Progesterone for the Prevention of Preterm Birth

Amy Murtha, MD
Associate Professor
Vice Chair for Research
Department of Ob/Gyn

Duke Medicine
Objectives

• Scope of the problem
• Role of progesterone in pregnancy
• Progesterone for preterm birth prevention in different populations
• Controversies in the US
Trends in Preterm Birth in the US

- Preterm (< 37 weeks)
- Late preterm (34 - 36 weeks)
- Early preterm (< 34 weeks)

Adapted from Source: CDC/NCHS, National Vital Statistics System.
Preterm Birth

PPROM 25%

Preterm labor 45%

World View: Land Area
World View: Low Birth Weight Related Deaths (<2500gms)

BUT.. Equal Preterm Birth RATES between 12.9 million preterm births in Africa & Asia in Africa & Africa
Ranking by Infant Mortality: US ranks 48th

Morbidity and Mortality of Preterm Birth as a Function of Gestational Age

Health and survival outcomes (%)

Survival
RDS
Sepsis
IVH
NEC

Gestational age at birth (wks)

0 20 40 60 80 100

24 26 28 30 32 34 36

Figure adapted with permission from Mercer BM. Obstet Gynecol. 2003;101(1):178-193.
Risk factors for preterm birth

**Medical risk factors:**
- PROM
- Infections (UTI, BV, STD)
- High blood pressure
- Diabetes
- Clotting disorders (thrombophilia)
- Maternal weight (underweight or obesity)
- Short time period between pregnancies
- Certain birth defects
- Vaginal bleeding

**Lifestyle risk factors:**
- Late or no prenatal care
- Smoking
- Drinking alcohol
- Using illegal drugs
- Domestic violence
- Lack of social support
- High levels of stress
- Long working hours
- Low income

- **Previous preterm birth**
- Multiple gestation
- Uterine/cervical anomalies

- **Decreased cervical length**
- African American race
- Age (<17, >35)
Risk Factor

PRIOR PRETERM BIRTH
## Risk of recurrent preterm birth

<table>
<thead>
<tr>
<th>First birth</th>
<th>Second birth</th>
<th>Subsequent preterm birth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not preterm</td>
<td></td>
<td>4.4</td>
</tr>
<tr>
<td>Preterm</td>
<td></td>
<td>17.2</td>
</tr>
<tr>
<td>Not preterm</td>
<td>Not preterm</td>
<td>2.6</td>
</tr>
<tr>
<td>Preterm</td>
<td>Not preterm</td>
<td>5.7</td>
</tr>
<tr>
<td>Not preterm</td>
<td>Preterm</td>
<td>11.1</td>
</tr>
<tr>
<td>Preterm</td>
<td>Preterm</td>
<td>28.4</td>
</tr>
</tbody>
</table>

PROGESTERONE
Progesterone

• Small hydrophobic steroid hormone
• Produced by ovaries (corpus luteum), adrenals, placenta
• Diffuses freely through the plasma membrane of all cells
• In target cells
  • Binds to progesterone receptor
  • Moves to nucleus
  • Binds to a progesterone response element
  • Transcription factor → mRNA → protein
How does progesterone work to prevent preterm birth?

1. Maintenance of uterine quiescence
2. Anti-inflammatory/immunosuppression
3. Cervical stroma
4. Autocrine/paracrine
Labor and Progesterone’s Role

• Change in contractility from uncoordinated contractures to coordinated contractions
  – Results in increase intrauterine pressure

• Labor requires formation of Gap junctions and expression of gap junction protein connexin 43

• Progesterone prevents formation of gap junctions and expression of connexin 43
ANTI-INFLAMMATORY & IMMUNOSUPPRESSION
Inflammation & Preterm Birth

Myometrium
Fetal membranes

Proinflammatory cytokines
(IL1β, IL6, IL8, TNFα)

Prostaglandins & MMPs

Contractions

Apoptosis

PPROM & PTL
Progesterone and Inflammation

• Progesterone, 17P, & MPA reduce TNF-α induced caspase-3 activity (Luo et al, Reprod Sciences, April 2010)

• Progesterone inhibits NFkβ induced activation of COX2 induced uterine contractility (Condon, Proc Natl Acad Sci USA, 2003)

• Progesterone protects chorion cells from oxidative stress induced apoptotic cell death (Murtha, SMFM 2012)
Progesterone Reduces TNF Induced MMP9 Activity

Normalized density of MMP9

Choi, SJ; Annual Meeting for SMFM 2012
ROLE IN CERVICAL REMODELING
Cervical Changes Preceding Labor

• Extracellular matrix

• Cervical ripening is result of
  – decreased collagen content
  – increased collagen solubility
  – increased collagenolytic activity
Cervical Changes Preceding Labor

• Influx of inflammatory cells into the cervix
  – Cytokines/prostaglandins affect extracellular matrix metabolism

