Preventing Preterm Birth

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Disclosures

• None

Preterm Birth

• An estimated 15 million babies are born preterm and this number is rising.

• Leading cause of death among children under 5 years of age (approximately 1 million deaths in 2015).

• Three-quarters of these deaths could be prevented with current, cost-effective interventions.

• Across 184 countries, the rate ranges from 5% to 18% of babies born.

WHO 2018
Preterm Births

• Adoption of fertility practices that reduce the likelihood of multi fetal pregnancies

• Adherence to guidelines IOL only for medical indications

• Progesterone and cerclage in women with a previous PTB

Mechanisms of Preterm Birth

Traditional Model of Contractions as the Initial Step Preceding Is Challenged by the following observations:
Mechanisms of Preterm Birth

• Current therapies to treat preterm labor are largely ineffective.

• Treatment of preterm birth has focused on inhibiting myometrial contractions.

• Growing body of clinical and animal studies now suggests that premature cervical shortening or ripening might be the primary mechanism.

Cervical Ripening (short cervix)
Driven by inflammation in the early second trimester is the most common initial manifestation.

How should women with a previous spontaneous preterm birth be evaluated for risk of subsequent preterm birth?

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- Evaluate obstetrical history
- Most common sequence for spontaneous PTB cervical ripening (short cervix) followed decidual-membrane activation and contractions.
- Review of medial records
  - Obstetrical: eg, preeclampsia, IUGR
  - Medical: eg, chronic hypertension, lupus
  - Fetal: eg, aneuploidy, polyhydramnios, fetal death

Risk Factors and Associations PTB
- Smoking
- Extremes of bodyweight
- Social disadvantage
- Maternal depression
- Pregnancy stress
- Poor diet
- Assisted fertility
- Periodontal disease

NEJM 370:3 January 16, 2014
Smoking Cessation

- Baby & Me: Tobacco Free™ babyandmetobaccofree.org
- The Smoking Cessation and Reduction in Pregnancy Treatment (SCRIPT) Program. A pregnant woman’s guide to quit smoking. Commit to quit smoking during and after pregnancy (a motivational DVD with stories from pregnant smokers who quit), counseling and assistance to create a non-smoking home. Visit sophe.org
- Telephone quitlines. www.cdc.gov/tobacco/quit_smoking/cessation/quitlines for more information.
- The 5 A’s (Ask, Advise, Assess, Assist and Arrange). The Agency for Healthcare Research and Quality (AHRQ) recommends this short intervention, a “gold standard” for pregnant women. There are a number of published studies documenting its effectiveness as a brief intervention model. Visit acog.org to view the Smoking Cessation eToolkit and learn more about the 5A’s.

History

- Prior pregnancy between 16 and 20 weeks — risk of recurrent preterm birth that = or exceeds the RR for women whose prior preterm birth occurred after 20 weeks.
- Women with a prior stillbirth are also often considered separately from those with a prior preterm birth — The risk of subsequent spontaneous preterm birth is also greater.
History

• The earlier the gestational age, the greater the risk of PTB

• Ranging from minimal if any for a twin birth after 34 weeks' versus 40% when the prior twin birth occurred before 30 weeks.

Interventions supported by firm evidence

• Smoking-cessation programs

• Screening and treatment for asymptomatic bacteriuria

• Prophylactic administration of progestational agents.

• Cervical cerclage

• Antenatal administration of corticosteroids
Screening Modalities

- The single most important predictor of preterm birth is a short cervix.
- In a review of 39,284 cases of preterm birth (<37 wk), short cervix was most important single predictor of preterm birth.

*Ultrasound Obstet Gynecol 2006; 27: 362–367*
How should the current pregnancy be managed in a woman with a prior spontaneous preterm delivery?

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Progestational Agents and the Prevention of Preterm Birth

Meis et al, US, 17OHP administration significantly reduces recurrent preterm birth.
DaFonseca et al, Brazil, Vaginal progesterone administration reduces preterm delivery in high risk patients.


Fonseca et al, UK, Vaginal progesterone administration reduces spontaneous premature delivery in women with a short cervix.

