UPDATE ON PROGESTERONE AND PREVENTION OF PRETERM BIRTH
Scope of the problem - US

- Preterm Birth – delivery <37 weeks EGA

% of Live Births

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>11.0%</td>
</tr>
<tr>
<td>2000</td>
<td>11.6%</td>
</tr>
<tr>
<td>2002</td>
<td>12.1%</td>
</tr>
<tr>
<td>2004</td>
<td>12.5%</td>
</tr>
<tr>
<td>2005</td>
<td>12.7%</td>
</tr>
<tr>
<td>2006</td>
<td>12.8%</td>
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</tbody>
</table>

Scope of the Problem - NC

Scope of the Problem - NC

Preterm Birth Rates
2003-2006 Average
Percent of live births (100 Counties)

- Over 14.8 (33)
- 13.1-14.8 (34)
- Under 13.1 (33)

Value ranges are based on an approximately equal number of counties in each range.

Implications of PTB

- Leading cause
  - neonatal morbidity and mortality
  - long term morbidity
    - cerebral palsy
    - developmental delay
Risk factors for preterm birth

- Prior PTB ***
- Multiple gestation
- Short cervical length
- Low maternal BMI
- African American
- Maternal age
- Smoking
Interventions to prevent PTB

- Prenatal care
  - Social support
- Lifestyle changes
  - Smoking cessation
  - Improved nutrition
- Cerclage
- Infections
- Home uterine activity monitoring
- Tocolytic medications

Trials of acute care of PTL show little benefit in prevention of PTB
Progesterone for prevention of PTB

- Small trials in 1970’s and 80’s
- Suggested
  - Reduction in preterm birth
- Variable dosing
  - IM
  - Vaginal
- Variable populations
Early progesterone trials

- 5 trials in high risk women with 17P vs. placebo
- Overall risks of:
  - preterm birth
    - OR 0.50, 95% CI: 0.30-0.85
  - low birth weight
    - OR 0.46, 95% CI: 0.27-0.80
- No difference in morbidity/mortality

Keirse MJNC. Brit J Obstet Gynecol 1990;97:149
Why may progesterone work?

- Functional prog withdrawal stimulates labor
  - Increase PR-A/PR-B expression
  - Decrease progesterone receptors
- Progesterone as anti-inflammatory
- Reduce myometrial gap junctions
  - Decrease conduction of contractions
- Reduces threshold for contractions
NICHD/MFMU
17 α-Hydroxyprogesterone Caproate

Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate

Paul J. Meis, M.D., Mark Klebanoff, M.D., Elizabeth Thom, Ph.D., Mitchell P. Dombrowski, M.D., Baha Sibai, M.D.,
Atef H. Moawad, M.D., Catherine Y. Spong, M.D., John C. Hauth, M.D., Menachem Miodovnik, M.D.,
Michael W. Varner, M.D., Kenneth J. Leveno, M.D., Steve N. Caritis, M.D., Jay D. Iams, M.D., Ronald J. Wapner, M.D.,
Deborah Conway, M.D., Mary J. O’Sullivan, M.D., Marshall Carpenter, M.D., Brian Mercer, M.D.,
Susan M. Ramin, M.D., John M. Thorp, M.D., and Alan M. Peaceman, M.D.,
for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network

New England Journal of Medicine, 2003; 348 (24)
17P – NICHD (Meis, 2003, NEJM)

N=463
Prior preterm birth
20 – 36 6/7 wks
SPTB, PPROM

N = 310
17 P

N= 153
Placebo

250mg IM weekly
16-20wks – 36wks

Primary outcome:
PTB < 37 weeks EGA
17-P NICHD trial (Meis, 2003, NEJM)

- **Study population**

<table>
<thead>
<tr>
<th></th>
<th>17 P</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA prior PTB</td>
<td>30.6 wk</td>
<td>31.3 wk</td>
</tr>
<tr>
<td># prior PTB</td>
<td>1.4</td>
<td>1.6 *</td>
</tr>
<tr>
<td>Married</td>
<td>51.3%</td>
<td>46.4%</td>
</tr>
<tr>
<td>BMI</td>
<td>26.9</td>
<td>26.0</td>
</tr>
<tr>
<td>&gt; 1 prior PTB</td>
<td>27.7%</td>
<td>41.2%</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>59.0%</td>
<td>58.8%</td>
</tr>
<tr>
<td>GA at randomization</td>
<td>18.4 wk</td>
<td>18.4 wk</td>
</tr>
</tbody>
</table>

