Screening for pre term labor

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Significance of Preterm Birth (PTB)

- 11.7% of births (US, 2011)
- Twice the rate EU
- One sixth of PTDs occur at 24-31 weeks, with highest rate of complications *
- Leading cause of neonatal mortality (early 75%, late 35%), morbidity (70%), and health care expenditures (57% of nursery costs; 10% of all healthcare costs for children)
- 26 bill $/year

Mortality & morbidity related to PTB (%)  
Ideal life...
Mortality & morbidity related to PTB (%)
Real life....

% Survival

% IVH Grade 3-4
Rationale for PTL screening

FOR

• <50% with PTL perceive typical symptoms
• 10-20% of uncomplicated patients have similar symptoms
• PTL is diagnosed only after gross structural change of the cervix
• no currently identifiable risk factor

AGAINST

• Inadequate criteria
• No treatment
• Inadequate intervention
• Unsure benefits
• Significant health care cost
Risk factors for PTL/PTB

- Prior PTB (spontaneous PTL) \( RR \ 1.5 - 2 \)
- Low socioeconomic status
- Teen and/or age >34
- Prepregnancy low BMI
- Uterine or cervical abnormality
- Maternal smoking
- Pregnancy associated...
Risk of subsequent PTB

Bakketeig LS, Hoffman HJ. Harley EE. The tendency to repeat gestational age and the birth weight in successive births. AJOG 1979;135:1086
Rationale for PTL screening

“providing opportunity to identify and treat prematurity related risk factors”

INTerventions

- Nutrition (Vit B and C, Ca)
  Buppasiri et al, Cochrane, 2011;10:CD007079

- BV treatment
  Carey et al, NEJM 2000;342:534

- Peridontal disease treatment
  Offenbacher et al, Obstet Gyecol 2009;114:551
Cervical length in pregnancy
Cervical length in pregnancy

NEJM 1996;334:567
... correlates with PTL
Short CL and high risk → Cerclage

<25 mm previous PTB (35 weeks)
Cerclage PTB RR 0.7, 95% CI 0.55-0.89
Consequently perinatal mortality and morbidity


NNT 11 PTL/PTD, NNT perinatal death 50

Alfirevic, Florence, ECPM, 2014
Ultrasound screening - options

Universal TV screening 18 – 24
- Need for large number of skilled sonographers, unnecessary examination, follow up
- NNT 11, 375 screened (<25 mm), 1 prevented {Romero, ECPM, Florence, 2014}

TA screening followed by TV
- Reproducibility of TA screening is uncertain

Selective TV screening of high risk
- High prevalence and low PPV

Iams JD. Prevention of preterm birth. NEJM 2014;370:254-61
RM, 2015
**TVS CL measurement for all?**

**FOR**

- Important condition (PTB)
- Technique well-described
- Safe and acceptable
- Reliable (reproducible)
- Recognizable early asymptomatic phase
- Valid (accuracy of prediction)
- ‘Early’ treatment is effective (Prevention)

**AGAINST**

- Identification of abnormal cervix does not determine etiology or direct treatment
TVS CL measurement for all?

FOR

Hassan SS. Et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Vaginal Progesterone (%)</th>
<th>Placebo (%)</th>
<th>Risk Reduction (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Neonatal Morbidity or Mortality Event</td>
<td>7.7%</td>
<td>13.5%</td>
<td>43%</td>
<td>0.04</td>
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<tr>
<td>Respiratory Distress Syndrome</td>
<td>3.0%</td>
<td>7.6%</td>
<td>61%</td>
<td>0.03</td>
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<tr>
<td>Birthweight &lt; 1500g</td>
<td>6.4%</td>
<td>13.6%</td>
<td>53%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

• ‘Early’ treatment is effective (Prevention)

RM, 2015
TVS CL measurement for all?

AGAINST


...insufficient evidence to recommend routine screening of asymptomatic or symptomatic pregnant women with TVU CL.

Non-significant association between knowledge of TVU CL results and a lower incidence of PTB at less than 37 weeks in symptomatic women

RM, 2015
Prevention of PTL

Iams JD. Prevention of preterm birth. NEJM 2014;370:254-61
Alternative options


... beneficial effect of cervical pessary in reducing preterm birth in women with a short cervix ...
Progestosterone vs. cerclage vs. pessary

Conde-Augudelo A et al. Vaginal progesterone vs. cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth and singleton gestation: a systematic review and indirect comparison meta analysis. AJOG 2013;208:42e1.42

Matijević Ratko
Application form
Preterm labor

Croatian Science Foundation

HRZZ Research Projects
(IP-09-2014)

Research project proposal

Ratko Matijević

Assessment of therapeutic intervention methods used in order to reduce the preterm labour in women with diagnosed cervical insufficiency. Randomised controlled trial

Preterm labor

University of Zagreb, School of medicine
Any other options in screening?
Clinical (bimanual) examination
Ultrasound vs. digital examination

RCT: n=282 (144 vs 138)

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>PPV</th>
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<tbody>
<tr>
<td>57.1</td>
<td>66.7</td>
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<tr>
<td>33.3</td>
<td>17.6</td>
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</tbody>
</table>

CL - 12-fold higher positive LR for PTL in low-risk population (37.4; 95%CI [8.2-170.7] versus 3.2; 95%CI [1.1-9.2]).