Elovitz 2008

Meis et al, NEJM 2003

• Women with a documented history of spontaneous preterm birth at less than 37 weeks
• Treatment started between 16 and 20 weeks
• Continued until 36 weeks or delivery

TABLE 1

Proposed mechanisms of action reported for progestogens to prevent preterm birth

- Stimulate transcription of ZEB1 and ZEB2, which inhibit connexin-43 (gap-junction protein that helps synchronize contractile activity and oocyte-receptor gene
- Decrease prostaglandin synthesis, infection-mediated cytokine production, and inflammatory effects by fetal membranes/placenta
- Changes in PR-A and PR-B expression (decreased PR-A/PR-B ratio keeps uterus quiescent)
- Membrane-bound PR in myometrium
- PRs, when stimulated by progesterone, help select and promote, or prevent binding of other factors
- Interferes with cortisol-mediated regulation of placental gene expression
- Non-genomic pathways
- Reduce cervical stromal degradation in cervix
- Alter barrier to ascending inflammation/infection in cervix
- Reduce contraction frequency in myometrium
- Alternates response to hemorrhage/inflammation in decidua
- Alter estrogen synthesis in fetal membranepicocites
- Alter fetal endocrine-mediated effects

Elovitz 2008
• 17P history of preterm birth at less than 37 weeks. (mean = delivery of index pregnancy 30.7 weeks).

• N = 306 to 17P and n = 153 placebo.

Meis et al, NEJM 2003

• PTB < 37 weeks 36.3% in progesterone vs 54.9% placebo
• PTB < 35 weeks 20.6% in progesterone vs 30.7% placebo
• PTB < 32 weeks 11.4% in progesterone vs 19.6% placebo

Meis et al, NEJM 2003

• NNT = 5 to prevent PTB before 37 weeks, NNT = 12 for PTB before 32 weeks.

• Progesterone group had less BW<2500 g, NEC, need for supplemental O2, and IVH.

• Results greatest for women with a prior PTB < 34 weeks.

Meis et al, NEJM 2003
Spong et al, Am J Obstet Gynecol 2005

• High rate of PTB in placebo group (36.3%)

• Study population was an especially high-risk group of women
17 – hydroxyprogesterone caproate

• While the best evidence for efficacy is for 17P to be started 21 weeks, beneficial effects have been reported when 17P is started by 27 weeks.

• 17P should **not be stopped early** as this is associated with increased incidence of PTB.
• MC, RCT examined role serial TV CL with cerclage placement for those with a short cervix
• Patients with singleton and history of spontaneous preterm birth at less than 34 weeks
• CL q 2 weeks starting at 16 weeks thru 23 weeks
• If length between 25 and 29 mm screening increased to q week.

• Primary Outcome was PTB at 35 weeks
  – No significant difference RR, 0.78; 95% CI, 0.58-1.04
• However, cerclage was associated with a reduction in:
  – Deliveries before 24 weeks RR, 0.44; 95% CI, 0.21-0.92
  – Deliveries before 37 weeks RR, 0.75; 95% CI, 0.60-0.93
  – Perinatal death RR, 0.54; 95% CI, 0.29-0.99

• Secondary Analysis
  – Cerclage for cervical length less than 15mm was associated significant decrease in preterm birth at less than 35 weeks (RR, 0.23; 95% CI, 0.08-0.66)
Should a woman with a current singleton pregnancy without a history of preterm birth be screened for a risk of preterm birth?

**Proponents**
- Potential to reduce preterm birth
- High quality evidence exists to support efficacy of treatment for positive test results (cervical length 20 mm or less)
- Cost Effective
- Safe
- Reliable (reproducible, variability <10%)
- Recognizable early asymptomatic phase
- Valid (accuracy of prediction)
- Accepted by patients (> 90% of pts)
- Widely available

**Opponents**
- Quality assurance of screening test
- Lack of availability of screening and patient access to qualified imaging
- Patient for patients to receive unnecessary interventions
What interventions have been shown to be beneficial for reducing the risk of preterm birth in women who do NOT have a history of preterm birth but who are found to have a short cervical length?

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**Progesterone and Short Cervix**

- Multicenter RCT
- Women underwent CL screening at 20-25 weeks (median 22 weeks)
- 1.7% of 24,640 screened CL less than or equal to 15 mm
- Excluded fetal anomalies, uterine contractions, ROM, cerclage
- Women with CL 15 mm or less randomized to: vaginal micronized progesterone 200 mg every night vs placebo between 24 and 34 weeks

**Progesterone and Short Cervix**

- 90% of the women in the study had a singleton
- 85% had no prior preterm birth
- Less PTB < 34 weeks in progesterone group (19.2 vs 34.4%; RR, 0.56; 95% CI, 0.36-0.86)
- 44% decrease in spontaneous preterm birth at less than 34 weeks

*The New England Journal of Medicine*

Original Article

Progesterone and the Risk of Preterm Birth among Women with a Short Cervix

Eduardo F. Forero, M.D., Elisabeth Celik, M.D., Mario Pena, M.D., Manjot Singh, M.D., and Kyrene H. Hockaday, M.D., for the Fetal Medicine Foundation Second Trimester Screening Group

King MD (3): www.nejm.org August 1, 2003
Progesterone and Short Cervix

- Number need to avoid one spontaneous preterm birth < 34 week
- Screen - 387
- Treat - 7

Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix
Hassan et al., UOG 2011

Phase III, prospective, randomized, placebo-controlled, double-masked, parallel-group, multi-center, international trial.

