Progesterone
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Prediction of sPTB

• Numerous risk factors
  • Short interpregnancy interval
  • Medical problems (e.g. hypertension)
  • Lifestyle (e.g. smoking)
  • Black race
  • Stress
  • etc ...

• The 2 strongest
  • History of PTB
  • Short cervix
Current Society Recommendations

- Women with singleton pregnancy + history of preterm birth should be offered progesterone supplementation starting at 16-24 weeks
  - level A (ACOG)

- Women with singleton pregnancy + history of preterm birth should undergo cervical length surveillance
  - grade 1A (SMFM), level A (ACOG)
Systematic Reviews & Meta Analyses

- **Singletons**: if the cervix is short, think about vaginal progesterone or cerclage
  - Targeted vs universal screening

- **Twins**: if the cervix is short, not unreasonable to consider vaginal progesterone or cerclage
  - No specified role for screening
Preterm Birth 2020
Brief History

• **2003**: MFM Units Network study of 17OHPC for prevention of recurrent sPTB stopped early by DSMC (“robust” evidence of efficacy)

• **2008**: ACOG and SMFM state, “progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and prior sPTB

• **2011**: FDA granted conditional approval of 17-OHPC for commercial use under Subpart-H accelerated approval pathway

• **2012**: FDA votes down 8% progesterone gel for prevention of SPTB in women with a short cervical length in the midtrimester

• **2015**: FDA recommends impossible studies for vaginal progesterone

• **2019**: FDA committee recommends withdrawing 17-OHPC
<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meis, 2003*</td>
<td>17α-hydroxyprogesterone caproate (250 mg weekly injections)</td>
<td>Women with a documented history of a spontaneous singleton preterm birth at less than 37 weeks of gestation; cervical length not measured at entry; treatment initiated between 16 weeks of gestation and 20 weeks of gestation and continued until 36 weeks of gestation or delivery, whichever occurred first</td>
</tr>
<tr>
<td>da Fonseca, 2003†</td>
<td>Vaginal progesterone (100 mg daily)</td>
<td>High-risk women with a history of spontaneous singleton preterm birth; treatment initiated at 24 weeks of gestation and continued until 34 weeks of gestation</td>
</tr>
<tr>
<td>O’Brien, 2007†</td>
<td>Vaginal progesterone (90 mg daily)</td>
<td>Women with a history of spontaneous preterm birth randomized and treated; cervical length measured at entry (mean length, 37 mm); treatment initiated between 18 weeks of gestation and 22 6/7 weeks of gestation and continued until 37 weeks of gestation, occurrence of premature rupture of membranes, or preterm delivery</td>
</tr>
<tr>
<td>Fonseca, 2007³</td>
<td>Micronized progesterone gel capsules (200 mg vaginally daily)</td>
<td>Asymptomatic women with a very short cervical length (15 mm or less); 90% of the women had a singleton gestation and 85% had no prior preterm delivery; treatment initiated at 24 weeks of gestation and continued until 34 weeks of gestation</td>
</tr>
<tr>
<td>Hassan, 2011Ⅱ</td>
<td>Vaginal progesterone gel (90 mg daily)</td>
<td>Women with a singleton gestation with a previous preterm birth between 20 weeks of gestation and 35 weeks of gestation; patients were randomized between 20 weeks of gestation and 23 6/7 weeks of gestation; treatment continued until 36 6/7 weeks of gestation, rupture of membranes, or delivery, whichever occurred first.</td>
</tr>
<tr>
<td>Hassan, 2011Ⅱ</td>
<td>Vaginal progesterone gel (90 mg daily)</td>
<td>Only women without prior preterm birth; patients were randomized between 20 weeks of gestation and 23 6/7 weeks of gestation; treatment continued until 36 6/7 weeks of gestation, rupture of membranes, or delivery, whichever occurred first.</td>
</tr>
</tbody>
</table>
da Fonseca et al., 2003

- VagP, singleton, “high-risk”

- Enrollment
  - 1996-2001
  - University of Sao Paolo Medical School
  - n=142 randomized
    - n=72 progesterone
    - n=70 placebo

- Included: history PTB, cerclage, uterine anomaly
  - EGA at previous PTB 33.3 ±2.7 (P) vs 33.4 ±2.6 (placebo)

Table II. Characteristics of women at randomization

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 70)</th>
<th>Progesterone (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>26.8</td>
<td>27.6</td>
</tr>
<tr>
<td>Ethnicity*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71.4%</td>
<td>68.0%</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>28.6%</td>
<td>32.0%</td>
</tr>
<tr>
<td>Parity (&gt;1 delivery)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>97.1%</td>
<td>90.2%</td>
</tr>
<tr>
<td>Risk factor*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous preterm delivery</td>
<td>97.2%</td>
<td>90.3%</td>
</tr>
<tr>
<td>Uterine malformation</td>
<td>1.4%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Incompetent cervix</td>
<td>1.4%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Gestational age at intake (wk)*</td>
<td>25.2</td>
<td>26.5</td>
</tr>
</tbody>
</table>

*Not significant. da Fonseca et al, AJOG 2003
da Fonseca et al., 2003

- VagP, singleton, “high-risk”
  - Intervention: VagP 100mg nightly
    - 24 to 34 weeks
  - Primary outcome: sPTB <34 weeks
da Fonseca et al., 2003

- VagP, singleton, “high-risk”

- **Results:** VagP (100mg) decreases sPTB
  
  - 2.8% (2/72) P vs 18.6% (13/70) placebo
  
  - OR 0.06 (95% CI 0.03 – 0.34)
Meis et al., 2003

- 17OHP (IM), singleton, hx sPTB

  - Enrollment
    - 1998-1999
    - 19 university hospitals in US
    - n=463 randomized (goal 500)
      - n=310 progesterone
      - n=153 placebo

  - Included: history of sPTB
    - 1/3 had >1 previous sPTB
    - Average EGA at previous sPTB 31 weeks

