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

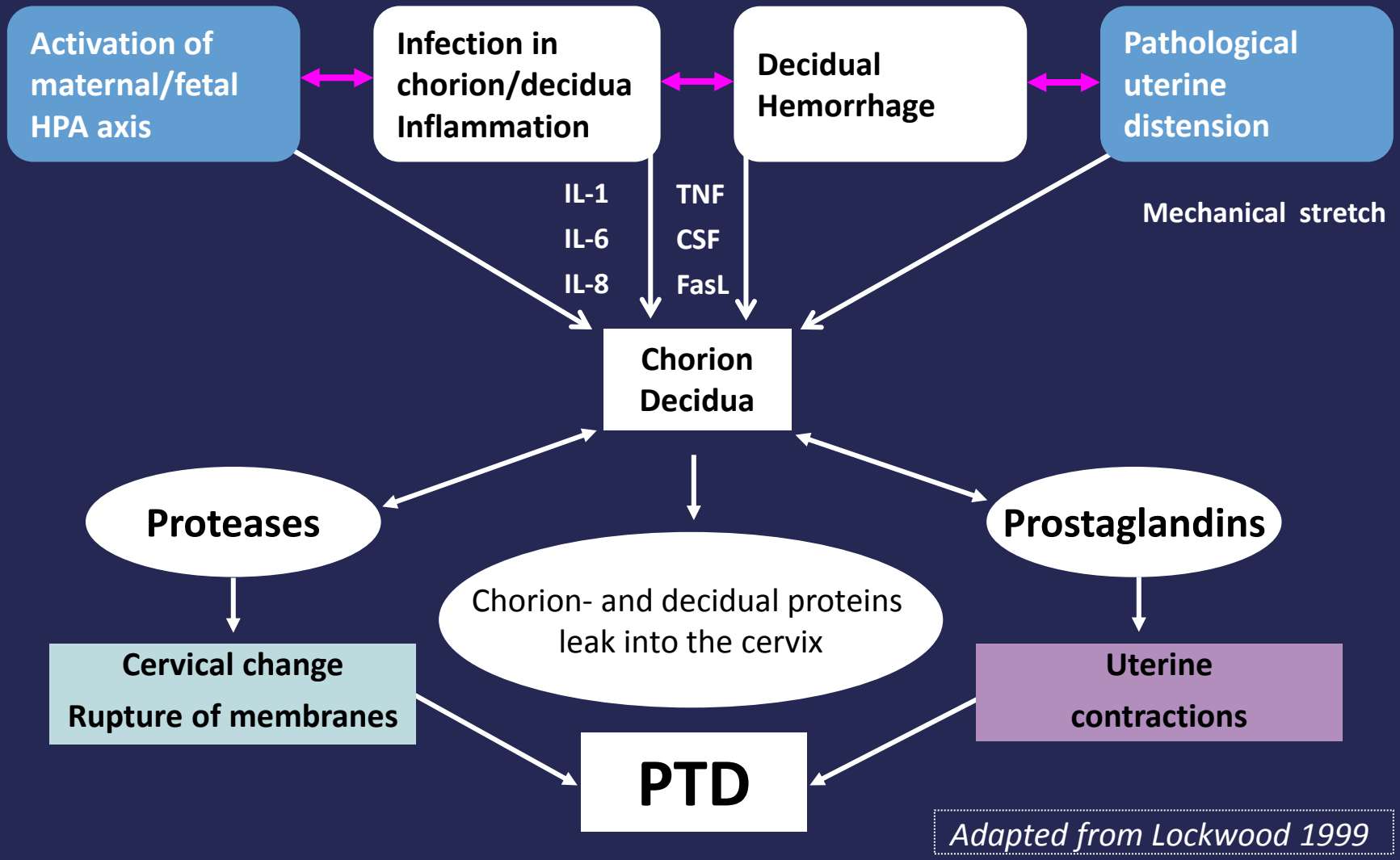
Professor Dr.med. Dr.h.c.mult.
Wolfgang Holzgreve, MS, MBA, FACOG, RCOG
Medical Director, University Bonn Medical Center, Germany

