Progesterone for the Prevention of Preterm Birth

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OBJECTIVE: We performed a systematic review to assess the benefits and harms of progesterone administration for the prevention of preterm birth in women and their infants.

DATA SOURCES: The Cochrane Controlled Trials Register was searched, and reference lists of retrieved studies were searched by hand. No date or language restrictions were placed.

METHODS OF STUDY SELECTION: Randomized trials comparing antenatal progesterone for women at risk of preterm birth were considered. Studies were evaluated for inclusion and methodological quality. Primary outcomes were perinatal death, preterm birth before 34 weeks, and neurodevelopmental handicap.

TABULATION, INTEGRATION AND RESULTS: Eleven randomized controlled trials (2,425 women and 3,187 infants) were included. For women with a history of spontaneous preterm birth, progesterone was associated with a significant reduction in preterm birth before 34 weeks (one study, 142 women, RR 0.15, 95% CI 0.04–0.64, number needed to treat 7, 95% CI 4–17), but no statistically significant differences were identified for the outcome of perinatal death. For women with a short cervix identified on ultrasound, progesterone was not associated with a significant difference in perinatal death (one study, 274 participants, RR 0.38, 95% CI 0.10–1.40), but there was a significant reduction in preterm birth before 34 weeks (one study, 250 women, RR 0.58, 95% CI 0.38–0.87, number needed to treat 7, 95% CI 4–25). For women with a multiple pregnancy, progesterone was associated with no significant difference in perinatal death (one study, 154 participants, RR 1.95, 95% CI 0.37–10.33). For women presenting after threatened preterm labor, no primary outcomes were reported. For women with “other” risk factors for preterm birth, progesterone was not associated with a significant difference in perinatal death (two studies, 264 participants, RR 1.10, 95% CI 0.23–5.29).

CONCLUSION: Progesterone is associated with some beneficial effects in pregnancy outcome for some women at increased risk of preterm birth.

Preterm birth, defined by the World Health Organization as birth before 37 completed weeks of gestation, is estimated to affect approximately 13 million births annually worldwide. The incidence of preterm birth is reported to be between 5% and 11%, ranging from 4.4% in Ireland, 7.6% in Canada, 8.2% in Australia, and 12.7% in the United States. The prevention of preterm birth remains elusive, with many reports indicating an increase in prevalence during recent years.

Infants who are born preterm are more likely to die during the neonatal period than are term infants, and although the risk is greatest for infants born at earlier gestational ages, it remains evident for infants born between 32 and 36 weeks of gestation. For surviving infants, the health implications of immaturity are significant, particularly in relation to respiratory distress syndrome, and the subsequent risk of developing chronic lung disease, and other long-term handicaps including cerebral palsy.
The cause of preterm birth is multifactorial, with the most significant and consistently identified risk factor being a woman’s history of previous preterm birth. Other characteristics in a woman’s current pregnancy placing her at increased risk of preterm birth include the identification of short cervix by ultrasound assessment and multiple pregnancy.

Progestrone has a role in maintaining pregnancy and is thought to act by suppressing smooth muscle activity in the uterus. We performed a systematic review to assess the benefits and harms of progestrone administration for the prevention of preterm birth in women and their infants.

SOURCES
We searched PubMed, the Cochrane Controlled Trials Register, and the International Clinical Trials Register using the free text search terms pregnancy, preterm birth, progestrone, progestogen, intramuscular, vaginal, oral, perinatal morbidity, perinatal mortality, and randomized controlled trial. The reference lists of retrieved studies were searched by hand, and no date or language restrictions were placed (date of last search was January 2008).

STUDY SELECTION
All published randomized controlled trials in which progesterone was administered for the prevention of preterm birth were considered. Studies were subdivided by reason the women were considered to be at risk for preterm birth, including past history of spontaneous preterm birth (including preterm premature rupture of membranes), multiple pregnancy, ultrasound-identified short cervical length, and after presentation with symptoms or signs of threatened preterm labor. Trials were excluded if progesterone was administered for the treatment of actual or threatened preterm labor, if progesterone was administered for preventing miscarriage, or if studies were available in abstract form only.

