Cervical Length Screening: Universal or Risk-based for Preterm Birth Prevention?

Learning Objectives
1. Appreciate the strengths & limitations of various cervical length screening strategies for preterm birth (PTB) prevention
2. Review the effectiveness data to reduce spontaneous preterm birth in women with shortened cervical length
3. Develop a reasonable protocol for the use of C.L. screening appropriate to your practice

Preterm Birth Rate in the U.S.A.
Who is having all the PTB’s?

- Only 10-20% of U.S. PTB’s happen in women with a prior SPTB
- 80-90% of U.S. PTB’s happen in women with no prior SPTB
  - Nulliparas
  - Multiparas with a prior term birth
Options for C.L. Screening

- None
- Risk-based
- Universal
- “Accidental”? 

No Screening Option

“Universal C.L. screening and vaginal progesterone prevents early preterm births, reduces neonatal morbidity and is cost saving: doing nothing is no longer an option”

Campbell, Editorial USOG, 2011

Risk Factors for SPTB

- Prior “early” SPTB (inc. Cerv Insufficiency)
- Multiple Gestation
- Cone Biopsy/multiple LEEPs
- Midtrimester “Bleeding”
- Uterine anomalies
- African American ethnicity
- Various clinical “Symptoms”
- BV/STDs
- Low/High Maternal BMI
- ART
- Periodontal Dz
- Single (Small) LEEP
- Smoking/drugs
- Family Hx
Accuracy of Risk-Scoring Systems for PTB Prevention: Systematic Review

- Considers multiple factors (~30)
  - SES/Habits, Past Med/OB Hx
  - Current Pregnancy Events
- Assigns total score - Risk status: Hi-Lo
  - Sensitivities <50%
  - PPV's <10%
- No effective interventions!

Honest, J Ob-Gyn, 2004

Risk-Based Cervical Length Screening

- Prior Spontaneous Preterm Birth
  - Level I Data support
- “Other” Risk Factors
  - No/Limited Data
  - Not proven effective
  - Investigate!
- Multiple Gestation
  - No effective Rx (yet?)
  - Cerclage harmful
  - Investigate!

Criteria for a Good Screening Test

- Is SPTB a clinically relevant problem?
- Are the screening test and treatments safe?
- Is the (C.L.) screening test widely available?
Criteria for a Good Screening Test

- Is screening test performance Dependable?
- Are the screening and treatments cost-effective?
- Is there a readily available, effective treatment?
- Have improvements in health outcomes been demonstrated?

How Dependable is Cervical Length for PTB Prediction? – Systematic Review

- Widely Investigated
  - Well-Defined protocols
  - Clinically useful prediction
- Consistent results across studies
- Predictive value varies by:
  - Exam GA: <20 weeks optimal
  - OB Hx: Prior SPTB - Higher PPV
  - C.L. cutoff: shorter - Higher PPV
  - Singletons better than twins

Honest, USOG, 2003

How Dependable are U.S. Clinicians and Sonographers?

- Cervical Length ultrasound certification highly recommended
  - Cervical Length Education & Review (CLER)
    - ACOG, SMFM, AIUM, ACR recognized
    - $150
    - https://clear.perinatalquality.org/
  - Fetal Medicine Foundation (U.K.)
    - Free
    - https://fetalmedicine.org/cervical-assessment
Criteria for a Good Screening Test

- Is screening test performance dependable?
- Are the screening and treatments cost-effective?
- Is there a readily available, effective treatment?
- Have improvements in health outcomes been demonstrated?

Universal C.L. Screening: Is it Cost Effective with Progesterone (P4) Rx?

- Odibo, 2000  Yes
- Cahill, 2010  Yes
- Werner, 2011 Yes

Universal C.L. Screening: Cost Effective with P4 Rx?

