Progesterone for the Prevention of Prematurity

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Disclosure

Neither I nor my partner/spouse have any financial relationships with relevant commercial interests.

Objectives

At the end of this session participants will be able to:

- Implement into practice the most recent data from published studies which support the use of progesterone to prevent preterm delivery
- Identify pregnant patients who may benefit from receiving antepartum progesterone for the prevention of preterm delivery
- Implement a screening for cervical length, as a risk factor, used to decide whether to treat with progesterone.
Progesterone as an option for the prevention of prematurity

Critical in the activation of Estrogen to continue the cascade leading to labor is the reduction in the inhibitory effects of progesterone.

Unlike estrogen, the only apparent reason for the massive production of progesterone by the placenta is to inhibit the rapidly expanding uterus from going into labor prematurely.

Removal of progesterone in animals leads to the onset of labor.

Physiological Effects of Progesterone which allows labor inhibition

- Inhibits oxytocin activation of myometrium
- Directly inhibits prostaglandin production
- Decreases myometrial excitation
- Inhibition of gap junction formation
“Progestins” = “Progestogens”

Natural
- Progesterone (Pregn-4-ene-3,20-dione, P4)
- 17α-hydroxyprogesterone (17P)
- Pregnenolone
- 17α-hydroxypregnenolone

Synthetic
- 17α-hydroxyprogesterone caproate (17Pc)
- Medroxyprogesterone acetate (MPA)
- Norgestrel
- Levonorgestrel
- Norgestimate
- Many others

Prevention of Preterm Birth with Progestins, Meta-Analysis

Prevention of Preterm Birth with 17Pc, Meta-Analysis
Prevention of Preterm Birth with 17Pc, Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>17Pc Dose</th>
<th>Frequency</th>
<th>Rx Start</th>
<th>Rx Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson</td>
<td>250 mg</td>
<td>Weekly</td>
<td>At booking</td>
<td>37w</td>
</tr>
<tr>
<td>Papiernik</td>
<td>250 mg</td>
<td>Q 3 days</td>
<td>28-32w</td>
<td>8 doses</td>
</tr>
<tr>
<td>Hartikainen</td>
<td>250 mg</td>
<td>Weekly</td>
<td>28-33w</td>
<td>37w</td>
</tr>
<tr>
<td>Levine</td>
<td>500 mg</td>
<td>Weekly</td>
<td>&lt; 10w</td>
<td>36w</td>
</tr>
</tbody>
</table>

Progestins for History of PTB
Recent Trials, PTB < 32 or <34 wks

Strategies to Prevent PTB
Twins & Triplets

Progestins for Twins & Triplets
RCTs, Outcome = PTB <32 or <34 wks

Twins: 7 Trials (Lim 2011 not shown), Total N = 2830
Triplets: 2 Trials, Total N = 215

Short Cervix – What to Do?
Cerclage for Short Cervix
Metaanalysis of 4 Randomized Trials

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>PTB &lt; 35w Cerclage</th>
<th>PTB &lt;35w No Cerclage</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton, Short Cvx, No Other Risk Factor</td>
<td>235</td>
<td>26%</td>
<td>33%</td>
<td>0.76</td>
</tr>
<tr>
<td>Singleton, Short Cvx, Prior PTB</td>
<td>208</td>
<td>23%</td>
<td>39%</td>
<td>0.61*</td>
</tr>
<tr>
<td>Twins, Short Cvx</td>
<td>49</td>
<td>75%</td>
<td>36%</td>
<td>2.15*</td>
</tr>
</tbody>
</table>

* P < 0.05

Berghella et al, Obstet Gynecol 106:181-9, 2005

Cerclage for Short Cervix, Prior PTB

17P for Short Cervix, Prior PTB
Subgroup analysis of Owen Trial


Cerclage Group: N = 47 with 17Pc, 101 without
No Cerclage: N = 52 with 17Pc, 100 without

Cerclage vs 17Pc for Short Cervix, RCT


N = 81 with TVCL < 25 mm at 16 – 24 wks
53% had prior PTB 16-36 wks
Randomized to 17Pc 250 mg/wk or McDonald cerclage

Short Cervix: One Solution

Fetal Medicine Foundation
Short Cervix: RCT of Pessary

FMF Trial, started 2008 (Current Controlled Trials)
- Plan for 1600 singletons with cervix < 25 mm
- Plan for 1180 twin pregnancies

