Prenatal Progesterone for Preventing Preterm Birth

This activity is jointly-provided by SynAptiv and the Colorado Hospital Association

Safe Deliveries Project Partnership

- Colorado Hospital Association
- Anthem Blue Cross and Blue Shield Foundation
- March of Dimes Colorado/Wyoming Chapter
- Colorado Perinatal Care Quality Collaborative
Thomas J. Garite, M.D.

- I have no conflicts of interest to disclose.

Impact of Prematurity

- 300,000 premature births/year
- Accounts for 60-70% of perinatal mortality
- Accounts for about 2/3 of cerebral palsy
- Accounts for 50% of total $$ spent on all of obstetric and newborn care in the U.S.
- Probably now most common reason for antepartum hospitalization
- No impact since records have been kept, rate is actually rising in the past 5-10 years

What does not work to prevent prematurity in at risk patients

**Singletons**
- Bed rest
- Prophylactic tocolytics
- Home uterine activity monitoring
- Baby ASA
- Antibiotics
- Risk Scoring and intensive antenatal surveillance

**Twins**
- Bed rest
- Cervical cerclage (routine)
- Multifetal reduction
Progesterone as an option for the prevention of prematurity

Endocrine Control of Parturition

- Progesterone Maintains Pregnancy
- Estrogens Promotes Parturition

PARTURITION

- Uterine contractions
- Cervical ripening
- Rupture of membranes

Progesterone Levels in Pregnancy
Progesterone

- 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

Physiologic Effects of Progesterone which allows labor inhibition

- Inhibits oxytocin activation of myometrium
- Directly inhibits prostaglandin production
- Decreases myometrial excitation
- Inhibition of gap junction formation

Prevention of Miscarriage with Progestins Meta-Analysis

Plot from data in:
Prevention of Preterm Birth with 17Pc, Meta-Analysis

<table>
<thead>
<tr>
<th>Year</th>
<th>Risk Factor</th>
<th>17Pc Dose</th>
<th>Frequency</th>
<th>Rx Start</th>
<th>Rx Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>2 or more PTBs and/or S/S</td>
<td>250 mg</td>
<td>Weekly</td>
<td>At booking</td>
<td>37w</td>
</tr>
<tr>
<td>1990</td>
<td>High PTB risk score</td>
<td>250 mg</td>
<td>Q 1 days</td>
<td>28-32w</td>
<td>8 doses</td>
</tr>
<tr>
<td>1991</td>
<td>Twins</td>
<td>250 mg</td>
<td>Weekly</td>
<td>28-33w</td>
<td>37w</td>
</tr>
<tr>
<td>1993</td>
<td>2 or more PTBs and/or S/S</td>
<td>250 mg</td>
<td>Weekly</td>
<td>At booking</td>
<td>37w</td>
</tr>
<tr>
<td>1994</td>
<td>3 or more S/A/S</td>
<td>500 mg</td>
<td>Weekly</td>
<td>&lt; 36w</td>
<td>36w</td>
</tr>
</tbody>
</table>

5 studies, Total N = 338
Summary OR = 0.49 (CI 0.3 to 0.8)

Prevention of Preterm Birth with 17Pc, Meta-Analysis

The NEW ENGLAND JOURNAL OF MEDICINE
June 24, 2003

- Prevention of Recurrent Preterm Delivery by alpha 17 hydroxy Progesterone Caproate

Multicenter RCT of Progesterone

- All patients with h/o previous preterm delivery due to PTL or PPROM
- Randomized between 15 and 20 3/7 weeks
- Singletons only
- Given trial placebo injection
- Started on weekly IM 17alpha OH Progesterone Caproate or placebo (2:1 randomization) until 36 weeks.

Multi-center RCT of Progesterone

- Randomized 463 women (310 Prog., 153 Plac.)
- Preterm Delivery:
  - 36% Progesterone
  - 55% Placebo (P < 0.001)
- Delivery before 35 weeks:
  - 21% Progesterone
  - 31% Placebo (P = 0.02)
- Delivery before 32 weeks:
  - 11% Progesterone
  - 20% Placebo (P = 0.02)
- Borderline statistically significant reduction in neonatal death, ventilatory support, IVH, any O2 requirement

Fonseca et al: Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind trial: Am J Obstet Gynecol 2003;18:

- Randomized patients with previous spont. preterm delivery, cerclage, uterine anomaly
- 100 mg progesterone suppositories or placebo every night from 24 to 34 weeks
- 142 patients randomize (70 Prog vs. 72 Plac.)
Fonseca et al: Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind trial: Am J Obstet Gynecol 2003;18:

- **Results**
  - **Preterm Delivery**
    - Progesterone 14%
    - Placebo 29% (p= 0.03)
  - **Delivery < 34 weeks**
    - Progesterone 3%
    - Placebo 19% (p= 0.002)
  - **Admitted for Preterm Labor**
    - Progesterone 19%
    - Placebo 31%

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

Short Cervix – What to Do?
Cervical Length at 14 Weeks and the Relative Risk of Premature Delivery (2915 Patients)

Cervical Length (cm)

One Solution

Cerclage for Short Cervix
Meta-analysis of 4 Randomized Trials

<table>
<thead>
<tr>
<th>Total N</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>
</tr>
<tr>
<td>Singleton, Short Cvx, Prior PTB</td>
<td>208</td>
<td>23%</td>
<td>39%</td>
</tr>
<tr>
<td>Twins, Short Cvx</td>
<td>49</td>
<td>75%</td>
<td>36%</td>
</tr>
</tbody>
</table>

* P < 0.05

Berghella et al, Obstet Gynecol 106:181-9, 2005
Effect of Vaginal Progesterone on Pregnancy Outcome in Singletons with an Ultrasonically Short Cervix (5 RCT’s)
An Individual Patient Meta-analysis

Romero et al: Am J Obstet Gynecol 2011;205(2) 124

Romero et al, AJOG 2012
Individual Patient Data Meta-analysis

- 5 trials, 775 women, 827 infants
- Vaginal progesterone treatment for TVUCCL ≤ 25 mm (asymptomatic)
- 42% reduction in PTB < 33 weeks
- 43% reduction in composite neonatal morbidity and mortality
- 25% significant reduction in NICU admissions
- No significant differences between treatment and placebo groups in rates of adverse maternal events or congenital anomalies

Results: Romero et al

![Figure 3: Effect of vaginal progesterone on preterm birth ≤33 weeks of gestation](image-url)
Primary Outcome

42% reduction in the rate of preterm birth <33 weeks

Effect of Vaginal Progesterone on Neonatal Outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Progesterone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU admission</td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>RDS</td>
<td>21%</td>
<td>32%</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>52%</td>
<td>52%</td>
</tr>
<tr>
<td>Composite neonatal morbidity/mortality</td>
<td>43%</td>
<td>46%</td>
</tr>
<tr>
<td>Birth weight &lt;1500g</td>
<td>4%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Need to Treat for Benefit

- Vaginal progesterone for short cervix
  - Treat 11 patients to prevent 1 PTB < 33 weeks
  - Treat 14 patients to prevent 1 case of RDS
- Magnesium sulfate for pre-eclampsia
  - Treat 100 patients to prevent 1 case of eclampsia
- Antenatal corticosteroids during preterm labor
  - Treat 13 patients to prevent 1 case of RDS
The Effect of Vaginal Progesterone on the Primary Outcome According to whether Patients had a Previous Preterm Birth

<table>
<thead>
<tr>
<th>Obstetric history</th>
<th>n</th>
<th>RR</th>
<th>95% CI</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With no previous preterm birth</td>
<td>606</td>
<td>0.61</td>
<td>(0.42-0.89)</td>
<td>0.68</td>
</tr>
<tr>
<td>With ≥1 previous preterm birth</td>
<td>169</td>
<td>0.54</td>
<td>(0.30-0.98)</td>
<td></td>
</tr>
</tbody>
</table>

The Effect of Vaginal Progesterone on Composite Neonatal Morbidity/Mortality According to Whether Mothers had a Previous Preterm Birth

<table>
<thead>
<tr>
<th>Obstetric history</th>
<th>n</th>
<th>RR</th>
<th>95% CI</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With no previous preterm birth</td>
<td>658</td>
<td>0.62</td>
<td>(0.43-0.91)</td>
<td>0.40</td>
</tr>
<tr>
<td>With ≥1 previous preterm birth</td>
<td>169</td>
<td>0.41</td>
<td>(0.17-0.96)</td>
<td></td>
</tr>
</tbody>
</table>

Does the effect of vaginal progesterone vary as a function of cervical length?

<table>
<thead>
<tr>
<th>Cervical length</th>
<th>PTB</th>
<th>Comp NN Morb</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10mm</td>
<td>0.83 (0.49-1.41)</td>
<td>0.62 (0.28-1.38)</td>
</tr>
<tr>
<td>10-20mm</td>
<td>0.52 (0.35-0.76)</td>
<td>0.54 (0.35-0.84)</td>
</tr>
<tr>
<td>21-25mm</td>
<td>0.50 (0.10-2.41)</td>
<td>0.89 (0.33-2.36)</td>
</tr>
</tbody>
</table>
Does the response to vaginal progesterone vary according to the dose used in the different trials?