• PTB often preceded by cervical ripening over weeks
Progesterone’s action on the cervix

- Reduction in mediators of inflammation and tissue destruction
  - IL-1, IL-8, iNOS, COX-2

- Block of 17-β-estradiol induced collagen degradation
Progesterone for preterm birth prevention

- Singleton with prior PTB
- Multiples gestation
- Cervical length
  - Vaginal progesterone
  - 17P
## Singleton with history of PTB

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Primary Outcome</th>
<th>Intervention</th>
<th>Delay in delivery</th>
<th>Improve infant outcome</th>
<th>Smile index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meis</td>
<td>463</td>
<td>PTB &lt;37 wk</td>
<td>17 OHP [16-20 until 36 wk]</td>
<td>Yes</td>
<td>Yes</td>
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<td><img src="image" alt="Smile" /></td>
</tr>
<tr>
<td>Fonseca</td>
<td>157</td>
<td>PTB &lt;37 wk</td>
<td>Vaginal progesterone [24 until 34 wk]</td>
<td>Yes</td>
<td>?</td>
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<td>Yes</td>
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<td>😊</td>
</tr>
<tr>
<td>O’Brien</td>
<td>659</td>
<td>PTB &lt;32 wk</td>
<td>Vaginal progesterone [18-37 wk]</td>
<td>No</td>
<td>No</td>
<td>😞</td>
</tr>
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</table>
Effectiveness of Progesterone in women with prior PTB

- 5-6 women with a previous sPTB would need to be treated to prevent one birth <37 weeks

- 12 women with a previous sPTB birth would need to be treated to prevent one birth <32 weeks

SHORTENED CERVIX
Shortened cervix

Mechanism of Effacement:

- **Canal Length**: Increase
- **Funnel Width**: Decrease
- **Functional Cervical length**: Increase

Relative Risk of SPTD < 35 wks by % of cervical length at 24 wks

<table>
<thead>
<tr>
<th>Length of cervix (cm)</th>
<th>No. of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.2</td>
<td>14</td>
</tr>
<tr>
<td>2.4</td>
<td>6</td>
</tr>
<tr>
<td>3.6</td>
<td>2</td>
</tr>
<tr>
<td>4.8</td>
<td>0</td>
</tr>
<tr>
<td>6.0</td>
<td>0</td>
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Percentile

1 5 10 25 50 75
# Short cervix

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<tbody>
<tr>
<td>Fonseca</td>
<td>250 with CL 15mm</td>
<td>PTB &lt;34 wk</td>
<td>Vaginal progesterone [24 until 33/6 wk]</td>
<td>Yes</td>
<td>+/-</td>
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Fonseca, NEJM, 2007
# Short cervix

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<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Hassan</td>
<td>458 with CL 10-20mm</td>
<td>PTB &lt; 33 wk</td>
<td>Vaginal progesterone [20-23 until 36/6 wk]</td>
<td>Yes</td>
<td>Yes</td>
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Fonseca, NEJM, 2007  
Hassan, Ultrasound Obstet Gynecol, 2011
Short Cervix Meta-analysis

• Meta-analysis of individual patient data from five placebo-controlled trials
• Progesterone supplementation for short cervix
  – 30 to 50 percent reduction in preterm birth <28, <33, and <35 weeks
• 40 percent reduction in neonatal morbidity and mortality
• Similar effects at 90, 100 and 200 mg daily and for women with and without a history of prior preterm birth

Romero et al, 2012
# Multiple gestation

<table>
<thead>
<tr>
<th>Author</th>
<th>Multiples</th>
<th>Primary Outcome (Drug vs placebo)</th>
<th>Results RR [95% CI]</th>
<th>Smile index</th>
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<tr>
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## Multiple gestation- TWINS

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<td>Briery</td>
<td>Twins N=30</td>
<td>PTB &lt; 35 wk</td>
<td>17-OHP [20-30 until 34 wk]</td>
<td>2.24 [0.8-6.3]</td>
<td>😞</td>
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<td>Rouse</td>
<td>Twins N=661</td>
<td>Delivery or death &lt; 35wk</td>
<td>17-OHP [16-20 until 34 wk]</td>
<td>1.1 [0.09-1.3]</td>
<td>😞</td>
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<td>1.1 [0.09-1.3]</td>
<td>😞</td>
</tr>
<tr>
<td>Norman</td>
<td>Twins N=500</td>
<td>PTB or death &lt;34 wk</td>
<td>Vaginal progesterone gel</td>
<td>1.27 [0.91-1.78]</td>
<td>😞</td>
</tr>
<tr>
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<td>Multiples</td>
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<td>Triplets N=134</td>
<td>Delivery or death &lt; 35wk</td>
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<td>1.0 [0.9-1.1]</td>
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</table>
## Multiple gestation- TRIPLETS

