Are Preterm Birth Prevention Strategies Effective? Yes…. No…. Maybe…..

UAB Progress in Ob/Gyn
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Learning Objectives

1. Appreciate important aspects of PTB epidemiology
2. Describe previously studied, ineffective interventions-the NO’s
3. Understand why PTB prevention research and clinical applications have become increasingly complex and frustrating
4. Be able to consider current effective prevention strategies

PTB Epidemiology

Preterm Birth Categories

- Spontaneous-Singleton: 55%
- Spont-Multiple Gestation: 20%
- Indicated: 2%

No Disclosures

- No Professional Conflicts
- No Financial Affiliations

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PTB Epidemiology

Preterm Birth Categories

- Spontaneous-Singleton: 55%
- Spont-Multiple Gestation: 20%
- Indicated: 2%
Risk Factors for sPTB

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Conditions</th>
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<tbody>
<tr>
<td>High</td>
<td>Prior “early” SPTB (Cervical Insufficiency)</td>
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<tr>
<td></td>
<td>Multiple Gestation</td>
</tr>
<tr>
<td></td>
<td>Shortened cervix/Cone Biopsy/multiple LEEP</td>
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<tr>
<td></td>
<td>Midtrimester “Bleeding”</td>
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<tr>
<td></td>
<td>Threatened PTL (+) fetal fibronectin</td>
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<tr>
<td></td>
<td>Uterine Anomalies</td>
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<tr>
<td></td>
<td>African American Ethnicity</td>
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<tr>
<td></td>
<td>UTI</td>
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<tr>
<td></td>
<td>Clinical “Symptoms”</td>
</tr>
<tr>
<td></td>
<td>BV/HPV/STDs</td>
</tr>
<tr>
<td>Med</td>
<td>Low/High Maternal BMI</td>
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<tr>
<td></td>
<td>ART</td>
</tr>
<tr>
<td></td>
<td>Periodontal Dz</td>
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<tr>
<td></td>
<td>Single (Small) LEEP</td>
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<tr>
<td></td>
<td>Smoking/drugs</td>
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<tr>
<td></td>
<td>Depression</td>
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<tr>
<td></td>
<td>Family Hx</td>
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<tr>
<td>Lo</td>
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Aren’t we all in search of this?

- Cerclage
- Progesterone (P4, 17-OHP)
- Pessary
- Mix & Match!

Strategic Interventions

- Home Uterine Activity Monitoring
- Teeth Cleaning
- Tocolytic medications
- Vitamins/supplements
- “Cadillac” care, stress reduction, etc.
- Antibiotics for ASx BV/TV, etc.

Cerclage Indications

- History
- Ultrasound Cervical Length
- Physical Exam
- Prior Cerclage Failures

History-indicated Cerclage

- Traditional approach (since 1950’s)
- Cervical insufficiency is a clinical diagnosis
- Little Randomized controlled data
- Can be replaced by serial CL and Ultrasound-Indicated cerclage for short CL

No

1. Home Uterine Activity Monitoring
2. Teeth Cleaning
3. Tocolytic medications
4. Vitamins/supplements
5. “Cadillac” care, stress reduction, etc.
6. Antibiotics for ASx BV/TV, etc.
7. Fetal fibronectin
8. Bed Rest
MRC/RCOG Multicentre Randomized Cerclage Trial

- N=1,292 “Risk factors” for Cervical Insufficiency, i.e. Physicians “unsure” if cerclage indicated
- Preterm Birth < 33 wks lower with cerclage: 13% vs 17%
- Risks: Increased medical interventions and puerperal fever
- 25 procedures to prevent one PTB < 33 wks

MRC/RCOG Multicentre Randomized Cerclage Trial

- Twin Gestation
- Cervical surgery
- Singletons-other
- (1) prior PTB/MT loss
- (2) prior PTB/MT losses
- (3) prior PTB/MT losses

<table>
<thead>
<tr>
<th>Effect</th>
<th>N</th>
<th>Effect</th>
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<tbody>
<tr>
<td>8% v. 31%</td>
<td>28</td>
<td>19% v. 22%</td>
</tr>
<tr>
<td>8% v. 10%</td>
<td>269</td>
<td>14% v. 17%</td>
</tr>
<tr>
<td>12% v. 14%</td>
<td>196</td>
<td>15% v. 32%</td>
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</tbody>
</table>

U/S-Indicated Cerclage: Benefit in Hi-risk women

- Level 1 data:
  - NICHD Cerclage Trial, 2009
  - Prior SPTB (16 - 33 wks)
  - Serial vaginal scans begin ~16 wks
  - If Cx Length < 25 mm at < 23 wks: Randomized to U/S-Indicated Cerclage

Owen, 2009

Effect of Randomization Cervical Length

- Cerclage for shortened CL (< 25 mm) effective only in singletons and only in women with a history of prior sPTB:
  - PTB < 35 wks, RR= 0.7
  - PN Composite M&M, RR=0.64
  - Harmful in Twins – Relative Risk = 2.2

Berghella, 2005, 2011
Clinical research suggested no benefit; outcomes research suggested harm

2019 Meta-analysis of 16 studies suggested ultrasound-indicated cerclage for CL (<15 mm) or physical exam-induced cerclage for dilation > 1 cm significantly prolonged pregnancy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Weeks Gained</th>
<th>PTB &lt; 34 Rel. Risk</th>
</tr>
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<tbody>
<tr>
<td>CL &lt; 15 mm</td>
<td>+3.9</td>
<td>0.57</td>
</tr>
<tr>
<td>A.C.I. &gt; 1 cm Dilated</td>
<td>+6.8</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Cerclage for Twins with short CL?