The primary outcomes were perinatal mortality, preterm birth before 34 weeks of gestation, and developmental delay in childhood. The secondary outcomes included threatened preterm labor, cesarean section, antenatal corticosteroids, use of antenatal tocolytics, preterm birth at less than 37 weeks of gestation, infant birth weight less than 2,500 g, respiratory distress syndrome, need for assisted ventilation, intraventricular hemorrhage, retinopathy of prematurity, necrotizing enterocolitis, patent ductus arteriosus, fetal death, and neonatal death.

Studies under consideration were evaluated independently for appropriateness for inclusion and methodological quality without consideration of their results by all authors, according to the QUOROM guidelines for systematic reviews of randomized trials. There was no blinding of authorship.

Assessment of quality considered generation of the randomization sequence, allocation concealment, blinding, and completeness of follow-up. We defined high-quality trials as those receiving an A rating for blinding of randomization, blinding of the intervention, and less than 20% loss to follow-up for major outcomes. For dichotomous data, relative risks (RRs) and 95% confidence intervals (CIs) were calculated. Primary analyses were based on intention to treat principles. Planned subgroup analyses included an assessment of the effect of 1) time of treatment commencing (before 20 weeks of gestation versus after 20 weeks of gestation), 2) route of administration (intramuscular, intravaginal, oral, intravenous), and 3) different dosage regimens (divided arbitrarily into a cumulative dose of less than 500 mg per week and a dose of greater than or equal to 500 mg per week).

Twenty-two studies were identified for consideration. Eleven studies met the inclusion criteria. For use of progesterone in women with a history of prior spontaneous preterm birth, four studies were included, involving 1,307 women with a past history of spontaneous preterm birth. Two of these compared weekly intramuscular injection with placebo, and two compared nightly vaginal progesterone with placebo. The primary outcomes reported related to preterm birth before 32 weeks of gestation and 37 weeks of gestation.

Intramuscular Progesterone
The method of generating the randomization sequence was adequate in one study with both studies using identical-appearing treatment packs (allocation concealment: A), and blinding of outcome assessment (blinding: A). There were no reported losses to follow-up in the study by Meis and 14% postrandomization exclusions in the study by Johnson. Both trials received a quality rating of A.

Vaginal Progesterone
The method of generating the randomization sequence was adequate in both studies, both using sequentially numbered identical-appearing treatment packs (allocation concealment: A) and blinded outcome assessors (blinding: A). Both studies re-
ported less than 20% loss to follow-up (DaFonesca 10%, O’Brien 7.3%), and received a quality rating of A.

For use of progesterone in women with a short cervix identified on transvaginal ultrasound examination, a single study was included involving 250 women who were identified as having short cervix (defined as less than 15 mm) at the time of transvaginal ultrasound examination. Women received either 200 mg nightly intravaginal progesterone or placebo from 24 to 33 completed weeks of gestation. The primary outcome related to the occurrence of preterm birth before 34 weeks of gestation.

Vaginal Progesterone

The method of generating the randomization sequence was not stated. The study used central randomization with identical-appearing treatment packs (allocation concealment: A) and blinded outcome assessors (blinding: A). There were no reported losses to follow-up. The trial received a quality rating of A.

For use of progesterone in women with a multiple pregnancy, two studies were included, involving 738 women with a twin pregnancy who received weekly intramuscular injections in a dose of 250 mg or placebo. The primary outcomes reported included a composite of death or birth before 35 weeks of gestation.

Intramuscular Progesterone

Hartikainen did not indicate the method of generation of the randomization sequence or allocation concealment (allocation concealment: B) but indicated the use of blinded outcome assessors (blinding: A) and reported no losses to follow-up, receiving an overall quality rating of B. The trial used a random number table to generate the randomization sequence, which was managed by a senior midwife (allocation concealment: B). The study did not use blinded outcome assessors (blinding: B), reported no losses to follow-up, and received a quality rating of B.

Vaginal Progesterone

The study by Borna used a random number table to generate the randomization sequence. There was no indication of the method of allocation concealment (allocation concealment: B), but both stated the use of blinded outcome assessors (blinding: A) and reported no losses to follow-up. Both trials received a quality rating of B.

Intramuscular Progesterone

Neither study indicated the method of randomization used or the process of allocation concealment (allocation concealment: B), but both stated the use of blinded outcome assessors (blinding: A) and reported no losses to follow-up. Both trials received a quality rating of B.