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the 463 Women at Randomization.†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Duration of gestation at the time of qualifying delivery — wk</td>
</tr>
<tr>
<td>No. of previous preterm deliveries</td>
</tr>
<tr>
<td>&gt;1 Previous preterm delivery — no. (%)</td>
</tr>
<tr>
<td>≥1 Previous term deliveries — no. (%)</td>
</tr>
<tr>
<td>Duration of gestation at randomization — wk</td>
</tr>
<tr>
<td>Age — yr</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Marital status — no. (%)</td>
</tr>
<tr>
<td>Married or living with partner</td>
</tr>
<tr>
<td>Never married</td>
</tr>
<tr>
<td>Divorced, widowed, or separated</td>
</tr>
<tr>
<td>Body-mass index before pregnancy§</td>
</tr>
<tr>
<td>Yr of education</td>
</tr>
<tr>
<td>Smoking during pregnancy — no. (%)</td>
</tr>
<tr>
<td>Alcohol use during pregnancy — no. (%)</td>
</tr>
<tr>
<td>Substance use during pregnancy — no. (%)</td>
</tr>
</tbody>
</table>
Meis et al., 2003

- 17OHP (IM), singleton, hx sPTB
  - Intervention: IM 17-OHPC 250mg weekly
    - 15+0 to 20+6 weeks through 36 weeks
  - Primary outcome: sPTB <37 weeks
Meis et al., 2003

• 17OHP (IM), singleton, hx sPTB

• Results: 17OHP (250mg) decreases sPTB

  • 29.4% (90/306) P vs 45.1% (69/153) placebo

  • RR 0.65 (95% CI 0.51-0.83)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progesterone Group (N=306)</th>
<th>Placebo Group (N=153)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery before 37 wk of gestation</td>
<td>111 (36.3)</td>
<td>84 (54.9)</td>
<td>0.66 (0.54–0.81)</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>90 (29.4)</td>
<td>69 (45.1)</td>
<td>0.65 (0.51–0.83)</td>
</tr>
<tr>
<td>Indicated because of complications</td>
<td>21 (6.9)</td>
<td>15 (9.8)</td>
<td>0.70 (0.37–1.32)</td>
</tr>
<tr>
<td>Black women</td>
<td>64 (35.4)</td>
<td>47 (52.2)</td>
<td>0.68 (0.51–0.90)</td>
</tr>
<tr>
<td>Nonblack women</td>
<td>47 (37.6)</td>
<td>37 (58.7)</td>
<td>0.64 (0.47–0.87)</td>
</tr>
<tr>
<td>Delivery before 35 wk of gestation</td>
<td>63 (20.6)</td>
<td>47 (30.7)</td>
<td>0.67 (0.48–0.93)</td>
</tr>
<tr>
<td>Delivery before 32 wk of gestation</td>
<td>35 (11.4)</td>
<td>30 (19.6)</td>
<td>0.58 (0.37–0.91)</td>
</tr>
<tr>
<td>Miscarriage at &lt;20 wk of gestation</td>
<td>5 (1.6)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Hospital visit for preterm labor</td>
<td>49 (16.0)</td>
<td>21 (13.8)</td>
<td>1.15 (0.72–1.86)</td>
</tr>
<tr>
<td>Tocolytic therapy</td>
<td>53 (17.3)</td>
<td>24 (15.9)</td>
<td>1.09 (0.70–1.69)</td>
</tr>
<tr>
<td>Corticosteroids for fetal lung</td>
<td>52 (17.8)</td>
<td>30 (19.7)</td>
<td>0.91 (0.60–1.35)</td>
</tr>
<tr>
<td>maturity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>77 (25.2)</td>
<td>41 (26.8)</td>
<td>0.94 (0.68–1.30)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>11 (3.6)</td>
<td>5 (3.3)</td>
<td>1.09 (0.39–3.09)</td>
</tr>
</tbody>
</table>
Meis et al., 2003

- 17OHP (IM), singleton, hx sPTB

  - Notes
    - Unexpectedly high PTB rate
      - sPTB 36.3% in P group
      - sPTB 54.9% in controls
      - Expected 37% in controls
    - May be ineffective in lower risk
  - FDA decision
Fonseca et al., 2007

- VagP, singleton or twins, CL ≤15mm

- Enrollment
  - 2003-2006
  - London (5 hospitals), Chile, Brazil, Greece
  - n=250 randomized (n=24 twins)
    - n=125 progesterone
    - n=125 placebo

- Included: CL ≤15mm at 20-25 weeks
Fonseca et al., 2007

- VagP, singleton or twins, CL <15mm
  - Intervention: VagP 200mg nightly
  - 24 to 34 weeks
- Primary outcome: sPTB <34 weeks

**Table 1. Characteristics of the Study Participants.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Progesterone Group (N=125)</th>
<th>Placebo Group (N=125)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Median</td>
<td>29</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>24–34</td>
<td>24–34</td>
<td></td>
</tr>
<tr>
<td>Obstetrical history — no. (%)</td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>71 (56.8)</td>
<td>69 (55.2)</td>
<td></td>
</tr>
<tr>
<td>Parous with no previous preterm births</td>
<td>39 (31.2)</td>
<td>33 (26.6)</td>
<td></td>
</tr>
<tr>
<td>Parous with ≥1 previous preterm birth</td>
<td>15 (12.0)</td>
<td>23 (18.4)</td>
<td></td>
</tr>
<tr>
<td>Race — no. (%)</td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>White</td>
<td>46 (36.8)</td>
<td>49 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>68 (54.4)</td>
<td>69 (55.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11 (8.8)</td>
<td>7 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Body-mass index†</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Median</td>
<td>23.3</td>
<td>25.4</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>21.6–27.7</td>
<td>22.3–28.4</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking during pregnancy — no. (%)</td>
<td>6 (4.8)</td>
<td>10 (8.0)</td>
<td>0.44</td>
</tr>
<tr>
<td>Single vs. multiple gestations — no. (%)</td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Singleton</td>
<td>114 (91.2)</td>
<td>112 (89.6)</td>
<td></td>
</tr>
<tr>
<td>Twin (dichorionic)</td>
<td>8 (6.4)</td>
<td>9 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Twin (monochorionic, diamniotic)</td>
<td>3 (2.4)</td>
<td>4 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Days of gestation at randomization</td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>Median</td>
<td>165</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>159–168</td>
<td>160–169</td>
<td></td>
</tr>
<tr>
<td>Cervical length at randomization — mm</td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>Median</td>
<td>11.0</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>9–14</td>
<td>9–14</td>
<td></td>
</tr>
<tr>
<td>Adherence rate &lt;80% — no. (%)</td>
<td>9 (7.2)</td>
<td>7 (5.6)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

