Vaginal progesterone does not prevent recurrent preterm birth in women with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester cervical length >25 mm

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Research Letter

Vaginal progesterone does not prevent recurrent preterm birth in women with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester cervical length >25 mm

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OBJECTIVE

We recently reported the results of a systematic review and meta-analysis that addressed the clinical question of whether vaginal progesterone is effective in preventing recurrent preterm birth and adverse perinatal outcomes in women with a singleton gestation and a history of spontaneous preterm birth. The results were conflicting. While the administration of vaginal progesterone was associated with a reduction in the risk of preterm birth <37 and <34 weeks of gestation in small, poor-quality trials, vaginal progesterone had no effect in large, high-quality trials. Therefore, we concluded that no convincing evidence supports prescribing vaginal progesterone to prevent preterm birth in singleton gestations with a history of spontaneous preterm birth.

Vaginal progesterone is clearly effective in reducing the risk of preterm birth and improving perinatal outcomes in women with a singleton gestation and a sonographic short cervix (≤25 mm), both with and without a history of spontaneous preterm birth. On the other hand, it is unclear if vaginal progesterone prevents preterm birth in patients with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester transvaginal sonographic cervical length >25 mm. Hence, we performed a post-hoc subgroup analysis of the recently published meta-analysis to assess the efficacy of vaginal progesterone in preventing preterm birth in this subset of patients.

STUDY DESIGN

A detailed description of the methods used in the conduct of our systematic review and meta-analysis can be found in the previous publication. Briefly, a protocol was registered with PROSPERO (number CRD42021275154) and a literature search was
performed in MEDLINE, EMBASE, LILACS, CINAHL, the Cochrane Central Register of Controlled Trials, and clinical trial registries (all from their inception to February 28, 2022), using the keywords *progesterone* and *preterm birth*. Randomized controlled trials were eligible if they compared vaginal progesterone vs placebo or no treatment for the prevention of preterm birth and/or adverse perinatal outcomes in women with a singleton gestation and a history of at least 1 spontaneous preterm birth in any of their previous pregnancies. The primary outcomes were preterm birth <37 and <34 weeks of gestation. The secondary outcomes were adverse maternal and perinatal outcomes. The risk of bias for each included study was assessed by using the Cochrane risk of bias tool 2, which classifies trials as at low risk of bias, some concerns of bias, or high risk of bias. Both authors independently retrieved and reviewed studies for eligibility, assessed their risk of bias, and extracted data. Relevant additional data of included trials supplied to previous meta-analyses were included in the meta-analysis.

The data synthesis was performed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions. We calculated the pooled relative risk (RR) with a 95% confidence interval (CI) by using a random-effects model. Heterogeneity of the results among studies was evaluated by visually inspecting forest plots and by estimating the $I^2$ quantity. A significant level of heterogeneity was defined as $I^2 \geq 30\%$. Heterogeneity was also addressed by performing several subgroup and sensitivity analyses and by calculating 95% prediction intervals. Standard and contour-enhanced funnel plots were constructed to investigate small-study effects and publication biases. Funnel plot asymmetry was assessed visually and with Egger’s and Harbord’s tests. Finally, we evaluated the quality of evidence for the primary and
secondary outcomes by using the GRADE approach, which categorizes the quality of
the evidence into four levels: high, moderate, low, and very low.

RESULTS

Ten trials, comprising 2958 women, met the inclusion criteria for the original systematic
review and meta-analysis.\(^1\) Six trials did not collect data on cervical length before
randomization (5 trials) or did not report results for patients with a cervical length >25 mm
(1 trial). We obtained data separately for women with a midtrimester transvaginal
sonographic cervical length >25 mm (N=1308) from the remaining 4 trials.\(^4-7\) The studies
by O’Brien et al\(^4\) and Norman et al\(^6\) were double-blind, placebo-controlled, registered,
 multicenter trials (1 conducted in high-income countries and 1 conducted in both high-
income and low/middle-income countries) and were judged to be at overall low risk of
bias. The studies by Cetingoz et al\(^5\) and Abdou\(^7\) were conducted in single centers located
in low/middle-income countries and were unregistered; 1 compared vaginal progesterone
vs placebo and was deemed to be at overall low risk of bias,\(^5\) whereas the other 1
evaluated vaginal progesterone vs no treatment and was considered to be at overall high
risk of bias.\(^7\) The daily dose of vaginal progesterone used in the trials was 200 mg in 2
studies,\(^6,7\) 100 mg in 1 study,\(^5\) and 90 mg in 1 study\(^4\) and the treatment was
administered from 18-24 to 34-37\(^{+0}\) weeks of gestation.

