Preterm Labor, the Cervix, and Progesterone

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Disclosure of Conflict of Interest

Dr. Hobbins has voluntarily disclosed that he does not have a financial affiliation with any commercial organization.

Nor does he intend to discuss or describe any off-label or investigational use of a medical device or pharmaceutical during this presentation.

The Cervix

Cervical stability depends upon a relationship between collagen and elastin. This, in turn, is affected by the presence of various hormones, cytokines, and infectious agents.
The Cervix

- Cervical length is a predictor of PTL well before labor occurs.

2nd Trimester Cervical Length Measurements (20-24 wks)

- Iams - seminal work
  - 10th percentile 2.5 cm
  - If <2.5 cm, then risk of PTB was 6x greater

2nd Trimester Cervical Length Measurements (20-24 wks)

- Iams (continued)
  - <35 wks
    - Overall population 4.3%
    - If <2.5 cm 17.6%
Cervical Length and Risk of Preterm Birth

Relative Risk (RR) of Preterm Birth for Cervical Length values Compared to those above the 75th Percentile (40 mm):

<table>
<thead>
<tr>
<th>Cervical Length (mm)</th>
<th>At or below Percentile</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>50</td>
<td>2.35</td>
<td>1.42 - 3.89</td>
</tr>
<tr>
<td>30</td>
<td>25</td>
<td>3.79</td>
<td>2.32 - 6.19</td>
</tr>
<tr>
<td>26</td>
<td>10</td>
<td>6.19</td>
<td>3.84 - 9.97</td>
</tr>
<tr>
<td>22</td>
<td>5</td>
<td>9.49</td>
<td>5.95 - 15.15</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>13.99</td>
<td>7.89 - 24.78</td>
</tr>
</tbody>
</table>

The Cervix

- The British Experience (Heath et al)
  - 50% of those delivering <32 weeks had CL of ≥ 1.5 cm

Cervical Shortening

- Cervical shortening generally follows a pattern which is a continuum
- Zilianti - “Trust your vaginal ultrasound”
TYVU
(Trust Your Vaginal Ultrasound)

T-shape / No funneling

T-shape / No funneling
Y-shaped funneling

![Image of Y-shaped funneling](image1)

Y-shaped funneling

![Image of Y-shaped funneling](image2)

Funneling

![Image of Funneling](image3)
V- shaped Funneling

Funneling

Funneling
Cervical Length - How to do it

- Minimal urine in bladder
- Slowly introduce probe; when you meet the cervix, pull back till image blurs then reapply with the slightest pressure—no squishing!
- Take 3 measurements and use "shortest best"
- Do not take average because 1st measure is often 3-5mm longer than 2nd and 3rd
- Scan should last at least 5 min to observe any dynamic changes such as funneling

The Cervix

- Beware of dynamic cervix

Dynamic cervix
Dynamic cervix
Funneling: Its importance

- Funneling is not as strong a predictor of PTB as cervical length – which is affected anyway if funneling is present
- However, it may be useful post cerclage.

Fundal Pressure

- Some studies show relationship with PTB when the cervix is shortened - others, not.
- My experience is that when the cervix shortens with pressure it is a late change in a sequence leading to PTB

CL between 18-24 weeks as a predictor of PTB

- <2.5 cm - odds go up
- <1.5 cm - odds go up a lot
- >3.0 cm - odds go down appreciably
- Much depends upon track record
- (Hx of PTB)
Current Guidelines

- The newest guidelines from AIUM suggest evaluating the “cervix” with every scan.
- But does that mean “with a trans vaginal approach”?

Can one effectively screen with TA scans?

- If CL > 3.5 cm by TAS, 96% chance the TVS will show CL > 2.5 cm.
- If < 3.5 cm by TAS, 40% specific but 100% sensitive for CL < 2.5 cm

- 2. Recent SMFM Abstract from St Louis shows same findings. If CL > 3.5 cm, all CLs by TVS were > 3 cm. Amount of amniotic fluid had no effect on results.

