Preterm Birth and Fetal Fibronectin:
Assessing Risk Along the Continuum

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At the conclusion of this presentation, the healthcare provider will be able to:

1. Describe the epidemiology and long-term consequences of preterm birth in the United States
2. Identify women at risk of spontaneous preterm birth (SPTB)
   1. Symptomatic
   2. Asymptomatic
3. Understand the role of fetal fibronectin (fFN) testing as an important tool for assessing risk
4. Describe strategies to benefit women at risk
Preterm Births in the United States: 1 in 8 Infants

Preterm Births in the US (\%)^{1-3}

1981: 9.4
1991: 10.8
2005: 12.7

35.1% Increase Since 1981
Healthy People 2010 goal: 7.6

US 2010: 9%
PR 2010: >19%

In the PR, preterm birth accounts for:

- 19% of all births
- 75% of all neonatal mortality and 50% of long-term neurological impairments in children
- 33% of all health care spending on infants and 10% of spending for children

Despite advances in OB care, the preterm birth rate has continued to rise
Prematurity Generates Enormous Health Care Costs

- Average newborn hospital charges: $4,300 vs. $58,000 for a preterm baby*

- Total U.S. hospital charges for infant stays due to prematurity/low birth weight: $11.9 Billion*

- Maternity & related expenses:
  - Often the largest cost to employers’ health care plans

* Source: Agency for Healthcare Research and Quality, 2000 Nationwide Inpatient Sample Prepared by March of Dimes Perinatal Data Center
Major Complications of Prematurity

- Major determinants of neonatal and infant illness:
  - Neurodevelopmental handicaps (CP, mental retardation)
  - Respiratory Distress Syndrome
  - Chronic pulmonary disease (bronchopulmonary dysplasia)
  - Intraventricular hemorrhage
  - Periventricular Leukomalacia
Continuation

– Patent Ductus Arteriosus
– Jaundice
– Infection
– Retrolental fibroplasia
– Necrotizing enterocolitis
– Neurosensory deficits (hearing, retinopathy of prematurity)
WHAT ARE THE RISK FACTORS FOR PRETERM LABOR
Preterm Labor Statistics

Spontaneous PTL
- 60% of all PTL
-- Screening tools are only:
  1. Fetal Fibronectin
  2. TV Cervical US

Indicated PTL
- 40% of all PTL
  -- 43% Ischemic (IUGR)
  -- 37% Placental Disease
- Preeclampsia
- Fetal growth Restriction
- Fetal Distress
- Abruption
Clinical Risk Factors for Spontaneous Preterm Birth

- Prior history of SPTB\textsuperscript{1, 2}
- Multiple gestation\textsuperscript{1, 2}
- Vaginal bleeding\textsuperscript{1, 2}
- African American or Hispanic\textsuperscript{1, 2}
- Low pre-pregnancy weight\textsuperscript{1, 2}
- Maternal age <17 and >35 years\textsuperscript{1}
- Low socioeconomic status\textsuperscript{1, 2}
- Maternal stress\textsuperscript{1, 2}
- Cigarette smoking, drug abuse\textsuperscript{1, 2}
- Anemia\textsuperscript{1}

These risk factors are also the same for Induced PTL!!

PROBLEM !!!
Most Clinical Risk Factors Are Poor Predictors

Risk factors fail in both directions

More than 1/2 of women who deliver preterm do not have identifiable risk factors and are nulliparous\(^1\)

Approximately 2/3 of women with traditional risk factors do not go on to deliver preterm\(^2\)

How Can We Screen for PTL?
Pathophysiologic Mechanisms for Prematurity

Activation of Maternal/Fetal HPA Axis
- Maternal/Fetal stress

Inflammation/Infection
- Chorio-decidual
- Systemic

Decidual Hemorrhage
- Abruption

Pathological Uterine Distension
- Multifetal pregnancy
- Polyhydramnios
- Uterine abnormality

