# The importance of accurate prediction of preterm labor and PROM (PPROM) diagnosis

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- **2011 statistics**
- 5641 deliveries (5808 infants)  (Finland cca 60 000/yr)
- 161 twin deliveries, 3 sets of triplets
- 20 stillbirths
- CS 24.1 %, vacuum delivery 11%
- Regional anaesthesia (epidural) 69%
- < 28 wk  1.2%
- < 32 wk  3% (Finland 0.8%)
- <37 wk  11.7% (Finland 5.5%)
- Perinatal mortality 0.4 %
- 25-30 IU transfusions,  1200 first/second trimester invasive procedures, 500 third trimester amniocentesis
- 40 specialist and 30 residents

# Preterm labor (PTL)

- PTL refers to the onset of uterine contractions of sufficient strength and frequency to effect progressive dilatation and effacement of cervix between 22 and 37 weeks of gestation
- PTL complicates 5-10% of pregnancies and is a leading cause of neonatal morbidity and mortality worldwide

# Why this lecture ?

It has been widely recognised that its

1.prevention

2.recognition and

3.effective management

will improve neonatal outcome and will have a profound impact on societal and long-term public health care costs

# (P)PROM and PTL
# The importance of diagnosis

The goal of early diagnosis of PTL and PPROM in symptomatic women is the appropriate application of four antenatal interventions that are recognized to reduce perinatal morbidity and mortality:

1) transfer of women with preterm labor to a facility with a neonatal intensive care unit and transfer tocolysis

2) administration of glucocorticoids to the mother

3) treatment of women in preterm labor with PROM with antibiotics

4) MgSO4 treatment to decrease neurological morbidity (in Helsinki since June 2012)

# If PTB is not imminent, withdrawal of treatment is better option

## WHY ?

1) transfer of women with preterm labor to a tertiary hospitals (unnecessary admissions, anxiety, costs)

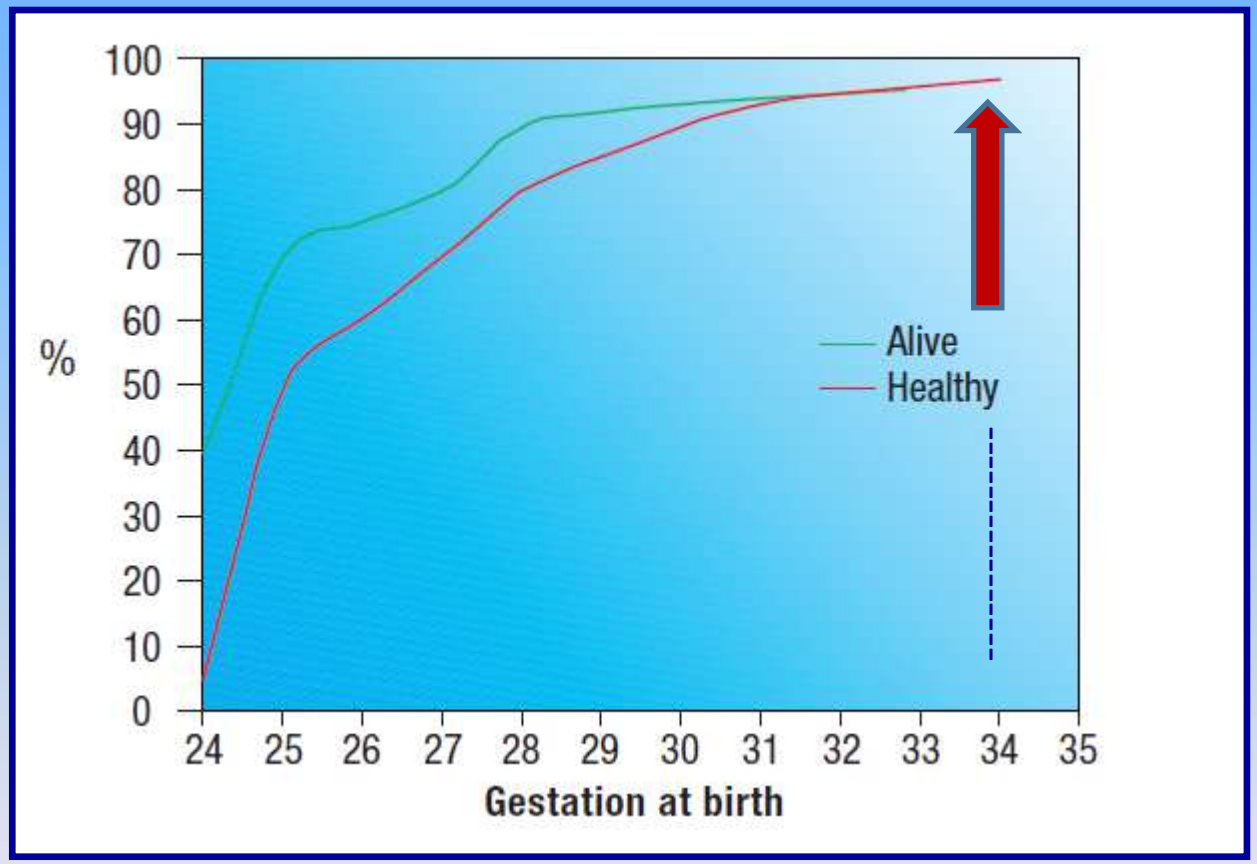
with a neonatal intensive care unit (tocolysis side-effects)