- Potential Problems: how valid are baseline assumptions? “Best-Case Scenario”
  - Overestimate P4 efficacy
  - Underestimate P4 costs
  - Failure to consider “indication creep”
  - Failure to consider “prevention creep”
  - Failure to consider real-world problems with protocol implementation
Criteria for a Good Screening Test

- Is screening test performance Dependable?
- Are the screening and treatments cost-effective?
- Is there a readily available, effective Rx?
- Have improvements in health outcomes been demonstrated?

Efficacy of Progestins for PTB Prevention

Vaginal Progesterone (P4) - Daily Dose 90-200 mg
Most clinical trial data for RX Short C.L.
17α hydroxyprogesterone caproate (17P)
250 mg/week m/c IM dosing
Most clinical trial data to Rx Prior SPTB
Few direct comparisons available

Multinational Trial of Vaginal Progesterone Gel for Short C.L.
- Phase III trial - 44 centers in 10 countries
- Screened 32,091 women (2.2% C.L. 10-20 mm)
- N=458: 90 mg Vaginal P4 gel or placebo

Hassan, USOG, 2011
Meeting of the FDA Advisory Committee for Reproductive Health Drugs  
January 20, 2012  
Lisa Soule, MD  
Clinical Team Leader  
Division of Reproductive and Urologic Products

FDA Analysis by Country: Preterm Birth at < 33 Weeks Gestation Study 302 (Hassan)

<table>
<thead>
<tr>
<th>Country (N)</th>
<th>Placebo</th>
<th>P4 Gel</th>
<th>Tx Diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (206)</td>
<td>19.2%</td>
<td>16.8%</td>
<td>-2.4%</td>
</tr>
<tr>
<td>Non-US (253)</td>
<td>12.0%</td>
<td>2.3%</td>
<td>-9.7%</td>
</tr>
</tbody>
</table>

Meeting of the FDA Advisory Committee for Reproductive Health Drugs

<table>
<thead>
<tr>
<th>Probabilities of Not Delivering</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age at Delivery (weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FDA Concerns about Treatment Effect

- Applicant’s analysis shows marginal overall significance
- FDA analysis shows no significant benefit
- Regional differences – no efficacy in US
- A few sites may be driving results
- Inconsistent results in subgroups

Criteria for a Good Screening Test

- Is screening test performance Dependable?
- Are the screening and treatments cost effective?
- Is there a readily available, effective treatment?
- Have improvements in health outcomes been demonstrated?

Does C.L. Screening + Progesterone Reduce SPTB?

- Grobman, 2014  RCT- 17P   No
- Berghella, 2014  Cohort- Vag P4   No
Committee Opinions

- ACOG
  - Does not mandate universal CL screening in women without prior SPTB, but this screening strategy may be considered
  - Vaginal progesterone recommended as management option to reduce risk of PTD in asymptomatic women with singleton gestation with incidentally identified CL < 20 mm before or at 24 weeks GA

- SMFM
  - There are no data regarding effectiveness of universal TVU screening for short cervix followed by vaginal progesterone for those with a short cervix, compared to no screening
  - Universal screening approach may not produce the same results in practice as those in a controlled trial

Universal Cervical Length Screening

- “Acceptable” to ACOG & SMFM
- Some trial data suggests utility
- Published clinical data not supportive
- No FDA-approved Rx for “Short C.L.”
- Not ready for Prime Time

Got Short Cervix?

- Serendipitous diagnoses not uncommon
  - Transabdominal cervical assessment (“looks kinda short”)
  - This leads to vaginal scan and the finding of a short C.L.

- If C.L. ≤ 20 mm, Safest option: Rx vag P4
PTB Prevention Algorithm

Singleton? yes → Usual Mult care*

Usual care no → SPTB Hx?

SPTB Hx? yes

Weekly 17P†, 16-36 wks and
C.L. Screen q 2 wk 16-22ª wks

no

C.L. 25-29 mm? yes → C.L. q 1 wk

C.L. <25 mm? no → Continue 17P

Continue 17P no

Counsel U/S-Indicated cerclage if <23 wks

Counsel U/S-Indicated cerclage if <23 wks

*Pending Clinical Trial  †17P=17α hydroxyprogesterone caproate