preterm birth <33 weeks of gestation. Six double-blind, placebo-controlled, high-quality trials [27, 28, 38–41], which provided IPD for 95 women and their 190 fetuses/infants, were included in this updated meta-analysis. Vaginal progesterone, as compared to placebo, was associated with a significant decrease in the frequency of preterm birth <33 weeks of gestation (38.5 vs. 55.8%; RR, 0.60; 95% CI, 0.38–0.95). Moreover, the treatment with vaginal progesterone significantly reduced the risk of preterm birth <34 weeks (RR, 0.68; 95% CI, 0.46–0.99), <32 weeks (RR, 0.56; 95% CI, 0.33–0.93), <30 weeks (RR, 0.45; 95% CI, 0.23–0.89) and <28 weeks (RR, 0.41; 95% CI, 0.19–0.91) of gestation, spontaneous preterm birth <33 weeks (RR, 0.53; 95% CI, 0.33–0.87) and <34 weeks (RR, 0.58; 95% CI, 0.38–0.89) of gestation, composite neonatal morbidity and mortality (RR, 0.59; 95% CI, 0.33–0.98), and birthweight <1,500 g (RR, 0.55; 95% CI, 0.33–0.94).

Although this updated IPD meta-analysis showed that vaginal progesterone reduces the risk of preterm birth occurring at <28 to <34 gestational weeks and improves perinatal outcomes, we think further evidence is required before recommending the use of this intervention among women with a twin gestation and a short cervix. The PROSPECT study (NCT02518594) is an ongoing randomized controlled trial assessing the use of vaginal progesterone 200 mg/day or cervical pessary vs. placebo to prevent preterm birth <35 weeks of gestation in 630 women with a twin gestation and a cervical length <30 mm between 16 and 23 weeks of gestation. The estimated completion date of this trial is February 2025. The results of this study will help to establish whether this promising intervention can be recommended to women with a twin gestation and a short cervix.

Women with a singleton gestation and a history of spontaneous preterm birth

In September 2022, we reported the results of a systematic review and meta-analysis that aimed to evaluate the

efficacy and safety of vaginal progesterone to prevent preterm birth and adverse perinatal outcomes in women with a singleton gestation and a history of spontaneous preterm birth [42]. The primary outcomes were preterm birth <37 and <34 weeks of gestation. A total of 10 randomized controlled trials, including 2,958 women, that compared vaginal progesterone to placebo/no treatment met the criteria for inclusion [26, 28, 30, 43–49]. Seven studies had a sample size <150 (small studies) [28, 43–47, 49] and 3 had a sample size >600 (large studies) [26, 30, 48]. The three large studies had high methodological quality. Among the 7 small studies, only 1 was deemed as high-quality [28]. The remaining 6 small studies were at high risk of bias (4 trials) [43, 45, 46, 49] or some concerns of bias (2 trials) [44, 47]. Overall, meta-analyses with substantial statistical heterogeneity that included data from all 10 trials showed that vaginal progesterone significantly reduced the risk of preterm birth <37 weeks (RR, 0.64; 95% CI, 0.50–0.81) and <34 weeks (RR, 0.62; 95% CI, 0.42–0.92), and the risk of admission to the NICU (RR, 0.53; 95% CI, 0.33–0.85). The quality of evidence according to the GRADE approach [31] for the outcomes of preterm birth <37 and <34 weeks of gestation was deemed as very low, which means that the true effect is probably markedly different from the estimated effect.