Intramuscular Progesterone

The study by Hauth involved 168 women who were considered to be at risk of preterm birth because of active military service. Women received either 1,000 mg of intramuscular progesterone weekly or placebo. The primary outcome for the study related to the incidence of preterm birth at less than 37 weeks of gestation.

Intramuscular Progesterone

One study compared an oral progesterogen with placebo but presented outcomes only as percentages. Five studies were excluded because they used a quasi-randomized method of treatment allocation. One study compared progesterone with cervical cerclage has been reported in abstract form.
RESULTS

Eleven randomized controlled trials involving a total of 2,425 women and 3,187 infants were included in the meta-analysis.

Progesterone Compared With Placebo for Women With a Past History of Spontaneous Preterm Birth

Primary Outcomes: For women administered progesterone during pregnancy, for the primary outcomes perinatal death and developmental delay in childhood, there were no statistically significant differences identified when compared with placebo. Women administered progesterone were significantly less likely to have a preterm birth at less than 34 weeks of gestation (one study, 142 women, RR 0.15, 95% CI 0.04–0.64, number needed to treat to benefit 7, 95% CI 4–17), See Table 1.

Secondary Infant Outcomes: For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant reduction in the risk of infant birth weight less than 2,500 g (two studies, 501 infants, RR 0.64, 95% CI 0.49–0.83, number needed to treat to benefit 7, 95% CI 5–17).

Secondary Maternal Outcomes: There were no statistically significant differences for the secondary maternal outcomes reported.

Route of Administration, Time of Commencing Therapy, and Dose of Progesterone: There was no differential effect on the outcomes when considering route of administration of progesterone, time of commencement of supplementation, or total weekly cumulative dose of progesterone.

Progesterone Versus Placebo for Women With a Short Cervix Identified on Ultrasound

Primary Outcomes: For women administered progesterone during pregnancy, for the primary outcome perinatal death, there were no statistically significant differences identified when compared with placebo. Women administered progesterone were significantly less likely to have a preterm birth at less than 34 weeks of gestation (one study, 250 women, RR 0.58, 95% CI 0.38–0.87, number needed to treat to benefit 7, 95% CI 4–25). See Table 2.

Secondary Infant Outcomes: For women administered progesterone during pregnancy, when compared with...

Table 1. Progesterone Versus Placebo in Women With a Prior Spontaneous Preterm Birth

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. Studies</th>
<th>Participants</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal death</td>
<td>3</td>
<td>1,114</td>
<td>0.65</td>
<td>0.38–1.11</td>
</tr>
<tr>
<td><strong>Preterm birth at less than 34 wk</strong></td>
<td>1</td>
<td>142</td>
<td><strong>0.15</strong></td>
<td><strong>0.04–0.64</strong></td>
</tr>
<tr>
<td>Developmental delay*</td>
<td>1</td>
<td>275</td>
<td>0.97</td>
<td>0.55–1.73</td>
</tr>
<tr>
<td>Secondary maternal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threatened preterm labor†</td>
<td>2</td>
<td>601</td>
<td>0.87</td>
<td>0.47–1.62</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>2</td>
<td>1,070</td>
<td>1.01</td>
<td>0.82–1.23</td>
</tr>
<tr>
<td>Antenatal corticosteroids</td>
<td>2</td>
<td>1,070</td>
<td>0.92</td>
<td>0.73–1.16</td>
</tr>
<tr>
<td>Antenatal tocolysis</td>
<td>3</td>
<td>1,114</td>
<td>1.11</td>
<td>0.81–1.52</td>
</tr>
<tr>
<td>Secondary infant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth at less than 37 wk†</td>
<td>4</td>
<td>1,255</td>
<td>0.68</td>
<td>0.45–1.02</td>
</tr>
<tr>
<td><strong>Birthweight less than 2,500 g</strong></td>
<td>2</td>
<td>501</td>
<td><strong>0.64</strong></td>
<td><strong>0.49–0.83</strong></td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>2</td>
<td>1,069</td>
<td>0.79</td>
<td>0.57–1.10</td>
</tr>
<tr>
<td>Need for assisted ventilation</td>
<td>1</td>
<td>459</td>
<td>0.59</td>
<td>0.35–1.01</td>
</tr>
<tr>
<td>Intraventricular hemorrhage, all grades†</td>
<td>2</td>
<td>1,070</td>
<td>0.54</td>
<td>0.12–2.47</td>
</tr>
<tr>
<td>Intraventricular hemorrhage, grade 3 or 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>2</td>
<td>1,069</td>
<td>1.59</td>
<td>0.21–11.75</td>
</tr>
<tr>
<td>Necrotizing enterocolitis†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>1</td>
<td>458</td>
<td>0.50</td>
<td>0.15–1.69</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>2</td>
<td>1,070</td>
<td>0.25</td>
<td>0.03–2.46</td>
</tr>
<tr>
<td>Fetal death</td>
<td>1</td>
<td>459</td>
<td>1.13</td>
<td>0.35–3.59</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>1</td>
<td>459</td>
<td>0.44</td>
<td>0.16–1.18</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,114</td>
<td>0.85</td>
<td>0.35–2.03</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1,114</td>
<td>0.56</td>
<td>0.28–1.10</td>
</tr>
</tbody>
</table>

