To Screen or Not to Screen: Cervical Length and Progesterone

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Disclaimer
- No discussion of off label use of FDA products
- No partnership or ownership of stock or vested interest
- Have served as consultant and Advisory Board member for TherRx and Watson Pharmaceuticals

Objective
- Clinical relevance and epidemiology of short cervix
- Review of clinical trials regarding use of progesterone to prevent preterm birth in women with short cervix
- Discuss current ACOG and SMFM guidelines

PTB rate in US 1990-2008

CDC/NCHS, May 2010
2010 Premature birth report cards

PTB: Quick Facts
- > 500,000/yr PTB in US
- 1 out of every 8 births
- Societal cost of PTB > $26 billion

Born Too Soon and Too Small in the United States

<table>
<thead>
<tr>
<th>In An Average Week in the United States</th>
<th>10,512</th>
<th>1,693</th>
<th>6,814</th>
<th>1,235</th>
</tr>
</thead>
<tbody>
<tr>
<td>babies are born prematurely</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>babies are born very premature</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>babies are born low birthweight</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>babies are born very low birthweight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Why is a short cervix important?

Iams et al. NEJM (2003)
Risk of PTB with “short cervix”

<table>
<thead>
<tr>
<th>Author (Yr)</th>
<th>Cervix</th>
<th>PTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassan (2001)</td>
<td>&lt; 15 mm</td>
<td>60% ≤ 34 wks</td>
</tr>
<tr>
<td>De Fonseca (2007)</td>
<td>&lt; 15 mm</td>
<td>21% ≤ 34 wks</td>
</tr>
<tr>
<td>Hassan (2011)</td>
<td>10-20 mm</td>
<td>9% &lt; 33 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30% &lt; 37 wks</td>
</tr>
<tr>
<td>Grobman (2012)</td>
<td>&lt; 30 mm</td>
<td>9% &lt; 32 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25% &lt; 37 wks</td>
</tr>
</tbody>
</table>

Short Cervix “Powerful” Predictor PTB

Trans-vaginal ultrasound best method to assess cervix in mid-trimester

Mid-trimester identification allow for treatment to prevent or delay PTB

How do you measure the cervix with ultrasound?

Definition of “short cervix” varies across different studies and populations:
examples: < 25 mm (high risk), < 30 mm (low risk)

What is cervical funnel?
What is a dynamic cervix?

What do the RCT’s indicate?

- Recruitment at UK, Brazil, and Greece
- Sept 2003 to May 2006
- Sponsored by Fetal Medicine Foundation

Eligibility Criteria

- Inclusion criteria
  - GA 20-24 wks
  - Singleton or twins
  - Cervical length ≤ 15 mm

- Exclusion criteria
  - Major anomalies, cerclage in situ, contractions, PROM

Treatment Protocol

- Tx GA 24 wks until 34 wks
- Self-administered capsule every evening
- Vaginal progesterone (200 mg) qd
  - Capsules of micronized progesterone
  - Utrogestan, Besins International Belgium
- Placebo
  - Identical-appearing capsules containing safflower oil (Medicaps)

Characteristics of Study Population

- Nulliparous women = 55%
- Parous with no PTB = 28%
- Parous with > 1 PTB = 15%
- Twins = 9%
- Cx length at randomization = 11-12 median
  - Inter-quartile range = 9-14.

Rate of PTB < 34 wks

- RR 0.56 (95% CI 0.36-0.86)
- Vag progesterone
- Placebo

Comments

- Heterogeneous population
  - Twins (~10%)
  - Prior PTB (~15%)
- Timing of cervical length = 20-24 wks
- Timing of progesterone therapy = Start at 24 wks
- Dose of vaginal progesterone = 200 mg daily

3 Key facts on RCT

1. Of women with cx ≤ 15 mm, PTB < 34 wks ~ 20%
2. Compliance high; minimal side effects; no safety issues
3. Need to screen 413 pts to treat 7 women with Cx ≤ 15 mm to prevent 1 case PTB < 34 wks

Eligibility Criteria

- Inclusion criteria
  - Singleton
  - GA 19 wks 0 days to 23 wks 6 days
  - Cx length 10-20 mm
- Exclusion criteria
  - Underlying medical complications
  - Major anomalies
  - Planned cerclage**
  - PTL symptoms or cervical dilation
  - Prior Tx progesterone

** Emergency cerclage allowed for certain Pts
**Treatment Protocol**

- Start GA 20 - 24wks
- Stop treatment at PROM or 37 wks
- Self-administered study medications every morning
- Vaginal progesterone (90 mg)
  - Prochieve 8%/Crinone 8% progesterone gel
  - A prefilled, single-use, disposable plastic applicator
- Placebo (Replens)

**Characteristics of Study Population**

- Nulliparous women = 55%
- Parous with no PTB= 87%
- Parous with > 1 PTB = 13%
- Twins = none
- Cx length at randomization = 18 median
  - Inter-quartile range = 15-19.

