Management of Shortened Cervix: Progesterone, Cerclage and Pessary

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Disclosure

• No financial relationship with any company whose products will be mentioned.

• No honorarium or speaker bureau relationship with any companies.

• I will be discussing FDA off-label indication for devices.
  – Arabin Pessary, Perforated
Management of Shortened Cervix

• Epidemiology and pathophysiology of PTD
  – Risk factors for PTD
  – Clinical pathway

• Tools for identification/risk stratification

• Treatment:
  – Progesterone
  – Cerclage
  – Pessary
PREVENTION OF PRETERM BIRTH (Singleton)

NO PRIOR PTB

UNIVERSAL TACL SCREENING at 18-24 weeks\(^3\)
if <35mm, do TVCL\(^#\)

CL ≤ 20 mm

CL 21-25 mm

CL >25 mm

Repeat TVCL once in 1-2 weeks\(^2\)

Vaginal Progesterone micronized compounded progesterone, 200 mg q hs through 36 wks with weekly TVCL until 24 wks\(^6,###\)

If further shortening, consider:
- Cerclage pessary\(^5\), vs.
- Exam-indicated cerclage after amniocentesis\(^12\)

Routine OB care

PRIOR PTB (between 20\(^{th}\) - 36\(^{th}/7\) weeks, including PPROM, SPTB, or abruption)

Recommend weekly 17-OHP
250 mg IM weekly, starting at 16-20 wks through 36 wks\(^###\)

Serial TVCL q 2 wks from 16-24 wks (every week if <30 mm)\(^2\)

CL <25 mm\(^3,4\)
(most effective if CL <15 mm)

Offer cerclage and Continue 17-OHP

CL ≥25 mm

Continue 17-OHP

HISTORY OF 1 or MORE SECOND TRIMESTER PREGNANCY LOSS in absence of labor or abruption or PRIOR CERCLAGE

Cerclage at 13-14 weeks\(^10,11\)

REFERENCES
1. Meis, NEJM 2003
2. Iams, NEJM 2014
4. Owen, AJOG 2009
5. Friedman, AJOG 2013
6. Hassan, Uf Obstet Gynecol 2011
7. Fonseca, NEJM 2007
8. Fonseca, AJOG 2003
10. ACOG Practice Bulletin #142
12. Pereira, AJOG 2007

# NOTE: Consider early screening at 16 wks in setting of prior cervical surgery\(^11\)

### NOTE: Consider initiation prior to 25 weeks

### NOTE: If declines injection, offer micronized compounded progesterone, 100 mg q hs through 36 wks\(^4\)
Prematurity

- Leading cause of perinatal morbidity and mortality
- 11.4% of deliveries in the United States
- Multiple gestation, and history of preterm delivery or midtrimester loss remain at highest risk

Martin JA, CDC, 2015
Why Do We Care?

- High rate of long term disability:
  - 20% children with developmental delay
  - 50% of children with cerebral palsy
  - 33% of children with vision impairment
  - Premature Delivery
Risk Factors

- Prior preterm delivery
- Multiple gestation
- Race
- Maternal age
- Genitourinary infection
- Smoking
- Change of partner between pregnancies
- Socio-economic status

Prior preterm delivery:
- 3-4 x increase in risk with one prior PTD
- Increases with each subsequent PTD
- 5-6 fold risk of singletons:
  - 50% of twins born preterm
  - 90% of triplets born preterm

African American women have a HR of 4.9 compared to Caucasian women

May be responsible for up to 50% of PTB prior to 28wks

Goldenbreg, Lancet 2008
Management of Shortened Cervix

• Epidemiology and pathophysiology of PTD

• Tools for identification/risk stratification
  – Transvaginal ultrasound

• Treatment:
  – Progesterone
  – Cerclage
  – Pessary
Prediction of PTB

• Measures sought to increase diagnostic accuracy
  – Transvaginal cervical length (TVUS)
  – Cervicovaginal fetal fibronectin assay (FFN)

