Preterm birth
Risk assessment &
The role of biomarkers in prediction

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Risk factors

- Identification of modifiable and nonmodifiable risk factors for PTB before conception or early in pregnancy
  - 2/3 occur among women with no risk factors
  - no adequate animal model
Risk factors
reproductive history

• history of spontaneous preterm birth (sPTB) or late abortion, particularly it is highest when the previous sPTB was early (23-27 weeks)
• Women who were born preterm
• A prior sPTB of twins
• Prior indicated PTB
• A short interpregnancy interval
• History of surgical uterine evacuation (???)
Risk factors
Genetic factors

• PTB susceptibility genes
• Women who were born preterm
• Women with a first degree female relative who had a PTB

• Paternal factors: NO paternal risk factors
Risk factors

• Age: in extremes of maternal age
• Cervical surgery: laser or cold knife conization, LEEP
• Diagnosis of precancerous change
• Uterine malformations: congenital (bicornuate, double uterus, uterine septum, T shaped uterus) & acquired (myoma)
• Chronic medical disorders
Risk factors

- Previous infant with sudden infant death syndrome & prior still birth
- Assisted reproduction: even in the absence of multifetal gestation
- Multifetal gestation: indicated and spontaneous
- Vaginal bleeding in early pregnancy: increased risk for both indicated and spontaneous PTB, PPROM, abruption, severe preeclampsia
- Pregnancies are complicated by a vanishing twin or unexplained elevation in maternal serum α fetoprotein
Risk factors

Infection

• Asymptomatic bacteriuria: unclear? Probably NO
• Perio dental disease:???, can be epidemiologically linked but not causally related
• Genital tract infection/colonization: GBS, chlamydia, .....????
• BV and preterm labor
• Candida species colonization is not a risk factor for PTB
Risk factors

• Short cervix at 16 to 28 weeks: inverse relationship (both singleton and twin)
• High Bishop score on digital examination: increased odds of PTB
• Dilated cervix: ≥ 1 cm before 24 weeks
• Occupational physical activity: OR 1.1 to 1.6 for all studies
• Exercise: not associated with an increased risk of PTB, optimal time: 2-4 hours /week, exercise may reduce PTB by reducing oxidative stress or increasing placental vascularization
• Coitus: not a risk factor
• Low socioeconomic status
Risk factors

• Smoking: indirectly (placenta abruption, PROM, ....) & directly
• Substance use: increase the risk of PTB
• Low pre pregnancy BMI, poor weight gain in pregnancy
• Women who are overweight or obese
• Height: increased risk with shorter stature
Risk factors

• Stress: ???, when stress has been associated: OR: 1.42
• Environment: fine particulate matter, ozone, high temperature, phthalate exposure – the effects are small
• Suboptimal prenatal care: is a risk factor, it is less clear whether this association is causal or a marker for other factors
• Fetal factors: male sex, congenital anomalies, growth restriction
Screening

• Screening for PTB is targeted to the population in which preventive intervention has been shown to be beneficial:
  ➢ those with previous sPTB or mid trimester abortion
  ➢ extensive cervical surgery or uterine abnormalities (may be)
interventions

• Progesterone
• Cerclage
• Smoking cessation
• Treatment of drug misuse
• Treatment of asymptomatic bacteriuria
• Maintenance of a normal body mass index
• Avoiding an interpregnancy interval of less than 6 and ideally less than 12 months
• Prevention and reduction of multifetal gestations
• Surgical correction of uterine anomalies
Predicting risk for preterm birth risk scoring systems

• Is a quantitative method
• Identify women at increased risk for PTB
• Epidemiologic, historical, and clinical risk factors
• An additive score

• **There is NO effective risk scoring system for prediction of PTB**
• Low sensitivity and poor predictive value particularly in nulliparous
• PPV of most risk scoring systems is low: 20-30 %
Predicting risk for preterm birth

Biomarkers

**Cervicovaginal fetal fibronectin (fFN)**

- Is a screening test for sPTB in women at high risk of PTB.
- > 50 ng/mL predicted spontaneous delivery in a high risk cohort before 34 weeks with AUC of 0.64
- Most of the value lies in high NPV (96 %)
- Low PPV (< 30 %)
- fFN is not useful as screening test for predicting risk of PTB in asymptomatic low risk nulliparous women with singleton pregnancy
- Predictive value more than 14 days: poor
Predicting risk for preterm birth
Biomarkers

• Quantitative bedside fFN test: enhanced prediction compared with the traditional qualitative (positive/ negative) test in both symptomatic and asymptomatic women.

• fFN concentration correlates directly with the subsequent incidence of sPTB.

• NPV remains high in all thresholds

• Incremental thresholds enhances PPV for sPTB

• Higher fFN concentration: greater the need for therapeutic intervention
Predicting risk for preterm birth
Biomarkers

• can be useful within 7 to 14 days in women with contractions and mild cervical dilation (< 3 cm) and effacement, particularly when combined with ultrasound assessment of cervical length and when a quantitative measurement is available.
• NPV: > 98 %
• Sensitivity > 70%
• More modest PPV
Predicting risk for preterm birth
Biomarkers

**Placental α-macroglobulin 1 (PAMG-1)**

- Vaginal swab inserted into vagina without speculum between 20-37 weeks
- Immunoassay bedside dipstick test (partosure)
- NPV: 97%
- PPV for delivery within 7 days in symptomatic women
- High predictive value for delivery within 2 weeks
- Prediction > 14 days after testing is not clear
- No evidence for its use compared to CL and other biochemical markers
Predicting risk for preterm birth Biomarkers

<table>
<thead>
<tr>
<th>Predictive test</th>
<th>threshold</th>
<th>Specimen collection</th>
<th>sen</th>
<th>spe</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>fFN</td>
<td>50 ng/mL</td>
<td>Via speculum 22-34 weeks</td>
<td>60-87</td>
<td>76-84</td>
<td>10-35</td>
<td>82-99</td>
</tr>
<tr>
<td>PAMG-1</td>
<td>4 pg/µL</td>
<td>Without speculum 20-37 weeks</td>
<td>80</td>
<td>96</td>
<td>87</td>
<td>93</td>
</tr>
</tbody>
</table>
Predicting risk for preterm birth
Biomarkers

• A test for two serum proteins,
  insulin like growth factor binding protein 4
  sex hormone binding globulin
Is available for clinical use to predict PTB
In asymptomatic pregnant women: sensitivity: 0.75  specificity:0.74

Not moving with serum screening for PTB until such screening has adequately tested and validated.
Predicting risk for preterm birth

Biomarkers

• 30 other biomarkers
• 72 observational studies
• 90,000 women
• None of these other biomarkers are useful in asymptomatic women
Self monitoring of contractions

• Self- measurement of the frequency of uterine contractions by self-palpation /detection of signs of labor or use of a home uterine activity monitor does not lead to a reduction in PTB rate.
Low-dose Aspirin

- Don’t routinely prescribe low-dose aspirin for prevention of sPTB. (ACOG)
- Meta analysis, 17 trials, 28797 women
  Aspirin in women at high risk for developing preeclampsia
  reduced sPTB < 34 RR: 0.8  sPTB < 37
- RCT
  aspirin in healthy nulliparous women at low risk for developing preeclampsia
  reduced sPTB < 34 RR: 0.46
- RCT, 12000 women, use of low dose aspirin for prevention of PTB
  81 mg Aspirin
  reduced sPTB < 34 RR: 0.75  sPTB < 37  RR: 0.89

The effect is due to prevention on indicated PTB due to preeclampsia