Use of Cervical Length in Patients with Preterm Contractions
Cervical Length

- Most patients presenting with contractions in late pregnancy prior to 36 weeks are NOT in labor.

- Our job is to identify those that are at greatest risk of delivering and then to leave the others alone.

Cervical Length


- 216 pts with painful preterm contractions (24-36 wks)
  - 43 pts - cervical length <1.5 cm
  - 16 of these (37%) delivery < 7 days
  - However, 132 had CL > 1.5 cm and only one delivered within 7 days
  - Negative predictive value of > 99%

Cervical length and preterm labor. Recent additions

- Malamed et al found the relationship between CL and PTB in those with preterm contractions to be only significant in those without a Hx of PTB.
- Ultrasound Obstet Gynecol 2014;661-8. Strong negative predictive value
- Hiersch et al noted that a single cut off (3.5 cm) did not have as strong a negative value for delivery within 14 days as a sliding threshold based on gestational age.
  - 32-34 weeks  3.6 cm
  - 30-32 weeks  3.25 cm
  - 27-29 weeks  2.4 cm
  - 24-26 weeks  2.0 cm
- AJOG 2014; 211: 532-3
Cervical length: the rate of change

- “Preterm labor with pain signifies contractions without prior cervical preparation while preterm labor with little or no pain suggests prior cervical change”.
- Meaning a single snapshot in time tells only a portion of the story

Fetal Fibrinectin
Where does it fit in?

Fibronectin—Earlier study

- It can be helpful
- Collaborative study from Chile and Detroit
  - 215 patients with PT Ctx
    - 20% delivered before 35 weeks
    - If <2.5 cm and fFN positive, 81% delivered <35 weeks
    - If both negative, 2.2% delivered <35 weeks
    - If CL >3 cm, fFN added little
CL and preterm contractions
Very recent study

- CL combined with fFN
- PTC in 702 pts, 12% delivered <7days
- CL<1.5 cm, 47% del < 7 days
- CL>3cm, <1% del < 7 days
- Cl 1.5 - 3.0 cm, and fFN neg, 2.1%<7 d

Van Baaren et al, Obstet Gynecol 2014;123:1185

The Role of Cervical Length in PROM

1. To determine whether or not membranes are actually ruptured
2. To estimate the length of the latent period

Are membranes really ruptured?

1. Assess the integrity of the amnion coursing over the cervix
Intact Membranes

Ruptured Membranes

PROM

Latency Period


- 100 pts pPROM:
  - if CL < 2 cm, average latency period 59 hrs
  - if CL ≥ 2 cm, average latency period 10 days

- 100 pts pPROM:
  - if CL < 2 cm, average latency period 59 hrs
  - if CL ≥ 2 cm, average latency period 10 days
Cervical Length and pPROM: Revisited

- 101 women with pPROM
  - 58 delivered within 7 days
  - Highly correlated with:
    - cervical length
    - presence or absence of contractions
    - gestational age


Cervical Length and pPROM: Revisited

The cervix as an arbiter of whom to treat for prevention of PTL

- Methods of prevention
  - Cerclage
  - Progesterone
  - 17-P
  - Vaginal progesterone gel
  - Pessary
Cerclage, in general

Many studies (and meta-analyses) had failed to show benefit of cerclage
1. In those with history of PTB when done at 13 weeks
2. In those with history of PTB when done later

Cerclage with short cx

- Despite earlier evidence to the contrary, an RCT by Owen et al, Am J Obstet Gynec 2010;201:375 emerged showing benefit in those with Hx of PTB and short cx.