• Accuracy depends on the population of women studied
  – Symptomatic women
  – Asymptomatic high risk women (h/o PTB)
  – Asymptomatic low risk women (w/out h/o PTB)
Transvaginal Ultrasound

Progression of cervical effacement
Usually begins at 32 weeks for term deliveries

Iams, NEJM 2014
Zilianti, J Ultrasound Med 1995
Shortened Cervix

- Inverse relationship between cervical length and risk of PTB
- Normal cervix ranges (10-50mm)
  - Median length 35mm
  - 10% = 25mm

Iams, NEJM, 1996
Figure 5. Survival Curves Showing the Duration of Pregnancy among Women Examined at 24 Weeks of Gestation, According to Cervical Length (≤25 mm or >25 mm).

Figure 3. Estimated Probability of Spontaneous Preterm Delivery before 35 Weeks of Gestation from the Logistic-Regression Analysis (Dashed Line) and Observed Frequency of Spontaneous Preterm Delivery (Solid Line) According to Cervical Length Measured by Transvaginal Ultrasonography at 24 Weeks.

Iams, NEJM 1996
## Test Characteristics for Mid-Trimester Cervical Length

### Predictive Values for Preterm Delivery before 35 weeks

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic Women</th>
<th></th>
<th>High Risk Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TVUS (mm)</td>
<td>≤20</td>
<td>≤ 25</td>
<td>≤ 30</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td>23</td>
<td>37</td>
<td>54</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td>97</td>
<td>92</td>
<td>76</td>
</tr>
<tr>
<td>PPV</td>
<td></td>
<td><strong>26</strong></td>
<td><strong>18</strong></td>
<td><strong>9</strong></td>
</tr>
<tr>
<td>NPV</td>
<td></td>
<td>97</td>
<td>97</td>
<td>97</td>
</tr>
</tbody>
</table>

Iams, NEJM 1996

Owens, JAMA 2001

- Positive predictive value is limited in low risk population
- RR of sPTD <35 weeks in high risk women with TVUS CL <2.5 of 3.3 (95% CI 2.1-5.0)
Fetal Fibronectin (FFN)

• FFN in women with symptoms
  – Ability to predict PTB in 7-14 days after the test:
    • PPV = 18% and NPV = 95%  
      Iams, Obstet and Gynecol 2003

• Meta analysis of FFN accuracy in asymptomatic women
  – Median LR for predicting spontaneous PTD <34:
    • +FFN = 3.99 (IQ range = 1.73-10.18)
    • -FFN = 0.38 (IQ range = 0.10-0.69)  
      Honest, BMJ 2002

• Evaluation of multiple markers in prediction of PTB in asymptomatic HR and LR women:
  • Bishop score (>4), CL (<25mm), +FFN
  – No test has a sensitivity >40% in HR or LR women
    Iams, AJOG 2001
Management of Shortened Cervix

- Epidemiology and pathophysiology of PTD
  - Risk factors for PTD

- Tools for identification/risk stratification

- Treatment:
  - Progesterone
  - Cerclage
  - Pessary
Shortened Cervix

No Prior PTB

- Cervical length (CL) \( \leq 20\text{mm} \)
  - Micronized compounded vaginal progesterone
    (Hassan, Ult Obstet Gynecol 2011; Fonseca, NEJM 2007)

Prior PTB

- Weekly 17-hydroxyprogesterone (Meis, NEJM 2003)
- CL <25 mm
  - Offer cerclage (Berghella, Obstet Gynecol 2011; Owen, AJOG 2009)
**Prevention of Preterm Birth (Singleton)**

### NO PRIOR PTB

**Universal TACL Screening**
- at 18-24 weeks
- if <35mm, do TVCL

- **CL < 20mm**
  - Vaginal Progesterone micronized compounded progesterone, 200 mg q hs through 36 wks with weekly TVCL until 24 wks
  - Routine OB care
  - If further shortening, consider:
    - Cerclage pessary
    - Exam-indicated cerclage after amniocentesis