Randomized Cerclage Trial: Emergency Cerclage with Bed rest vs. Bed rest alone

- Entry < 27 weeks
- Cervix dilated – Membranes at E.O.
- N=23 (13 cerclage, 10 bed rest)
- Singletons and multiples
- Empiric Indocin and Augmentin for 1 wk
- McDonald Stitch (1 intraop ROM)
- Bed Rest until 30 weeks

Randomized Trial of Abdominal vs Repeat Transvaginal Cerclage

- RCT- 3 Cerclage arms
- Prior 14-28 wk birth with TV cerclage
- 9 centers in U.K., 6 years!
  1. Transabdominal (Benson)
  2. Low vaginal (McDonald)
  3. High vaginal (Shirodkar)

Randomized Trial of Abdominal vs Repeat Transvaginal Cerclage

- N= 39 39 33
- PTB < 32 wks 8% 38% 33%
- PTB < 34 wks 10% 46% 39%
- Fetal loss 3% 21% 21%

Survival Curves, P=.03

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Abd</th>
<th>Hi Vag</th>
<th>Lo Vag</th>
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</thead>
<tbody>
<tr>
<td>PTB &lt; 32 wks</td>
<td>8%</td>
<td>38%</td>
<td>33%</td>
</tr>
<tr>
<td>PTB &lt; 34 wks</td>
<td>10%</td>
<td>46%</td>
<td>39%</td>
</tr>
<tr>
<td>Fetal loss</td>
<td>3%</td>
<td>21%</td>
<td>21%</td>
</tr>
</tbody>
</table>
Pessary Strategies

- Prior sPTB
- Cervical shortening
- (arrested preterm labor)

Pessaries for PTB Prevention

- Arabin Pessary
- Bioteque Pessary

Pessary for Short CL: Meta-Analysis of 9 RCTs

Singletons Relative Risks and 95% CI

- (GBR) Nicolaides, 2016: 1.1 (0.8, 1.6)
- (CHN) Hui, 2012: 1.7 (0.4, 7)
- (ESP) Goya, 2012: 0.24 (0.1, 0.4)
- (USA) Dugoff, 2017: 1.1 (0.6, 1.9)
- (ITA) Saccone, 2017: 0.48 (0.2, 0.95)

Overall: 0.72 (0.57, 0.9)

Progesterone Strategies (P4, 17-OHP)

- Prior sPTB
- Cervical shortening
- (arrested preterm labor)

Is Anyone Here Surprised?

The PROLONG Trial

- Double-blind RCT, Phase 3, Pharma-funded
- 2:1 active:placebo, patterned after 2003 NICHD MFMU “Meis” trial, IM 250 mg 17-OHP weekly
- 93 centers in 9 countries, 9 years!
- Participants ≥ 1 Prior sPTB
- 1,130 received 17-OHP, 578 placebo (450 U.S.)
- Primary outcome - birth < 35 weeks
  - 17-OHP 11.0% Placebo 11.5%
  - 2003: 17-OHP 36% Placebo 55%
FDA versus Makena

- Expert panel recommended withdrawing approval
- FDA requirements were not satisfied
- No trial is perfect!
- Will Insurance keep paying for it? (~$10k/preg)
- Will compounding shops start making it again?
  Will the FDA let them?
- Will patients demand it?
- What will ACOG & SMFM say about it?
- If it’s not harmful, Should we use it anyway?

Vaginal Progesterone vs 17-OHP to Prevent Recurrent sPTB

- Randomized trial – All Prior sPTB, N=518
- IM 17-OHP: 250 mg/wk vs. Vaginal P4: 90 mg/d

How Effective is C.L. Screening?

Cutoff ≤20 mm for PTB<32 wks

| 14.9% Sensitivity | 1.2% FPR | 8.6% PPV |

Multinational Trial of 90 mg Vaginal Progesterone (P4) Gel for Shortened C.L.