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

	GA (wk)	Incidence
Extreme prematurity	<28	5%
Severe prematurity	28-31	15%
Moderate prematurity	32-33	20%
Near term	34-36	60-70%

Pathways leading to PTD



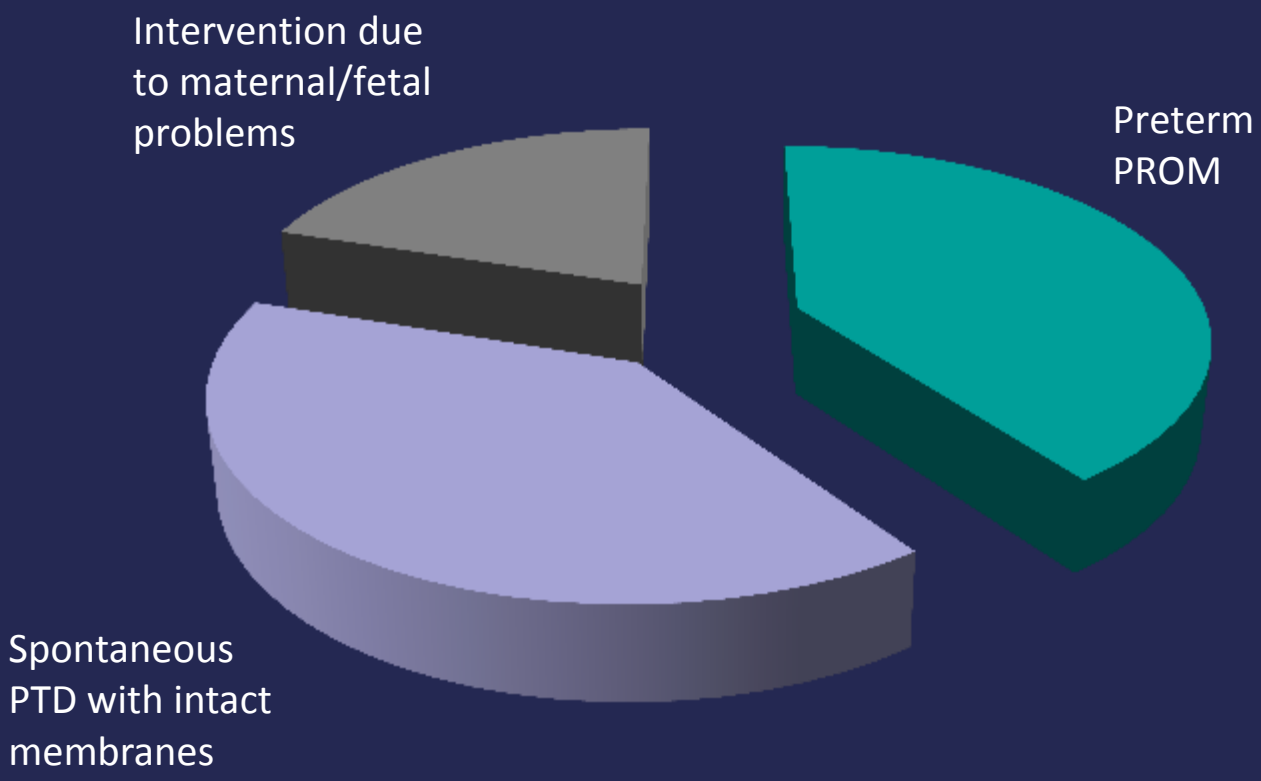
Adapted from Lockwood 1999

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



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 **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 ferning, 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

