Progesterone Therapy for Preterm Birth Prevention

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Learning Objectives

By the end of this session, participants will be able to:

• Recognize benefits of screening patients for progesterone use
• Identify indications for 17P
• Identify indications for vaginal progesterone
• Identify indications for cerclage for short cervix
• Recognize controversial management areas

17P = 17α-hydroxyprogesterone caproate
Background

Preterm Birth: Why worry?

1) Very common (~ 450,000 infants/yr)
2) Very expensive (~ $26 billion/yr)*
3) #1 cause of infant deaths
4) Intervention can reduce the risk

Preterm birth in North Carolina

Infants born <37 weeks (12% of births)
- 13,410 infants
  - 1:8 overall
  - 1:6 African American infants

Infants born <26 weeks
- 806 infants

2010-2013 Average
National Center for Health Statistics, natality data.
2014 March of Dimes Report Card

North Carolina

Preterm (< 37 weeks)

<table>
<thead>
<tr>
<th>Year</th>
<th>2006</th>
<th>2010</th>
<th>2014</th>
<th>2020 Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13.6%</td>
<td>12.7%</td>
<td>12.0%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>
Preterm Birth: Etiology

- Preterm labor/PROM: 70%
- Medical/obstetrical indications: 30%
## Recurrence Risks for Spontaneous Preterm Birth

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Risk of SPTB in next pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2\textsuperscript{nd} pregnancy; 1\textsuperscript{st} at term</td>
<td>9%</td>
</tr>
<tr>
<td>2\textsuperscript{nd} pregnancy; 1\textsuperscript{st} SPTB</td>
<td>22%</td>
</tr>
<tr>
<td>3\textsuperscript{rd} pregnancy; 2 Prior SPTBs</td>
<td>42%</td>
</tr>
<tr>
<td>both &lt; 32 weeks</td>
<td>57%</td>
</tr>
<tr>
<td>3\textsuperscript{rd} pregnancy; 2 Term births</td>
<td>5%</td>
</tr>
</tbody>
</table>

Mercer (1999)  
McManemy (2007)
Progesterone Therapy

Two different preparations *with* two different indications

17P:
- prior spontaneous preterm birth

Vaginal progesterone:
- incidentally detected short cervix (ultrasound)
17α-hydroxyprogesterone (17P)
**Prevention of sPTB**

**Preterm Birth History/Cervical Length Screening Flowchart**

- History of spontaneous preterm birth (<37 weeks) or 2nd trimester pregnancy loss?
  - Yes
    - Consider MFM/high-risk OB consult
    - Obtain MFM/high-risk consult if history of spontaneous preterm birth <32 weeks or 2nd trimester loss
  - No
  - Current singleton pregnancy?
    - Yes
      - Recommended intramuscular progesterone (see Box 2)
      - Measure cervical length every two weeks by transvaginal ultrasound from 15-16 weeks to 23-24 weeks or weekly if cervical length <30mm or if internal os abnormalities
      - Consider cerclage up to 23-24 weeks if cervical length <25mm
      - For history of spontaneous preterm birth <34 weeks or 2nd trimester loss in a multiple gestation, obtain MFM/high-risk OB consult for progesterone recommendation
    - No
      - Usual care for multiple gestation

*Funding for this project is provided in part by The Duke Endowment*
Evidence supporting 17P

NICHD randomized controlled trial (2003)

Eligible participants:
- Prior spontaneous preterm birth 200 – 366
- Enrolled at 16-20 weeks
- Weekly 17P (250 mg) vs. placebo until 36 weeks

Meis (2003)
## Evidence for 17P

<table>
<thead>
<tr>
<th>Gestation</th>
<th>Placebo</th>
<th>17P</th>
<th>RR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 37 weeks</td>
<td>55%</td>
<td>36%</td>
<td>0.66</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; 35 weeks</td>
<td>31%</td>
<td>21%</td>
<td>0.67</td>
<td>0.017</td>
</tr>
<tr>
<td>&lt; 32 weeks</td>
<td>20%</td>
<td>11%</td>
<td>0.58</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Approximately 33% reduction in preterm births