* Race was self-reported.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

Fonseca et al, NEJM 2007
VagP, singleton or twins, CL ≤15mm

Results: VagP (200mg) decreases sPTB

- 19.2% (24/125) P vs 34.4% (43/125) placebo
- RR 0.56 (95% CI 0.36-0.86)
Fonseca et al., 2007

- VagP, singleton or twins, CL ≤15mm
  - Notes (data available on n=23,795)
    - 2.1% of entire cohort (n=490) had sPTB
    - 1.7% (413/24,620) had CL ≤15mm
      - 30.9% (n=126) of these had sPTB (25.9% of total)
    - 8.3% (n=1975) had CL 16-25mm
      - 5.1% of these (100/1975) had sPTB (20.4% of total)
  - Less than 1/3 of the women who delivered preterm had CL <15mm
O’Brien et al., 2007

- VagP (90mg gel), singleton, hx sPTB

- Enrollment
  - 2004-2007
  - 53 medical centers on 5 continents
    - 17 US sites
  - n=659 randomized
    - n=332 progesterone
    - n=327 placebo

- Included: sPTB at 20+0 to 35+0 in immediately preceding pregnancy
O’Brien et al., 2007

- VagP (90mg gel), singleton, hx sPTB

- Intervention
  - VagP (8% bioadhesive gel) 90mg nightly
  - 18+0 to 22+6 weeks through 37 weeks

- Primary outcome: sPTB ≤32 weeks

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Table 1 Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Progesterone (n = 309)</th>
<th>Placebo (n = 302)</th>
<th>Mean difference* or odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27.1 (5.8)</td>
<td>27.3 (5.6)</td>
<td>−0.19 (−1.1 to 0.72)*</td>
</tr>
<tr>
<td>Range</td>
<td>16.1–44.2</td>
<td>17.9–40.8</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity (n/%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>111 (35.9)</td>
<td>99 (32.8)</td>
<td>1.14 (0.82 to 1.6)</td>
</tr>
<tr>
<td>African–American</td>
<td>76 (24.6)</td>
<td>85 (28.1)</td>
<td>0.83 (0.58 to 1.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>22 (7.1)</td>
<td>14 (4.6)</td>
<td>1.37 (0.79 to 2.34)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>55 (17.8)</td>
<td>60 (19.9)</td>
<td>0.87 (0.58 to 1.3)</td>
</tr>
<tr>
<td>Native American</td>
<td>0</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>45 (14.6)</td>
<td>43 (14.2)</td>
<td>1.02 (0.82 to 1.6)</td>
</tr>
<tr>
<td>Country of study site (n/%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>200 (64.7)</td>
<td>195 (64.6)</td>
<td>1.0 (0.70 to 1.4)</td>
</tr>
<tr>
<td>India</td>
<td>54 (17.5)</td>
<td>57 (18.9)</td>
<td>0.91 (0.6 to 1.4)</td>
</tr>
<tr>
<td>South Africa</td>
<td>44 (14.2)</td>
<td>40 (13.2)</td>
<td>1.1 (0.68 to 1.7)</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>7 (2.3)</td>
<td>6 (2.0)</td>
<td>1.14 (0.37 to 3.4)</td>
</tr>
<tr>
<td>Chile/El Salvador</td>
<td>4 (1.3)</td>
<td>4 (1.3)</td>
<td>1.0 (0.2 to 3.9)</td>
</tr>
<tr>
<td>Body mass index (mean (SD))</td>
<td>26.6 (6.5)</td>
<td>26.4 (7.1)</td>
<td>0.23 (−0.8 to 1.2)*</td>
</tr>
<tr>
<td>Parity (mean (SD))</td>
<td>1.5 (1.1)</td>
<td>1.5 (1.1)</td>
<td>−0.02 (−0.19 to 0.15)*</td>
</tr>
<tr>
<td>Prior preterm births (n, mean (SD))</td>
<td>1.3 (0.6)</td>
<td>1.4 (0.7)</td>
<td>−0.98 (−0.17 to 0.04)*</td>
</tr>
<tr>
<td>&gt; 1 prior preterm birth (n/%)</td>
<td>73 (23.6)</td>
<td>77 (25.5)</td>
<td>0.90 (0.6 to 1.3)</td>
</tr>
<tr>
<td>Prior cervical surgery (n/%)</td>
<td>22 (7.1)</td>
<td>28 (9.3)</td>
<td>0.73 (0.44 to 1.3)</td>
</tr>
<tr>
<td>&gt; 1 spontaneous miscarriage (n/%)</td>
<td>99 (32.0)</td>
<td>100 (33.1)</td>
<td>0.95 (0.67 to 1.3)</td>
</tr>
<tr>
<td>GA at randomization (weeks, mean (SD))</td>
<td>19.9 (2.1)</td>
<td>20.1 (3.3)</td>
<td>−0.14 (−0.57 to 0.29)*</td>
</tr>
<tr>
<td>Cervical length at randomization (cm, mean (SD))</td>
<td>3.7 (0.7)</td>
<td>3.7 (0.7)</td>
<td>−0.002 (−0.13 to 0.13)*</td>
</tr>
</tbody>
</table>