- **CL 21-25 mm**
  - Repeat TVCL once in 1-2 weeks
  - Routine OB care

- **CL > 25 mm**
  - Continue TVCL

### PRIOR PTB

**(between 20\(\frac{0}{7}\) – 36\(\frac{6}{7}\) weeks, including PPROM, SPTB, or abruption)**

- Recommend weekly 17-OHP
  - 250 mg IM weekly, starting at 16-20 wks through 36 wks

- **Serial TVCL q 2 wks from 16-24 wks**
  - (every week if <30mm)

- **CL < 25 mm**
  - (most effective if CL < 15 mm)
  - Offer cerclage and Continue 17-OHP

- **CL > 25 mm**
  - Continue 17-OHP

### HISTORY OF 1 or MORE SECOND TRIMESTER PREGNANCY LOSS in absence of labor or abruption or PRIOR CERCLAGE

- Cerclage at 13-14 weeks

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**REFERENCES**

1. Meis, NEJM 2003
2. Iams, NEJM 2014
3. Bergthold, Obstet Gynecol 2011
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5. Friedman, AJOG 2013
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# NOTE: Consider early screening at 16 wks in setting of prior cervical surgery

## NOTE: Consider initiation prior to 25 weeks

### NOTE: If declines injection, offer micronized compounded progesterone, 100 mg q hs through 36 wks
No Prior Preterm Birth

Vaginal Progesterone versus Placebo with Mid-Trimester Shortened Cervix (<15 mm)

- 200 mg vaginal progesterone nightly
- 44% Reduction in PTD <34 weeks
  Fonseca, NEJM 2007

- RCT with 44 centers and 10 countries
  - Vaginal progesterone in asymptomatic singleton pregnancies with TVUS CL <20 mm, <24 weeks
  - 45% reduction in PTD <33 weeks, P = 0.02
  Hassan, Ult Obstet Gynecol 2011
What if cervical shortening is progressive?

- Exam-induced cerclage
  - After amniocentesis to rule out intra-amniotic infection
- Cerclage pessary
PREVENTION OF PRETERM BIRTH (PTB)

NO PRIOR PTB

UNIVERSAL TAACL SCREENING at 18-24 weeks\(^5\)
if <35 mm, do TVCL\(^#\)

CL ≤ 20 mm

CL 21-25 mm

CL > 25 mm

Repeat TVCL once in 1-2 weeks\(^3\)

Vaginal Progesterone micronized compounded progesterone, 200 mg q hs through 36 wks with weekly TVCL until 24 wks\(^6,7,##\)

If further shortening, consider:
- Cerclage pessary\(^9\), vs.
- Exam-indicated cerclage after amniocentesis\(^12\)

NOTE: Consider early screening at 16 wks in setting of prior cervical surgery\(^13\).

NOTE: Consider initiation prior to 25 weeks.

## HISTORY OF 1 or MORE SECOND TRIMESTER PREGNANCY LOSS in absence of labor or abruption or PRIOR CERCLAGE

Cerclage at 13-14 weeks\(^10,11\)

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Prior Preterm Delivery

• Reduction in sPTD <37 weeks among asymptomatic HR women
  – **34%** reduction in PTD with weekly IM 17-hydroxyprogesterone caproate (Meis, NEJM 2003)
    • Initiate 250 mcg 17-OHP injections between 16-20 weeks, continue through 36 weeks
  – **60%** reduction in PTD with progesterone vaginal suppositories (da Fonseca, AJOG 2003)
    • 100 mg per vagina nightly
When should we offer a cerclage with a prior PTD?