N = 192 Pessary
N = 193 Expectant
Prior PTB = 11% of both groups

Goya et al, Lancet ePub: 3 Apr 2012

Strategies to Prevent PTB

17Pc Vag P4 Cerclage
Singleton, Prior PTB
Keirse meta Yes
No

Singleton, Short Cervix, Prior PTB
Berghella meta

Singleton, Short Cervix, No Prior PTB

Twins, Short Cervix
Berghella meta

Single, Short Cervix, Prior PTB
Keirse meta

Single, Short Cervix, No Prior PTB

Twins, Short Cervix

Blue = Benefit (✔ = P < 0.05), Light blue = Favorable trend, underpowered
Brown= No effect (✗ = well-powered), Red = Harm (☠ = P< 0.05)
17P for Short Cervix, Prior PTB
Subgroup analysis of Owen Trial

Strategies to Prevent PTB

Effect of Vaginal Progesterone on Pregnancy Outcome in Singletons with an Ultrasonically Short Cervix (5 RCT's)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progesterone</th>
<th>Placebo</th>
<th>Pooled RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB &lt; 33 wks</td>
<td>41/365 (.12)</td>
<td>72/358 (.21)</td>
<td>0.56 (.40–.80)</td>
</tr>
<tr>
<td>PTB &lt; 37 wks</td>
<td>127/365 (.35)</td>
<td>141/358 (.40)</td>
<td>0.91 (.75–1.10)</td>
</tr>
<tr>
<td>PTB &lt; 35 wks</td>
<td>67/365</td>
<td>100/358</td>
<td>0.67 (.51–.87)</td>
</tr>
<tr>
<td>PTB &lt; 28 wks</td>
<td>20/365</td>
<td>39/358</td>
<td>0.51 (.31–.85)</td>
</tr>
<tr>
<td>RDS</td>
<td>17/365</td>
<td>37/358</td>
<td>0.47 (.27–.81)</td>
</tr>
</tbody>
</table>

Also significant reductions in composite morbidity, mechanical ventilation, NICU admissions, and higher birthweights with progesterone.
Romero et al IPD Metanalysis
Progesterone for Women with Short Cervix

- Reduction in rates of spontaneous premature delivery at all gestational ages from < 28 to < 37 weeks.
- Impact greatest in preventing PTD at the very earliest gestational ages.
- Impact in women with Cervical lengths < 10-25 mm, but only in subgroups 10-20mm.
- Reduction seen in women with and without a history of previous preterm delivery.
- No significant reduction in twins (underpowered/positive trend).

Universal Cervical Length Screening?
Cost-Benefit Analysis

Assumptions (based on Fonseca data)
Singleton
- Prior PTB cases (7.3%) would get 17Pc if no TVCL
- One TVCL screen during anatomy scan, cost $52
- TVCL < 15 mm in 1.2% of population
- Vaginal P4 will reduce PTB<34 wks from 30% - 18%.

Results (per 100,000 women screened)
- $125 Million saved
- 200 quality-adjusted life-years gained
- 141 cases of serious neonatal morbidity prevented
- Universal screening better than screening targeted at women with prior PTB.

Universal Cervical Length Screening?
Cost-Benefit Analysis

Assumptions (based on Fonseca data)
Singleton
- No prior PTB
- Single TVCL screen at 18-24 wks, cost $187
- TVCL < 15 mm in 1.7% of population
- Vaginal P4 will reduce PTB<34 wks from 32% to 17%

Results (per 100,000 women screened)
- $12.1 Million saved
- 434 quality-adjusted life-years gained
- 22 neonatal deaths or neuro deficit prevented
- Robust across wide range of costs & assumptions.
### Progestins after Arrest of PTL