CI, confidence interval.
Bold indicates statistically significant results.
* Developmental assessment using Ages and Stages Questionnaire.†
† Significant statistical heterogeneity identified (I² statistic in excess of 50%); random effects model used.
placebo, there was a statistically significant reduction in
the risk of neonatal sepsis (one study, 274 infants, RR
0.28, 95% CI 0.08–0.97, number needed to treat to
benefit 18, 95% CI 9–163), but no other differences
were identified for other secondary infant outcomes.

Route of Administration, Time of Commencing Ther-
apy, and Dose of Progesterone: It was not possible to
assess the effect of route of progesterone administra-
tion, gestational age at commencement of therapy, or
total cumulative dose of medication.

Progesterone Versus Placebo for Women With
a Multiple Pregnancy

Primary Outcomes: For women administered progester-
one during pregnancy, for the primary outcomes
perinatal death and preterm birth at less than 34
weeks of gestation, there were no statistically signifi-
cant differences identified when compared with pla-
cebo. See Table 3.

Secondary Infant Outcomes: For women administered
progesterone during pregnancy, when compared with
placebo, there were no statistically significant differences
for the reported secondary infant outcomes.

Secondary Maternal Outcomes: For women adminis-
tered progesterone during pregnancy, when com-
pared with placebo, there was a statistically significant
reduction in the need for antenatal tocolysis (one
study, 654 women, RR 0.75, 95% CI 0.57–0.97,
number needed to treat to benefit 14, 95% CI 8–123).

Route of Administration, Time of Commencing Ther-
apy, and Dose of Progesterone: There was no differential
effect observed when considering time of commence-
ment of supplementation.

Table 2. Progesterone Versus Placebo in Women With a Short Cervix Identified on Ultrasound

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. Studies</th>
<th>Participants</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal death</td>
<td>1</td>
<td>274</td>
<td>0.38</td>
<td>0.10–1.40</td>
</tr>
<tr>
<td>Preterm birth at less than 34 wk</td>
<td>1</td>
<td>250</td>
<td>0.58</td>
<td>0.38–0.87</td>
</tr>
<tr>
<td><strong>Secondary infant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight less than 2,500 g</td>
<td>1</td>
<td>274</td>
<td>0.96</td>
<td>0.73–1.27</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>1</td>
<td>274</td>
<td>0.59</td>
<td>0.29–1.19</td>
</tr>
<tr>
<td>Need for assisted ventilation</td>
<td>1</td>
<td>274</td>
<td>0.65</td>
<td>0.36–1.16</td>
</tr>
<tr>
<td>Intraventricular hemorrhage, all grades</td>
<td>1</td>
<td>274</td>
<td>0.51</td>
<td>0.05–5.53</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>1</td>
<td>274</td>
<td>5.07</td>
<td>0.25–104.70</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>1</td>
<td>274</td>
<td>0.34</td>
<td>0.01–8.23</td>
</tr>
<tr>
<td><strong>Neonatal sepsis</strong></td>
<td>1</td>
<td>274</td>
<td>0.28</td>
<td>0.08–0.97</td>
</tr>
<tr>
<td>Fetal death</td>
<td>1</td>
<td>274</td>
<td>1.01</td>
<td>0.06–16.06</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>1</td>
<td>274</td>
<td>0.29</td>
<td>0.06–1.37</td>
</tr>
</tbody>
</table>

CI, confidence interval.
Bold indicates statistically significant results.