General screening not recommended

Bacterial vaginosis

PTD OR 1.8 - 2.2

18 studies > 20,000 pregnant women

Miscarriage OR 9.91 (1.99-49.34)
Endometritis OR 2.53 (1.26-5.08)


Leitich H et al. Bacterial vaginosis as a risk factor for preterm delivery: a meta analysis. AJOG 2003;189:139-47
BV vs. CL

BV assessed by vaginal pH  5.0 (95th-percentile threshold)
CL assessed by TVS  26 mm
n=316
PTL (<37) and EPTL (<34)

BV vs. CL

BV assessed by vaginal pH       5.0 (95th-percentile threshold)       14 (4.4%)
CL assessed by TVS               26 mm                                   15 (4.7%)
n=316
PTL (<37) and EPTL (<34)         7.2% vs. 2.5%

CL was significantly correlated with PTL (likelihood ratio [LR] weighted by prevalence; 2.7; 95% CI, 1.1-6.7) but not with early PTL (LR, 0.8; 95% CI, 0.4-1.8)
BV and CL was a better predictor of PTL (LR, 3.7; 95% CI, 1.3-10.4) and early PTL (LR, 1.7; 95% CI, 1.1-3.1)

An elevated vaginal pH was a better predictor of early PTL than a shortened CL in this cohort of pregnant women at low risk.

Effect of BV treatment
RR of PTD

Meta-analysis confirms reduction in PTB only in high risk patients (prior PTB)

AJOG 1995;173:157
AJOG 1995;173:1527
300 mg BID
250 mg TDS + 333 mg TDS
NEJM 1995;333:1732
RM, 2014
Bacterial vaginosis: summary

- BV increases risk of PTD
- Screen high risk patients
- Systemic treatment for BV (Clinda, Metro,...)
- Other antibiotics (Nifuratel,...)

General screening not recommended

Screening for risks of PTL by means other than history is not beneficial in the general obstetric population

ACOG Practice Bulletin # 31, 10/01
Fibronectins

- glycoproteins in plasma and ECM
- fFN in ECM of decidua basalis and cytотrophoblasts
- fFN rarely present in cervical/vaginal secretion of women without PTL/PROM (3%)
- fFN common in cervical/vaginal secretion of women with PTL (50%) or PROM (94%)

**HYPOTHESIS**: mechanical or inflammatory damage to placenta or membranes releases fFN into cervical/vaginal secretions
<table>
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<tr>
<th>Peaceman (1997)</th>
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<td>Malagrande (1995)</td>
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<td>Surbek (1997)</td>
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<td>Negecze (1992)</td>
<td>0.34700</td>
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<td>Morrison (1995)</td>
<td>0.91400</td>
<td>0.08600</td>
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<tr>
<td>Overall (95% CI)</td>
<td>2.27 (2.74 to 3.02)</td>
<td>0.48 (0.41 to 0.56)</td>
</tr>
</tbody>
</table>

Honest H et al. Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth BMJ 2002;325:1-10
Fibronectin: summary

- fFN is fairly sensitive marker for PTD in high risk patients (55-97%)
- High short term NPV (71-100%) may identify women not needing tocolysis
- General screening not recommended
- No intervention
Electromyography (uterine electrical activity measurement)

Uterine electrical activity – result of the depolarization and repolarization of thousands of myometrial smooth muscle cells
- causes action potentials (AP)
- by spreading unchanged, through gap junctions, result in electrical activity
- organized uterine electrical activity precedes uterine contractions and the associated cervical shortening

Electromyography vs. (and with) CL

n=308
CL  ≤25 mm (≤5th centile)
EMG  ≥20 action potentials in 20 min (≥95th centile)
Outcome measures: prediction of PTD and early PTD (≤34 weeks).

Electromyography vs. (and with) CL

n=308
CL  ≤25 mm (≤5th centile)
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Outcome measures: prediction of PTD and early PTD (≤34 weeks).

7.4%  2.9%

LR wp                  PTD                  EPTD
CL                      1.9, 95% CI 1.0-3.5      0.4, 95% CI 0.2-0.8
EMG                      9.5, 95% CI 2.5-35.7      0.6, 95% CI 0.3-1.7
BOTH                           4,95% CI 1.3-14.3

Electromyography

Problem:

- General screening not recommended

“Do not do a test which will not change your clinical management”
The Genetics of Preterm Birth: True Labor or False Labor?

News | May 21, 2014 | Pregnancy and Birth, Prenatal Genetic Testing By Sarah Bruyn Jones

... the predictive efficacy of the nine gene signature coupled with clinical blood data outperformed the fetal fibronectin test ...
PTB prediction and prevention: Conclusions

- Most routine screening (BV, fFN, EMG) \textit{not} indicated for \textit{low risk} patients
- Possible ultrasound screening for all (US)
- Consider progesterone supplementation for women at high risk for PTB (whatabout all...?)
Finally...

The UK NSC recommendation on Preterm labour screening in pregnancy

Recommendation: Systematic population screening programme not recommended

Last review completed: January 2015

Next review due in: 2017/18

Key downloads:
- Last external review - Preterm Labour and Bacterial Vaginosis
- Last policy review summary
- Recommendation statement

Find general information about population health screening.
Why not (UK)

- The measurement of cervical length in asymptomatic women is not reliable enough for use as a screening tool. There are unanswered questions over the timing of the test and there is no standardised 'normal' measurement of cervical length in order to establish what an 'abnormal' measurement is.

- Not known when the test should be offered or whether it is reliable in identifying which pregnancies are at risk and which are not. Screening would identify many women as at risk when they are not, leading to unnecessary preventative treatment.

- There is not enough evidence to be sure that vaginal progesterone (a hormone treatment) is an effective treatment for preventing preterm labour or that it reduces the most severe outcomes (death or disability) for the baby.
Next congress
Zagreb, Croatia, December 4-6, 2015

www.penta-pco/SEESPM2015