Cerclage (con’t)

- 1014 patients with hx of PTB
- All had CL q 2 weeks 16-24 weeks
- 1/3 had CL <2.5cm
- Half randomized to cerclage or not
Cerclage (con’t)

- Cerclage vs no cerclage
- If CL < 2.5 cm: PTB 32% vs 42%
- If CL 1.5 cm-2.5 cm: OR= 0.84 NS
- If CL < 1.5 cm (in 6.4%); OR= 0.63 ***

Cerclage and PTB
Middle ground (1.5-2.5cm)

- Recent meta-analysis with Owen data added.
- CL 1.5-2.5 cm- significance in 2 categories:
  - PTB <37 weeks (47.5% vs 62%)
  - PTB <24 weeks (6.4% vs 13.6%)

Benefit of cerclage with short CL

1. Effective in those with CL< 1.5 cm with Hx. Maybe in those 1.5-2.5.
2. Is not beneficial in twins with short CL
3. No evidence of benefit in patients without Hx of PTB
4. Not indicated at 13 weeks unless Hx of >2 second trimester losses
Early Cerclage

- Unfortunately, cerclage is invasive and not innocuous as it puts a foreign body in the cervix.
- Study from Chile showed that outcomes were better when decision for cerclage was based on CL in the second trimester, rather than when a cerclage was empirically placed at the end of the first trimester.

So ... what about progesterone?

- 17α OH progesterone caproate (17-P)
  - Initial study by Meis et al in patients with history of PTB
  - Double-blind, placebo-controlled trials of 463 pregnant women with history of sPTD—Treatment with IM 17 P
    - Treatment initiated at 16-20 wks of gestation and continued to delivery or 36 wks gestation
    - Delivery <37 wks of gestation
      - 36.3% vs. 54.9% with placebo (p <0.001)
      - 42% reduction in delivery <32 wks of gestation
      - 11.4% vs. 19.6% with placebo (p = 0.02)
    - Need to treat
      - 6 women with a previous sPTB to prevent 1 birth <37 wks
      - 12 women with previous sPTB to prevent 1 birth <32 wks

Now ...

- Most importantly can progesterone be used effectively in patients with a short cervix?
- Natural progesterone suppositories

Block buster study

- 458 pts with CL 1.0-2.0.
- All comers for screening
- Half got vaginal progesterone suppositories (Prochieve 8%, 90mg) daily. Rest got placebos


Vaginal progesterone RCT (con’t)

- Delivery < 37 weeks: Prog, 8.9% vs placebo, 16.7%, RR= 0.54 (95% CI 0.33-0.92)
- RDS: 3% vs 7.6%, RR= 0.39
- Neonatal M and M: 7.7% vs 13.5% (RR=0.57)
- BW <1500gms: 6.4% vs 13.6% (RR=0.47)
Aftermath of this study

- A Yale study showing cost effectiveness using the above data in all comers
- An FDA challenge re the data
- A brand new study not showing benefit in low risk patients
- A vindication of the data and statistics in the Haasan study

Prevention of PTB

The pessary: an old theory reworked

- Study by Arabin
  - 12 singletons and 23 twins with short CL
  - No births < 32 weeks
- Study by Goya
  - 385 singletons with short CL, half controls and half with pessary
  - Risk of PTB and PPROM reduced appreciably (OR 0.18 and 0.16, respectively)

Pessary in Twins

- An abstract at the SMFM last year suggested the benefit
- A study is now ongoing to evaluate the efficacy of this method
Summary of methods to decrease PTB in patients with short CL

- Cerclage can work in singletons with CL < 1.5 cm, but could double risk in twins
- IM progesterone (17P) can work when CL < 2.0 cm in patients with Hx of PTB. Not in twins
- Vaginal progesterone may work in those with short CL regardless of Hx
- Pessary may work in patients with short Cx and twins, but needs more study

Protocol for patients with singletons and Hx of PTB

1. Workup includes urine culture, BV, and R/O uterine anomalies
2. Start progesterone at 15-16 weeks
3. CL exams q 2 weeks between 18-24 weeks, unless 2.5 cm-3.0 cm, then q 1 week.
4. If CL 1.5-2.5, offer cerclage
5. If CL < 1.5, recommend cerclage

Preterm birth protocol (con’t)

6. If doing cerclage, R/O signs of infection/inflammation
7. Empirical cerclage at 13-14 weeks not recommended unless there is a very worrisome story for early preterm loss (2 or more 2nd trimester losses, or 3 or more 3rd trimester preterm deliveries.)