A prespecified subgroup analysis according to study sample size indicated that the results were highly conflicting because vaginal progesterone was associated with a large decrease in the risk of preterm birth <37 weeks (RR, 0.43; 95% CI, 0.33–0.55) and <34 weeks (RR, 0.27; 95% CI, 0.15–0.49) and of NICU admission (RR, 0.30; 95% CI, 0.18–0.51) in the small, poor-quality trials, whereas it had no effect in the large, high-quality trials (RR, 0.98; 95% CI 0.88–1.09 for preterm birth <37 weeks; RR, 0.94; 95% CI, 0.78–1.13 for preterm birth <34 weeks; and RR, 0.87; 95% CI, 0.69–1.09 for NICU admission) (Figure 1). Small-study effects, defined as the tendency of small trials to report larger benefits of treatment than large trials do, were clearly demonstrated in these meta-analyses. Sensitivity analyses restricted to the trials at overall low risk of bias showed that vaginal progesterone did not decrease the risk of preterm birth <37 weeks (RR, 0.96; 95% CI, 0.84–1.09) and <34 weeks (RR, 0.90; 95% CI, 0.71–1.15) and the risk of NICU admission (RR, 0.77; 95% CI, 0.53–1.14). In addition, the adjustment for small-study effects resulted in a markedly reduced and nonsignificant effect of vaginal progesterone on preterm birth <37 weeks (RR, 0.86; 95% CI, 0.68–1.10) and <34 weeks (RR, 0.92; 95% CI, 0.60–1.42). There were no substantial differences between the vaginal progesterone and the placebo/no treatment groups in other adverse perinatal and maternal outcomes. Based on these analyses, it was concluded that

no convincing evidence supports prescribing vaginal progesterone to prevent preterm birth in singleton gestations with a history of spontaneous preterm birth.

In summary, vaginal progesterone should not be recommended for preventing preterm birth in women with a singleton gestation based solely on the history of spontaneous preterm birth.

Women with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester transvaginal sonographic cervical length >25 mm

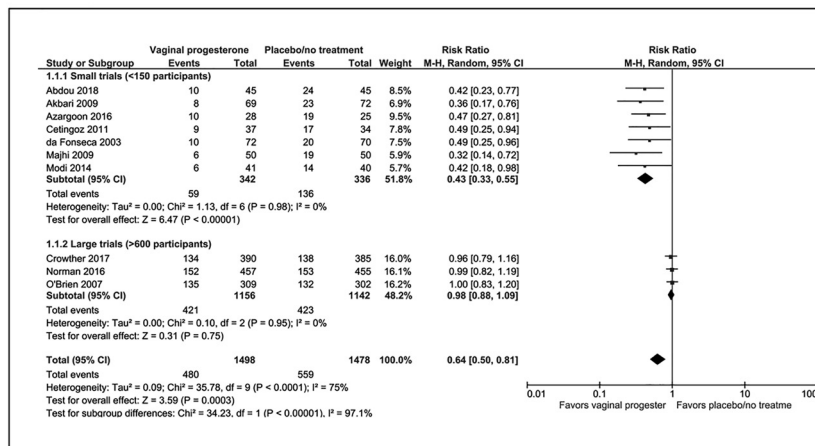
We recently reported the results of a post-hoc subgroup analysis [50] of the recently published meta-analysis [42], which evaluated the efficacy of vaginal progesterone in preventing preterm birth in women with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester transvaginal sonographic cervical length >25 mm. The primary outcomes were preterm birth <37 and <34 weeks of gestation. Four randomized controlled trials [26, 28, 30, 49], comprising 1,308 women with these characteristics, fulfilled the inclusion criteria. The frequency of preterm birth <37 weeks of gestation among women allocated to receive vaginal progesterone was remarkably similar to that observed in women in the placebo/no treatment group (35.4 vs. 35.4%; RR, 0.99; 95% CI, 0.84–1.16; $p=0.88$). The quality of evidence according to the GRADE approach [31] was considered high for this outcome. There were no significant differences between the vaginal progesterone and placebo/no treatment groups in the risk of preterm birth <34 and <28 weeks of gestation and of adverse perinatal outcomes. Hence, it was concluded that vaginal progesterone does not prevent preterm birth, nor does it improve perinatal outcomes in women with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester transvaginal sonographic cervical length >25 mm.

