Progesterone for the prevention of preterm birth in women with a short cervix

William A. Grobman, MD MBA
Associate Professor of Obstetrics and Gynecology
Northwestern University Medical School

Evidence for progesterone as a modulator of labor

- In vivo:
  - An increase in plasma estrogen and a decrease in plasma progesterone precedes the onset of labor in many mammalian species

Implications for preterm labor: May be related to a pathologically early progesterone withdrawal

Hypothesis: Exogenous progesterone will offset withdrawal and preterm delivery

Johnson et al

- RCT: 43 women with history of 2 SAB, 2 PTB < 36 weeks, or one of each
- 17-P 250mg IM weekly vs. placebo
- No uniform GA for starting therapy
- Included patients with cerclage

<table>
<thead>
<tr>
<th></th>
<th>17-P</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGA*</td>
<td>38.6 ± 1.4</td>
<td>35.3 ± 6.2</td>
<td>-----</td>
</tr>
<tr>
<td>PTB</td>
<td>11%</td>
<td>48%</td>
<td>0.14 (0.03-0.72)</td>
</tr>
</tbody>
</table>

*P = 0.03

Johnson et al, N Engl J Med 1975
Hauth et al

- RCT: 168 women on active military duty
- 17-P 1000 mg IM weekly vs. placebo
- Initiation of treatment 16-20 weeks

BW < 2500g:
- 17-P: 7.5%
- Placebo: 9.0%
- OR 0.81 (0.24 – 2.73)

Issue with biologic plausibility

- There is no evidence of a fall in maternal plasma progesterone levels or P/E ratios before the onset of human labor, either term or preterm

The progesterone paradox

- Progesterone is still involved in labor and preterm labor, even though no differences in serum levels
  - “Functional” progesterone withdrawal
  - Paracrine-type function
  - Changes in the mediators of progesterone’s “message”
Progesterone: Anti-inflammatory mechanisms

- Progesterone withdrawal associated with inflammation-mediated preterm birth
- LPS given to mice resulted in decreased progesterone levels followed by PTD (Fidel et al., 1998)
- LPS-initiated fall in progesterone followed by increase in myometrial PGE2, which is implicated in PTD in mice (Zeng et al., 2002)

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da Fonseca et al

- RCT: 142 women at “high risk” for preterm delivery (at least one previous PTD, prophylactic cerclage or uterine malformation).
- 100mg progesterone vaginal suppository daily vs. placebo
- Initiation of treatment at 24 weeks

Preterm delivery:
- Progesterone: 13.8%
- Placebo: 28.5%
- OR 0.40 (0.17 – 0.94)


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da Fonseca et al

- Study Issues
  - Inclusion of women with CI and uterine malformations
  - Did not report any outcome other than PTD
Vaginal progesterone and PTD

  - 659 women with prior sPTB randomized

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Meis et al

- RCT: 463 women with a history of a spontaneous PTD
- 17-P 250mg IM weekly vs. placebo
- Initiation of treatment 16-20 weeks

<table>
<thead>
<tr>
<th></th>
<th>17-P</th>
<th>Placebo</th>
<th>OR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB &lt; 37 w</td>
<td>36%</td>
<td>55%</td>
<td>0.66 (0.54 – 0.81)</td>
<td>~6</td>
</tr>
<tr>
<td>PTB &lt; 32 w</td>
<td>11%</td>
<td>20%</td>
<td>0.58 (0.37 – 0.91)</td>
<td>~12</td>
</tr>
</tbody>
</table>

Meis et al, NEJM 2003

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Meis et al: Neonatal outcomes

<table>
<thead>
<tr>
<th></th>
<th>17-P</th>
<th>Placebo</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing</td>
<td>0%</td>
<td>2.6%</td>
<td>P = 0.81</td>
</tr>
<tr>
<td>enmetocolitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any IVH</td>
<td>1.3%</td>
<td>5.2%</td>
<td>0.25 (0.08 – 0.82)</td>
</tr>
<tr>
<td>Supplemental O₂</td>
<td>15%</td>
<td>24%</td>
<td>0.63 (0.46 – 0.92)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>1.6%</td>
<td>3.3%</td>
<td>0.50 (0.15 – 1.70)</td>
</tr>
<tr>
<td>BPD</td>
<td>1.3%</td>
<td>3.3%</td>
<td>0.40 (0.11 – 1.46)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>2.6%</td>
<td>5.9%</td>
<td>0.44 (0.17 – 1.13)</td>
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ACOG Committee Opinion #291: Use of progesterone to prevent preterm birth