*Calculation for mean difference = Progesterone − Placebo, with 95% CI for the difference (significant if zero not included in the range). There were no significant differences for any comparisons in mean difference or odds ratio between groups, P > 0.03. GA, gestational age.
Results

- VagP (90mg) does not decrease sPTB
- 10% (31/309) P vs 11.3% (34/302) placebo
- OR 0.9 (95% CI 0.52-1.56)

O’Brien et al., 2007

Table 2: Maternal and neonatal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progesterone (n = 309)</th>
<th>Placebo (n = 302)</th>
<th>Mean difference* or odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA at birth (weeks, mean (SD))</td>
<td>36.6 (3.8)</td>
<td>36.6 (4.2)</td>
<td>0.0 (-0.64 to 0.64)*</td>
</tr>
<tr>
<td>Preterm birth (n (%))</td>
<td>129 (41.7)</td>
<td>123 (40.7)</td>
<td>1.08 (0.76 to 1.52)</td>
</tr>
<tr>
<td>&lt; 37 weeks</td>
<td>79 (25.6)</td>
<td>75 (24.8)</td>
<td>1.14 (0.98 to 1.37)</td>
</tr>
<tr>
<td>≥ 37 weeks</td>
<td>50 (16.1)</td>
<td>48 (15.9)</td>
<td>0.95 (0.80 to 1.13)</td>
</tr>
<tr>
<td>Admission for preterm labor (n (%))</td>
<td>79 (25.6)</td>
<td>75 (24.8)</td>
<td>1.14 (0.98 to 1.37)</td>
</tr>
<tr>
<td>Death due to preterm labor (n (%))</td>
<td>31 (10.0)</td>
<td>34 (11.3)</td>
<td>0.9 (0.52 to 1.56)</td>
</tr>
<tr>
<td>Intrauterine fetal demise (n (%))</td>
<td>10 (3.2)</td>
<td>9 (3.0)</td>
<td>1.07 (0.38 to 2.96)</td>
</tr>
<tr>
<td>Infants weighing &lt; 2000 g at birth (n (%))</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>PPROM (n (%))</td>
<td>37 (12.0)</td>
<td>38 (12.6)</td>
<td>0.95 (0.58 to 1.53)</td>
</tr>
<tr>
<td>Maternal intensive care admission (n (%))</td>
<td>79 (25.6)</td>
<td>75 (24.8)</td>
<td>1.14 (0.98 to 1.37)</td>
</tr>
<tr>
<td>Mode of delivery (n (%))</td>
<td>218 (71.0)</td>
<td>216 (72.2)</td>
<td>0.94 (0.66 to 1.34)</td>
</tr>
<tr>
<td>Cesarean section (n (%))</td>
<td>89 (29.0)</td>
<td>85 (27.8)</td>
<td>0.96 (0.75 to 1.25)</td>
</tr>
<tr>
<td>Study medication compliance (mean, SD)</td>
<td>96.2 (9.4)</td>
<td>96.4 (7.8)</td>
<td>-0.2 (-1.5 to 1.2)*</td>
</tr>
<tr>
<td><strong>Neonatal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APGAR score (median (SD))</td>
<td>8.9 (2.3)</td>
<td>8.8 (2.2)</td>
<td>0.1 (-0.2 to 0.4)*</td>
</tr>
<tr>
<td>Birth weight (g, mean (SD))</td>
<td>2680 (710)</td>
<td>2661 (738)</td>
<td>19 (-96 to 133)*</td>
</tr>
<tr>
<td>NICU admission (n (%))</td>
<td>54 (17.5)</td>
<td>63 (21.1)</td>
<td>0.75 (0.51 to 1.11)</td>
</tr>
<tr>
<td>Days in NICU per admission (n, mean (SD))</td>
<td>14.2 (14.6)</td>
<td>20.5 (10.7)</td>
<td>-6.2 (-15.2 to 2.8)*</td>
</tr>
<tr>
<td>Head circumference (cm, mean (SD))</td>
<td>32.3 (3.4)</td>
<td>32.5 (3.7)</td>
<td>-0.2 (-0.8 to 0.4)*</td>
</tr>
<tr>
<td>Respiratory distress syndrome (n (%))</td>
<td>34 (11.6)</td>
<td>36 (11.9)</td>
<td>0.91 (0.56 to 1.50)</td>
</tr>
<tr>
<td>Intracranial hemorrhage (n (%))</td>
<td>6 (1.9)</td>
<td>5 (1.6)</td>
<td>0.0 (0.0 to 0.0)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (1.3)</td>
<td>4 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Necrotizing enterocolitis (n (%))</td>
<td>3 (1.0)</td>
<td>5 (1.7)</td>
<td>0.58 (0.14 to 2.46)</td>
</tr>
<tr>
<td>Surgical intervention (n (%))</td>
<td>0 (0.0)</td>
<td>3 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Clinical intervention (n (%))</td>
<td>3 (1.0)</td>
<td>2 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Neonatal death (&lt; 28 days) (n (%))</td>
<td>6 (1.9)</td>
<td>7 (2.3)</td>
<td>0.87 (0.29 to 2.60)</td>
</tr>
</tbody>
</table>

*Calculation for mean difference as Progesterone – Placebo, with 95% CI for the difference (significant if zero not included in the range).
† Data for mode of delivery were not obtained for every patient. GA, gestational age; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes.
O’Brien et al., 2007

• Notes
  
  • Fewer short cervixes than expected
    • 4% (n=24/611) had CL ≤ 25 mm
      • (10% = ~60)
    
    • Perhaps highest risk women (CL <25mm + history) were excluded for planned cerclage
  
  • Similar population to Meis
    • 24.6% (n=150/611) delivered ≤ 35 weeks (Meis 25.3%)
    