In summary, findings from this analysis indicate that vaginal progesterone should be offered to patients with a singleton gestation and a history of spontaneous preterm birth only if they have a midtrimester transvaginal sonographic cervical length ≤ 25 mm.

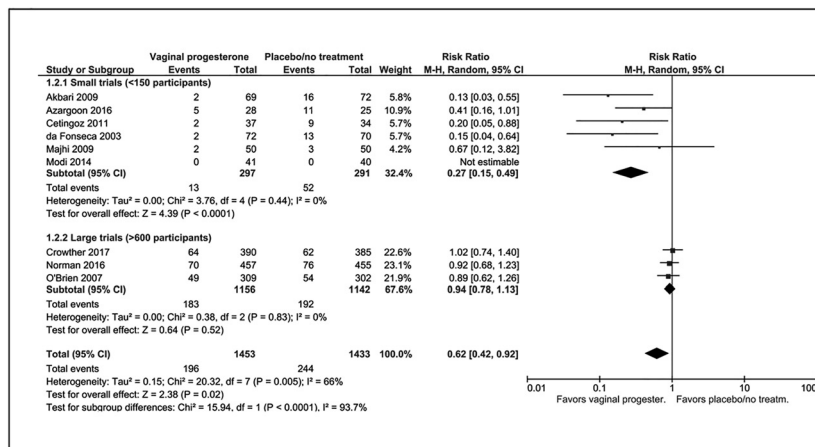
Women with a singleton gestation conceived by assisted reproductive technologies

We identified a single center, double-blind, placebo-controlled trial that evaluated the efficacy of vaginal

(A) Preterm birth <37 weeks



(B) Preterm birth <34 weeks



(C) Admission to the neonatal intensive care unit

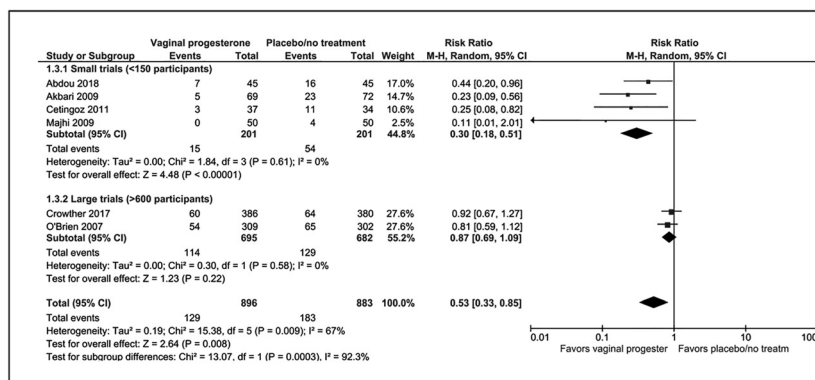


Figure 1: Effect of vaginal progesterone on preterm birth <37 and <34 weeks and on admission to the neonatal intensive care unit in women with a singleton gestation and a history of spontaneous preterm birth according to study sample size.

progesterone (400 mg/d) from 16–22 to 36 weeks of gestation to prevent preterm birth in 215 singleton gestations conceived by *in vitro* fertilization or intracytoplasmic sperm injection [51]. Vaginal progesterone administration was associated with a significant reduction in the risk of preterm birth <37 weeks (RR, 0.63; 95% CI, 0.40–0.98).

There were no significant differences between the vaginal progesterone and placebo groups in the risk of preterm birth <34 weeks of gestation and adverse perinatal outcomes. Therefore, although vaginal progesterone appears promising to reduce the risk of preterm birth in women with a singleton gestation conceived by assisted reproductive technologies,

further trials are needed to confirm the findings of this study before recommending its use in this subset of patients.