2) administration of glucocorticoids to the mother (optimal if administered not more than 7 days prior birth)

3) treatment of women in preterm labor with PROM with antibiotics (if membranes intact->> more harm than the benefit, harmful labor inductions etc.)

4) MgSO4 treatment to decrease neurological morbidity (in Helsinki since June 2012) (close to birth)

# Focus on labor before 34 weeks of gestation



# How to identify a black tulip ?

- The majority of women with symptoms of preterm labor will go on to deliver at term
- However, for the minority who are destined to deliver preterm, there are some beneficial obstetric interventions
- 40% of women have no known risk factors for PTL

# Conventional methods for estimation of risk of preterm delivery

- **Cervical length measurement with ultrasound**
  - The shorter the cervix the greater is the risk to deliver preterm (great risk when cervical length <20 mm)
  - Outcome is not clear especially when cervical length is between 20 and 30 mm.
  - Requires expensive equipment and instrument expertise.
- **Bishop scores**
  - Pre-labor scoring system, which assists in predicting if induction is required
  - For estimating the risk of preterm delivery
- **Biochemical tests**:
  - **Actim Partus test**
  - Fetal Fibronectin test (fFN)

# Assessment of the Patient Presenting with Premature Contractions

- What is the likelihood that the patient will delivery prematurely?
- Are the membranes ruptured?
- Is infection present?
- Is there any other factor causing contractions (polyhydramnion etc)

- Dunn et al: Antepartal Bed Rest: Conflicts, Costs, Controversies and Ethical Considerations

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# What is the likelihood that the patient will delivery prematurely?

- Risk fators (absent in 40%)
- Ultrasound of the cervix (not available everywhere, needs experience)

- Biochemical markers

# Actim PARTUS test

- Bedside rapid test to estimate the risk of preterm delivery
- Detects phIGFBP-1 (phosphorylated insulin-like growth factor binding protein) in cervical samples
- Based on highly unique monoclonal antibodies - no effect from semen or urine or lubricants
- Suitable from 22$^{nd}$ gestational week until term

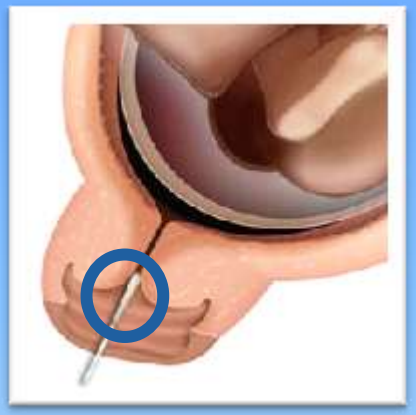
# Performing the Actim PARTUS test

1. The sample is collected with a speculum from the **cervical os**. Hold the swab in for **10-15 seconds**

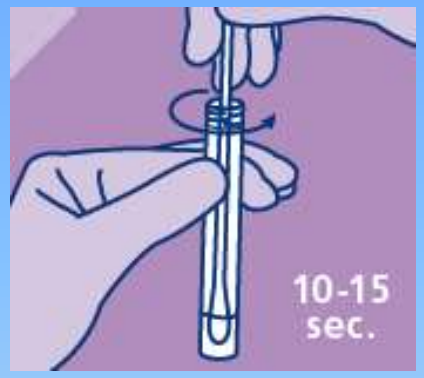
2. Extraction: Stir the swab in the buffer for **10-15 seconds**

3. Dip the dipstick into the Extraction Solution.

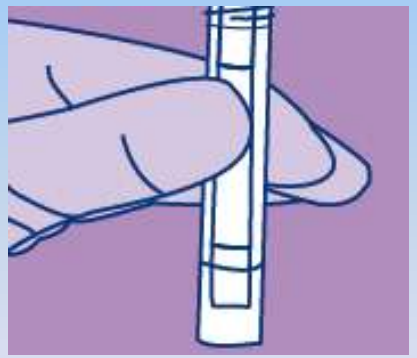
4. Read the results **in 5 minutes**. **Positive result can be interpreted as soon as the line becomes visible**.