- Phase III trial - 44 centers in 10 countries
- Screened 32,091 women (2.2% C.L. 10-20 mm)
- N=458: Randomized-Daily VagP4 gel v. Placebo

<table>
<thead>
<tr>
<th>% PTB&lt;33 Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Vag P4</td>
</tr>
<tr>
<td>16.1</td>
</tr>
<tr>
<td>8.9</td>
</tr>
</tbody>
</table>

| RR=0.56 |

44% PTB Reduction

Hassan, 2011

Meeting of the FDA Advisory Committee for Reproductive Health Drugs

- Overall, in the FDA analysis, the Rx effect of P4 gel vs. placebo was not statistically significant for either PTB <33 weeks or the neonatal morbidity index; the applicant analysis showed only marginal significance
- The FDA analysis showed large variations in treatment effect of P4 gel across countries and by maternal age.
- In both the FDA and Applicant analyses, P4 gel did not significantly reduce the rate of preterm birth at any evaluated gestational age or improve the neonatal morbidity/mortality index in U.S. subjects (45% of total)
Committee Opinions-Singletons

ACOG PB#130, 2012-reaffirmed 2016

- Does not mandate universal screening in women with no prior sPTB, but this strategy may be considered.
- Vaginal P4 recommended as management option to reduce PTB in asymptomatic women with singletons & incidentally identified CL ≤ 20 mm, at ≤ 24 weeks’ GA.

SMFM Guideline, 2012-reaffirmed 2016

- There are no data regarding effectiveness of universal screening for short cervix followed by vaginal P4 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 (efficacy) trial.
- Cervical length screening in singletons w/o prior sPTB cannot yet be mandated universally.

Committee Opinions-Multiples

ACOG PB#130, 2012-reaffirmed 2016

- Progesterone does not reduce the incidence of preterm birth in women with twin or triplet pregnancy and is not recommended (Level A)
- Cerclage may increase the risk of preterm birth in women with a twin pregnancy and a cervical length < 25 mm and is not recommended (Level B)

Yes

1. Ultrasound-indicated Cerclage for short cervix in Hi-risk Women, i.e. prior sPTB or a cervical insufficiency Hx, +/- progesterone
2. Physical Exam-indicated cerclage for acute cervical insufficiency in singletons
3. Transabdominal Cerclage for prior vaginal cerclage “failures” (rare, specialized training)
Maybe (OK)

1. Daily vaginal P4 for short CL in low-risk (U.S.) women (??Universal screening??)
2. Daily Vaginal P4 for Hi-risk women (i.e. prior sPTB) instead of 17-OHP
3. Cerclage backup for vaginal P4 “failures”
4. Cerclage in twins for very short CL < 15 mm or acute cervical insufficiency

NICHD MFMU Network Trials

• TOPS - RCT: 2 Arms
  ➢ Singletons with CL ≤ 20 mm + Vag P4 (412/850 enrolled)
  1. Arabin pessary
  2. No Pessary
• PROSPECT - RCT: 3 Arms
  ➢ Twins with CL < 30 mm (293/630 enrolled)
  1. Vag P4
  2. Arabin Pessary
  3. Control (placebo vag P4)

PTB Prevention: One Strategy?

1) Assess risk factors for sPTB
   • Prior sPTB, Multiples, Modifiable?
2) Assess ongoing Symptoms
   • Pressure, vag d/c, bleeding, Ctx.
3) Cervical evaluations
   • Ultrasound (CL), Physical exam, Both
   • U/S: Indicated v. Universal screening
4) “Best” intervention
   • Cerclage, Progesterone, Both?

Who’s Better, Who’s Best?

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Yes…. No…. Maybe…..

Thank You!

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Stepwise Approach?

- Limited research data
- Makes biologic “sense”
- Use cerclage for progesterone “failures”
- What’s a “failure”

**Pathways**

**FACTORS**

- Preterm Labor
- External Environment
- Medical Interventions
- Nutrition
- Medical Conditions
- Immune Status
- Behaviors
- Psychosocial
- Genetics/Family History/Race

**PRETERM BIRTH**

**Spontaneous PTB Package**

**Levels of Prevention**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Primary</th>
<th>Secondary</th>
<th>Tertiary</th>
</tr>
</thead>
<tbody>
<tr>
<td>An intervention implemented before there is any evidence of Dz</td>
<td>An intervention implemented after the Dz has begun but is ASx</td>
<td>An intervention implemented after the Dz is established</td>
<td></td>
</tr>
<tr>
<td>Reduce or eliminate causative risk factors</td>
<td>Early identification by screening Rx (+)</td>
<td>Attenuate Dz severity Reduce/prevent sequelae</td>
<td></td>
</tr>
<tr>
<td>Ablate/Attenuate known PTB risk factors (i.e. preconception)</td>
<td>Treat ASx shortened cervical length</td>
<td>Tocolytics, corticosteroids for NN benefit</td>
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</tr>
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**Randomized Cerclage Trial: Emergency Cerclage with Bed rest vs. Bed rest alone**

<table>
<thead>
<tr>
<th></th>
<th>Cerclage</th>
<th>Bed rest</th>
<th>P</th>
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<tbody>
<tr>
<td>Mean entry GA</td>
<td>22.2</td>
<td>23.0</td>
<td>NS</td>
</tr>
<tr>
<td>Days gained</td>
<td>54 ± 47</td>
<td>20 ± 28</td>
<td>.046</td>
</tr>
<tr>
<td>Delivery GA</td>
<td>30</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>NN Survival</td>
<td>9/16</td>
<td>4/14</td>
<td>NS</td>
</tr>
<tr>
<td>NN Morbidity</td>
<td>10/16</td>
<td>14/14</td>
<td>.02</td>
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*Althuisius, 2003*