Women with an unselected twin gestation

Currently, we are performing a systematic review and meta-analysis on the efficacy of vaginal progesterone in twin gestations (registered with the PROSPERO database of systematic reviews; number CRD42020205184). The primary outcome is preterm birth <34 weeks of gestation. We identified 9 randomized controlled trials that compared vaginal progesterone vs. placebo/no treatment in unselected twin gestations conceived either naturally or by assisted reproductive technologies [28, 38–41, 51–54]. All but 1 study [54] were double-blind, placebo-controlled trials. The daily dose of vaginal progesterone used in the trials was 90–100 mg in 3 studies [28, 52, 53], 200 mg in 2 studies [38, 40], 400 mg in 2 studies [51, 54], 600 mg in 1 study [41], and 200 or 400 mg in 1 study [39]. All 9 trials reported that there were no significant differences between the vaginal progesterone and the placebo/no treatment groups in the risk of preterm birth <34 weeks of gestation and adverse perinatal outcomes. Only 1 small trial [28] reported that vaginal progesterone significantly reduced the risk of preterm birth <37 weeks of gestation. The remaining 8 trials reported no significant differences between the vaginal progesterone and the placebo/no treatment groups in preterm birth <37 weeks. A meta-analysis with data from the 9 trials, comprising 3,368 women, showed that there was no significant difference between the vaginal progesterone and the placebo/no treatment groups in the risk of preterm birth <34 weeks of gestation (pooled RR, 1.00; 95% CI, 0.84–1.19). We concluded that vaginal progesterone, regardless of the daily dose used, does not prevent preterm birth nor does it improve perinatal outcomes in unselected twin gestations.

Women with a triplet or higher-order multifetal gestation

Only the study by Wood et al. [53], comparing vaginal progesterone to placebo in multiple gestations, included 3 triplet gestations (two in the vaginal progesterone group and 1 in the placebo group). No results were reported for this subset of patients. Therefore, currently there is no evidence supporting the use of vaginal progesterone to prevent preterm birth in triplet and higher-order multifetal gestations.

Women with a singleton gestation and a positive fetal fibronectin test result combined with other clinical risk factors

The trial by Norman et al. [30] included a subset of patients with a positive fetal fibronectin test at 22–24 weeks of gestation combined with other clinical risk factors for preterm birth such as a history of preterm birth, a second-trimester loss, preterm premature rupture of the membranes, or a history of a cervical procedure to treat abnormal smears ($n=343$). There were no significant differences between patients allocated to receive vaginal progesterone and those allocated to receive placebo in preterm birth or fetal death before 34 weeks of gestation (odds ratio, 0.91; 95% CI, 0.57–1.46), a composite outcome of neonatal death, bronchopulmonary dysplasia, or brain injury on cerebral ultrasound (odds ratio, 0.69; 95% CI, 0.37–1.30), and a Bayley-III cognitive composite score at 2 years of age (mean difference, -1.09 ; 95% CI, -5.41 to 3.23). In conclusion, vaginal progesterone does not reduce the risk of preterm birth and adverse neonatal outcomes in women with a singleton gestation and a positive fetal fibronectin test result combined with other clinical risk factors.

Women with congenital uterine anomalies

To date, only 4 randomized controlled trials assessing vaginal progesterone in women at high risk of preterm birth have included patients with congenital uterine anomalies [28, 43, 45, 47]. The studies by Da Fonseca et al. [43] and Akbari et al. [45], comprising a total of 10 women with congenital uterine anomalies, did not report results separately for these patients. We were able to perform meta-analyses including data from the studies by Cetingoz et al. [28] ($n=12$) and Azargoon et al. [47] ($n=15$). Overall, no significant differences were observed between the vaginal progesterone and the placebo groups in the risk of preterm birth <37 weeks (pooled RR, 2.10; 95% CI, 0.21–21.27) and <34 weeks (pooled RR, 0.89; 95% CI, 0.40–1.99). Thus, the current evidence suggests that the use of vaginal progesterone in patients with congenital uterine anomalies has no benefit in preventing preterm birth.

