Prevention of Preterm Delivery:

Progestosterone, Cerclage, and Pessaries

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Preterm Birth

- Single most important cause of perinatal mortality (28 weeks gestation through 6 days of life) in the U.S. (accounts for approx 75% of these losses)
- Leading cause of neonatal mortality (0-27 days) in U.S.
- Second leading cause of infant mortality in U.S.
- Leading cause of black infant mortality in U.S.
- Major determinant of neonatal and infant illness.
- Major contributor of short and long term morbidity and disability.

Source: National Center for Health Statistics, period linked birth/infant death data
Prepared by March of Dimes Perinatal Data Center, 2006
Preterm Births

- Adoption of fertility practices that reduce the likelihood of multifetal 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 Riepening (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?
• Evaluate obstetrical history

• Most common sequence for spontaneous PTB cervical ripening (short cervix) followed decidual-membrane activation and contractions.

• Review of medial records
  – Obstetrical: e.g., preeclampsia, IUGR
  – Medical: e.g., chronic hypertension, lupus
  – Fetal: e.g., aneuploidy, polyhydramnios, fetal death

Risk Factors and Associations PTB

• Smoking
• Extremes of bodyweight
• Social disadvantage
• Maternal depression
• Pregnancy stress
• Poor diet
• Assisted fertility
• Peridontal disease

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
History

- Gyn Hx: Cervical Surgery

- Ovulation promotion (clomiphene) and stimulation (gonadotropins) – associated with a 2-fold increased risk of PTB

- Superovulation /fresh eggs has a GREATER risk of preterm birth than does use of frozen eggs.


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

Mothers with a prior preterm birth

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 women with a prior spontaneous preterm delivery?

Practice Bulletin No. 130 ACOG

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.

2003

2007

Elovitz 2008
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.

Meis et al, NEJM 2003

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 women 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 intervention 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?
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

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**

**Inclusion criteria**

1) Singleton
2) GA 19\textsuperscript{th} – 23\textsuperscript{rd} weeks
3) Cervical length (TV US): 10 – 20 mm
4) Asymptomatic (no symptoms or signs of preterm labor)

**Exclusion criteria**

1) Planned cerclage
2) Acute cervical dilation
3) Allergy to progesterone
4) Recent progestogen treatment (within 4 weeks)
5) Chronic medical conditions
6) Major fetal anomaly or chromosomal abnormality
7) Uterine malformations
8) Vaginal bleeding
9) Known/suspected chorioamnionitis

**Outcomes**

Primary outcome
- Preterm birth <33 weeks

Secondary outcomes
- Neonatal morbidity
  - RDS
  - Bronchopulmonary dysplasia
  - Intraventricular hemorrhage (Grade III or IV)
  - Periventricular leukomalacia
  - Sepsis
  - Necrotizing enterocolitis
  - Perinatal mortality
  - PTB <28, <35, and <37 weeks
  - Neonatal biometry at birth
  - Congenital abnormalities

**ITT analysis**

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Neonatal morbidity

RDS 0.03 0.04 NS
Any morbidity/mortality 0.04 NS NS
Birth weight < 1500g 0.01 0.01 NS

*Primary study outcome

†Adjustment for study site and risk strata

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

- 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)

Does cerclage placement or progesterone treatment decrease the risk of preterm birth in women with multiple gestations?

• 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]


• Progesterone treatment does not reduce the incidence of PTB in women with twin or triplet gestations.

• Cerclage 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.

ClinicalTrials.gov

- 7 trails actively recruiting
  - Pessary to Prevent Prematurity in Twins in Case of Short Cervix
  - Cerclage vs Cervical Pessary in Women With Cervical Incompetence
  - Prevention of Preterm Birth in Pregnant Women at Risk Identified by Ultrasound: Evaluation of Two Treatment Strategies
  - Arabin Cervical Pessary for Prevention of Preterm Birth in Cases of Twin-to-twin Transfusion Syndrome Treated by Fetoscopic Selective Laser Coagulation: The PECEP Laser Trial
  - Prevention of Preterm Birth With a Pessary in Twin Gestations
  - Prevention of Preterm Birth With a Pessary in Singleton Gestations
  - Efficacy Study of a Cervical Pessary Containing Progesterone for the Prevention of Preterm Delivery

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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.