The frequency of preterm birth <37 weeks of gestation among women with a
cervical length >25 mm allocated to receive vaginal progesterone was remarkably similar
to that observed in women in the placebo or no treatment group (35.4% vs 35.4%; RR,
0.99; 95% CI, 0.84-1.16; \(P = 0.88; I^2 = 8\%\); high-quality evidence) (Figure). As in the
original meta-analysis, there was a tendency of small trials to report a beneficial effect of vaginal progesterone on the risk of both outcomes, whereas in large studies, this intervention had no effect. The effect of vaginal progesterone on the risk of preterm birth <37 weeks of gestation significantly differed between the subgroup of women with a singleton gestation, a history of spontaneous preterm birth, and a cervical length ≥25 mm (RR, 0.99; 95% CI, 0.84-1.16) and that of women with a singleton gestation, a history of spontaneous preterm birth, and a cervical length ≤25 mm (RR, 0.72; 95% CI, 0.58-0.90; high-quality evidence; \( P \) for interaction = 0.02).

Similarly, among women with a cervical length ≥25 mm there was no evidence that vaginal progesterone reduced the frequency of preterm birth <34 and <28 weeks of gestation compared to placebo or no treatment (for preterm birth <34 weeks: 13.6% [86/634] vs 15.0% [94/625]; RR, 0.86; 95% CI, 0.51-1.44; \( P = 0.57; I^2 = 58\% \); low-quality evidence); (for preterm birth <28 weeks: 3.9% [25/634] vs 2.4% [15/625]; RR, 1.65; 95% CI, 0.88-3.11; \( P = 0.12; I^2 = 0\% \); moderate-quality evidence). The effect of vaginal progesterone on adverse perinatal outcomes is shown in the Table. No significant differences were observed between the vaginal progesterone and the placebo or no treatment groups in the risk of fetal death, neonatal death, perinatal death, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, neonatal sepsis, admission to the neonatal intensive care unit (NICU), use of mechanical ventilation, and birthweight <1500 g and <2500 g. The quality of evidence was considered low for 7 of 11 perinatal outcomes evaluated and moderate for the remaining 4.

CONCLUSION
Based on the subgroup analysis reported herein, 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.

The limitations of subgroup analyses are well known and include the increased likelihood of statistically significant false positive results due to multiple comparisons and false negative results due to inadequate statistical power. In addition, most subgroup analyses that are not specified a priori in the protocol should be considered as hypothesis-generating rather than as hypothesis-testing. Though this subgroup analysis was post-hoc, we think there are several reasons for considering its results as reliable: (1) according to the interaction $P$ value of 0.02, differences in the treatment effect of vaginal progesterone on preterm birth <37 weeks of gestation between the subgroup of women with a cervical length >25 mm and those with a cervical length ≤25 mm would occur by chance only 2% of the time. When chance alone is unlikely to explain subgroup differences, a subgroup effect may be present; (2) the evidence was deemed to be high-quality for the outcome of preterm birth <37 weeks of gestation in both patients with a cervical length >25 mm and those with a cervical length ≤25 mm, which means that we are very confident that the true effect lies close to that of the estimate of the effect, and further research is unlikely to change our confidence in the estimate of the effect; (3) the subgroup effect was consistent across related outcomes. In fact, vaginal progesterone had no effect on preterm birth <34 and <28 weeks of gestation or on perinatal morbidity and mortality in patients with a cervical length >25 mm, whereas it reduced preterm birth <35 and <32 weeks of gestation, perinatal morbidity and mortality, and admission to the
NICU in those with a cervical length ≤25 mm in a prior analysis; 3 (4) the sample size of the subgroup analysis was relatively large (1308 women); and (5) there is growing evidence that treatment with vaginal progesterone may prevent preterm birth in women with a sonographic short cervix by altering molecular pathways involved in premature cervical ripening and/or by its anti-inflammatory effects. 8,9 Such evidence could explain the differential effect of vaginal progesterone on the risk of preterm birth in patients with a cervical length ≤25 mm and those with a cervical length >25 mm.

Ideally, the findings of the present subgroup analysis should be confirmed or refuted in subsequent trials. However, we were unable to identify ongoing or planned randomized controlled trials comparing vaginal progesterone vs placebo or no treatment in women with a singleton gestation and a history of spontaneous preterm birth in major clinical trial registries. Therefore, until the results of such trials are available, the subgroup analysis reported herein is the best available evidence about the effect of vaginal progesterone in singleton gestations with a history of spontaneous preterm birth and a cervical length >25 mm.