- Recommended progesterone use for women with a prior spontaneous PTD

Total Live Births 4,021,726

Multiparous & Singleton: 2,313,718

PNC started ≤ 20 w: 2,037,292

Previous sPTB: 132,933

Estimated 33% reduction in PTD

A decrease in US PTD rate from 12.1% to 11.8%

Can we extend the benefits of progesterone to other high-risk populations?

Petrini et al, Obstet Gynecol 2005
Predicted probability of delivery before week 32, by cervical length (mm) and time of measurement (week of pregnancy)

Short cervix and progesterone: Epidemiologic rationale

  - Two factors most associated with PTD:
    - Prior PTD PAR = 18.9% (AA), 14.7% (W)
    - Short Cervix PAR = 16.3% (AA), 14.6% (W)
Progesterone and short cervix

- Fonseca et al, NEJM 2007
  - RCT: 250 women with cervical length ≤ 15mm
  - Progesterone 200 mg PV daily vs. placebo
  - Initiation of treatment at 24 weeks

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<tr>
<td>PTD &lt; 34 weeks</td>
<td>21%</td>
<td>36%</td>
</tr>
<tr>
<td>Composite morbidity</td>
<td>8%</td>
<td>14%</td>
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**Issues:**
- Very heterogeneous study group
- Includes women with prior PTD, multiple gestations
- Very short cervix (1.7% of the population, less in lower risk women)
- Use of vaginal progesterone

**Accompanying editorial:** Not yet indicated to use progesterone for women with a short cervix
Progesterone and short cervix

- DeFranco et al, Ultrasound Obstet Gynecol 2007
  - Planned randomized trial of women with short cervix ≤ 25 mm and no history of PTB (in parallel with O'Brien trial of 2007)
  - Secondary analysis that included women with short cervix and prior preterm delivery
    - 25 mm did not provide enough patients for analysis
    - Initially defined as that in the lowest quartile (32 mm)
    - Survival curves no different based on study medication (P < 0.05)
    - Assessed cutoffs of 30 and 28 mm as well
    - No significant difference in survival curves at either of these cutoffs
    - Further evaluated dichotomous outcomes at 28 mm

Progesterone and short cervix

- 46 women with ≤ 28 mm cervical length
  - 19 progesterone
  - 27 placebo

"...these conclusions must be considered tentative...and...hypothesis...and...further investigation is necessary. Specifically randomized clinical trials designed to test the effect of progesterone in women with short cervix..."

Progesterone and a short cervix: Hassan et al, 2011

- 19 to 23 6/67 weeks
- Singleton
- Cervix 10-20 mm
- Nullips and multips (with prior term and preterm birth)
- Outcome: PTB < 33 weeks
- N = 465
60 women were enrolled in violation of protocol
- 55 of these were with respect to EGA at enrollment
  - Significantly more women who were enrolled early randomized to placebo
  - Significantly more women who were enrolled late randomized to progesterone

What are we left with?
- Good evidence that progesterone reduces frequency of recurrent preterm birth
  - Several properly powered + 17OHP trials
  - Brazilian vaginal progesterone trial +/ US based vaginal progesterone trial
  - Progesterone for this indication will make little dent in the burden of preterm birth
What are we left with?

- A short cervix is associated with preterm birth
- Definition of short varies with gestational age
- Two studies of vaginal progesterone for reduction of PTB in women with a short cervix
  - Anyone with cervix < 15 mm (1%)
  - Singleton with cervix 10-20 mm (2%)
  - Issues with protocol violations
  - Ideal formulation, cervical length, GA at initiation, and certainty of benefit remain uncertain