    • 10.6% (n=65/611) delivered ≤ 32 weeks (Meis 14.2%)
deFranco et al., 2007 planned 2⁰ analyses

- VagP (90mg gel), singleton, hx sPTB, CL <28mm

- **Enrollment**
  - 2004-2007
  - 53 medical centers on 5 continents
    - 17 US sites
    - So Africa, India, Czech Republic
  - Screened at 16+0 to 22+6
  - n=46 randomized
    - n=19 with CL <28mm progesterone
    - n=27 with CL <28mm placebo
deFranco et al., 2007 planned 2^0 analyses

- VagP (90mg gel), singleton, hx sPTB, CL <28mm
  - Included: sPTB at 20+0 to 35+0 in immediately preceding pregnancy (and/or, at US sites, CL <25mm)
    - Insufficient numbers
      - CL <25mm only (1.3%, n=9)
      - CL <28mm
    - Lowest quartile was <32mm
      - Divided into <30mm and <28mm
      - 28mm = 9%ile of population

Table 1 Baseline demographic and obstetric characteristics of women with a short cervix (<28 mm)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Progesterone (n = 19)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 27)</td>
</tr>
<tr>
<td></td>
<td>P</td>
</tr>
<tr>
<td>Maternal age (years, mean (SD))</td>
<td>27.4 (4.9)</td>
</tr>
<tr>
<td>Race/ethnicity (n (%))</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>African-American</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>6 (31.6)</td>
</tr>
<tr>
<td>Body mass index (mean (SD))</td>
<td>28.5 (8.3)</td>
</tr>
<tr>
<td>Prior preterm births (n, mean (SD))</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>&gt; 1 prior preterm birth (n (%))</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Prior cervical surgery (n (%))</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Prior spontaneous miscarriages (n, mean (SD))</td>
<td>0.8 (1.4)</td>
</tr>
<tr>
<td>GA at randomization (weeks, mean (SD))</td>
<td>20.4 (1.3)</td>
</tr>
</tbody>
</table>

deFranco et al, UOG 2007
• VagP (90mg gel), singleton, hx
  sPTB, CL <28mm

• Intervention
  • VagP (8% bioadhesive gel) 90mg nightly
  • 18+0 to 22+6 weeks through 37 weeks

• Primary outcome: sPTB ≤32 weeks

deFranco et al., 2007 planned 2⁰ analyses
deFranco et al., 2007 planned 2⁰ analyses

• Results

• VagP (90mg) decreases sPTB

• 0% (0/19) P vs 29.6% (8/27) placebo, p=0.014

Table 2: Preterm birth outcomes in women with a cervical length < 28 mm at enrollment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progesterone (n = 19)</th>
<th>Placebo (n = 27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at birth (weeks, mean (SD))</td>
<td>36.3 (2.4)</td>
<td>34.6 (4.6)</td>
<td>0.160</td>
</tr>
<tr>
<td>Preterm birth (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 37 weeks</td>
<td>8 (42.1)</td>
<td>16 (59.3)</td>
<td>0.370</td>
</tr>
<tr>
<td>≤ 33 weeks</td>
<td>7 (36.8)</td>
<td>13 (48.1)</td>
<td>0.551</td>
</tr>
<tr>
<td>≤ 32 weeks*</td>
<td>0</td>
<td>8 (29.6)†</td>
<td>0.014§</td>
</tr>
<tr>
<td>≤ 28 weeks</td>
<td>0</td>
<td>3 (11.1)</td>
<td>0.257</td>
</tr>
<tr>
<td>Cervical length at enrollment (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>24 (0.2)</td>
<td>22 (0.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Median (range)</td>
<td>25 (19–27)</td>
<td>25 (11–27)</td>
<td>0.27</td>
</tr>
<tr>
<td>Cervical length at 28 weeks (mm, mean (SD))</td>
<td>25 (0.8)</td>
<td>22 (0.8)</td>
<td>0.70</td>
</tr>
<tr>
<td>Admission for preterm labor (n (%))</td>
<td>6 (31.6)</td>
<td>7 (25.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Latency period to delivery after tocolysis for preterm labor (days, mean (SD))</td>
<td>42.7 (52.3)†</td>
<td>10.0 (18.0)</td>
<td>0.287</td>
</tr>
<tr>
<td>Compliance (% (SD))†</td>
<td>93.9 (9.77)</td>
<td>94.7 (13.03)</td>
<td></td>
</tr>
</tbody>
</table>

*Primary outcome. †Percent compliance was assessed as total treatment duration compliance (total applicators used/total dosing days) × 100. A compliance of 96% represents missing one application every 25 dosing days. ‡Four of these patients had a baseline cervical length < 25 mm and one had a baseline cervical length < 15 mm. §Adjusted for cervical length at baseline using logistic regression, P = 0.016. GA, gestational age.
Notes

• 30% sPTB in CL <28mm (many also + hx sPTB)

• sPTB in CL <25mm only (n=9)
  • 0% (n=0/4) vs 40% (n=2/5)

• ? ‘responders’ in previous trials of vagP may have been those who also had short CL

deFranco et al., 2007 planned 2^{0} analyses
Hassan et al., 2011

- VagP (90mg gel), singleton, CL 10-20mm

- Enrollment
  - 2008-2010
  - 10 countries
    - 19 centers in US: AL, AZ, CA, FL, HI, IA, KY, KS, MD, MA, MI, MS, NY, NJ, NC, PA, TN, VA, WV
    - US, Belarus, Chile, Czech Republic, India, Israel, Italy, Russian Federation, So Africa, Ukraine
  - n=465 with CL 10-20mm randomized
    - n=235 progesterone
    - n=223 placebo
      - Stratified by center and risk (eg hx sPTB)
      - Emergent cerclage in n=16
        - n=10 progesterone, n=6 placebo

Figure 1 Participant flow diagram.
Hassan et al., 2011

- VagP (90mg gel), singleton, CL 10-20mm
  - Included: asymptomatic, CL 10-20mm at 19+0 to 23+6