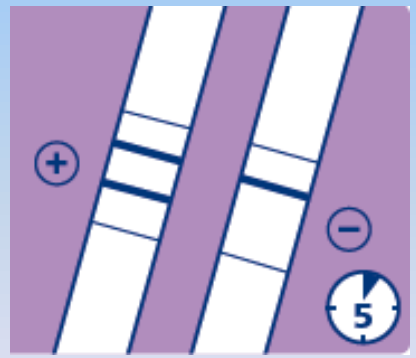
1. Sample collection




2. Sample extraction



3. Test performance




4. Result in 5 minutes

# Positive result of Actim Partus is related to preterm delivery

- Patients with a positive result deliver at earlier GA than those with a negative result

| Study | n | GA (wk) | | Actim Partus + | Actim Partus - | P-value |
|---|---|---|---|---|---|---|
| Lembet 2005 | 36 | 20-36 | GA at birth | 34.4 (± 3.0) | 37.9 (± 2.3) | <0.01 |
| Elizur 2005 | 45 | 24-36 | GA at birth | 34.6 (± 3.3) | 38.1 (± 2.3) | <0.01 |
| Eroglu 2007 | 51 | 24-35 | GA at birth | 32.8 (± 3.7) | 37.7 (± 2.1) | 0.001 |
| Ting 2007 | 94 | 24-34 | GA at birth | 32.9 (± 4.0) | 37.4 (± 1.8) | <0.001 |
| Altinkaya2009 | 105 | 24-34 | GA at birth | 32.8 (± 3.8) | 37.8 (± 2.5) | <0.05 |
| Tanir 2009 | 68 | 24-37 | GA at birth | 34.3 (± 2.1) | 36.6 (± 1.8) | 0.03 |

# Actim Partus combined with CL

| Study | End point | GA (wk) | Test Results | Sensitivity % | Specificity % | PPV % | NPV % |
|---|---|---|---|---|---|---|---|
| Eroglu et al. 2007 N=51 | <7 d | 24-35 | Actim Partus | 83.3 | 84.4 | 41.7 | 97.4 |
| | | | CL <25 mm | 66.7 | 88.9 | 44.4 | 95.2 |
| | | | Combined | 80.0 | 97.1 | 80 | 97.1 |
| Rahkonen et al. 2009 N=246 | <14 d | 22-34 | Actim Partus | 71.4 | 87.0 | 13.9 | 99 |
| | | | CL <25 mm | 57.1 | 94.1 | 22.2 | 98.7 |
| | | | Combined | 42.9 | 99.6 | 75.0 | 98.3 |
| Azlin et al. 2010 N=51 | <7 d | 24-35 | Actim Partus | 80.0 | 93.5 | 57.1 | 97.7 |
| | | | CL <25 mm | 80.0 | 71.7 | 23.5 | 97.1 |
| | | | Combined | 80.0 | 97.8 | 80.0 | 97.8 |

Combined use of Actim Partus and CL measurement **improves PPV** value of both methods.

Actim Partus can be used **also independently to exclude imminent delivery**.

# Prediction of imminent preterm delivery with Actim Partus:

- Symptomatic patients

| Study | n | GA (wk) | End-point | Sensitivity % | Specificity % | PPV % | NPV % |
|---|---|---|---|---|---|---|---|
| Lembet 2005 | 36 | 20-36 | < 7d | 93.8 | 85 | 83.3 | **94.1** |
| Eroglu 2007 | 51 | 24-35 | < 7d | 83.3 | 84.4 | 41.7 | **97.4** |
| Ting 2007 | 94 | 24-34 | < 7 d | 69 | 78 | 39 | **92** |
| Ting 2007 | 94 | 24-34 | < 14d | 72 | 80 | 46 | **92** |
| Tanir 2009 | 68 | 24-37 | < 7 d | 93.3 | 79.2 | 56 | **97.6** |
| Spinelli 2009 | 276 | 24-34 | < 7 d | 73.1 | 66.2 | 21.8 | **95** |
| Azlin 2010 | 51 | 24-36 | < 7 d | 80.0 | 93.5 | 57.1 | **97.7** |

