What's with Ultrasound and the cervix?

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Fellow, Maternal Fetal Medicine
Yale University
Objectives

• Cervical anatomy and its relation to preterm labor
• Cervical length measurement
  – Who, how and when?
• What to do if you find a short CL?
• Should we be doing cervical length in all pregnancies?
Cervical anatomy

- 25% circular smooth muscle fibers
- Rest is collagen fibers

- 6% smooth muscle fibers
- Remaining is collagen and connective tissue
Stages of normal cervical changes in pregnancy

- **Softening**
  - Collagen reorganization
  - Growth
  - Increased vascularity
  - Edema

- **Ripening**
  - Collagen concentration
  - HA and GAGs
  - Collagen dispersal
  - Collagen solubility

- **Dilation**
  - Collagen concentration
  - iNOS and vascular permeability
  - IL-8, cytokines
  - Leukocyte infiltration
  - Prolyase activation
  - Collagen degradation

- **Repair**
  - Inflammation
  - Tissue hydration
  - Mechanical stretch
  - Collagen density

Weeks gestation
Distinct and similar features during preterm and term cervical remodeling

**Inflammation-induced PTD**
- Complement dependent
- Leukocyte dependent (macrophages)
- No changes in progesterone

**Term delivery**
- Complement independent
- Non-leukocyte dependent
- Progesterone withdrawal

**Common pathway**
- Increased MMP-9 activity
- Increased collagen degradation

**Main source of MMP-9:**
- Macrophages

**Stimulus for MMP release:**
- C5a

**Main source of MMP-9:**
- Endocervical epithelial cells
- Cervical fibroblasts

**Stimulus for MMP release:**
- Progesterone withdrawal

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Why measure the cervix?

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 mm CL at 24 weeks</td>
<td>6-14</td>
</tr>
<tr>
<td>History of PTB</td>
<td>6-8</td>
</tr>
<tr>
<td>African American</td>
<td>3.3</td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td>1.83-2.65</td>
</tr>
<tr>
<td>Age&lt;17 years</td>
<td>1.47 – 1.95</td>
</tr>
<tr>
<td>Age&gt;35 years</td>
<td>1.47-1.95</td>
</tr>
</tbody>
</table>

Iams, NFJM 1996
ACOG Practice Bulletin #130
PTB increases as CL decreases

<25 mm: 10%
<15 mm: 2%

at 20-24 weeks

J Iams et al. NEJM, 1996
## Risk of spontaneous PTB in subsequent pregnancies

<table>
<thead>
<tr>
<th>Outcome of First Birth</th>
<th>Outcome of Second Birth</th>
<th>Subsequent Preterm Birth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>Preterm</td>
<td>4.4</td>
</tr>
<tr>
<td>Preterm</td>
<td>Term</td>
<td>17.2</td>
</tr>
<tr>
<td>Term</td>
<td>Term</td>
<td>2.6</td>
</tr>
<tr>
<td>Preterm</td>
<td>Preterm</td>
<td>5.7</td>
</tr>
<tr>
<td>Preterm</td>
<td>Preterm</td>
<td>11.1</td>
</tr>
<tr>
<td>Preterm</td>
<td>Preterm</td>
<td>28.4</td>
</tr>
</tbody>
</table>

High risk cervical conditions

• Congenital disorders
  – Hypoplastic cervix
  – DES Exposure in utero

• Surgical trauma- Conization
  – Cold knife conization: PTB <30 wks (RR 5.33 x (1.63- 17.4)
  – LEEP increases the risk → 2x, repeat LEEP→5x
  – h/o CIN III increases risk for PTB

• Traumatic damage
  – Repeated cervical dilation
  – Cervical tear in labor

Jakobsson et al, Obstet Gynecol. 2009 Sep;114(3):504-10
Measuring the cervix

Funnel

Cervical Length

A

B

C_A

C_P

Berghella, Ultrasound Obstet Gynecol 1997
Burger, Ultrasound Obstet Gynecol 1997
Trans abdominal vs. Transvaginal

TAU missed 57% of short cervices found on TVUS
Hernandez-Andrade, J Mat-Fet Neonat Med 2012

Short cervices often missed on TAU
Rust, Am J Obstet Gynecol 2001
To, Lancet 2004
Althusisius, Am J Obstet Gynecol 2001

Sensitivity of TAU for PTB is low (8%)
Owen, JAMA 2001

Saul, JUM 2008
Problems with trans abdominal approach

- Bladder filling may elongate cervix and mask funnel
- Long distance from probe decreases resolution
- Manual pressure may compress lower uterine segment and mimic cervix
Technique for transvaginal approach