- Intervention
  - VagP (8% bioadhesive gel)
  - 20+0 to 23+6 through 36 weeks

- Primary outcome: sPTB <33 weeks
Hassan et al., 2011

- VagP (90mg gel), singleton, CL 10-20mm

- Results: vagP (90mg) decreases sPTB

- 8.9% (21/235) P vs 16.1% (16/223) placebo

- RR 0.55 (95% CI 0.33-0.92)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vaginal progesterone (n (%))</th>
<th>Placebo (n (%))</th>
<th>Relative risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth &lt; 33 weeks</td>
<td>21/235 (8.9)</td>
<td>36/223 (16.1)</td>
<td>0.55 (0.33–0.92)</td>
<td>0.020</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth &lt; 28 weeks</td>
<td>12/235 (5.1)</td>
<td>23/223 (10.3)</td>
<td>0.50 (0.25–0.97)</td>
<td>0.036</td>
</tr>
<tr>
<td>Preterm birth &lt; 35 weeks</td>
<td>34/235 (14.5)</td>
<td>52/223 (23.3)</td>
<td>0.62 (0.42–0.92)</td>
<td>0.016</td>
</tr>
<tr>
<td>Preterm birth &lt; 37 weeks</td>
<td>71/235 (30.2)</td>
<td>76/223 (34.1)</td>
<td>0.89 (0.68–1.16)</td>
<td>0.376</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>7/235 (3.0)</td>
<td>17/223 (7.6)</td>
<td>0.39 (0.17–0.92)</td>
<td>0.026</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>4/235 (1.7)</td>
<td>5/223 (2.2)</td>
<td>0.76 (0.21–2.79)</td>
<td>0.678</td>
</tr>
<tr>
<td>Proven sepsis</td>
<td>7/235 (3.0)</td>
<td>6/223 (2.7)</td>
<td>1.11 (0.38–3.24)</td>
<td>0.853</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>5/235 (2.1)</td>
<td>4/223 (1.8)</td>
<td>1.19 (0.32–4.16)</td>
<td>0.797</td>
</tr>
<tr>
<td>Intraventricular hemorrhage, Grade III/IV</td>
<td>0/235 (0.0)</td>
<td>1/223 (0.5)</td>
<td>0.32 (0.01–7.73)*</td>
<td>0.305</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>0/235 (0.0)</td>
<td>0/223 (0.0)</td>
<td>Not estimable</td>
<td>NA</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>8/235 (3.4)</td>
<td>11/223 (4.9)</td>
<td>0.69 (0.28–1.68)</td>
<td>0.413</td>
</tr>
<tr>
<td>Fetal death</td>
<td>5/235 (2.1)</td>
<td>6/223 (2.7)</td>
<td>0.79 (0.25–2.57)</td>
<td>0.700</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>3/235 (1.3)</td>
<td>5/223 (2.2)</td>
<td>0.57 (0.14–2.33)</td>
<td>0.431</td>
</tr>
<tr>
<td>Composite outcome scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any morbidity/mortality event</td>
<td>18/235 (7.7)</td>
<td>30/223 (13.5)</td>
<td>0.57 (0.33–0.99)</td>
<td>0.043</td>
</tr>
<tr>
<td>0–4 without NICU†</td>
<td></td>
<td></td>
<td></td>
<td>0.048</td>
</tr>
<tr>
<td>0–4 with NICU†</td>
<td></td>
<td></td>
<td></td>
<td>0.068</td>
</tr>
<tr>
<td>0–6 without NICU†</td>
<td></td>
<td></td>
<td></td>
<td>0.048</td>
</tr>
<tr>
<td>Birth weight &lt; 2500 g</td>
<td>60/234 (25.6)</td>
<td>68/220 (30.9)</td>
<td>0.83 (0.62–1.11)</td>
<td>0.213</td>
</tr>
<tr>
<td>Birth weight ≥ 1500 g</td>
<td>13/234 (6.4)</td>
<td>30/220 (13.6)</td>
<td>0.47 (0.26–0.83)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Unadjusted relative risk (RR) and 95% CI calculated using the Cochran–Mantel–Haenszel (CMH) test. *Based on Logit estimator with continuity correction. †Frequency of perinatal mortality/neonatal morbidity composite scores are provided in Appendix S4 online. NA, not applicable; NICU, neonatal intensive care unit.
Hassan et al., 2011

• Notes
  
  • 2.3% (733/32,091) had CL 10-20mm
    • <10mm have increased risk of triple-I (less likely to benefit)
    • Explore benefit beyond 15mm
  
  • Compared to Fonseca et al. 2007
    • No twins
    • Evaluated >15mm
  
  • FDA decision
Blackwell et al., 2019

- 17OHPC (IM), singleton, hx sPTB

- Enrollment
  - 2009-2018
  - 9 countries, 93 centers
    - AL, AZ, CA, CO, FL, GA, HI, ID, KY, MD, MI, MS, NC, ND, OH, PA, SC, TN, TX, UT, VA, WA, WI
    - US, Bulgaria, Canada, Czechia, Hungary, Italy, Russian Federation, Spain, Ukraine
  - n=1708 women randomized (23%, n=391 US)
    - n=1130 17OHPIC
    - n=578 placebo

Fig. 1. Patient eligibility, randomization, and assessment. HPC, hydroxyprogesterone caproate; PROLONG, Progesterone's Role in Optimizing Neonatal Gestation; PTB, preterm birth; sPTB, spontaneous PTB.
Blackwell et al., 2019

• 17OHPC (IM), singleton, hx sPTB

• Included: 16+0 to 20+6 weeks, hx sPTB at 20+0 to 36+6 weeks

• Intervention: IM 17-OHPC 250mg weekly
  • 15+0 to 20+6 weeks through 36 weeks

• Co-Primary outcomes: sPTB <35 weeks and composite neonatal morbidity and mortality index