<table>
<thead>
<tr>
<th>Daily dose of vaginal progesterone</th>
<th>n</th>
<th>RR (95% CI)</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-100 mg</td>
<td>511</td>
<td>0.58 (0.35-0.95)</td>
<td>0.92</td>
</tr>
<tr>
<td>200 mg</td>
<td>316</td>
<td>0.56 (0.34-0.94)</td>
<td></td>
</tr>
</tbody>
</table>

Romero et al IPD Meta-analysis
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)
Vaginal Progesterone – The OPPTIMUM Study
- Multicenter RCT in UK of patients with either a short cervix (<25mm) or a previous PTB
- Randomized 1228 women daily 200mg vaginal P vs. placebo
- Outcome
  - Delivery < 34 weeks: P 16.0%, Placebo 18.1% (0.64-1.17)
- Outcomes
  - NN Morbidity or Death: P 6.6%, Placebo 10.2% (0.38-1.03)
  - NN Death: P 0.01%, Placebo 1.0% (0.06-0.49)
  - Mod. to Severe Neurologic Impairment: P 12%, Placebo 9% (0.98-2.15)

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 weeks 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

Assumptions (based on Fonseca data)
Singleton
- No prior PTB
- Single TVCL screen at 18-24 weeks, cost $187
- TVCL < 15 mm in 1.7% of population
- Vaginal P4 will reduce PTB<34 weeks 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
**Transabdominal Ultrasound**

- Designed to image the baby
- Routine fetal anatomy scan at 18-22 weeks
  - Protocol includes looking at the cervix
  - Full bladder often elongates and distorts cervix
- Per ACOG/SMFM
  - Not reliable nor reproducible as a screening method
  - Not sufficient evidence to suggest benefit of TAU screening for progesterone or other intervention

**Transvaginal Ultrasound**

- Designed to image the reproductive organs
- Identify anomalies
- Diagnose complications (e.g., cervical shortening, funneling, amniotic fluid or debris)
- Used in clinical trials of vaginal progesterone
- Per ACOG/SMFM
  - Diagnostic exam for intervention
  - Proper technique, quality control, monitoring essential
  - Certification recommended
  - Perinatal Quality Foundation
    - 3 lectures
    - Exam
    - Image review
    - CME credit

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Friedman et al: Can transabdominal ultrasound be used as a screening test for short cervical length? AJOG 2013 208 (3):190

- Screened 1217 Patients at 16-24 weeks with both TA and TV US
- 76 had a TV CL <= 25 mm
- To have a 96% confidence of identifying these 76 women they needed to have a TA CL of <= 36 mm
- 6.2% could not be screened due to technical difficulty
- 54% (657/1217) had a TA CL <36 mm
- So with screening with TA US you will still need to do TV on 60% of women to identify almost all women who will have a TV CL <25mm

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Cervical Length Education and Review
The Arabin Pessary for the Prevention of PTB with a Short Cervix

Two Large RCT’s of Pessary for a Short Cervix

- PECEP Study (Goya et al. Lancet 2012;379, 1800-06)
  - 385 women with CL < 25mm
  - Delivery < 34 weeks (primary outcome)
    - 6% pessary, 27% control (RR 0.24, 0.13-0.43)
  - Delivery < 28 weeks
    - 2% pessary, 8% control (RR 0.24, 0.09-0.73)
  - 108 women with CL < 25
  - Delivery < 34 weeks
    - 9% pessary, 6% control

RCT of Pessary in Twins (Liem et al. Lancet, 2013 382:194)

- RCT of all women with multiple pregnancy
- 40 Hospitals in the Netherlands
- 403 pessary, 410 control
- No overall difference in preterm birth or composite overall outcome
- In women with cervical length < 25th %
  - Composite mn morbidity – 12% pessary, 23% control (RR 0.42, 0.19-0.91)
  - PTD < 32 weeks – 12% pessary, 28% control (RR 0.43, 0.21-0.89)
Recent RCT of Pessary in Twins
Nicolaides et al: AJOG 2016

- Randomized unselected twins to pessary at 20-24 weeks vs. routine care
- N = 1180 (590 in each group)
- No differences in outcome
  - Delivery < 34 weeks – 13.6% vs. 12.9%
  - Adverse NN outcome – 10.0% vs. 9.2%
- Subanalysis of 214 women with a short cervix <25mm showed no benefit either

Bioteque Cup Pessary

Available in the U.S., Bioteque, Inc. San Jose, CA
FDA approved for use in pregnancy

Society Guidelines:
Progesterone to Prevent Preterm Birth

SMFM  ACOG  ACNM
Recommendations for Routine Cervical Length Screening

- **SMFM**
  - The issue of universal TVU CL screening of singleton gestations without prior PTB for the prevention of PTB remains an object of debate. CL screening in singleton gestations without prior PTB cannot yet be universally mandated. Nonetheless, implementation of such a screening strategy can be viewed as reasonable, and can be considered by individual practitioners.