* p<0.007
17P – NICHD (Meis, 2003, NEJM)

PTB rates

- **17P**: 11.4%, 19.6%, 54.9%
- **Placebo**: 20.6%, 30.7%, 36.3%

*p < 0.01*
17P – NICHD (Meis, 2003, NEJM)

PTB rates

- African American
  - 17P: 52.2%
  - Placebo: 35.4%

- Non-African American
  - 17P: 37.6%
  - Placebo: 58.7%

\( p < 0.05 \)
17P – NICHD (Meis, 2003, NEJM)

Neonatal morbidity

- Birthweight < 2500gram: 41.1% *
- Birthweight < 1500gram: 27.2%
- Neonatal death: 13.9%
- IVH: 5.2% *
- Supplemental O2: 14.9%

* p < 0.05
17P – NICHD (Meis, 2003, NEJM)

- **Summary**

- **Weekly 17P**
  - 34% reduction in PTB < 37 weeks
  - 33% reduction in PTB < 35 weeks
  - 42% reduction in PTB < 32 weeks

- **Number need to treat**
  - 5-6 (95% CI 3.6, 11) for prevention of 1 PTB < 37
  - 12 (95% CI 6.3, 74.6) for PTB < 32
17 – P: Safety

- Rebarber, 2007, Diabetes Care
  - 17-P associated with 3 x increased risk of GDM (95% CI 2.1, 4.1)
  - 12.9% vs. 4.9%

- 4 year outcome of exposed children
  - No congenital anomalies
  - Normal neurological development

17 –P side effects

- Meis, 2003 NEJM – injection site s/s

<table>
<thead>
<tr>
<th>Symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soreness</td>
<td>34.2</td>
</tr>
<tr>
<td>Swelling</td>
<td>14.1</td>
</tr>
<tr>
<td>Itching</td>
<td>11.3</td>
</tr>
<tr>
<td>Bruising</td>
<td>6.7</td>
</tr>
</tbody>
</table>
Cost effective

  - Modeled 17P costs vs. costs of PTB
- 17P cost effective
  - Prevention of PTB
    - Prior preterm birth <32 weeks
    - Prior preterm birth 32-37 weeks
17 P costs/savings

- Modeled costs of 17 P and PTB
- Use of 17 P with prior SPTB
  - Savings
    - $3800 per woman treated
    - $15,900 per infant treated
  - Total - $2 billion annual savings

Bailit JL, Votruba ME. Am J Obstet Gynecol
Use of 17 P among MFM physicians

- Ness, 2006 AJOG, survey

% use of 17 P

- 2003: 38%
- 2005: 67%
17 – P twins and triplets

- High risk populations
- NICHD trials of 17P vs. placebo
- Twins – no difference in PTB
  - No difference in morbidity
- Triplets – no difference in PTB

Rouse, NEJM, 2007
Caritis, Obstet Gynecol 2009
Other progesterone trials

- O’Brien, Ultrasound Ob/Gyn, 2007
  - Vaginal progesterone gel, similar population
  - 90 mg progesterone (Crinone®)
  - No difference in PTB < 32 weeks

  - 100mg micronized vaginal progesterone
  - Reduction in PTB <34 weeks in progesterone group (2.7% vs. 18.6%)
Other progesterone trials

- Fonseca, NEJM, 2007
  - Cervical length at 22 weeks <15mm
  - 200mg micronized vaginal progesterone
  - 44% reduction in PTB <34 weeks in progesterone group (19% vs. 34.4%)
ACOG/SMFM Recommendations

- How to give it
  - 17 alpha OHP – 250 mg IM weekly
    - Start 16-20 weeks EGA
    - Continue to completed 36th week
    - Ok to use in diabetes
ACOG/SMFM Recommendations

- Not recommended
  - Tocolytic
  - Supplement to cerclage
  - + FFN in asymptomatic patient
  - Therapeutic agent after tocolysis
  - Multiple gestations
Questions or to discuss if a patient is a 17 P candidate:
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