Women with uterine leiomyoma

The trial by Azargoon et al. [47], which compared vaginal progesterone to placebo in women at high-risk for preterm

birth, was the only one that included patients with uterine leiomyoma (≥ 7 cm; $n=5$). No results were reported separately for this subset of patients. Consequently, there is no evidence supporting the administration of vaginal progesterone to women with uterine leiomyoma aiming to prevent preterm birth.

Recommendations for the clinical use of vaginal progesterone in women at high risk for preterm birth

Based on the evidence presented herein, we propose the following recommendations for the clinical use of vaginal progesterone in women at high-risk for preterm birth:

- (1) Vaginal progesterone at a dose of 90–100 mg/d should be offered from 18–24 to 36 weeks of gestation to women with a singleton gestation and a transvaginal sonographic cervical length ≤ 25 mm at 18–24 weeks of gestation, with and without a history of spontaneous preterm birth.
- (2) Vaginal progesterone at a dose of 90–100 mg/d should be offered from 18–24 to 36 weeks of gestation to women with a singleton gestation and a history of spontaneous preterm birth only if they have a transvaginal sonographic cervical length ≤ 25 mm at 18–24 weeks of gestation.
- (3) Vaginal progesterone appears promising to reduce the risk of preterm birth in women with a twin gestation and a midtrimester transvaginal sonographic cervical length ≤ 25 mm and in women with a singleton gestation conceived by assisted reproductive technologies, but further research is needed before recommending its use in these subsets of patients.
- (4) Vaginal progesterone should not be offered to women with a singleton gestation and a history of spontaneous preterm birth based solely on such history.
- (5) Vaginal progesterone should not be offered to women with an unselected twin gestation and to women with a singleton gestation, a history of spontaneous preterm birth, and a transvaginal sonographic cervical length >25 mm at 18–24 weeks of gestation.
- (6) There is no evidence supporting the use of vaginal progesterone in women with a triplet or higher-order multifetal gestation, in women with a singleton gestation and a positive fetal fibronectin test result combined with other clinical risk factors, and in women with congenital uterine anomalies or uterine leiomyoma.

A revised, evidence-based clinical algorithm for the use of vaginal progesterone in preventing preterm birth among women with a singleton gestation is presented in Figure 2.

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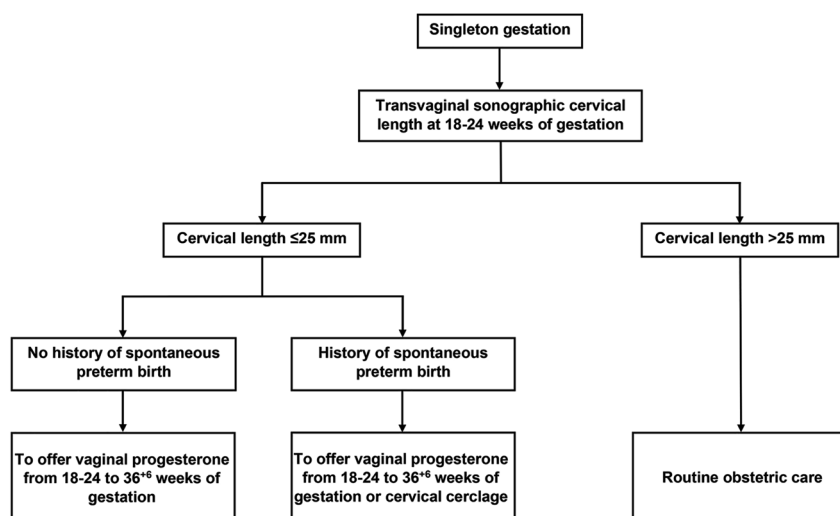


Figure 2: Evidence-based clinical algorithm for the use of vaginal progesterone in preventing preterm birth among singleton gestations.

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