**PTB Outcomes**

- Primary outcome PTB < 33 wks
  - RR 0.55 (95% CI 0.33-0.92)
  - Number needed to treat (NNT)= 14
**Neonatal Outcomes**

Hassan *et al.* (UOG 2011)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vag Progesterone</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Morbidity</td>
<td>7.7%</td>
<td>3%</td>
<td><em>P</em> = 0.043</td>
</tr>
<tr>
<td>RDS</td>
<td>13.5%</td>
<td>6.5%</td>
<td><em>P</em> = 0.026</td>
</tr>
<tr>
<td>BPD</td>
<td>7.6%</td>
<td>1.7%</td>
<td><em>P</em> = 0.678</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2.2%</td>
<td>2.7%</td>
<td><em>P</em> = 0.853</td>
</tr>
</tbody>
</table>

**3 Key facts on RCT**

1. Cx 10-20 mm, PTB < 34 wks ~ 20%
2. Compliance high; minimal side effects; no safety issues
3. Need to screen 616 women to prevent 1 PTB < 33 wks

**Limitations**

1. Study does not address women with Cx < 10 mm or 20-30 mm
2. Study included women with prior PTB, prior cervical surgery, and thus NNS maybe much higher (less efficient) for nulliparous or parous women without PTB

**Last Key Fact**

4. There were NO differences in PTB < 33 wks in women with a prior PTB (20-35 wks)
   - Vaginal progesterone = 15.8% [6/38]
   - Placebo = 20.6% [7/34]
   - Relative Risk 0.77, 95% CI 0.29-2.06; P=0.60

Hassan *et al.* (UOG 2011)
Meeting of the Advisory Committee for Reproductive Health Drugs

January 20, 2012

Lisa Soule, MD
Clinical Team Leader
Division of Reproductive and Urologic Products

Is Efficacy Consistent across Countries?

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

<table>
<thead>
<tr>
<th>Country (N)</th>
<th>Placebo</th>
<th>Progesterone 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>
<tr>
<td>So. Africa (21)</td>
<td>36.4%</td>
<td>0.0%</td>
<td>-36.4%</td>
</tr>
<tr>
<td>Belarus (11)</td>
<td>50.0%</td>
<td>0.0%</td>
<td>-50.0%</td>
</tr>
<tr>
<td>India (149)</td>
<td>7.9%</td>
<td>2.7%</td>
<td>-5.2%</td>
</tr>
<tr>
<td>Ukraine (54)</td>
<td>3.8%</td>
<td>0.0%</td>
<td>-3.8%</td>
</tr>
<tr>
<td>Others* (18)</td>
<td>16.7%</td>
<td>8.3%</td>
<td>-8.4%</td>
</tr>
</tbody>
</table>

* Others include Chile (2), Czech Republic (4), Israel (3), Italy (8) and Russia (1)

Primary Endpoint: Preterm Birth at < 33 Weeks Gestation
Study 302 (ITT)

<table>
<thead>
<tr>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicant Analysis</td>
<td>0.56 (0.33, 0.93)</td>
</tr>
<tr>
<td>FDA Analysis</td>
<td>0.62 (0.37, 1.02)*</td>
</tr>
</tbody>
</table>

- Applicant analysis adjusted for risk strata & primary pool site
- FDA analysis adjusted for region (US vs. non-US), maternal age & cervical length

* CI of RR includes 1, indicating there is no significant reduction in preterm birth at < 33 weeks gestation
FDA Review

- Not FDA approved for use in US
  - Advisory and formal panel reports
  - Additional studies necessary
- Rationale
  - Did not meet threshold for approval as a single RCT
  - Statistical questions with analysis (post-hoc adjustments)
  - Potential spurious results at 2 low recruiting non-US sites drive findings of benefit

Randomized controlled trial of progesterone treatment for preterm birth prevention in nulliparous women with a short cervical length (CL).

