Prediction and Prevention of Preterm Birth

Juan M. Gonzalez, MD
Assistant Professor
Maternal-Fetal Medicine
Department of Ob/Gyn & RS
University of California, San Francisco

Preterm Birth

- Single most important cause of perinatal mortality (28 weeks gestation through 6 days of life) in the U.S. (accounts for approx 75% of these losses)
- Leading cause of neonatal mortality (0-27 days) in U.S.
- Second leading cause of infant mortality in U.S.
- Leading cause of black infant mortality in U.S.
- Major determinant of neonatal and infant illness.
- Major contributor of short and long term morbidity and disability.

Source: National Center for Health Statistics, period linked birth/infant death data
Prepared by March of Dimes Perinatal Data Center, 2006

Mechanisms of Preterm Birth

- Current therapies to treat preterm labor are largely ineffective.
- Treatment of preterm birth has focused on inhibiting myometrial contractions.
- Growing body of clinical and animal studies now suggests that premature cervical shortening or ripening might be the primary mechanism.
Screening Modalities

- The single most important predictor of preterm birth is a short cervix.
- In a review of 39,284 cases of preterm birth (<37 wk), short cervix was most important single predictor of preterm birth.

Cervical Length Screening for Prevention of Preterm Birth

Technical Aspects of Screening

1. Have the woman empty her bladder just before ultrasound
2. Prepare the clean probe covered by a condom
3. Insert the probe (probe can be inserted by the woman for her comfort)
4. Guide the probe in the anterior fornix of the vagina
5. Obtain a sagittal long-axis view of the entire endocervical canal
6. Withdraw the probe until the image is blurred, and reapply just enough pressure to restore the image (to avoid excessive pressure on the cervix, which can elongate it)
Cervical Length Screening for Prevention of Preterm Birth

Technical Aspects of Screening

7. Enlarge the image so that the cervix occupies at least 2/3 of the screen, and both external and internal os are seen
8. Measure the cervical length from the internal to the external os along the endocervical canal
9. Obtain at least three measurements, and record the shortest best measurement in millimeters
10. Apply transfundal pressure for 15 seconds, and record cervical length again at least 3 times, recording best measurement
11. Entire examination should last at least 5 minutes; record only the shortest best cervical length obtained for clinical management.

Semin Perinatol 33:317-324
How should women with a previous spontaneous preterm birth be evaluated for risk of subsequent preterm birth?

- Evaluate obstetrical history
- Most common sequence for spontaneous PTB cervical ripening (short cervix) followed decidual-membrane activation and contractions.
- Review of medical records
  - Obstetrical: eg, preeclampsia, IUGR
  - Medical: eg, chronic hypertension, lupus
  - Fetal: eg, aneuploidy, polyhydramnios, fetal death

How should the current pregnancy be managed in a women with a prior spontaneous preterm delivery?

Care Algorithm for Women With a History of Birth at 16 to 34 Weeks:*

- Evaluate obstetrical, medical, or fetal causes thorough record review
  - Obstetrical: eg, preeclampsia, IUGR
  - Medical: eg, chronic hypertension, lupus
  - Fetal: eg, aneuploidy, polyhydramnios, fetal death

- Offer 17P progesterone prophylaxis and serial cervical ultrasound at 16-23 weeks
- Evaluate according to additional specific risk identified

- Cervical length <25 mm -> offer cerclage

• Women with a documented history of spontaneous preterm birth at less than 37 weeks

• Treatment started between 16 and 20 weeks

• Continued until 36 weeks or delivery

• 17P history of preterm birth at less than 37 weeks. (mean = delivery of index pregnancy 30.7 weeks).

• N = 306 to 17P and n = 153 placebo.

• PTB < 37 weeks 36.3% in progesterone vs 54.9% placebo

• PTB < 35 weeks 20.6% in progesterone vs 30.7% placebo

• PTB < 32 weeks 11.4% in progesterone vs 19.6% placebo

Meis et al, NEJM 2003
• NNT = 5 to prevent PTB before 37 weeks, NNT = 12 for PTB before 32 weeks.

• Progesterone group had less BW<2500 g, NEC, need for supplemental O2, and IVH.

• Results greatest for women with a prior PTB < 34 weeks.

Meis et al, NEJM 2003
Spong et al, Am J Obstet Gynecol 2005

• High rate of PTB in placebo group (36.3%)

• Study population was an especially high-risk group of women

• MC, RCT examined role serial TV CL with cerclage placement for those with a short cervix

• Patients with singleton and history of spontaneous preterm birth at less than 34 weeks

• CL q 2 weeks starting at 16 weeks thru 23 weeks

• If length between 25 and 29 mm screening increased to q week.
• Primary Outcome was PTB at 35 weeks
  – No significant difference RR, 0.78; 95 % CI, 0.58-1.04

• However, cerclage was associated with a reduction in:
  – Deliveries before 24 weeks RR, 0.44; 95 % CI, 0.21-0.92
  – Deliveries before 37 weeks RR, 0.75; 95 % CI, 0.60-0.93
  – Perinatal death RR, 0.54; 95 % CI, 0.29-0.99

Secondary Analysis
  – Cerclage for cervical length less than 15mm was associated significant decrease in preterm birth at less than 35 weeks (RR, 0.23; 95% CI, 0.08-0.66)

Should a women with a current singleton pregnancy without a history of preterm birth be screened for a risk of preterm birth?
Proponents

- Potential to reduce preterm birth
- High quality evidence exists to support efficacy of treatment for positive test results (cervical length 20 mm or less)
- Cost Effective
- Safe
- Reliable (Reproducible, variability <10%)
- Recognizable early asymptomatic phase
- Valid (accuracy of prediction)
- Accepted by patients (> 90 % of pts)
- Widely available

Opponents

- Quality assurance of screening test
- Lack of availability of screening and patient access to qualified imaging
- Patient for patients to receive unnecessary interventions

What intervention have been shown to be beneficial for reducing the risk of preterm birth in women who do NOT have a history of preterm birth but who are found to have a short cervical length?