Table 3. Progesterone Versus Placebo in Women With a Multiple Pregnancy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. Studies</th>
<th>Participants</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal death</td>
<td>1</td>
<td>154</td>
<td>1.95</td>
<td>0.37–10.33</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>1</td>
<td>652</td>
<td>0.99</td>
<td>0.88–1.12</td>
</tr>
<tr>
<td>Antenatal corticosteroids</td>
<td>1</td>
<td>654</td>
<td>0.91</td>
<td>0.70–1.17</td>
</tr>
<tr>
<td><strong>Antenatal tocolysis</strong></td>
<td>1</td>
<td>654</td>
<td>0.75</td>
<td>0.57–0.97</td>
</tr>
<tr>
<td><strong>Secondary infant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth at less than 37 wk</td>
<td>2</td>
<td>732</td>
<td>1.01</td>
<td>0.92–1.12</td>
</tr>
<tr>
<td>Birth weight less than 2,500 g</td>
<td>1</td>
<td>1,276</td>
<td>0.94</td>
<td>0.86–1.02</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>1</td>
<td>1,280</td>
<td>1.13</td>
<td>0.86–1.48</td>
</tr>
<tr>
<td>Need for assisted ventilation</td>
<td>1</td>
<td>1,280</td>
<td>0.93</td>
<td>0.69–1.26</td>
</tr>
<tr>
<td>Intraventricular hemorrhage, grades 3 or 4</td>
<td>1</td>
<td>1,280</td>
<td>1.20</td>
<td>0.40–3.54</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>1</td>
<td>1,280</td>
<td>NE*</td>
<td>NE*</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>1</td>
<td>1,280</td>
<td>0.77</td>
<td>0.17–3.42</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>1</td>
<td>1,280</td>
<td>0.95</td>
<td>0.55–1.63</td>
</tr>
<tr>
<td>Patent ductus arterosus</td>
<td>1</td>
<td>1,280</td>
<td>0.60</td>
<td>0.34–1.05</td>
</tr>
</tbody>
</table>

CI, confidence interval; NE, not estimable.
Bold indicates statistically significant results.
Progesterone Versus Placebo for Women After Presentation with Threatened Preterm Labor

**Primary Outcomes:** For women administered progesterone during pregnancy, for the primary outcomes perinatal death and preterm birth at less than 34 weeks of gestation, there were no statistically significant differences identified when compared with placebo.

**Secondary Infant Outcomes:** For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant reduction in the risk of infant birth weight less than 2,500 g (one study, 70 infants, RR 0.52, 95% CI 0.28–0.98, number needed to treat to benefit 5, 95% CI 2–45) and respiratory distress syndrome (one study, 70 infants, RR 0.30, 95% CI 0.11–0.83, number needed to treat to benefit 5, 95% CI 2–45). There were no statistically significant differences for the outcomes need for mechanical ventilation or sepsis.

**Secondary Maternal Outcomes:** For women administered progesterone during pregnancy, when compared with placebo, there was a statistically significant reduction in the risk of preterm birth at less than 37 weeks (one study, 60 women, RR 0.29, 95% CI 0.12–0.69, number needed to treat to benefit 3, 95% CI 2–6).

**Route of Administration, Time of Commencing Therapy, and Dose of Progesterone:** It was not possible to assess the effect of route of progesterone administration, gestational age at commencement of therapy, or total cumulative dose of medication.

Progesterone Versus Placebo for Women With “Other” Risk Factors for Preterm Birth

**Primary Outcomes:** For women administered progesterone during pregnancy, for the primary outcome perinatal death, there were no statistically significant differences identified when compared with placebo (two studies, 264 participants, RR 1.10, 95% CI 0.23–5.29).

**Secondary Infant Outcomes:** There were no statistically significant differences for the outcomes perinatal death, infant birth weight less than 2,500 g, intraterine fetal death, or neonatal death.

**Secondary Maternal Outcomes:** There were no statistically significant differences for the outcome preterm birth at less than 37 weeks of gestation.