Objective: To determine whether 17 alpha hydroxyprogesterone caproate (17-OHPc) reduces preterm birth in nulliparous women with a short cervical length (CL).

Methods: In this multicenter randomized controlled trial, nulliparous women with a singleton gestation between 16 and 22 3/7 weeks underwent transvaginal ultrasound CL measurement by centrally certified sonographers. Consenting women with a CL <30 mm (<10th percentile in gestational age range) were randomly assigned to either 17-OHPc (250 mg IM weekly through 36 weeks) or an identically appearing placebo. The primary outcome was preterm birth before 37 weeks (PTB).

Results: Of 15,436 screened women, 1,588 (10.3%) had a CL <30 mm. The DSMB halted the study after 657 women had been randomized (N=327 17-OHPc and 330 placebo) due to a planned interim analysis that revealed further enrollment was statistically very unlikely to demonstrate a significant difference between the groups. The frequency of PTB did not differ between the 17-OHPc and placebo groups (25.1% vs 25.2%, P = 0.80). There also was no difference in delivery <35 weeks (13.3% vs 16.1%, P = 0.35) or <32 weeks (8.6% vs 9.7%, P = 0.61). While the power to show a difference was limited, subgroup analyses failed to demonstrate benefit from 17-OHPc in women with a CL <15 mm or at 10-20 mm.

Conclusions: Weekly IM 17-OHPc does not reduce the frequency of PTB in nulliparous women with a short cervix <30 mm and should not be used for this indication.
**PTB Outcomes**

![Graph showing PTB outcomes for 17P and Placebo groups](image)

**Grobman et al SMFM 2012**

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**Is Vaginal Progesterone Therapy Cost-Effective?**

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**Table 1** Summary of results of Werner et al.'s decision-analytic model: effect (per 100,000 women) of universal cervical-length screening/vaginal progesterone administration, compared with no screening in 2010

<table>
<thead>
<tr>
<th>Original analysis (Fonseca et al.(^1) data)</th>
<th>Re-analysis(^*) (Hassan et al.(^1) data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost savings</td>
<td>$12,119,947</td>
</tr>
<tr>
<td>QALY gained</td>
<td>424</td>
</tr>
<tr>
<td></td>
<td>$19,603,380</td>
</tr>
<tr>
<td></td>
<td>735</td>
</tr>
</tbody>
</table>

Table provided by Dr Erica Werner. \(^*\)Assumes a reduction in preterm birth with progesterone in women with cervical length 1.5–2.5 cm. QALY, quality of life years.
How would prenatal care change if we adopted Hassan RCT protocol?

1. Routine vaginal ultrasound screening for low-risk women is not currently performed
   - Trans-abdominal approach inadequate
   - Thus will need to do in >75% of singleton pregnancies
   - Additional time for routine scans (productivity, access)

2. Screening policy may add additional interventions
   - Another Cx length if Cx is slightly above 20mm
   - Perform cerclage for short cervix

3. May require delay in timing of routine prenatal ultrasound for fetal anatomy (or additional scans)
   - ACOG recommends anatomy survey at 18-20 wks

Advocates of Screening

Doing something positive for PTB prevention

- Two RCT's demonstrated positive results
- 17P was widely endorsed prior to FDA approval
- Don't need to do screening RCT: efficacy RCT + CEA are adequate evidence
- Vaginal progesterone relatively inexpensive + low side effects
- Screening of Cx length is tolerated by pts, relative inexpensive, and reliable
- Given huge consequences and cost of PTB, the strategy of screening + Tx makes sense to readily adopt

What are current ACOG and SMFM guidelines?
Incidently Detected Short Cervical Length

ABSTRACT: Occasionally, a short cervical length may be incidently detected during transabdominal scanning of the lower uterine segment. The American College of Obstetricians and Gynecologists and the American Institute of Ultrasound in Medicine recommend that a cervical length measurement be performed at the time the ultrasound examination is undertaken for fetal anatomic survey at around 18-22 weeks of gestation. It also is recommended that a subsequent transvaginal ultrasound examination be performed to confirm the presence of a short cervix length, defined as less than or equal to 20 mm or 14-28 weeks of gestation. Cervical length measured by transvaginal ultrasound examination is a useful screening test for predicting spontaneous preterm birth. Once a short cervix length is confirmed, the patient’s risk factors for preterm birth should be reviewed, specifically, the number of fetuses and a history of spontaneous preterm birth, for a discussion of management options. Ideally, transvaginal ultrasound examination of cervical length should be used as a screening test in clinical care only when interventions that reduce the risk of subsequent preterm birth in the event of a positive result (i.e., short cervix length) are available. The utility of universal cervical length screening for the prevention of preterm birth is controversial and is being debated.