Table 1 Demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>17-OHPC</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td>30.0 ± 5.2</td>
<td>29.9 ± 5.2</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>73 (6.5)</td>
<td>41 (7.1)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1,004 (88.8)</td>
<td>504 (87.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>23 (2.0)</td>
<td>22 (3.8)</td>
</tr>
<tr>
<td>Other</td>
<td>30 (2.7)</td>
<td>11 (1.9)</td>
</tr>
<tr>
<td>Hispanic or Latino ethnicity</td>
<td>101 (8.9)</td>
<td>54 (9.3)</td>
</tr>
<tr>
<td>No. of prior spontaneous PTB &gt; 1</td>
<td>148 (13.1)</td>
<td>70 (12.2)</td>
</tr>
<tr>
<td>Prior elective abortion</td>
<td>28 (24.9)</td>
<td>142 (24.6)</td>
</tr>
<tr>
<td>Prior indicated PTB</td>
<td>19 (1.7)</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td>Gestational age at qualifying prior sPTB (wk)</td>
<td>32 (28–35)</td>
<td>33 (29–35)</td>
</tr>
<tr>
<td>Prepregnancy BMI (kg/m²)</td>
<td>23 (21–27)</td>
<td>23 (21–27)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living with a partner</td>
<td>1,013 (89.6)</td>
<td>522 (98.3)</td>
</tr>
<tr>
<td>Never married</td>
<td>86 (7.6)</td>
<td>40 (6.9)</td>
</tr>
<tr>
<td>Divorced/widowed/separated</td>
<td>31 (2.7)</td>
<td>16 (2.8)</td>
</tr>
<tr>
<td>Years of education</td>
<td>13 (11–15)</td>
<td>13 (11–15)</td>
</tr>
<tr>
<td>Smoked during current pregnancy</td>
<td>92 (8.1)</td>
<td>41 (7.1)</td>
</tr>
<tr>
<td>Drank alcohol during current pregnancy</td>
<td>24 (2.1)</td>
<td>18 (3.1)</td>
</tr>
<tr>
<td>Used any “street drugs” during current pregnancy</td>
<td>16 (1.4)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>Transvaginal cervical length &lt;25 mm, n/N* (%)</td>
<td>10 (833) (1.2)</td>
<td>8 (420) (1.9)</td>
</tr>
<tr>
<td>Prior vaginal progesterone therapy in pregnancy</td>
<td>16 (1.4)</td>
<td>10 (1.7)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; OHPC, 17-hydroxyprogesterone caproate; PTB, preterm birth; sPTB, spontaneous preterm birth. 
Note: n is number of patients in the intent to treat population. Data expressed as n (%) median (inter-quartile range), or mean (± standard of deviation).
*NI = number of patients with cervical length measurement performed prior to first dose of study drug; measured prior to the first dose of study drug.

Blackwell et al, Am J Perinat 2019
• 17OHP (IM), singleton, hx sPTB

• Results: no difference in sPTB <35 weeks
  • 11.0% (122/1113) vs 11.5% (66/574)
  • RR 0.95 (95% CI 0.71-1.26)

• Results: no difference in neonatal outcome
  • 5.6% vs 5.0%
  • RR 1.12 (95% CI 0.70-1.66)
Blackwell et al., 2019

- 17OHP (IM), singleton, hx sPTB
  - sPTB higher in US than elsewhere, but still no difference
    - 15.6% (340/256) P vs 17.6% (23/131) placebo
    - RR 0.88 (95% CI 0.55-1.40)
    - Same for sPTB <37 weeks; 29.9% placebo

- CL documented in n=1253
  - CL <25 mm in 1.4% (18/1253)
    - 1.2% (10/833) P, 1.9% (8/420) placebo
    - 22.2% (n=4/18) vs 44.4% (n=4/9) had sPTB <35 weeks
  - CL >25 mm in 1220
    - 9.6% (78/810) P vs 9.5% (39/410) placebo had sPTB <35 weeks
    - Much lower than expected

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**Table S1. Relationship between PTB < 35⁰ weeks based on Treatment Group by Geographic Region of Enrollment**

<table>
<thead>
<tr>
<th>Country of Enrollment</th>
<th>Total Enrolled</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>17-OHPC  Placebo</td>
</tr>
<tr>
<td></td>
<td>n/N1</td>
<td>n/N1</td>
</tr>
<tr>
<td>US</td>
<td>391</td>
<td>15.6% (40/256) 17.6% (23/131)</td>
</tr>
<tr>
<td>Russia</td>
<td>621</td>
<td>6.7% (27/406) 8.7% (18/206)</td>
</tr>
<tr>
<td>Ukraine</td>
<td>420</td>
<td>10% (27/270) 9.9% (14/142)</td>
</tr>
<tr>
<td>Hungry</td>
<td>91</td>
<td>18.6% (11/59) 12.5% (4/32)</td>
</tr>
<tr>
<td>Spain</td>
<td>85</td>
<td>14% (8/57) 10.7% (3/28)</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>50</td>
<td>12.1% (4/33) 0% (0/17)</td>
</tr>
<tr>
<td>Canada</td>
<td>31</td>
<td>26.3% (5/19) 25% (3/12)</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>14</td>
<td>0% (0/9) 20% (1/5)</td>
</tr>
<tr>
<td>Italy</td>
<td>5</td>
<td>0% (0/4) 0% (0/1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,708</strong></td>
<td><strong>11% (122/1,113) 11.5% (66/574 11.5))</strong></td>
</tr>
</tbody>
</table>

N1 = Number of subjects within the geographic region with non-missing delivery data or with missing delivery data who were known to be pregnant at ≥35⁰ weeks of gestation.