• Empty maternal bladder
• Introduce probe all the way into the anterior fornix
• Withdraw probe until blurred, then reapply pressure until anterior=posterior width
• Rotate probe for best long axis of canal
• Make image 75% screen
• Measure along canal (Internal to external os)
• Apply fundal pressure
• Correct caliper placement
• Repeat 3x, use shortest best
Ideal image
Measurement in a curved cervix

If A > 5mm, use B+C
Pitfalls of TVU

- Excessive pressure
- Not allowing enough time to view dynamic changes (3-5 minutes)
- Uterine contractions
- Underdevelopment of lower uterine segment <14wks
- Prior cervical surgery
T-Y-V-U: Cervical length shortening
Reliability of cervical measurement

Preterm Prediction (MFMU) -> ~ 20 % Fail
SCAN Trial (MFMU) -> ~ 15 % Fail
Nulliparous Network -> 30% Fail
CerviLenz Study -> 11.5% Fail
PREGNANT Trial -> ~ 10 % Fail
Learning curve for Cervical length measurement

• Takes approximately 23 supervised US scans to train someone with no experience in transvaginal US.

• Substantially fewer (∼5-15) for operator already familiar with transvaginal US

• Fetal Medicine Foundation CL Training

When to measure the CL?
Timing and indications for CL

• 14 weeks
  – Prior history of second trimester loss
  – Planning for an early history based cerclage

• 18-24 weeks
  – Previous history of spontaneous preterm delivery before 36 weeks
  – Uterine anomalies and cervical surgeries (eg. History of conization, CIN III)
  – Symptomatic - cramping, contractions, spotting

• 24-32 weeks
  – Symptomatic
  – Follow-up US
  – Multiple gestation
When to repeat or stop CL?

- Risk factors present
  - Repeat every 3-4 weeks until 32 weeks

- Cervical length 15-25 mm
  - If asymptomatic, repeat q 2 weeks
  - If symptomatic, fFN and observe

- CL < 15 mm
  - Admit and observe
  - May consider discharge if stable and asymptomatic
  - Stop CL measurement for CL< 10mm, use speculum examination for dilatation*
CL: Special circumstances

- Post-cerclage
  - Immediately after to examine the change
  - A week later for possible failed cerclage
  - Q 3-4 weeks until 28-30 weeks
    - To consider admission
    - case-by-case

- PPROM
  - CL not a predictor of early delivery
  - No change the management based on CL

What to do if you find a short CL?
Cerclage for short cervix with prior history of PTB

- Reduces delivery before 28, 30, 32, 34 weeks

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<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cerclage Events</th>
<th>Total</th>
<th>No Cerclage Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
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<tbody>
<tr>
<td>Rust 2001</td>
<td>13</td>
<td>53</td>
<td>16</td>
<td>49</td>
<td>16.0%</td>
<td>0.75 [0.40, 1.40]</td>
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<tr>
<td>Althuisius 2001</td>
<td>0</td>
<td>14</td>
<td>6</td>
<td>12</td>
<td>6.7%</td>
<td>0.07 [0.00, 1.07]</td>
</tr>
<tr>
<td>To 2004</td>
<td>5</td>
<td>21</td>
<td>8</td>
<td>23</td>
<td>7.3%</td>
<td>0.68 [0.27, 1.77]</td>
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<tr>
<td>Berghella 2004</td>
<td>5</td>
<td>14</td>
<td>11</td>
<td>17</td>
<td>9.5%</td>
<td>0.55 [0.25, 1.21]</td>
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<tr>
<td>Owen 2009</td>
<td>48</td>
<td>148</td>
<td>64</td>
<td>153</td>
<td>60.5%</td>
<td>0.78 [0.58, 1.04]</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>250</strong></td>
<td><strong>510</strong></td>
<td><strong>254</strong></td>
<td><strong>100%</strong></td>
<td>0.70 [0.55, 0.89]</td>
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</tbody>
</table>

Total events: 71, 105
Heterogeneity: Chi² = 3.63, df = 4 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.91 (P = 0.004)

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Cerclage for short cervix with prior history of PTB

- Improves composite neonatal outcome

**Study or Subgroup**

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<td>14</td>
<td>2</td>
<td>12</td>
<td>4.3%</td>
<td>0.17 [0.01, 3.29]</td>
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<tr>
<td>To 2004</td>
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<td>21</td>
<td>1</td>
<td>23</td>
<td>2.3%</td>
<td>0.36 [0.02, 8.47]</td>
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<tr>
<td>Berghella 2004</td>
<td>4</td>
<td>14</td>
<td>11</td>
<td>17</td>
<td>15.8%</td>
<td>0.44 [0.18, 1.09]</td>
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<td>26</td>
<td>148</td>
<td>40</td>
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<td>0.67 [0.43, 1.04]</td>
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<td><strong>254</strong></td>
<td>100.0%</td>
<td></td>
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<td><strong>0.64 [0.45, 0.91]</strong></td>
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Vaginal Prometrium for short CL in singleton pregnancies