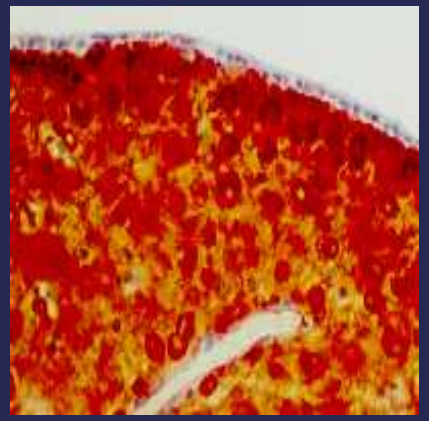
Better diagnostic methods are necessary

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

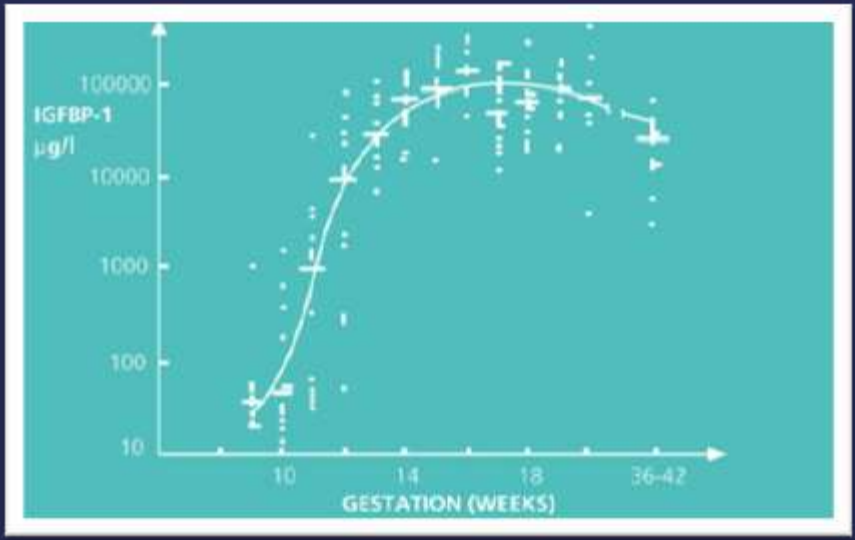
Insulin-like growth factor binding protein-1 (IGFBP-1)

- 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

Ref 1. Wathen et al. J Endocrinol 1993
Ref 2. Rutanen et al. Clin Chim Acta 1993

Principle of the Actim PROM test – detection of amniotic fluid

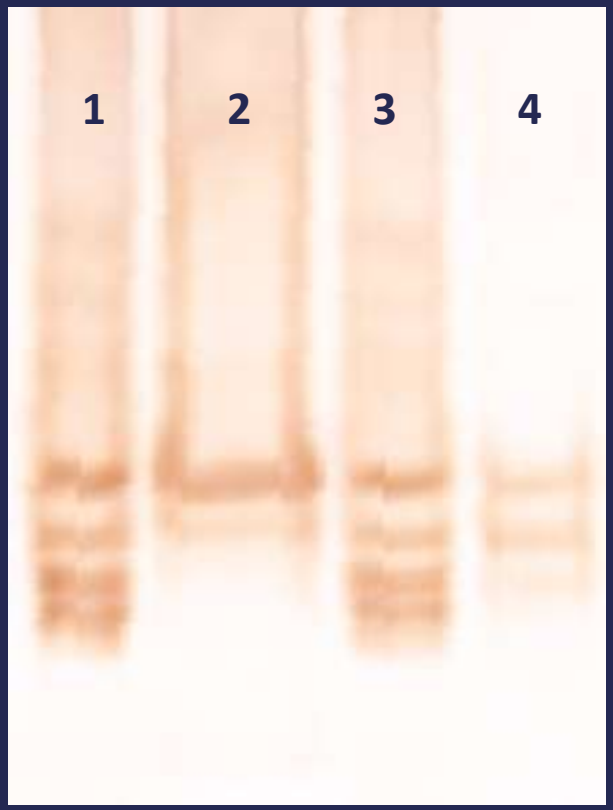
- Produced by the decidual cells
- Exists in large amounts in amniotic fluid
- Not present in vaginal secretions
- In PROM, amniotic fluid leaks into the vagina