In summary, our findings reaffirm 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 (18-24 weeks of gestation) transvaginal sonographic cervical length ≤25 mm.
REFERENCES


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FIGURE LEGEND

Legend for Figure: Effect of vaginal progesterone on preterm birth <37 weeks of gestation in women with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester transvaginal sonographic cervical length >25 mm.
Table 1. Effect of vaginal progesterone on perinatal outcomes in women with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester sonographic cervical length >25 mm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of trials</th>
<th>Vaginal progesterone</th>
<th>Placebo or no treatment</th>
<th>Relative risk (95% CI)</th>
<th>P value</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal death</td>
<td>273,74</td>
<td>5/330 (1.5%)</td>
<td>3/313 (1.0%)</td>
<td>1.59 (0.38-6.58)</td>
<td>0.52</td>
<td>NA</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>378,40</td>
<td>16/641 (2.5%)</td>
<td>11/638 (1.7%)</td>
<td>1.40 (0.56-3.53)</td>
<td>0.47</td>
<td>19</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>273,74</td>
<td>12/330 (3.6%)</td>
<td>10/313 (3.2%)</td>
<td>1.12 (0.50-2.52)</td>
<td>0.79</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>260,81</td>
<td>36/330 (10.6%)</td>
<td>33/313 (10.5%)</td>
<td>1.01 (0.64-1.58)</td>
<td>0.97</td>
<td>0</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>273,74</td>
<td>3/330 (0.9%)</td>
<td>4/313 (1.3%)</td>
<td>0.71 (0.16-3.16)</td>
<td>0.66</td>
<td>NA</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>273,75</td>
<td>6/330 (1.8%)</td>
<td>5/313 (1.6%)</td>
<td>1.14 (0.35-3.70)</td>
<td>0.82</td>
<td>NA</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>273,76</td>
<td>4/306 (1.3%)</td>
<td>5/300 (1.7%)</td>
<td>0.79 (0.21-2.91)</td>
<td>0.72</td>
<td>NA</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>273,74</td>
<td>55/330 (16.7%)</td>
<td>65/313 (20.8%)</td>
<td>0.51 (0.12-2.13)</td>
<td>0.35</td>
<td>75</td>
</tr>
<tr>
<td>Use of mechanical ventilation</td>
<td>273,76</td>
<td>19/304 (6.3%)</td>
<td>29/300 (9.7%)</td>
<td>0.65 (0.37-1.13)</td>
<td>0.13</td>
<td>0</td>
</tr>
<tr>
<td>Birthweight &lt;1500 g</td>
<td>273,74</td>
<td>25/329 (7.6%)</td>
<td>17/309 (5.5%)</td>
<td>1.36 (0.76-2.46)</td>
<td>0.30</td>
<td>0</td>
</tr>
<tr>
<td>Birthweight &lt;2500 g</td>
<td>273,76</td>
<td>97/329 (29.5%)</td>
<td>103/309 (33.3%)</td>
<td>0.88 (0.70-1.11)</td>
<td>0.30</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are presented as number/total number. CI, confidence interval; NA, not applicable; NICU, neonatal intensive care unit.
<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (Random) (95% CI)</th>
<th>Vaginal progesterone n/N</th>
<th>Placebo/no treatment n/N</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Brien 2007</td>
<td></td>
<td>128/297</td>
<td>122/283</td>
<td>56.5</td>
<td>1.00 (0.83 - 1.21)</td>
</tr>
<tr>
<td>Cetingoz 2011</td>
<td></td>
<td>8/33</td>
<td>13/30</td>
<td>4.7</td>
<td>0.56 (0.27 - 1.16)</td>
</tr>
<tr>
<td>Norman 2016</td>
<td></td>
<td>91/304</td>
<td>87/312</td>
<td>35.7</td>
<td>1.07 (0.84 - 1.38)</td>
</tr>
<tr>
<td>Abdou 2018</td>
<td></td>
<td>6/25</td>
<td>8/24</td>
<td>3.1</td>
<td>0.72 (0.29 - 1.77)</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td>233/659</td>
<td>230/649</td>
<td>100.0</td>
<td>0.99 (0.84 - 1.16)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2 = 8\%$
Test for overall effect: $Z = 0.15, P = 0.88$