- 24,620 singleton screened
- 413 (2%) included: cervical length < 15 mm
  - Gest age 20-24 weeks
- 250 participated
  - 125 in each arm
  - 80% adherence
- PTL <34wks
  - 19% vs. 34% (RR 0.56; CI 0.36-0.86)
- Neonatal mortality
  - Non-significant (RR 0.59; CI 0.26-1.25)

Vaginal progesterone 90 mg gel for short CL

- Multicenter, double blind, placebo controlled
- Included cervical length: 10-20 mm
  - Gest age 19-23+6wks
- 465 enrolled
- Primary outcome: PTL < 33 weeks
  - 8.9% vs. 16.1% (RR 0.55; 95% CI 0.31-0.91)
- Secondary outcomes
  - Improved <28 weeks, <35 weeks PTL
  - RDS (RR 0.39; 95% CI 0.33-0.99)

Clinical Scenarios
Case 1

- 33 yr old G₂ P₀₁₀₁ at 19 weeks on 17-hydroxyprogesterone acetate IM weekly injection, was noted to have cervical length of **14 mm** on TVU during the anatomy ultrasound.

  - What will you do?
    - Change the form of progesterone to vaginal?
    - Cerclage vs. no cerclage?
    - Bed rest
Singleton and prior PTB

• Shortened cervical length before 24 weeks
  – CL between 15-25 mm
    • Some consider cervical cerclage
    • Vaginal Prometrium 200 mg or progesterone 90 mg gel
  – CL below 15 mm
    • Offer cervical cerclage
    • Vaginal Prometrium 200 mg or progesterone 90 mg gel

• Ultrasound-indicated cerclage is as effective as history indicated cerclage
  – avoids cerclage in 60% of cases

Prior preterm delivery on 17-OHP and currently has shortened cervical length at <24 wks gestation

• Cerclage may be offered for CL < 15 mm to reduce PTB < 34 weeks
• No evidence to change the form for progesterone

Case 2

- 26 yr old G₁ P₀ at 22 with history of LEEP x2, was noted to have cervical length of 8 mm on TVU during a follow-up ultrasound
  - What will you do?
    - Vaginal progesterone?
    - Cerclage vs. no cerclage?
Singleton, no prior birth, and has risk factors for cervical insufficiency

- No role for cerclage
- For CL below 20 mm
  - Vaginal Prometrium 200 mg or progesterone 90 mg at night until 36 weeks
Case 3

• 35 yr old G₄ P₂₀₁₂ at 20 weeks with uncomplicated obstetrical history, was noted to have cervical length of **16 mm** on TVU during an anatomy ultrasound (suspicious on a trans abdominal US)
  
  – What will you do?
    • Vaginal progesterone?
    • Cerclage vs. no cerclage?
Singleton, no prior PTD, and has NO risk factors

• No role for cerclage
• For CL below 20 mm
  – Vaginal Prometrium 200 mg or progesterone 90 mg at night until 36 weeks
• Pessary is an option for CL <25 mm*
  – Delivery <28 weeks RR 0.23 (95% CI 0.06-0.74)
  – Delivery <34 weeks RR 0.18 (95% CI 0.08-0.37)

Case 4

• 35 yr old G₃ P₁₀¹¹ at 26 weeks with uncomplicated obstetrical history, came for preterm labor evaluation and was noted to have cervical length of 10 mm on TVU.
  – What will you do?
    • fFN?
    • Vaginal progesterone?
    • Tocolysis?
    • Bed rest?
Threatened preterm labor evaluation (<3 cm dilation and 80% effacement)

- CL ≥ 30 mm - PTL unlikely
- Cervical length < 15 mm
  - 37% delivered within 7 days
  - has 44% (RR 5.5) chance for delivery < 32 weeks
- Cervical length between 15-30 mm
  - Variable rates
  - Use fFN for further triage
Management of threatened preterm labor