Meis (2003)
ACOG Practice Bulletin 130 (2012)

Initial recommendation (2008)

Progesterone (17P) supplementation should be offered to women with a current singleton pregnancy and a prior spontaneous singleton preterm birth (start at 16-24 weeks)

Use in multiple gestations is not recommended

NC Pregnancy Medical Home (2011) requires PMH providers to offer and provide 17P to eligible patients
17P Candidates and use

- Take a good history. Not indicated, if prior preterm birth was secondary to a medical or obstetrical indication.
- Previous singleton spontaneous preterm birth < 37 weeks
- Begin at 16-20 weeks and continue until 36 weeks
  - Start by 24 weeks at latest*
  - 250 mg IM weekly
- If dose is missed, resume therapy as soon as possible

*NC Medicaid will reimburse for 17p treatment for any patient with a history of spontaneous preterm birth regardless of weeks of gestation at initiation of therapy.
Management dilemmas

- Prior SPTB of a twin gestation and now has a singleton
  - High-risk Ob consult
  - Consider 17P, if prior birth was “early” (i.e. < 30-32 weeks)

- Should 17P be continued, if a cerclage is done for a short cervix?
  - Yes

- Should 17P be used following tocolysis?
  - No, unless she was previously receiving it prior to tocolysis

- Should it be used in patients with risk factors for preterm birth, but no prior SPTB (multiples, uterine anomaly, + fFN, etc.)?
  - No
Vaginal Progesterone
Prevention of sPTB

No Preterm Birth History/ Cervical Length Screening Flowchart
Evidence for Vaginal Progesterone

Randomized controlled trial:
- Asymptomatic women with cervix < 15 mm (20-25 wks)
- Vaginal progesterone (200 mg daily) vs. placebo
- 24-34 weeks

- Delivery < 34 weeks
  - Progesterone: 19%  (44% reduction)
  - Placebo: 34%

Fonseca (2007)
Evidence: Intervention for Short Cervix Effective

Vaginal progesterone (90mg gel)

- RCT n=32,091 screened, n=458 randomized
- High and low risk women with CL 10-20 mm
- Reduced risk by 45%

Hassan, Ultrasound Obstet Gynecol 2011;38:18
Assess cervical length by transabdominal ultrasound at time of fetal anatomic survey. If cervix appears short (i.e. < 25-35 mm), perform transvaginal ultrasound
- (transabdominal cervical length for low-risk patients only)

Consider vaginal progesterone for asymptomatic women with a singleton gestation and no prior spontaneous preterm birth who have an incidental finding of short cervix (< 20 mm) before 24 weeks
Assessing Cervical Length

Options for assessing Cervical Length include

– Digital Examination
  • Unable to see intraamniotic debris or choriodecidual separation

– Transabdominal Ultrasound
  • Factors that may affect reliability include obesity, fetal shadowing, and cervix position

– Transvaginal Ultrasound
  • Shown to be safe, reliable, and reproducible
Regardless of whether practitioners choose to screen universally or selectively, correct technique is critical to avoiding incorrect diagnosis and treatment.
Normal Cervix

Bladder Empty
Fetal Head
Internal Os
Ext Os
Posterior Cervix

Dist = 2.55 cm
Cervical Screening Measurement Image Criteria

- Transvaginal Image
- Cervix ~ 75% of the image
- Anterior = Posterior Width
- Maternal Bladder Empty
- Internal Os Seen
- External Os Seen
- Cervical Canal Visible throughout
- Caliper Placement Correct
- Cervix Mobility Considered
Dynamic Technique

- Withdraw probe until blurred / Reapply
- Enlarge image (2/3 of screen)
- Measure Ext Os → Int Os along endocervical canal
- Apply fundal or suprapubic pressure
- Obtain 3 measurements, use shortest best

Berghella, Clin Obstet Gynecol 2003;46:947
Other Factors Affecting Cervical Measurement

Gestational age:

Lower segment of uterus may be difficult to distinguish from cervix until somewhere between 16 and 20 weeks