Objective
To determine the efficacy and safety of vaginal progesterone gel in reducing the rate of PTB < 33 weeks in asymptomatic women with a mid-trimester sonographic short cervix.

Methodology

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Singleton</td>
<td>1) Planned cerclage</td>
</tr>
<tr>
<td>2) GA 19th – 23rd weeks</td>
<td>2) Acute cervical dilation</td>
</tr>
<tr>
<td>3) Cervical length (TV US): 10 – 20 mm</td>
<td>3) Allergy to progesterone</td>
</tr>
<tr>
<td>4) Asymptomatic (no symptoms or signs of preterm labor)</td>
<td>4) Recent progestogen treatment (within 4 weeks)</td>
</tr>
<tr>
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<td>5) Chronic medical conditions</td>
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<td>6) Major fetal anomaly or chromosomal abnormality</td>
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<td></td>
<td>7) Uterine malformations</td>
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<td></td>
<td>8) Vaginal bleeding</td>
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<td></td>
<td>9) Known/suspected chorioamnionitis</td>
</tr>
</tbody>
</table>
**Primary study outcome**

**Adjustment for study site and risk strata**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ITT analysis</th>
<th>Treated patient</th>
<th>Compliant analysis</th>
<th>P value</th>
<th>P value</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Preterm birth</strong></td>
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<tr>
<td>PTB &lt; 28 weeks</td>
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<td>NS</td>
<td>0.04</td>
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<tr>
<td>PTB &lt; 33 weeks</td>
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<td>0.02</td>
<td>0.01</td>
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<td></td>
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<tr>
<td>PTB &lt; 35 weeks</td>
<td>0.02</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PTB &lt; 37 weeks</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
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<tr>
<td><strong>Neonatal morbidity</strong></td>
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<tr>
<td>RDS</td>
<td>0.03</td>
<td>0.04</td>
<td>NS</td>
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<td></td>
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<tr>
<td>Any morbidity/mortality</td>
<td>0.04</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>Birth weight &lt; 1500g</td>
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<td>0.01</td>
<td>0.01</td>
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</tbody>
</table>

Journal Club slides prepared by Dr Asma Khalil (UOG Editor for Trainees)

**Progesterone for the prevention of preterm birth in women with short cervix**

N = 458
Cervix: 10 to 20 mm (median 15.1 mm)
GA: 20 – 22+6 weeks (median 21 weeks)
Progestrone: Bioadhesive gel 90 mg PV daily
Duration: 20 – 34 weeks
No serious adverse events

N = 550
Cervix: ≤ 15 mm (median 11.5 mm)
GA: 20 – 22 weeks (median 22 weeks)
Progestrone capsule 200 mg PV daily
Duration: 20 – 34 weeks
No serious adverse events

Journal Club slides prepared by Dr Asma Khalil

**Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix**

Hassan et al., UOG 2011

**Clinical utility – Number needed to treat (NNT) to prevent adverse outcome**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone for prevention of PTB &lt; 33 weeks*</td>
<td>14</td>
</tr>
<tr>
<td>Progesterone for prevention of RDS†</td>
<td>22</td>
</tr>
<tr>
<td>MgSO4 for prevention of eclampsia†</td>
<td>100</td>
</tr>
<tr>
<td>Antenatal steroids for prevention of RDS‡</td>
<td>13</td>
</tr>
</tbody>
</table>

*Hassan S et al., UOG 2011
†Altman D et al., Lancet 2002
‡Sinclair JC et al., AJOG 1995

Journal Club slides prepared by Dr Asma Khalil (UOG Editor for Trainees)

**Should cerclage placement be considered in women who do NOT have a history of preterm birth but who are found to have a short cervical length? (closed internal os)**

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Incidentally detected short cervical length is not diagnostic of cervical insufficiency
  – Cerclage is not indicated

Vaginal progesterone is recommended in this population

Cerclage placement in women WITHOUT a prior spontaneous preterm birth and a cervical length less than 25 mm detected between 16 and 24 weeks has not been associated with a significant reduction of preterm birth. (Level A)

Vaginal progesterone is recommended in this population

Cerclage placement in women WITHOUT a prior spontaneous preterm birth and a cervical length less than 25 mm detected between 16 and 24 weeks has not been associated with a significant reduction of preterm birth. (Level A)