Suspected PTL <33+6

Contractions + Cervix dilation < 3 cm or < 80% effaced

CL < 20 mm
- Preterm labor

CL 20 – 30 mm
- fFN
  - fFN Negative
    - Observation
    - Manage individually

CL ≥ 30 mm
- PTL unlikely, discharge

Contractions + Cervix dilation ≥ 3 cm or 80% effaced

Preterm labor

fFN Positive
- Steroids
- Tocolysis
- admission

Case 5

• 27 yr old, a medical student, G₁ P₀ at 16 weeks with no risk factors, came for an anatomy ultrasound and requests for TVU to evaluate her cervical length.
  – What will you do?
Cervical length as a universal screening for PTL
Cervical length as a screening test for predict PTB

<table>
<thead>
<tr>
<th>Criterion: Disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease is clinically important</td>
<td>PTB is leading cause of perinatal morbidity/mortality, with more than 1 million deaths annually worldwide</td>
</tr>
<tr>
<td>Disease is clearly defined</td>
<td>Birth &lt; 37 weeks</td>
</tr>
<tr>
<td>Disease prevalence is well known</td>
<td>12% in US, about 10% worldwide</td>
</tr>
<tr>
<td>Disease natural history is known/recognizable early asymptomatic phase</td>
<td>CL is inversely related to spontaneous PTB, and early cervical changes occurs at the internal os.</td>
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</table>
Cervical length as a screening test for predict PTB in low risk population

<table>
<thead>
<tr>
<th>Criterion: Intervention, cost-effectiveness, feasibility</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Early intervention is effective</td>
<td>2 RTCs: Results show improved survival</td>
</tr>
<tr>
<td></td>
<td>Controversy in methods and interpretation</td>
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<tr>
<td>Cost-effectiveness</td>
<td>2 studies demonstrate cost-effectiveness, but</td>
</tr>
<tr>
<td></td>
<td>based on the above RCTs</td>
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<tr>
<td>Facilities for screening</td>
<td>All pregnancies have anatomy US at 18-24 weeks</td>
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<tr>
<td></td>
<td>Trained personnel for TVUs is unknown</td>
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<tr>
<td>Facilities for treatment</td>
<td>Vaginal prometrium is easy to administer</td>
</tr>
<tr>
<td></td>
<td>-80-90% compliance rate</td>
</tr>
</tbody>
</table>
Why is the controversy about universal CL screening?

• Fonseca trial <15 mm
  – 44% reduction in delivery <34 weeks
  – No significant improvement in perinatal mortality or morbidity

• Hassan trial- 10-20 mm
  – 45% improvement in delivery <33 weeks
  – Significant improvement in perinatal morbidity or mortality
  – Significant beneficial effect was seen only in 2 non-North American countries
    • Once excluded the findings were not significant
    • The findings were not significant for US subjects

• Cost-effective studies were based the above RCTs

• Additional studies based in United States are warranted
SMFM on CL screening

• Level I evidence of prevention of PTB and neonatal benefits based on treating with vaginal progesterone low-risk singleton gestations identified with TVU screening to have a short CL.

• Strategy is not only beneficial. But also cost-effective, and in fact cost-saving.

• TVU CL is safe, acceptable, reproducible and accurate screening test, with potentially widespread availability.

Barghella, SMFM Publication Committee, AM J Obstet Gynecol 2012
ACOG on CL Screening

• Transvaginal US is reliable and reproducible
• Recent RCTs of vaginal progesterone have initiated consideration of whether the current standard should be changed.
• Although this document does not mandate universal cervical lengths screening in women without a prior preterm birth, this screening strategy may be considered.
Clinical approach to shortened cervical length

Short cervix noted on TVU

Singleton pregnancies

Prior preterm birth ± 17-OHP wkly inj.

- Prior PTB < 34 weeks: Consider cerclage for CL < 25mm <24wks
- Offer cerclage for CL <15 mm

Multiple gestation*

No prior preterm birth

Vaginal prometrium for CL ≤ 20mm, <24 wks.
Summary

• Transvaginal Ultrasound must be performed for cervical length measurement

• H/o of PTL and high risk cervical history are indications for cervical length measurement

• Follow-up Ultrasound
  – Every 3-4 weeks if normal CL (>3 cm)
  – CL 2-3 cm, repeat in 2 weeks
  – 1-2 cm, repeat weekly, consider progesterone
  – < 1 cm, no follow-up US, perform speculum or digital exam
Summary

- Prior history of PTL, give 17-hydroxy progesterone
  - CL <15 mm, consider cerclage
- No benefit of cerclage in short cervix in the following conditions:
  - Prior normal pregnancy
  - High risk cervical disorder
  - Nulliparous
  - Give vaginal progesterone for CL < 20 mm
- Threatened preterm labor
  - > 3 cm CL, unlikely preterm labor
  - CL < 15 mm < 24 weeks is associated with 30-50% chance of delivery before 34 weeks
Thank you!