If can’t tell at 16-18, ask her to come back at 18-20 wks

Duration of scan – A scan < 3 minutes is inadequate

OPERATOR experience & training

Standardize method
Trans-Abdominal Pitfalls

- Fetal parts may obscure cervix
- Bladder filling may elongate cervix and mask funnel
- Long distance from probe decreases resolution
- Manual pressure may compress lower uterine segment and mimic cervix
Cervical Length Education and Review Course
Available online through the Perinatal Quality Foundation at
https://clear.perinatalquality.org/
Progesterone Formulations

17P
- Makena®
- Compounded

Vaginal progesterone
- Prometrium® 200 mg (oral tablets, but use per vagina)
- Crinone® 90mg gel
  * per vagina nightly

Continue through 36th week of pregnancy

All of these preparations are covered by NC Medicaid; for more information or technical assistance, contact your local CCNC OB team.
17P versus vaginal progesterone

• What if my patient can’t/won’t take 17P for the indication of prior sPTB?
  • Are 17P and vaginal progesterone equally effective & interchangeable?
  • Can I give her vaginal progesterone in lieu of 17P?
• Unfortunately this is unknown…
Cerclage
Prior SPTB and short cervix

Meta-analysis (5 studies)
- singleton gestation
- prior SPTB
- current cervical length < 25 mm before 24 weeks
- randomized to cerclage vs. no cerclage

- Delivery < 35 weeks
  - cerclage: 28.4%  RR: 0.70 (30% reduction)
  - no cerclage: 41.3%

Berghella (2011)
Multiple Gestation
Twins and short cervix

- **Cerclage**
  - not recommended
  - associated with 2-fold increase in preterm births*

- **Vaginal progesterone**
  - no effect on preterm delivery rate
  - ACOG: not recommended
  - some experts recommend**:
    ~ 50% decreased risk of adverse perinatal outcome (RDS, IVH, NEC, sepsis, or neonatal death)

*Berghella (2005)  
**Romero (2012)
Recommendations:
Singleton gestation

Prior spontaneous preterm birth < 37 weeks
  - consider high risk pregnancy consultation
  - weekly 17P from 16-36 weeks

Prior spontaneous preterm birth < 32 weeks
  - obtain high-risk pregnancy consultation
  - weekly 17P from 16-36 weeks
  - TV cervical length every 2 weeks from 15-23 weeks
  - if cervix is 25-29 mm, assess weekly
    - consider cerclage, if cervix is < 25 mm
Recommendations: Singleton gestation

No prior spontaneous preterm births
- transabdominal cervical length at anatomy scan (18-24 wks)
  - if cervix is < 30-35 mm, perform transvaginal ultrasound
  - if cervix is < 25 mm by transvaginal ultrasound:
    - vaginal progesterone
      - 200mg tablets (Prometrium®) nightly
      - 90mg gel(Crinone®) nightly
Recommendations:
Multiple gestation (DFZ)

Prior SPTB:
- consider 17P

Short cervix:
- no cerclage (doubles risk for preterm delivery)
- consider vaginal progesterone
## Grand Summary

<table>
<thead>
<tr>
<th>Current pregnancy</th>
<th>Past SPTB</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton</td>
<td>Singleton</td>
<td>17P; cerclage (if cervix &lt; 25 mm, 16-23 wks)</td>
</tr>
<tr>
<td>Singleton</td>
<td>Multiple</td>
<td>unclear; consider 17P</td>
</tr>
<tr>
<td>Singleton</td>
<td>No</td>
<td>not 17P candidate</td>
</tr>
<tr>
<td>Multiple</td>
<td>Singleton</td>
<td>unclear; consider 17P</td>
</tr>
<tr>
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<tr>
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<td>not 17P candidate</td>
</tr>
<tr>
<td>Multiple</td>
<td>----------</td>
<td>cervix &lt; 25 mm: NO cerclage consider vaginal progest</td>
</tr>
</tbody>
</table>
References

• Meis et al. NEJM 2003;348:2379-85
References

• ACOG:

• www.marchofdimes.org
Questions and Comments?

Thank you.

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