The very high NPV means that a patient with a negative result is highly unlikely to deliver within 7-14 days

# Using Actim Partus for long term prediction of PTD:

Symptomatic patients end point: PTD at <35-37 weeks of gestation

| Study | n | GA (wk) | End-point | Sensitivity % | Specificity % | PPV % | NPV % |
|---|---|---|---|---|---|---|---|
| Lembet 2002 | 36 | 20-36 | <37 wk | 89.5 | 94.1 | 94.4 | 88.9 |
| Kwek 2004 | 47 | 23-33 | <36 wk | 73.7 | 82.6 | 77.8 | 79.2 |
| Elizur 2005 | 64 | 24-35 | <35 wk | 81.8 | 64.1 | 32.1 | 94.4 |
| Elizur 2005 | 64 | 24-35 | <37 wk | 69.6 | 70.7 | 57.1 | 80.5 |
| Eroglu 2007 | 51 | 24-35 | <35 wk | 70 | 87.8 | 58.3 | 92.3 |
| Altinkaya 2009 | 105 | 24-34 | <37 wk | 70.00 | 87.05 | 56.00 | 92.50 |

⇨ No detectable phIGFBP-1 (Actim Partus negative) **indicates that the delivery will not occur preterm** with high probability.

- 85% percent of neonatal morbidity and mortality is a result of prematurity.
- PPROM is associated with 30-40% of preterm deliveries and is the leading identifiable cause of preterm delivery
- PPROM complicates 3% of all pregnancies and occurs in approximately 150,000 pregnancies yearly in the USA

# Preterm PROM

1. Mortality
2. Respiratory distress syndrome (RDS)
3. Intraventricular hemorrhage (IVH)
4. Sepsis etc.

# Diagnosis of PROM

- Conventional methods have many false positives and false negatives
- Often several tests are needed to establish diagnosis
- High rate of false results due to interfering factors
- The IGFBP-1 based Actim PROM test solves these problems

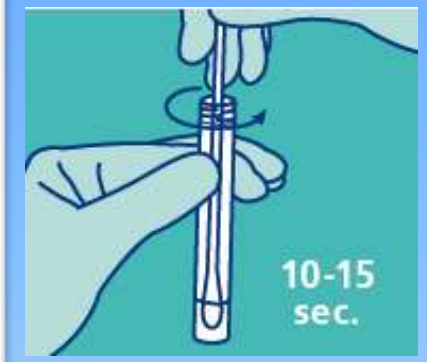
# Performing the Actim PROM test

1. The sample is collected with or without the speculum from the **vagina (posterior fornix)**. Hold the swab in for **10-15 seconds**

2. Extraction: Stir the swab in the buffer for **10-15 seconds**

3. Dip the dipstick into the Extraction Solution.
4. Read the results **in 5 minutes**. **Positive result can be interpreted as soon as the line becomes visible**.

1. Sample collection

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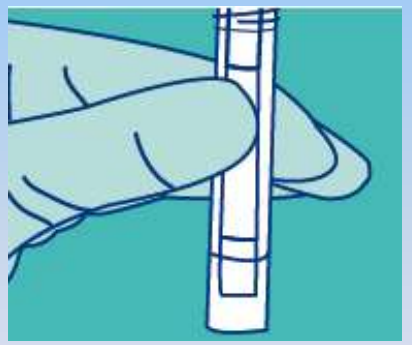