➡ 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

Mab 6303

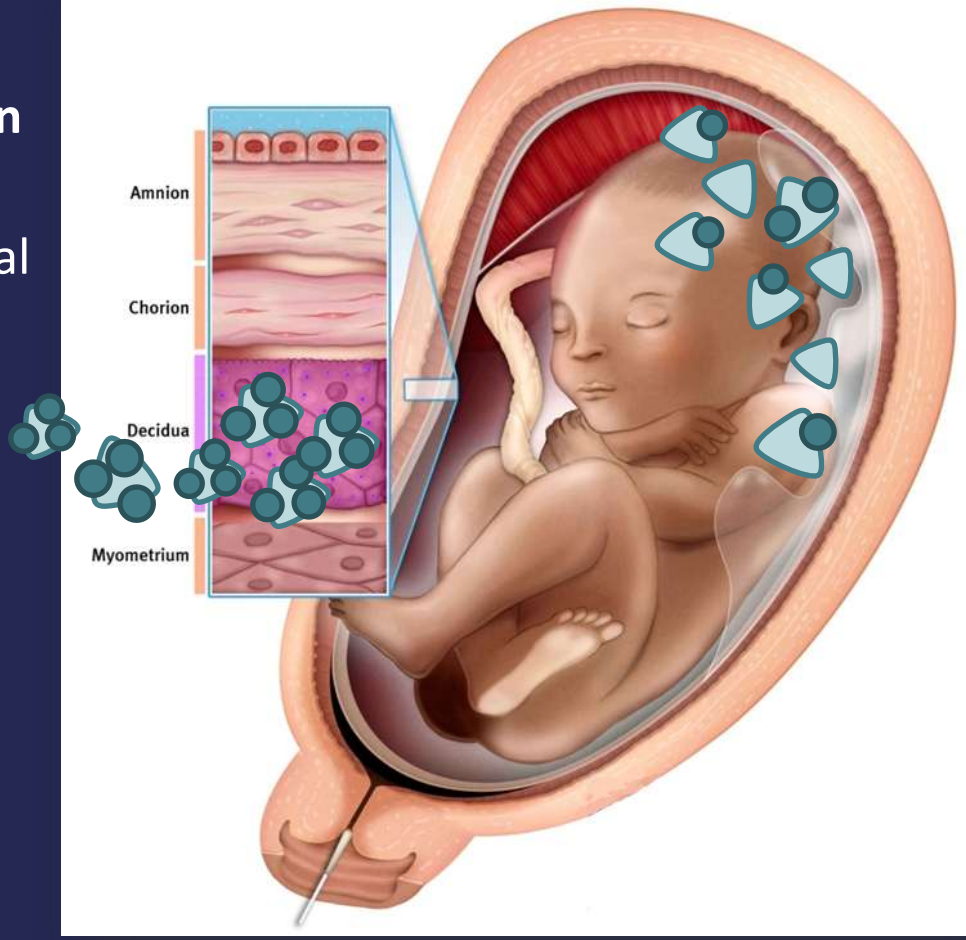
Mab 6305

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



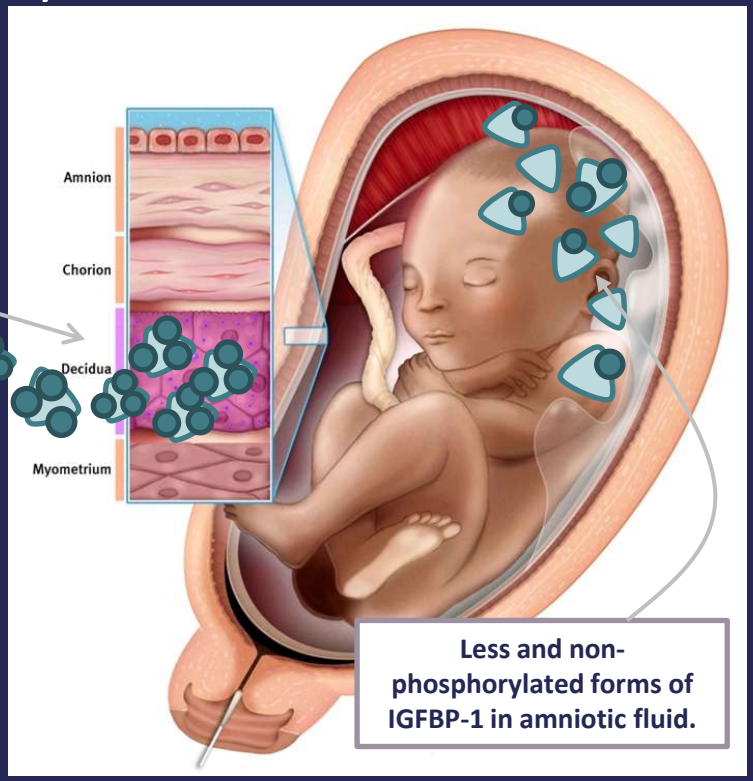
Less phosphorylated forms

- are located in **amniotic fluid**
- **Identify membrane rupture**

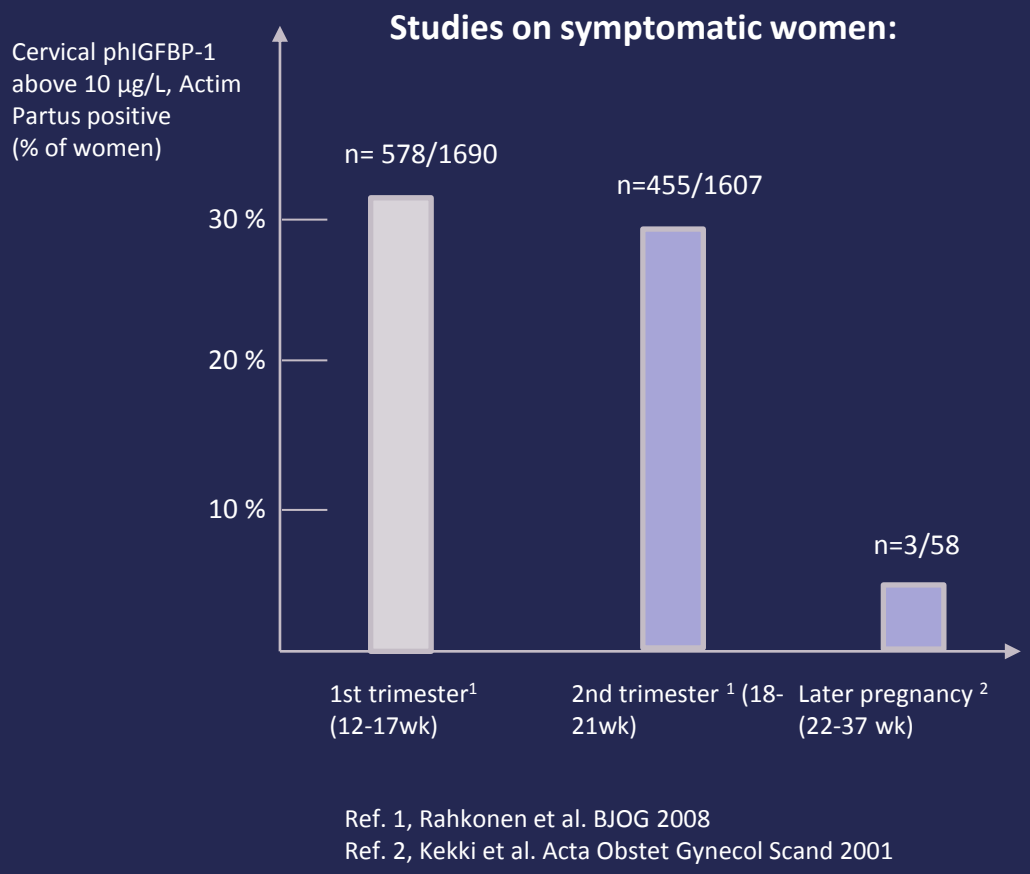
Principle of the Actim Partus test: Detecting phIGFBP-1 in cervical fluid

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



Ref. 1, Rahkonen et al. BJOG 2008
Ref. 2, Kekki et al. Acta Obstet Gynecol Scand 2001

- 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.

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 judious manner
- To plan the place of delivery (in utero transfer?)