Chorion Decidua

fFN is the single common biochemical marker

fFN +

Uterine Contraction
Cervical Change
Preterm PROM

Preterm Birth

Relative Risk of SPTB <32 Weeks

Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
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</thead>
<tbody>
<tr>
<td>Contractions (+)</td>
<td></td>
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<tr>
<td>Race (Black)</td>
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<tr>
<td>Pelvic Infection (+)</td>
<td></td>
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<tr>
<td>Bacterial Vaginosis (+)</td>
<td></td>
</tr>
<tr>
<td>Vaginal Bleeding (+)</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index &lt;19.8</td>
<td></td>
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<tr>
<td>Previous SPTB (+)</td>
<td></td>
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<tr>
<td>Cervical Length ≤25 mm</td>
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<tr>
<td>Fetal Fibronectin (+)</td>
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</tbody>
</table>

Risk (%) for SPTB at <37 Weeks
Multiparas Only

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Risk of PTB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL ≤25 mm</td>
<td>15.6</td>
</tr>
<tr>
<td>Prior SPTB</td>
<td>17.6</td>
</tr>
<tr>
<td>(+) fFN</td>
<td>19.2</td>
</tr>
<tr>
<td>CL ≤25 mm and (+) fFN</td>
<td>43.8</td>
</tr>
<tr>
<td>ALL three</td>
<td>60</td>
</tr>
</tbody>
</table>

Biomarkers for Risk Assessment

Allows Physicians to:
- More accurately identify women at risk
- Develop ongoing surveillance programs
- Institute appropriate interventions
- Increase patient education and preparation

Allows Patients to:
- Avoid unnecessary treatment and expense
- Maintain personal, family, and professional lifestyle

Biochemical
Fetal fibronectin (fFN)

Biophysical
Cervical length by TVUS

TVUS = transvaginal ultrasound

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**Biophysical**

- Cervical length by TVUS

**Biochemical**

- Fetal fibronectin (fFN)

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TVUS = transvaginal ultrasound
Fetal Fibronectin: Key Biochemical Marker for Risk Assessment

- Adhesive glycoprotein “glue” at the maternal-fetal interface
- Presence in cervicovaginal secretions highly associated with risk of preterm delivery

Cervicovaginal Presence of Fetal Fibronectin from 22 to 35 Weeks Is Abnormal

Fetal Fibronectin (ng/mL)

Gestational Age (Weeks)

Clinically Relevant Time Frame (22 to 35 weeks)

Fetal Fibronectin (ng/mL)

Gestational Age (Weeks)

Clinically Relevant Time Frame (22 to 35 weeks)

50 ng/mL Cutoff Level

### Guidelines for Performing fFN Test

<table>
<thead>
<tr>
<th>Obtain Specimen <strong>Prior</strong> to Any Examination or Manipulation of the Cervix:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Digital examination</td>
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<tr>
<td>- Vaginal ultrasound</td>
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<tr>
<td>- Microbiologic culture</td>
</tr>
<tr>
<td>- Pap test</td>
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<table>
<thead>
<tr>
<th>Specimen Should <strong>Not</strong> be Obtained in the Presence of:</th>
</tr>
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<tbody>
<tr>
<td>- Cervical dilatation ( \geq 3 \text{ cm} )</td>
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<tr>
<td>- PPROM</td>
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<tr>
<td>- Soaps, gels, lubricants, or disinfectants</td>
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<tr>
<td>- Cervical cerclage</td>
</tr>
<tr>
<td>- Moderate or gross vaginal bleeding</td>
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<tr>
<td>- Sexual intercourse within 24 hours</td>
</tr>
</tbody>
</table>

fFN Specimen Collection Procedure

- During speculum examination, lightly rotate swab across posterior fornix of vagina for 10 seconds to absorb cervicovaginal secretions.

- Remove swab and immerse polyester tip in buffer; break shaft at score even with top of tube.

- Align the shaft with hole inside the tube cap and push down tightly over shaft, sealing tube; ensure shaft is aligned to avoid leakage.

Cervical length as a screening Test

- Have validity
  - Digital vs TVU examinations of CL every 2 wks (GA 14 ~GA 30) predict PTB ➔ TVU superior
    - Sonographic cervical length : 11 mm longer than manual estimations.
    - ➔ TVU superior to manual exam for evaluation of Cx & prediction of preterm birth.
The association between a short cervix and preterm delivery is significant.