TABLE 9

Current Society for Maternal-Fetal Medicine recommendations regarding use of progesterone for prevention of preterm birth

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation regarding use of progesterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>No evidence of effectiveness</td>
</tr>
<tr>
<td>Singleton without prior preterm birth and abnormal cervix length</td>
<td>No evidence of effectiveness</td>
</tr>
<tr>
<td>Singleton with prior preterm birth</td>
<td>17P 250 mg IM weekly from 16-20 weeks until 36 weeks</td>
</tr>
<tr>
<td>Singleton without prior preterm birth but with short cervix length &lt;2 cm at &lt;24 weeks</td>
<td>Vaginal progesterone 9g/mg gel or 200-mg suppository daily from diagnosis of short cervix until 36 weeks</td>
</tr>
<tr>
<td>Multiple gestations</td>
<td>No evidence of effectiveness</td>
</tr>
</tbody>
</table>

Symptomatic

<table>
<thead>
<tr>
<th>Condition</th>
<th>No evidence of effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic inflammatory disease</td>
<td>No evidence of effectiveness</td>
</tr>
</tbody>
</table>

17P: 17 alpha hydroxyprogesterone capsule; CL, cervical length; IU, intramuscularly; PPROM, preterm prematurity; t(17p), paternal carrier of t(17p), presumed present at fertilization; (P), placebo; (T), transdermal testosterone; SMFM: Progesterone and preterm birth. Jama Obstet Gynecol 2012.
ARGUMENT AGAINST PARADIGM SHIFT

Adoption of routine (universal) cervical length screening in low risk women to reduce PTB is premature and NOT support by available evidence.

Lack of Evidence

- No RCT addressed the question regarding EFFECTIVENESS of cervical length screening
  - Fonseca #2
  - Pregnant Trial
- Only evaluated EFFICACY once short cervix identified

Trial Profile

<table>
<thead>
<tr>
<th>Hassan et al. UOG 2011 Apr 6.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Singleton</strong></td>
</tr>
<tr>
<td>GA 20-24 wks</td>
</tr>
<tr>
<td>N= 32,091</td>
</tr>
<tr>
<td><strong>Cx 10-21 mm</strong></td>
</tr>
<tr>
<td>N=733</td>
</tr>
<tr>
<td><strong>Randomized</strong></td>
</tr>
<tr>
<td>N=465</td>
</tr>
<tr>
<td><strong>Declined or exclusion criteria</strong></td>
</tr>
<tr>
<td>N=268 (36.6%)</td>
</tr>
<tr>
<td><strong>Vaginal Progesterone</strong></td>
</tr>
<tr>
<td>N=236</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>N=229</td>
</tr>
<tr>
<td><strong>Subjects Analyzed</strong></td>
</tr>
<tr>
<td>N=235</td>
</tr>
<tr>
<td><strong>Subjects Analyzed</strong></td>
</tr>
<tr>
<td>N=223</td>
</tr>
</tbody>
</table>

Lost to follow-up

N=1

Lost to follow-up

N=6
Question

How could cervical length screening cause increased harm or costs?

Potential utilization outcomes

- Health care visits or interventions
  - Repeat or follow-up ultrasound examination
  - Hospitalizations and/or triage visits
  - Treatment for PTL
  - Cervical cerclage
- Other
  - Activity restriction (s)
  - Off-work

Theoretical models (decision analysis) do not adequate answer question RCT feasible, and necessary

Industry Sponsored Trials

- Why do companies do studies?
  - To show their drug works
  - To expand the indications
  - To show its better than other drugs/devices
- Study design to optimize chance for (+) findings
  - Narrow, Inclusion criteria (10-21 mm)
  - Multiple small recruitment sites
  - Attempt to expand threshold to 25 mm after trial
RCT’s are necessary to answer the question regarding EFFECTIVENESS of routine screening

Independent RCT’s should be conducted by trialists with clinical equipoise and designed to answer important clinical question (not primary for drug approval)

Why Scrutinize “New Therapy”?