Survival Curves, CL <25 mm

Survival Curves, CL <15 mm

Reduction in PTD <35 weeks in cerclage patients:

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL &lt;25 mm</td>
<td>0.84</td>
<td>(0.49 – 1.40)</td>
</tr>
<tr>
<td>CL &lt;15 mm</td>
<td>0.23</td>
<td>(0.08 – 0.66)</td>
</tr>
</tbody>
</table>

TVUS < 15 mm: 77% reduction in sPTD

Owen, AJOG 2009
Berghella, Obstet Gynecol 2011
**PRIOR PTB**
**(between 20^{0/7} - 36^{6/7} weeks, including PPROM, SPTB, or abruption)**

**Recommend weekly 17-OHP**
250 mg IM weekly, starting at 16-20 wks through 36 wks

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**Serial TVCL**
qu 2 wks from 16-24 wks
(every week if <30mm)

**CL <25 mm**
(most effective if CL <15 mm)

**Offer cerclage and Continue 17-OHP**

**CL >25 mm**

**Continue 17-OHP**

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**# # # NOTE:** If declines injection, offer micronized compounded progesterone, 100 mg q hs through 36 wks

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**NOTE:** Consider early screening at 16 wks in setting of prior cervical surgery

**NOTE:** Consider injection prior to 25 weeks
Cerclage Pessary

Mechanical support:

- Maintains the physiologic angle between the cervix and uterus
- Displaces the uterine weight on the pelvis
Clinical Trials: Pessary vs. no treatment

- PECEP trial in Spain (n=385)
  - Cerclage pessary for CL < 25 mm
  - Reduction in PTB < 34 weeks
    - 6% VS 27% (OR 0.18, p<0.0001)

- Reduction not supported by 2 subsequent trials
  - Hui, et al (n=108)
    - 9.4% and 5.5% (p = 0.46)
  - Nicolaides, et al (n=932)
    - 12.0% and 10.8% (p=0.57)

Nicolaides, *NEJM* 2016
Open questions

• Is there a subgroup of patients that would benefit from the pessary?

• Appropriate comparison:
  • What about cerclage vs pessary?
Hypothesis

The efficacy of cervical pessary is similar to cerclage in women with an ultrasound detected mid-trimester shortened cervix as measured by:

- Delivery prior to 34 weeks
- Gestational age at delivery
- Previable delivery (prior to 24 weeks)
Methods: Study Population

• Retrospective chart review
  – Swedish Medical Center, Maternal Fetal Medicine
  – August 2010 – August 2016
  – Patients identified by procedure CPT code
  – IRB exemption obtained

• Chart abstraction for clinical variables
  – Progesterone supplementation, tocolysis or other intervention at discretion of physician

• Clinical consent process included discussion of non-FDA approved use of pessary
## Inclusion/Exclusion

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton non-anomalous pregnancies</td>
<td>Planned termination of pregnancy</td>
</tr>
<tr>
<td>Dating confirmed by ACOG criteria prior to 16w</td>
<td>Clinical features consistent with labor, abruption, chorioamnionitis, or preeclampsia at enrollment</td>
</tr>
<tr>
<td>Cervical length &lt;25 mm between 16w0d to 26w0d</td>
<td>Cervical dilation</td>
</tr>
</tbody>
</table>
Methods: Study Population

• Sample size calculation:
  – Expected ratio of cerclage to pessary: 3:1
  – Assume 24% preterm delivery rate < 34 wks in setting of cerclage (Berghella, Obstet Gynecol 2005)
  – 80% power to detect 15% reduction in preterm delivery rate < 34 weeks
    • Sample size: 153 cerclage and 51 pessary patients
<table>
<thead>
<tr>
<th></th>
<th>Pessary Group (n=44)</th>
<th>Cerclage Group (n=81)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior PTD &lt;24 wks, n (%)</td>
<td>3 (7) 16%</td>
<td>34 (42) 60%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior PTD 24-34 wks, n (%)</td>
<td>4 (9)</td>
<td>21 (26)</td>
<td>0.012</td>
</tr>
<tr>
<td>GA at CL&lt; 25mm, (wks) mean ± SD</td>
<td>21.1 ± 2.4</td>
<td>19.4 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GA at intervention, (wks) mean ± SD</td>
<td>23.0 ± 2.1</td>
<td>20.4 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CL at intervention, (mm) mean ± SD</td>
<td>10.0 ± 5.4</td>
<td>12.2 ± 6.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Progesterone, n (%)</td>
<td>44 (100)</td>
<td>74 (91)</td>
<td>0.089</td>
</tr>
</tbody>
</table>
## Results: Primary Outcomes