<table>
<thead>
<tr>
<th>Study</th>
<th>Total N</th>
<th>Progestin</th>
<th>Control (Latency)</th>
<th>Latency (Progestin)</th>
<th>Δ Latency</th>
<th>New Malay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facchinetti, 2007</td>
<td>60</td>
<td>17Pc</td>
<td>17Pc</td>
<td>17Pc</td>
<td>17Pc</td>
<td>...</td>
</tr>
<tr>
<td>Borna, 2009</td>
<td>70</td>
<td>Vag P4</td>
<td>No Rx</td>
<td>36 d</td>
<td>12 d</td>
<td>+</td>
</tr>
<tr>
<td>Sharami, 2010</td>
<td>173</td>
<td>Vag P4</td>
<td>Placebo</td>
<td>24 d</td>
<td>17 d</td>
<td>NS</td>
</tr>
<tr>
<td>Bomba-Opon, 2011</td>
<td>196</td>
<td>Vag P4</td>
<td>No Rx</td>
<td>53 d</td>
<td>44 d</td>
<td>NS</td>
</tr>
</tbody>
</table>

* P < 0.05

**Facchinetti, AJOG 194:453.e1-4, 2007**
**Borna, ANZJOG 48: 58-63, 2008**
**Sharami, Int J Fertil Steril 4:45-50, 2010**
**Bomba-Opon, J Matern-Fetal Neonatal Med e-pub 2011**

### Strategies to Prevent PTB

<table>
<thead>
<tr>
<th>Strategy</th>
<th>17Pc</th>
<th>P4</th>
<th>Cerclage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton, Prior PTB</td>
<td>✔</td>
<td>✔</td>
<td>Keirse meta</td>
</tr>
<tr>
<td>Single, Short Cmx, Prior PTB</td>
<td>✔</td>
<td>✔</td>
<td>Bernharinda meta</td>
</tr>
<tr>
<td>Single, Short Cmx, No Prior PTB</td>
<td>✔</td>
<td>✔</td>
<td>Bernharinda meta</td>
</tr>
<tr>
<td>Twins</td>
<td>✔</td>
<td>✔</td>
<td>Berghella meta</td>
</tr>
<tr>
<td>Twins, Short Cmx</td>
<td>✔</td>
<td>✔</td>
<td>Berghella meta</td>
</tr>
<tr>
<td>Twins, Short Cmx, No Prior PTB</td>
<td>✔</td>
<td>✔</td>
<td>Berghella meta</td>
</tr>
</tbody>
</table>

**Keirse meta**
**Berghella meta**

### Safety Issues

- Blue = Benefit (✔ = P < 0.05), Light blue = Favorable trend, underpowered
- Brown = No effect (✗ = well-powered), Red = Harm (☠ = P < 0.05)
Perinatal Losses with Progestins
(Miscarriages < 20 wks, stillbirths, neonatal deaths)

11 placebo-controlled trials, Total N = 6166 offspring.
3.5% Losses with Progestin
3.1% Losses with Placebo

Followup, Mean Age 48 months
From Meis 2003 Trial, history of prior PTB

Scores below Cut-off on Ages & Stages Questionnaire

<table>
<thead>
<tr>
<th></th>
<th>17Pc (n=193)</th>
<th>Placebo (n=82)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication</td>
<td>11%</td>
<td>11%</td>
<td>NS</td>
</tr>
<tr>
<td>Gross motor</td>
<td>3%</td>
<td>4%</td>
<td>NS</td>
</tr>
<tr>
<td>Fine motor</td>
<td>21%</td>
<td>18%</td>
<td>NS</td>
</tr>
<tr>
<td>Problem-solving</td>
<td>10%</td>
<td>11%</td>
<td>NS</td>
</tr>
<tr>
<td>Diagnoses from Health Prof®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor skills problem</td>
<td>1%</td>
<td>1%</td>
<td>NS</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>7%</td>
<td>8%</td>
<td>NS</td>
</tr>
<tr>
<td>Attention or learning problem</td>
<td>8%</td>
<td>10%</td>
<td>NS</td>
</tr>
</tbody>
</table>


Followup to 18 months
From Rode 2011 Trial, Twins

Ages & Stages Questionnaire

<table>
<thead>
<tr>
<th></th>
<th>P4</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASQ Mean Score at 6 months</td>
<td>215 ± 38</td>
<td>218 ± 37</td>
<td>NS</td>
</tr>
<tr>
<td>ASQ Mean Score at 18 months</td>
<td>193 ± 43</td>
<td>194 ± 41</td>
<td>NS</td>
</tr>
<tr>
<td>Score &lt; 115 at 18 months</td>
<td>3.8%</td>
<td>3.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>