- **ACOG**
  - Although this document does not mandate universal cervical length screening in women without a prior preterm birth, this screening strategy may be considered. Practitioners who decide to implement universal cervical length screening should follow one of the protocols for transvaginal measurement of cervical length from the clinical trials on this subject.

- **ACNM**
  - Application of evidence-based strategies to effectively screen women at potential risk for preterm birth should be accessible and available to every woman including strategies to assess cervical length in order to implement timely prevention strategies.

**SMFM Recommendations**

- In women with singletons, no prior ptb, <24 weeks with cervical length < 20 mm, vaginal progesterone 90 or 200 mg is associated with a reduction in PTB and PN morbidity and mortality and can be offered in these cases.

- The issue of routine screening of all pregnant women is a subject of debate but such a screening strategy can be viewed as reasonable.
SMFM Recommendations (cont.)

- In singleton pregnancies with a prior (spontaneous) PTB prior to 37 weeks, 17 OH Progesterone 250 mg IM q week starting at 16-20 weeks until 36 weeks is recommended.
- In these women with a prior PTB and whom the cervix shortens to < 25 mm, cervical cerclage may (also) be offered.
- Progesterone has NOT been associated with a reduction in PTB in patients with multiple pregnancy, preterm labor or PPROM.
- Transabdominal screening for cervical length is not recommended.

What are the concerns with routine endovaginal ultrasound screening?

- Lack of training and consistency in doing transvaginal US for cervical length
- “Indication Creep”
- What to do with 20-25 mm
- Lack of availability in some areas
- Applies to only about 2% of women
- Many ultrasounds for those needed to treat
Other Indications for Progesterone in Prematurity Prevention

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

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

Progesterone in Patients with Preterm Labor

Sacco et al: AJOG 2015: PTB <37 weeks
Vaginal P

Suhag et al: AJOG 2015: PTB <37 weeks
Progesterone for PPROM
RCT of patient with PPROM
23 – 31 weeks
17OHP Weekly vs. Placebo
Combs, Garite et al: AJOG2015

Safety Issues

Perinatal Losses with Progestins
(Miscarriages < 20 weeks, stillbirths, neonatal deaths)
NO EVIDENCE OF TERATOGENICITY

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

<table>
<thead>
<tr>
<th>Scores below cut-off on</th>
<th>17Pc (n=193)</th>
<th>Placebo (n=82)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages &amp; Stages Questionnaire</td>
<td>Communication</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Gross motor</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Fine motor</td>
<td>21%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>Problem-solving</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Diagnoses from Health Profi</td>
<td>Motor skills problem</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Developmental delay</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Attention or learning problem</td>
<td>8%</td>
<td>10%</td>
</tr>
</tbody>
</table>


Long Term Follow up of Babies from Progesterone Trials

- Rode et al (2011): US Ob Gyn: N = 433. Mean ASQ scores at 6 months and 18 months were not significantly different between the two groups. 215 for infants in the progesterone group and 216 for infants in the placebo group at 6 months (P = 0.45) and 193 and 194, respectively, at 18 months (P = 0.89).
- McNamara et al (2015): N=759. There was no evidence of difference between the progesterone and placebo groups in global health status assessed using the Health Utilities Index.

Cognitive Composite score at 2 years, mean (SD)
87.7 (17.8; n=193) 93.1 (17.6; n=82) 0.48 (2.77, 1.81) 0.093, p<0.000
Progesterone Costs

- Makena (17OHP)
  - Retail $680/dose, copay about $70
  - Compounded – generally not available due to FDA bulletin

- Vaginal Progesterone
  - Crinone gel – about $15/day
  - Prometrium – about $1/day
  - Compounded Progesterone – cheap if available

Summary

- Progesterone lowers the rate of premature delivery and avoids many associated morbidities in:
  - Patients with a history of a prior PTB
  - Patients with a short cervix
  - In patients with a short cervix and a prior preterm birth both a cerclage and progesterone used together creates the optimum outcome

- Progesterone does not lower the rate of preterm birth in patients with multiple gestations

- Vaginal ultrasound for cervical length may become routine in all pregnant women

- Based on available data, progesterone is safe.