NICHD Maternal-Fetal Medicine Network Trial
- RR less than 4 cm at 28 weeks: 2.8
- RR less than 3 cm at 28 weeks: 5.39
- RR less than 2.2 cm at 28 weeks: 13.88
- RR less than 1.3 cm at 28 weeks: 24.94
Comparison of Risk Factors (TVUS+FFN)

Cervical length measurement and fFN testing were performed at 22 to 24 weeks.

Spontaneous Preterm Birth < 32 Weeks

Relative Risk

- African American: 1.5
- BMI <19.8: 2.6
- (+) BV: 2.7
- Previous SPTB: 7.1
- CL ≤25 mm: 7.7
- (+) fFN: 14.1

fFN in Symptomatic Patients:
High NPV

NPV for delivery within:
7 days = 99.5%
14 days = 99.2%
<37 weeks = 84.5%

N = 763
Mean gestational age at fFN testing = 30.3±3.0 weeks
Mean gestational age at delivery = 38.4±2.6 weeks

Benefits of a Negative Test
• Less intervention
• Avoid hospitalizations
• Physician and patient reassurance

fFN in Symptomatic Patients: Helpful PPV

Benefits of a Positive Test

- Identify group that can be targeted for intervention
- Opportunity for antenatal steroids
- Preparation for optimal neonatal care

PPV for delivery within:
7 days = 12.7%
14 days = 16.7%
<37 weeks = 44.7%

N = 763
Mean gestational age at fFN testing = 30.3±3.0 weeks
Mean gestational age at delivery = 38.4±2.6 weeks

NICHD Preterm Prediction Study: Asymptomatic Patients

If fFN positive at 22 to 24 weeks:

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Sensitivity</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28 weeks</td>
<td>63</td>
<td>59.2</td>
</tr>
<tr>
<td>&lt;30 weeks</td>
<td>54</td>
<td>39.9</td>
</tr>
<tr>
<td>&lt;32 weeks</td>
<td>38</td>
<td>21.2</td>
</tr>
<tr>
<td>≤34 weeks</td>
<td>21</td>
<td>8.9</td>
</tr>
</tbody>
</table>

N=2929. Single testing at 22 to 24 weeks.
NICHD=National Institute of Child Health and Human Development.

Potential Interventions for Symptomatic Patients Based on fFN Results

Obtain fFN and cultures
Assess membranes
Cervical dilatation <3 cm

fFN (-)
Consider:
- Cervical length measurement
- Normal or modified ADLs
- Heightened antenatal surveillance

If Hospitalized:
- Consider stopping tocolytics
- Rule out infection
- Release home when appropriate
- Close office follow-up

fFN (+)
Consider:
- Cervical length measurement
- Admission for steroids and observation
- Transfer to tertiary care
- Fetal assessment
- Rule out infection
- Modified ADLs
- Tocolysis

ADLs=activities of daily living
### Potential Interventions for Asymptomatic Women at Risk Based on fFN Results

<table>
<thead>
<tr>
<th>fFN (-)</th>
<th>fFN (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider:</strong></td>
<td><strong>Consider:</strong></td>
</tr>
<tr>
<td>▪ Routine follow-up</td>
<td>▪ Increase intensity of prenatal observation</td>
</tr>
<tr>
<td>▪ Biweekly fFN testing</td>
<td>▪ Educate on signs and symptoms</td>
</tr>
<tr>
<td>▪ Cervical length measurement</td>
<td>▪ Examine for other risk factors</td>
</tr>
<tr>
<td></td>
<td>▪ Cervical length measurement</td>
</tr>
<tr>
<td></td>
<td>▪ Rule out infection</td>
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<tr>
<td></td>
<td>▪ Antenatal Steroids</td>
</tr>
<tr>
<td></td>
<td>▪ Serial fFN testing</td>
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Summary

- Preterm birth remains a serious problem
- Women at risk need to be identified early for evaluation and intervention
- fFN is a powerful, actionable predictor of SPTB
  - A negative test can avoid unnecessary interventions and provide reassurance
  - A positive test can be used to target interventions in women most likely to benefit
  - Cervical length can further improve prediction
Conclusions

fFN determination has an essential place in management of women at increased risk of spontaneous preterm birth