<table>
<thead>
<tr>
<th>Author</th>
<th>Multiples</th>
<th>Primary Outcome</th>
<th>Intervention (Drug vs placebo)</th>
<th>Results RR [95% CI]</th>
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<td>Triplets N=134</td>
<td>Delivery or death &lt; 35wk</td>
<td>17-OHP [16-20 until 35 wk]</td>
<td>1.0 [0.9-1.1]</td>
<td>😞</td>
</tr>
<tr>
<td>Combs</td>
<td>Triplets N=81</td>
<td>Composite neonatal morbidity</td>
<td>17-OHP [16-22 until 34 wk]</td>
<td>0.9 [0.65-1.27]</td>
<td>😞</td>
</tr>
</tbody>
</table>
• Formulations
• Timing of initiation & cessation
• Dose
• Frequency of use

ADMINISTRATION OF PROGESTERONE
Formulations

• Oral micronized
• Intramuscular
  – Compounded
  – Makena
• Vaginal
  – Crinone
  – Compounded

Either IM or vaginal depending on indication

Which one to use???
Dose

• *What dose of progesterone should I use?*
  – IM: 250 mg weekly of 17-hydroxyprogesterone caproate
  – Intravaginal: unclear
    • Compounded: 100-200 mg micronized progesterone
    • Crinone 8% gel (90mg)
Summary of recommendations

- Women with history of prior spontaneous PTB between 20/0 and 36/6 SHOULD BE OFFERED progesterone therapy

- Women with short (≤25mm) cervix SHOULD BE OFFERED vaginal progesterone

- There are NO DATA to support use of progesterone in women multiple gestation or preterm labor
Prior spontaneous PTD
- Only one risk factor
- Small % of all PTD

Major initiatives into:
- Understanding the cause(s)
- Methods of prevention and treatment in pregnant women
- Optimal management/treatment of neonates
CONTROVERSIES IN THE US
Progesterone and the US FDA- 17-P

• 17-P was initially denied FDA approval
  – Insufficient evidence that it reduces preterm birth <37 weeks
  – Concern over pregnancy loss <20 weeks

• In 2011 FDA gives provisional approval for 17-P to be marketed as Makena
  – Company must complete new randomized trial to answer
    • Safety concerns
    • Efficacy at <37 weeks
Progesterone and the US FDA- 17-P

- TherRx begins marketing Makena at inflated cost
- FDA decides to let compounding pharmacies continue to make 17-P at a reduced cost
  - First time FDA has approved a drug and allowed compounding pharmacies to continue
- Controversy continues over quality and potency of compounded 17-P
Progesterone and the US FDA- Crinone

• Crinone gel is micronized progesterone used in the Hassan trial

• Marketed by Columbia Laboratories and now moved to Watson Pharmaceuticals

• Columbia applied for FDA approval of Crinone 8% gel for the prevention of preterm birth in setting of short cervix
Progesterone and the US FDA- Crinone

- 2012 FDA Special Advisory committee recommended that FDA not approve Crinone
- Hassan trial did not meet the targeted P value of .01
- Sub-analysis suggested that Crinone was not effective in US population (P=0.2)
- Main Problem- in US without FDA approval most insurance carriers will not pay for vaginal progesterone
AMERICAN COLLEGE OF OBSTETRICS AND GYNECOLOGY (ACOG)
American College of Obstetrics and Gynecology (ACOG)

- ACOG recommends screening by trans-abdominal ultrasound

- A short cervix (<25 mm long) during pregnancy may help predict the risk of having a spontaneous preterm birth
American College of Obstetrics and Gynecology (ACOG)

- Transvaginal ultrasound screening for cervical length should reserved for pregnant women with a prior preterm birth carrying a single fetus
- Pregnant women with a prior preterm birth should be offered progesterone (17-P) starting at 16 weeks
- Vaginal progesterone in setting of incidental short cervix
- No effective treatments to prevent preterm birth for women with a short cervix who are carrying multiple fetuses

The following College documents were withdrawn in May 2012:

ACOG Committee Opinion No. 483: Primary and Preventive Care: Periodic Assessments (Obstet Gynecol 2011;117:1008–15) has been withdrawn. The recommendations have been transitioned to a new online format available at http://www.acog.org/About_ACOG/ACOG_Departments/Annual_Womens_Health_Care/Assessments_and_Qualifications.

SUMMARY AND RECOMMENDATIONS

• For women with a prior spontaneous preterm birth, intramuscular injections of 17-P (250 mg) rather than vaginal progesterone

• For women with midtrimester cervical shortening (defined as ≤20 mm before 24 weeks) and no prior spontaneous preterm birth vaginal progesterone treatment
  – Options include a vaginal suppository (100 or 200 mg), gel (90 mg), or tablet (100 mg micronized progesterone)