Blackwell et al, Am J Perinat 2019
Blackwell et al., 2019

• Notes
  
  • sPTB rate ~50% lower than in MFMU trial
    • Underpowered
      • Needed 3600 women
      • MFMU: sPTB rates among women receiving placebo
        • PTB < 37 weeks 54.9%, <35 weeks 30.7%, <32 weeks 19.6%
      • PROLONG: sPTB rates among women receiving placebo
        • <37 weeks 21.9%, <35 weeks 11.5%, and <32 weeks 5.2%
        • Among US women: sPTB <37 weeks 29.9%

  • Selection bias
    • US enrollees not the highest risk?
• How best to adjudicate the findings of the PROLONG trial, given it was underpowered and ... will be challenging for clinicians, patients, and policy makers

• The feasibility of conducting another placebo controlled RCT seems improbable, especially in the US
Practice Advisory: Clinical guidance for integration of the findings of the PROLONG study: Progestin’s Role in Optimizing Neonatal Gestation

• ACOG is not changing clinical recommendations at this time

• Consideration for offering 17-OHPC to women at risk of recurrent preterm birth should continue to take into account the body of evidence for progesterone supplementation, the values and preferences of the pregnant woman, the resources available, and the setting in which the intervention will be implemented.

• Additional information from planned meta-analysis and secondary analyses will need to be evaluated to assess the impact this intervention has on women at risk of recurrent preterm birth in the United States.
### Table 1. Characteristics of the 463 Women at Randomization.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Progesterone Group (N=310)</th>
<th>Placebo Group (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of gestation at the time of qualifying delivery — wk</td>
<td>30.6±4.6</td>
<td>31.3±4.2</td>
</tr>
<tr>
<td>No. of previous preterm deliveries</td>
<td>1.4±0.7</td>
<td>1.6±0.9†</td>
</tr>
<tr>
<td>&gt;1 Previous preterm delivery — no. (%)</td>
<td>86 (27.7)</td>
<td>63 (41.2)</td>
</tr>
<tr>
<td>≥1 Previous term deliveries — no. (%)</td>
<td>153 (49.4)</td>
<td>71 (46.4)</td>
</tr>
<tr>
<td>Duration of gestation at randomization — wk</td>
<td>18.4±1.4</td>
<td>18.4±1.4</td>
</tr>
<tr>
<td>Age — yr</td>
<td>26.0±5.6</td>
<td>26.5±5.4</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>183 (59.0)</td>
<td>90 (58.8)</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>79 (25.5)</td>
<td>34 (22.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>43 (13.9)</td>
<td>26 (17.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (0.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.0)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Marital status — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living with partner</td>
<td>159 (51.3)</td>
<td>71 (46.4)</td>
</tr>
<tr>
<td>Never married</td>
<td>119 (38.4)</td>
<td>64 (41.8)</td>
</tr>
<tr>
<td>Divorced, widowed, or separated</td>
<td>32 (10.3)</td>
<td>18 (11.8)</td>
</tr>
<tr>
<td>Body-mass index before pregnancy§</td>
<td>26.9±7.9</td>
<td>26.0±7.0</td>
</tr>
<tr>
<td>Yr of education</td>
<td>11.7±2.3</td>
<td>11.9±2.3</td>
</tr>
<tr>
<td>Smoking during pregnancy — no. (%)</td>
<td>70 (22.6)</td>
<td>30 (19.6)</td>
</tr>
<tr>
<td>Alcohol use during pregnancy — no. (%)</td>
<td>27 (8.7)</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td>Substance use during pregnancy — no. (%)</td>
<td>11 (3.5)</td>
<td>4 (2.6)</td>
</tr>
</tbody>
</table>

### Table 1. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>17-OHPC n=1,130</th>
<th>Placebo n=578</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td>30.0 ± 5.2</td>
<td>29.9 ± 5.2</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>73 (6.5)</td>
<td>41 (7.1)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1,004 (88.8)</td>
<td>504 (87.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>23 (2.0)</td>
<td>22 (3.8)</td>
</tr>
<tr>
<td>Other</td>
<td>30 (2.7)</td>
<td>11 (1.9)</td>
</tr>
<tr>
<td>Hispanic or Latino ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of prior spontaneous PTB &gt; 1</td>
<td>148 (13.1)</td>
<td>70 (12.1)</td>
</tr>
<tr>
<td>Prior elective abortion</td>
<td>281 (24.9)</td>
<td>142 (24.6)</td>
</tr>
<tr>
<td>Prior indicated PTB</td>
<td>19 (1.7)</td>
<td>13 (2.3)</td>
</tr>
<tr>
<td>Gestational age at qualifying prior SPTB (wk)</td>
<td>32 (28–35)</td>
<td>33 (29–35)</td>
</tr>
<tr>
<td>Prepregnancy BMI (kg/m²)</td>
<td>23 (21–27)</td>
<td>23 (21–27)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living with a partner</td>
<td>1,013 (89.6)</td>
<td>522 (90.3)</td>
</tr>
<tr>
<td>Never married</td>
<td>86 (7.6)</td>
<td>40 (6.9)</td>
</tr>
<tr>
<td>Divorced/widowed/separated</td>
<td>31 (2.7)</td>
<td>16 (2.8)</td>
</tr>
<tr>
<td>Years of education</td>
<td>13 (11–15)</td>
<td>13 (11–15)</td>
</tr>
<tr>
<td>Smoked during current pregnancy</td>
<td>92 (8.1)</td>
<td>41 (7.1)</td>
</tr>
<tr>
<td>Drank alcohol during current pregnancy</td>
<td>24 (2.1)</td>
<td>18 (3.1)</td>
</tr>
<tr>
<td>Used any &quot;street drugs&quot; during current pregnancy</td>
<td>16 (1.4)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>Transvaginal cervical length &lt;25 mm, n/N1* (%)</td>
<td>10/833 (1.2)</td>
<td>8/420 (1.9)</td>
</tr>
<tr>
<td>Prior vaginal progesterone therapy in pregnancy</td>
<td>16 (1.4)</td>
<td>10 (1.7)</td>
</tr>
</tbody>
</table>
Stay Tuned ....
Thank you!