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<tr>
<td>PTB &lt;34 weeks, n (%)</td>
<td>15 (34)</td>
<td>15 (19)</td>
<td>0.052</td>
</tr>
<tr>
<td>GA at delivery, (wks) mean ± SD</td>
<td>35.5 ± 4.6</td>
<td>36.5 ± 4.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Preivable delivery &lt;24 weeks, n (%)</td>
<td>1 (2)</td>
<td>3 (4)</td>
<td>0.99</td>
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### Results: Primary Outcomes

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<tr>
<td>PTB &lt;32 weeks, n (%)</td>
<td>9 (21)</td>
<td>12 (15)</td>
<td>0.42</td>
</tr>
<tr>
<td>PTB &lt;28 weeks, n (%)</td>
<td>3 (7)</td>
<td>5 (6)</td>
<td>0.89</td>
</tr>
<tr>
<td>PTB &lt;24 weeks, n (%)</td>
<td>1 (2)</td>
<td>3 (4)</td>
<td>0.99</td>
</tr>
</tbody>
</table>
# Results: Secondary Outcomes

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<th>Pessary Group (n=44)</th>
<th>Cerclage Group (n=81)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorioamnionitis n (%)</td>
<td>1 (2)</td>
<td>7 (9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Medically indicated PTB, n (%)</td>
<td>6 (14)</td>
<td>14 (17)</td>
<td>0.59</td>
</tr>
<tr>
<td>Neonatal survival to hospital discharge, n (%)</td>
<td>42 (98)</td>
<td>77 (96)</td>
<td>0.99</td>
</tr>
<tr>
<td>Interval: intervention to delivery (days), mean ± SD</td>
<td>87.6 ± 34</td>
<td>112.5 ± 32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPROM, n (%)</td>
<td>15 (34)</td>
<td>9 (11)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Conclusions

- Cerclage may be superior to pessary at reducing the incidence of preterm delivery
- PPROM was significantly more common in the pessary group
  - Biologically plausible:
    - Mechanical
    - Exposed membranes with continued dilation
    - Change in microbiome with pessary in place
Conclusions

• Mean latency between intervention and delivery in the cerclage group was longer than pessary group
  – Not significant when adjusted for those with history of PTD and <24 weeks at intervention

• Identification of a subgroup who may benefit from pessary:
  – Shortened cervix at periviability not responsive to progesterone
PREVENTION OF PRETERM BIRTH (Singleton)

NO PRIOR PTB

- UNIVERSAL TACL SCREENING at 18-24 weeks³
  - if <35mm, do TVCL #

  - CL < 20mm
  - CL 21-25 mm
  - CL >25 mm

  - Repeat TVCL once in 1-2 weeks²
  - Vaginal Progesterone micronized compounded progesterone, 200 mg q hs through 36 wks with weekly TVCL until 24 wks⁶,7,###
  - Routine OB care

  - If further shortening, consider:
    - Cerclage pessary⁶, vs.
    - Exam-indicated cerclage after amniocentesis¹²

# NOTE: Consider early screening at 16 wks in setting of prior cervical surgery⁴

### NOTE: Consider initiation prior to 25 weeks

PRIOR PTB (between 20⁷/⁸ - 36⁶/⁷ weeks, including PPROM, SPTB, or abruption)

- Recommend weekly 17-OHP
  - 250 mg IM weekly, starting at 16-20 wks through 36 wks⁴,###

  - Serial TVCL q 2 wks from 16-24 wks (every week if <30mm)³

  - CL <25 mm³,⁴ (most effective if CL <15 mm)

  - Offer cerclage and Continue 17-OHP

  - CL >25 mm

  - Continue 17-OHP

HISTORY OF 1 or MORE SECOND TRIMESTER PREGNANCY LOSS in absence of labor or abruption or PRIOR CERCLAGE

- Cerclage at 13-14 weeks¹⁰,¹¹

REFERENCES
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