Practice Bulletin No. 130 ACOG
Progesterone and Short Cervix

- Multicenter RCT
- Women underwent CL screening at 20-25 weeks (median 22 weeks)
- 1.7 % of 24,640 screened CL less than or equal to 15 mm
- Excluded fetal anomalies, uterine contractions, ROM, cerclage
- Women with CL 15 mm or less randomized to: vaginal micronized progesterone 200 mg every night vs placebo between 24 and 34 weeks

- 90 % of the women in the study had a singleton
- 85 % had no prior preterm birth
- Less PTB < 34 weeks in progesterone group (19.2 vs 34.4%; RR, 0.56; 95% CI, 0.36-0.86)
- 44 % decrease in spontaneous preterm birth at less than 34 weeks

• Number need to avoid one spontaneous preterm birth < 34 week
• Screen - 387
• Treat - 7
**Methodology**

**Inclusion criteria**
1) Singleton
2) GA 19<sup>th</sup> – 23<sup>rd</sup> weeks
3) Cervical length (TV US): 10 – 20 mm
4) Asymptomatic (no symptoms or signs of preterm labor)

**Exclusion criteria**
1) Planned cerclage
2) Acute cervical dilation
3) Allergy to progesterone
4) Recent progestogen treatment (within 4 weeks)
5) Chronic medical conditions
6) Major fetal anomaly or chromosomal abnormality
7) Uterine malformations
8) Vaginal bleeding
9) Known/suspected chorioamnionitis

Journal Club slides prepared by Dr Asma Khalil (UOG Editor for Trainees)

**Outcomes**

**Primary outcome**
Preterm birth <33 weeks

**Secondary outcomes**
- Neonatal morbidity
  - RDS
  - Bronchopulmonary dysplasia
  - Intraventricular hemorrhage (Grade III or IV)
  - Periventricular leukomalacia
  - Sepsis
  - Necrotizing enterocolitis
- Perinatal mortality
- PTB <28, <35, and <37 weeks
- Neonatal biometry at birth
- Congenital abnormalities

Journal Club slides prepared by Dr Asma Khalil (UOG Editor for Trainees)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ITT analysis</th>
<th>Treated patient</th>
<th>Compliant analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjusted*</td>
<td>Adjusted*</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td>Preterm birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTB &lt; 28 weeks</td>
<td>0.04</td>
<td>NS</td>
<td>0.04</td>
</tr>
<tr>
<td>PTB &lt; 33 weeks</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>PTB &lt; 35 weeks</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>PTB &lt; 37 weeks</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Neonatal morbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDS</td>
<td>0.03</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Any morbidity/mortality</td>
<td>0.04</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight &lt; 1500g</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Journal Club slides prepared by Dr Asma Khalil (UOG Editor for Trainees)

**Primary study outcome**

- Adjustment for study site and risk strata

Journal Club slides prepared by Dr Asma Khalil (UOG Editor for Trainees)

**Progestrone for the prevention of preterm birth in women with short cervix**

- Placebo N=225
- Progesterone N=233

Journal Club slides prepared by Dr Asma Khalil (UOG Editor for Trainees)

**Hassan et al., UOG 2011**

**Fonseca EB et al., NEJM 2007**
Does cerclage placement or progesterone treatment decrease the risk of preterm birth in women with multiple gestations?

Summary

- All women with a singleton and a prior history of spontaneous PTB should be offered progesterone supplementation starting between 16 – 24 weeks.
- Regardless of TV ultrasound cervical length, to reduce the risk of recurrent preterm birth.

• Progesterone treatment does not reduce the incidence of PTB in women with twin or triplet gestations.

• Cerclage may increase the risk of PTB in women with a twin pregnancy and an US detected cervical length less than 25 mm.

Practice Bulletin No. 130 ACOG

Clinical utility – Number needed to treat (NNT) to prevent adverse outcome

<table>
<thead>
<tr>
<th>Interventions</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone for prevention of PTB ≤ 33 weeks*</td>
<td>14</td>
</tr>
<tr>
<td>Progesterone for prevention of RDS*</td>
<td>22</td>
</tr>
<tr>
<td>MgSO4 for prevention of eclampsia†</td>
<td>100</td>
</tr>
<tr>
<td>Antenatal steroids for prevention of RDS‡</td>
<td>13</td>
</tr>
</tbody>
</table>

* Hassan S et al., UOG 2011
† Altman D et al., Lancet 2002
‡ Sinclair JC et al., AJOG 1995

Journal Club slides prepared by Dr Asma Khalil
(UOG Editor for Trainees)
Summary

• Vaginal progesterone can reduce the risk of preterm birth in asymptomatic women with a singleton without prior PTB and short cervix less than or equal to 20 mm before or at 24 weeks.