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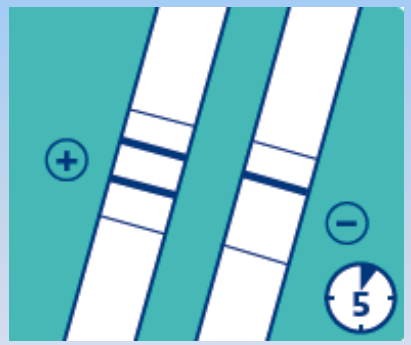
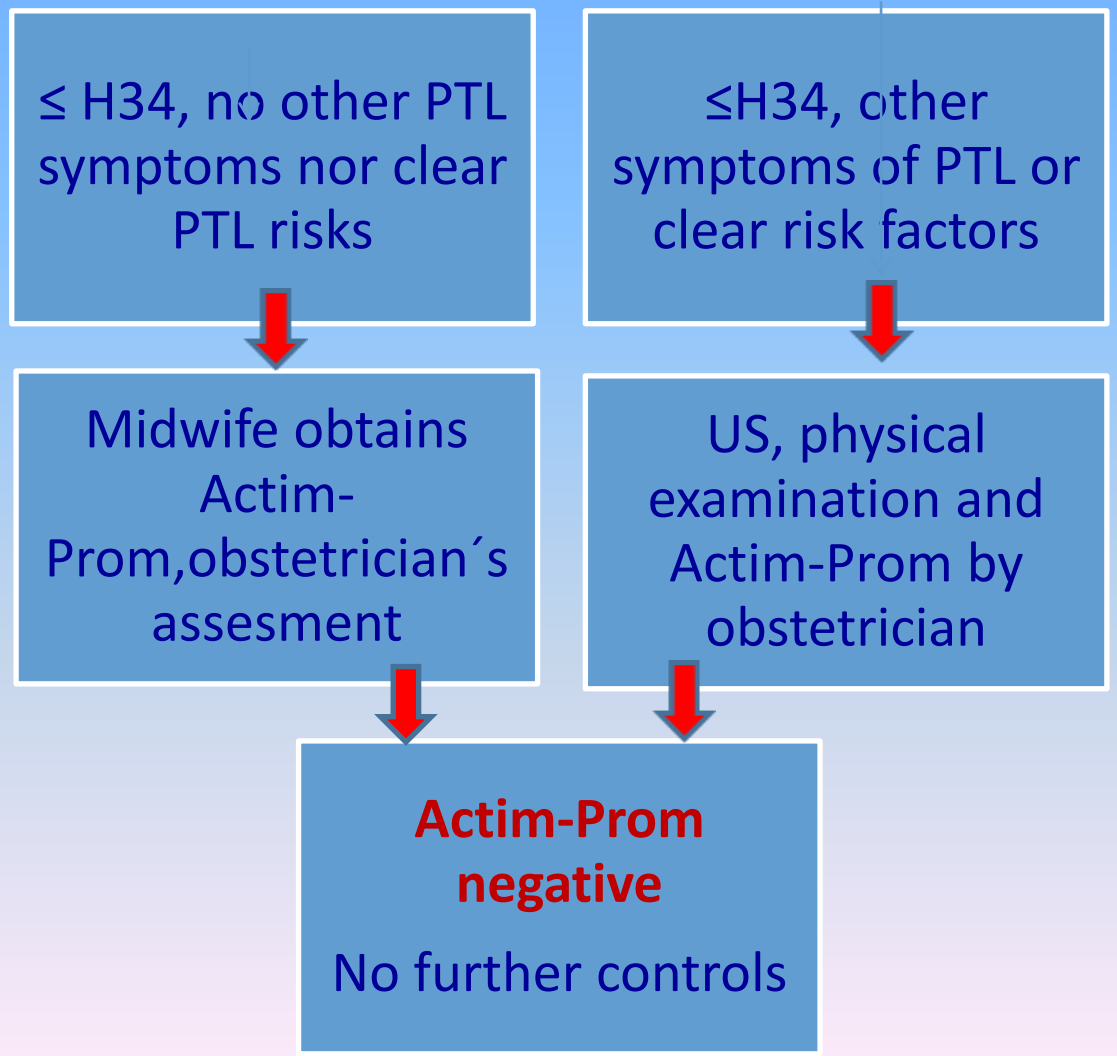



4. Result in 5 minutes

# Suspected PROM :from accurate diagnosis to optimal management



# Actim-Prom positive < H32

Prenatal steroids
Tocolysis
Broad spectrum antibiotics
In-patient surveillance
Amniocentesis (gluc,LD and bakt-PCR

If signs of MIAC/failed tocolysis
MgS04 neuroprophylaxis

If no signs of MIAC and ≥ H34

**DELIVERY**

# Clinical evidence on Actim PROM test performance

- Clinical studies constantly show an excellent performance of the test
- All studies have included all the main patient groups that need testing of PROM – **including women with vaginal bleeding**.

