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

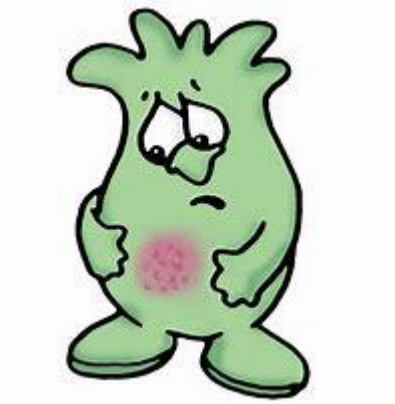
Risk factors

- 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 ά fetoprotein

Risk factors
Infection

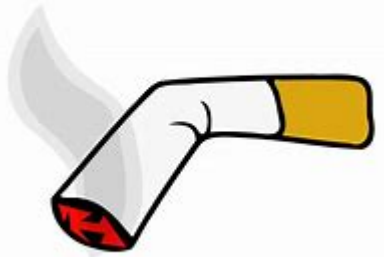


- Asymptomatic bacteriuria: unclear? Probably NO
- Perio dental disease:???, can be epidemiologically linked but not causally related
- Genital tract infection/colonization: GBS, chlamydia, …..????
- BV and preterm labor
- Candida species colonization is not a risk factor for PTB

Risk factors

- Short cervix at 16 to 28 weeks: inverse relation ship (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 pragnancy 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:

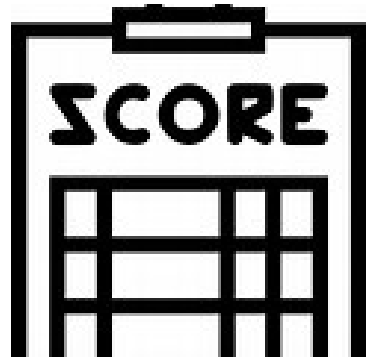
➢ those with previous sPTB or mid trimester abortion

➢ 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 therapeotic 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 ά-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

Predictive test	threshold	Specimen collection	sen	spe	PPV	NPV
fFN	50 ng/mL	Via speculum 22-34 weeks	60-87	76-84	10-35	82-99
PAMG-1	4 pg /µL	Without speculum 20-37 weeks	80	96	87	93

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 spesificity: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
- 90000 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