Preterm labor and premature rupture of fetal membranes: Accurate diagnosis is vital

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Preterm delivery (PTD)

- Delivery at <37 weeks
- Affects 5-9% of pregnancies, in the US 12-13%
- The rate has risen in most industrialized countries
- In the US 38% increase since 1981!
- Accounts for 75% of perinatal mortality

<table>
<thead>
<tr>
<th>Incidence</th>
<th>GA (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme prematurity</td>
<td>&lt;28</td>
</tr>
<tr>
<td>Severe prematurity</td>
<td>28-31</td>
</tr>
<tr>
<td>Moderate prematurity</td>
<td>32-33</td>
</tr>
<tr>
<td>Near term</td>
<td>34-36</td>
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</tbody>
</table>
Pathways leading to PTD

Activation of maternal/fetal HPA axis
Infection in chorion/decidua
Inflammation
Decidual Hemorrhage
Pathological uterine distension
Mechanical stretch

IL-1
IL-6
IL-8
TNF
CSF
FasL

Chorion Decidua

Proteases
Cervical change
Rupture of membranes

Prostaglandins

Chorion- and decidual proteins leak into the cervix

PTD

Adapted from Lockwood 1999
Etiology of spontaneous preterm birth

- Multifactorial
  - Obstetric
  - Immunologic, biochemical
  - Histopathologic and anatomic factors
  - Infections

In 1/3 no risk factors can be identified
Preterm delivery precursors

- Intervention due to maternal/fetal problems
- Preterm PROM
- Spontaneous PTD with intact membranes
Premature rupture of fetal membranes (PROM)

• The major single identifiable cause of PTD
• Occurs in 5-15% of all pregnancies, preterm in 1-3%
• In 60% of cases, spontaneous labor occurs within 24 hrs
• The latency is longer, if PROM occurs preterm
What may cause PROM?

- Infection
- Physiological changes in membranes
- Smoking
- Vaginal bleeding
- Previous PROM (recurrence 20%)
- Stress
- Low socio-economic status

However, often PROM \textit{cannot be predicted}
What makes PROM diagnosis difficult?

• The symptoms may be unclear or leakage may have stopped when the patient is examined

• The loss of fluid may be small – yet, even a small rupture may cause complications.

• The traditional diagnostic methods are affected by several interfering factors
  • Bleeding, cervical mucus
  • Seminal fluid
  • Infections
  • Medication
Traditional methods for PROM diagnosis

- Visualization of amniotic fluid in the posterior fornix or clear fluid passing from cervical canal = pooling AND
- Vaginal pH (=nitrazine test) AND
- Arborization (aka fering, amniotic crystallization)
- Dye injection ("gold standard")
- Ultrasound, measuring amniotic fluid index, AFI
Limitations of the traditional methods

• Interfering factors affect the test results:
  • Bleeding, cervical mucus, intercourse, medication

• Accuracy may depend on GA
• Require a remarkable fluid loss
• Are invasive

Better diagnostic methods are necessary
Requirements for an ideal method

• The test should **differentiate** between amniotic fluid and other vaginal fluids even when no fluid is visible at the time of examination.

• It should have **minimal interference** and should work even after intercourse and on patients with vaginal bleeding. It should not be affected by intravaginal medications.

• The test should be **rapid** and **available** bed-side for 24 h a day.

• The test should be able to ”see” the changes before they become clinically visible.
Insulin-like growth factor binding protein-1 (IGFBP-1)

- Originally called PP12 (placental protein-12)
- Early 80’s: Found to be present in very high levels in amniotic fluid
- Mid 80’s: Shown to originate from decidua
- Early 90’s: Identified as an optimal PROM marker
- Late 90’s: Different forms in AF and tissues – identified as a marker of PTD
IGFBP-1 concentrations in body fluids

IGFBP-1 levels in amniotic fluid rise in early pregnancy and remain high until term.¹

Concentrations in body fluids:²

- Serum (in pregnancy) 58-600 µg/l
- Amniotic fluid 10.000 - 350.000 µg/l
- Undetectable in seminal plasma and urine

Principle of the Actim PROM test – detection of amniotic fluid

- Produced by the decidual cells
- Exists in large amounts in amniotic fluid
- Not present in vaginal secretions
- In PROM, amniotic fluid leaks into the vagina

Detection of IGFBP-1 indicates rupture
IGFBP-1 - a protein with many forms

- IGFBP-1 has different forms that exist in different tissues
- Different forms are released in different conditions
- An accurate test needs to distinguish these forms
- This can be achieved by different monoclonal antibodies
Monoclonal antibodies Mab 6305 and 6303 (Medix Biochemica, Finland) detect different phosphorylation patterns of IGFBP-1

1 decidua
2 decidua and alkaline phosphatase
3 decidua
4 amniotic fluid

The tissue form, also predominating in blood is not detected by the key antibody of the PROM test.
Different forms of IGFBP-1 - a pathway to another clinical application

**Highly** phosphorylated forms
- Are located in **decidual cells** and in **whole blood**
- Indicate changes in chorio-decidual interface

**Less** phosphorylated forms
- are located in **amniotic fluid**
- **Identify membrane rupture**
Principle of the Actim Partus test: Detecting phIGFBP-1 in cervical fluid

When there are clinically significant changes in fetal membranes (e.g. due to contractions)

- Decidua and chorion start to detach
- Decidual cells are damaged
- Decidual proteins (including phIGFBP-1) leak into the cervix
Tissue form of IGFBP-1 in early pregnancy

• phIGFBP-1 protein is located in decidual cells. Before fetal membranes fuse completely (1st and 2nd trimester), phIGFBP-1 can leak into the cervix.

• By week 22, the fetal membranes have completely fused. This prevents phIGFBP-1 from leaking into the cervix.

Studies on symptomatic women:

Cervical phIGFBP-1 above 10 µg/L, Actim Partus positive (% of women)

- 1st trimester\(^1\) (12-17wk) n= 578/1690
- 2nd trimester\(^1\) (18-21wk) n= 455/1607
- Later pregnancy\(^2\) (22-37 wk) n=3/58

Ref. 1, Rahkonen et al. BJOG 2008
Why is it necessary to use two tests?

• The management of patients is different if they have ruptured membranes, or if they have an increased risk of PTD.
• If a test can distinguish between these two conditions, correct management can be done.
• Actim PROM and Actim Partus tests provide this possibility
Benefits of the accurate diagnosis

• To differentiate between "true" and "false" contractions
• To diagnose occult rupture of membranes
• To make decision of inpatient admission
• To avoid unnecessary treatment
• To give steroids in a more judicious manner
• To plan the place of delivery (in utero transfer?)