Cerclage

Low-risk population, cerclage cervical length less than 25 mm
  – 16–24 weeks of gestation has not been associated with a significant reduction in preterm birth at less than 35 weeks of gestation [RR, 0.76; 95% CI, 0.52–1.15]

Cerclage for detection of a cervical length of 15 mm or less
  – 22–24 weeks of gestation has not been shown to significantly decrease the rate of preterm birth at less than 33 weeks of gestation [RR, 0.84; 95% CI, 0.54–1.31]

Does cerclage placement or progesterone treatment decrease the risk of preterm birth in women with multiple gestations?
• Progesterone treatment does not reduce the incidence of PTB in women with twin or triplet gestations.

• Cervix may increase the risk of PTB in women with a twin pregnancy and an US detected cervical length less than 25 mm.

Choosing Wisely® is an initiative of the ABIM Foundation
to help physicians and patients engage in conversations to reduce overuse of tests and procedures, and support physician efforts to help patients make smart and effective care choices.

Does a pessary in women with a short cervix decrease the risk of preterm birth?
Pessary

• One trial of women with an incidentally diagnosed short cervix
  — less than or equal to 25 mm at 18–22 weeks of gestation

• open-label randomization: cervical pessary or expectant management (no pessary)

• 385 women, the rate of spontaneous delivery at less than 34 weeks of gestation was significantly lower in the pessary group than in the no pessary group (6% compared with 27%; OR, 0.18; 95% CI, 0.08–0.37).


Pessary

• If the results of this small trial are validated, cervical pessary placement may have additional benefit for prevention of preterm birth in otherwise low-risk women with a short cervix.

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Birth Spacing

• Wait until at least 18 months before getting pregnant again.
• Use effective birth control.
• Take a multivitamin with 400 micrograms of folic acid in it every day before and during pregnancy.
• Get to a healthy weight before pregnancy.
• Get a preconception checkup.
  – Medication Review
  – Family health history
  – Vaccinations
  – high blood pressure or diabetes, under control before pregnancy.

https://beyondthepill.ucsf.edu/educational-materials
Summary

- All women with a singleton and a prior history of spontaneous PTB should be offered progesterone supplementation starting between 16 – 24 weeks.

- Regardless of TV ultrasound cervical length, to reduce the risk of recurrent preterm birth.

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Summary

- Vaginal progesterone can reduce the risk of preterm birth in asymptomatic women with a singleton without prior PTB and short cervix less than or equal to 20 mm before or at 24 weeks.

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The New England Journal of Medicine

Initial prenatal visit
- Comprehensive obstetrical history
- Ultrasonographic confirmation of gestational age and number of fetuses

Is there a history of spontaneous preterm birth?
(i.e., a singleton live birth at 18^{th}-36^{th} wk of gestation or stillbirth before 24 wk presenting as labor, ruptured membranes, advanced cervical dilatation, or effacement)

Yes
- Prescribe 17OHPC, 250 mg IM weekly from 16^{th}-36^{th} wk of gestation
- Measure TVCL every 14 days from 16-24 wk of gestation, every 7 days if CL <30 mm

If TVCL <25 mm before 24 wk of gestation:
- Consider cerclage suture, especially if patient had prior spontaneous preterm birth at <28 wk or if membranes are visible
- Continue progesterone treatment

TVCL >25 mm
- Provide routine prenatal care

TVCL 21-25 mm
- Measure TVCL once more in 7-14 days
- Have TVCL performed by credentialed ultrasonographer

TVCL ≥20 mm
- Prescribe vaginal progesterone daily (200-mg capsules or suppositories or 90-mg gel) until 36 wk of gestation

No
- Is this a singleton pregnancy?

Yes
- Does the patient have signs or symptoms of parturition (e.g., persistent pelvic pressure, cramps, or spotting or vaginal discharge)?
- Progestogens are ineffective and cerclage may increase the risk of preterm birth

No
- Use one of the following suggested site-specific screening strategies:
  - Universal TVCL screening at 18-24 wk of gestation
  - Universal TACCL screening at 18-24 wk of gestation, until CL <35 mm
  - Selective TVCL screening of women with the following risk factors:
    - Prior preterm birth at <34 wk of gestation with unknown cause, or twin birth
    - History of genitourinary infection
    - Concepcion with fertility drugs
    - Black race
    - Previous cervical surgery
    - BMI <19.6 or >35.0
    - Renal disease

TVCL >25 mm
- Provide routine prenatal care

TVCL 21-25 mm
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