**Route of Administration, Time of Commencing Therapy, and Dose of Progesterone:** There was no differential effect observed related to cumulative dose of progesterone administered or gestational age at commencement of therapy.

CONCLUSION

The randomized trials identified assessed the use of progesterone in women considered to be at increased risk of preterm birth due to a variety of risk factors. For women with a past history of spontaneous preterm birth, there was a significant reduction in the risk of preterm birth at less than 34 weeks demonstrated in one study. There were no statistically significant differences identified for the primary outcome perinatal death. Further information is required about the optimal route of administration of progesterone, with the largest study to date using vaginal progesterone gel suggesting no benefit in this group of women. There are three ongoing randomized trials assessing the role of intramuscular (P. Rozenberg, e-mail communication, February 14, 2008) and vaginal (C.A. Crowther, J.M. Dodd, A.J. McPhee, V. Flenady, e-mail communication, February 14, 2008; Y. Perlitz, e-mail communication, February 14, 2008) progesterone in women with a history of spontaneous preterm birth, which will contribute information about the role of progesterone in this group of women.

In the single trial to date assessing the role of progesterone in women with a short cervix identified on ultrasound, there were no statistically significant differences identified for the primary outcome perinatal death. Women administered progesterone were significantly less likely to have preterm birth at less than 34 weeks of gestation, although further information is required about the risk of other infant and maternal health outcomes in this group of women. There is a single ongoing randomized trial assessing the role of intramuscular (W. Gorbman, e-mail communication, February 14, 2008) progesterone in nulliparous women with short cervices identified on transvaginal ultrasound, which will contribute information in the future.

The role of progesterone in women with a multiple pregnancy is less clear, with no identified differences in the primary outcomes perinatal death and preterm birth at less than 34 weeks of gestation. Although the use of progesterone was associated with a reduction in the use of antenatal tocolysis, there were no differences identified for the other secondary infant and maternal health outcomes. There are several ongoing randomized trials assessing the role of intramuscular (H.W. Bruinse, e-mail communication, February 14, 2008; K. Maurel, A. Combs, e-mail communication, February 14, 2008; A. Nassar, e-mail communication, February 14, 2008) and vaginal (L. Rode, e-mail communication, February 14, 2008; V. Serra, e-mail communication, February 14, 2008; S.
Wood, e-mail communication, February 14, 2008) progesterone in women with a multiple pregnancy.

The role of progesterone for women after presentation with threatened preterm labor remains uncertain because the combined sample size of these studies was small and underpowered to detect differences in both maternal and infant health outcomes. Furthermore, the failure to use a placebo and lack of blinding in the assessment of outcomes increases the potential for bias. There is an ongoing randomized trial assessing the role of vaginal progesterone (B. Matinez de Tajada, e-mail communication, February 14, 2008) in women presenting with symptoms or signs of threatened preterm labor, which will contribute information in the future.

The role of progesterone in women considered to be at risk of preterm birth for “other” reasons is uncertain, with the two randomized trials to date indicating no benefit in terms of perinatal death or preterm birth. However, the combined sample size of these two trials is underpowered to detect all but large differences in these outcomes.

There remains limited information about the benefits and harms of progesterone, particularly in relation to long-term outcomes for the infants. Information is available from the follow-up of a single randomized trial related to long-term infant and childhood health outcomes. Although this report indicates no statistically significant differences in health and developmental assessment at 2 years of age, ongoing assessment of participants in randomized trials remains a priority. Maternal outcomes after antenatal progesterone therapy, including treatment side effects, preferences of mode of administration, and satisfaction with care, were poorly reported in the available literature. Further information is required on these important issues. Uncertainty remains about the optimal dose, route of administration, and gestational age at which to commence progesterone therapy. The American College of Obstetricians and Gynecologists has issued a statement indicating the need for further information about the optimal mode of administration.

To date only three studies have been reported detailing the use of vaginal progesterone therapy. Further information is required from randomized trials relating to the effect of vaginal progesterone on maternal and infant health outcomes for women at risk of preterm birth.

Progesterone is associated with some beneficial effects in pregnancy outcome for some women at increased risk of preterm birth. Over time, the results of current randomized trials will assist in further elucidating the precise role of progesterone therapy for women considered to be at increased risk of preterm birth.

REFERENCES