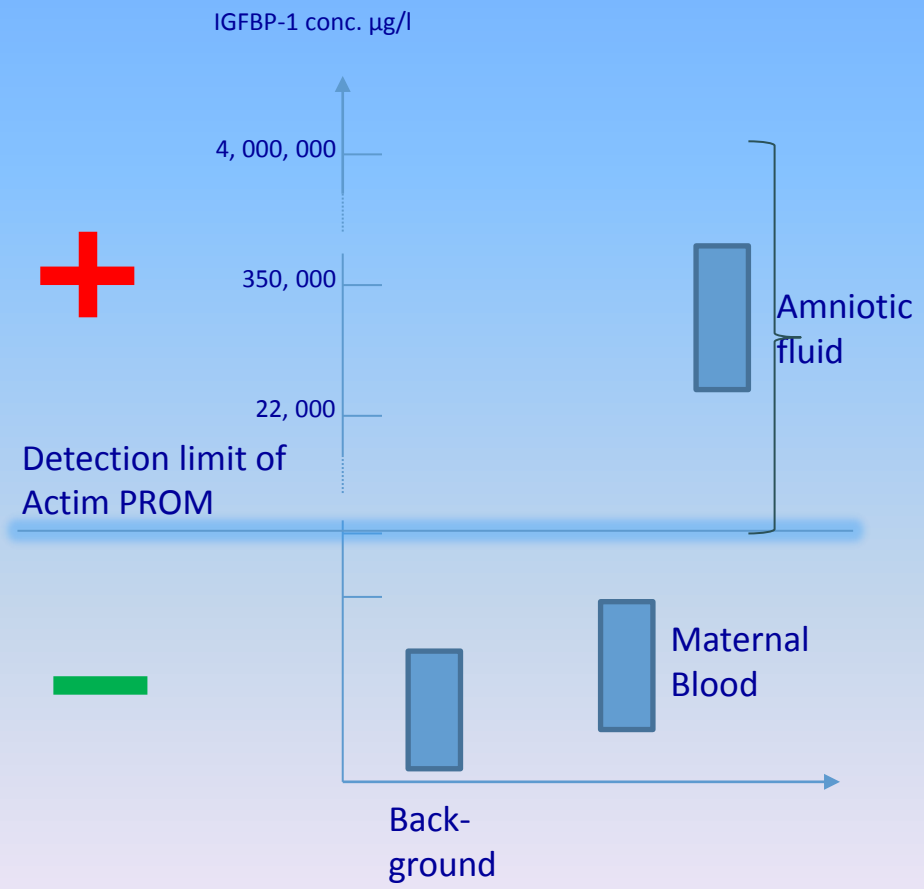
| Reference | Number of patients | Sensitivity % | Specificity % |
|---|---|---|---|
| Hupfner et al. 1997 | 54 | 100 | 93 |
| Ragosch et al. 1996 | 75 | 100 | 83 |
| Rutanen et al. 1996 | 130 | 100 | 95 |
| Gaucherand et al. 1997 | 100 | 95 | 98 |
| Jain & Morris 1998 | 100 | 100 | 89 |
| Kubota & Takeuchi 1998 | 90 | 95 | 93 |
| Darj & Lyrenäs 1998 | 75 | 96 | 93 |
| Akercan et al. 2004 | 87 | 100 | 92 |
| Erdemoglu and Mungan 2004 | 151 | 97 | 97 |

# Optimal specificity

- Unlike with other methods**, also bleeding patients can be tested with Actim PROM**
- **Even 20%** of the patients that need PROM test have vaginal bleeding and cannot be reliably tested with other methods
- Correct results with bleeding patients have been **proven in clinical studies**:
  - Rutanen et al. 1996
  - Kubota et al. 1998
  - Guibourdenche et al. 1999
  - Erdemoglu and Mungan 2004
  - Novikova et al. 2007

# Why is Actim PROM test result not affected by blood?

- The **antibodies** in Actim PROM do not detect the predominant form of IGFBP-1 found in blood.
- The **detection limit** of the test has been set above the known concentration in maternal blood



# Optimal sensitivity

- The sample is seldom pure amniotic fluid, it can be contaminated or diluted by e.g.,
  - Urine
  - Seminal plasma
  - Bath water
  - Blood
  - Vaginal discharge
  - **No interference with any of these substances**
  - Even amniotic fluid volumes less than 0.5 µl can be **detected**

# Conclusions (1)

- **Actim Partus** test gives a rapid and reliable answer to estimate the risk of PTD or imminent delivery
- A negative result means that it is highly unlikely that the patient will deliver soon
- The test helps limit unnecessary medication and to focus treatment to those patients that really need it

# Conclusions (2)

- Actim PROM test can be used to reliably identify patients that have ruptured membranes
- The test can be used on **all patients** suspected of having ruptured membranes

- The correct diagnosis ensures the correct clinical management of your patients