• Emotional Investment
• Financial Investment
• Academic Investment

1. Clinical algorithm for > 3 million pregnancies per Yr
2. Difficult to STOP therapy once on-going

SCRUTINY
• Critical appraisal + > 1 independent RCT
• FDA approval process

Potential Risks of Adopting Without Adequate Scrutiny

• Unknown or unintended harm
  – Repeat antenatal corticosteroids
  – Treatment BV to prevent PTB
  – Electronic fetal monitoring

• Therapy in reality NOT effective
  • Fetal pulse oximetry
  • Cerclage for short cervix
  • Anti-oxidants for PIH, Omega 3 for PTB

6 Reasons to NOT start screening

1. Flaws in existing trials combined with FDA denial
2. Neither RCT evaluated screening: efficacy of treatment doesn’t prove effectiveness
3. Shouldn’t underestimate potential non compliance and overuse of screening and treatment
4. Huge public health consequences if incorrect
5. RCT’s, not CEA should guide Tx decisions (unless can’t do RCT)
6. We have been wrong in the past and can’t go back
**Table 1** | Probability and utility estimates in support of the model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female birth at 38 weeks</td>
<td>0.1 (0.0–0.1)</td>
</tr>
<tr>
<td>Male birth at 38 weeks</td>
<td>0.1 (0.0–0.1)</td>
</tr>
<tr>
<td>Probability of preterm delivery <strong>&lt; 34 weeks</strong></td>
<td>0.1 (0.0–0.1)</td>
</tr>
<tr>
<td>Probability of preterm delivery <strong>34–37 weeks</strong></td>
<td>0.1 (0.0–0.1)</td>
</tr>
<tr>
<td>Probability of preterm delivery <strong>38–40 weeks</strong></td>
<td>0.1 (0.0–0.1)</td>
</tr>
</tbody>
</table>

**Table 2** | Cost estimates of the model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range (2019)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical-length ultrasound scan (cost per scan)</td>
<td>$70 (50–100)</td>
</tr>
<tr>
<td>Vaginal progesterone supplementation (total cost for gestation)</td>
<td>$205 (100–400)</td>
</tr>
<tr>
<td>Admission cost for short cervix, including corticosteroids</td>
<td>$0 (0–10,000)</td>
</tr>
<tr>
<td>Cost of maternal care if delivery at <strong>&lt; 20 weeks</strong></td>
<td>$10,951 (5,767–23,907)</td>
</tr>
<tr>
<td><strong>≥ 20 weeks, &lt; 34 weeks</strong></td>
<td>$815 (407–1,607)</td>
</tr>
<tr>
<td><strong>≥ 34 weeks, &lt; 37 weeks</strong></td>
<td>$442 (224–925)</td>
</tr>
<tr>
<td><strong>≥ 37 weeks</strong></td>
<td>$3,577 (1,789–7,555)</td>
</tr>
<tr>
<td>Cost of neonatal care if delivery at <strong>&lt; 20 weeks</strong></td>
<td>$207,927 (87,251–419,922)</td>
</tr>
<tr>
<td><strong>≥ 20 weeks, &lt; 34 weeks</strong></td>
<td>$37,139 (13,231–78,129)</td>
</tr>
<tr>
<td><strong>≥ 34 weeks, &lt; 37 weeks</strong></td>
<td>$469 (223–1,092)</td>
</tr>
<tr>
<td><strong>≥ 37 weeks</strong></td>
<td>$1,056 (241–3,643)</td>
</tr>
<tr>
<td>Cost of early intervention (0–3 years if delivery at <strong>&lt; 20 weeks</strong></td>
<td>$847 (442–1,769)</td>
</tr>
<tr>
<td><strong>≥ 20 weeks, &lt; 34 weeks</strong></td>
<td>$420 (210–948)</td>
</tr>
<tr>
<td><strong>≥ 34 weeks, &lt; 37 weeks</strong></td>
<td>$162 (85–228)</td>
</tr>
<tr>
<td><strong>≥ 37 weeks</strong></td>
<td>$562 (331–1,723)</td>
</tr>
<tr>
<td>Cost of severe disability <strong>≥ 20 weeks</strong></td>
<td>$245,664 (61,533–525,335)</td>
</tr>
<tr>
<td>Income and domestic productivity losses due to bed rest</td>
<td>$0 (0–13,505)</td>
</tr>
</tbody>
</table>

**Notes**: *Range of values used in sensitivities and Monte Carlo simulations.*