Improving Pregnancy Outcomes: The Challenge of Prematurity

Geeta K. Swamy, MD
Duke Maternal Fetal Medicine
Preterm Birth: A Global Issue

Estimated preterm birth rates by country for the year 2010
Preterm Birth: Trends in the US

- Preterm (< 37 weeks)
- Late preterm (34 - 36 weeks)
- Early preterm (< 34 weeks)

Source: CDC/NCHS, National Vital Statistics System
Preterm Birth: Short-term Morbidity & Mortality by Gestational Age

Health and survival outcomes (%)

- Survival
- RDS
- Sepsis
- IVH
- NEC

Gestational age at birth (wks)

24 26 28 30 32 34 36

Figure adapted with permission Mercer BM. ObGyn 2003;101(1):178-193.
Preterm birth: Long-term Effects

• Childhood sequelae
  • Chronic lung disease
  • Visual and hearing impairments
  • Neurodevelopmental disabilities

• Adolescent & adult sequelae
  • Increased mortality risk
  • Reduced reproductive capacity/potential
  • Increased risk for psychiatric conditions

Swamy, JAMA 2008
Preterm Birth is an unusual . . .

• Disease?
• Syndrome?
• Health Outcome?
• Condition defined by time rather than a distinct clinical phenotype
Risk factors for Preterm Birth

**Lifestyle-Societal factors**
- Inadequate prenatal care
- Tobacco, alcohol, illicit substances
- Domestic violence
- Poor social support
- Psychosocial stress
- Excessive work hours
- Low socioeconomic status
- Short inter-pregnancy interval
- Environmental exposures

**Medical risk factors:**
- Hypertension
- Diabetes
- Clotting disorders
- Extremes of maternal weight
- Genitourinary Infections
- Fetal congenital anomalies
- Vaginal bleeding
- Prior preterm birth/poor outcome
- Multiple gestation
- Uterine/cervical anomalies
- Decreased cervical length

**Host factors**
- Extremes of maternal age
- Minority race
- Hereditary trait
Preterm Birth Phenotype

- PPROM: 25%
- Preterm labor: 45%

Referenced from JM Moutquin – BJOG, 2003
Multifactorial Etiology of Preterm Birth

- Inflammation
  - IL-1β, IL-8, TGF-β, GCSFR, Calgranulin A, GRO2, Complement C5A

- Decidual haemorrhage
  - MCP1, MCP3, MIP1α, MIP1β

- Maternal/fetal HPA axis

- Gestational tissues

- Uterine distention

- Proteases
  - PAI-1

- Cervical change
  - PROM

- Uterotropins
  - Thrombospondin 1, PGHS2, FLAP

- Endothelin converting enzyme

- Uterine contractions

- Delivery

Esplin & Warner, BJOG 2005
Phenotypic components of preterm birth

Villar. The preterm birth syndrome. AJOG 2012
Interventions to Reduce Preterm Birth

• Primary – directed to all women

• Secondary – aimed at eliminating or reducing existing risk

• Tertiary – aimed at improving outcomes in preterm infants

Tertiary Interventions for women with immediate risk of preterm birth

- Regionalized care
- Antenatal corticosteroids
- Tocolytic agents
- Antibiotics
  - PPROM latency
  - GBS prophylaxis
- Magnesium sulfate for CP prophylaxis
- While these measures have reduced perinatal morbidity and mortality, they have had no significant impact on preterm birth incidence

Secondary prevention for women at risk for preterm birth

- Prevention of indicated preterm birth
  - Low dose aspirin, calcium supplementation
- Modified maternal activity
- Nutritional supplementation
- Improved prenatal care
- Antibiotics
- Cervical cerclage
- Cervico-Vaginal Pessary
- Progesterone
Secondary prevention for women at risk for preterm birth

- ECM Degradation
- Inflammation
- Uterine Contractility
- Progesterone

Short Cervix

Preterm Birth
## Progesterone use in singleton gestation with history of spontaneous PTB

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Primary Outcome</th>
<th>Intervention</th>
<th>Delay in Delivery</th>
<th>Improved Infant outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meis</td>
<td>463</td>
<td>PTB &lt; 37wks</td>
<td>17-OHP from 16 - 36 wks</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fonseca</td>
<td>142</td>
<td>PTB &lt; 37wks</td>
<td>Vaginal progesterone 24 - 34 wks</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>O’Brien</td>
<td>659</td>
<td>PTB &lt; 32wks</td>
<td>Vaginal progesterone 18 – 37 wks</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Meis, NEJM 2003 Jun 12;348(24):2379-85  
Fonseca, AJOG 2003 Feb;188(2):419-24  
Effectiveness of Progesterone in women with prior sPTB

- 5-6 women need to be treated to prevent 1 birth <37 weeks
- 12 women need to be treated to prevent 1 birth <32 weeks
Primary prevention during pregnancy

- Primary - directed to all women
- Nutritional supplementation
- Smoking cessation
- Periodontal care
- Screening-treatment
  - Benefit in cancer and cardiovascular disease
  - Involves decades of effort through education and public policy built on sound science
  - Cervical length
  - Maternal serum proteomic profiling

Relative Risk of sPTB < 35 wks by cervical length at 24 wks

Relative risk of premature delivery

No. of women

Length of cervix (cm)

Percentile

1 5 10 25 50 75

Iams et al, NEJM 1996
## Progesterone for Short cervix

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Primary Outcome</th>
<th>Intervention</th>
<th>Delay in Delivery</th>
<th>Improved Infant outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fonseca</td>
<td>250</td>
<td>PTB &lt; 34wks</td>
<td>Vaginal progesterone 24 – 34 wks</td>
<td>Yes</td>
<td>+/-</td>
</tr>
<tr>
<td>Hasson</td>
<td>458</td>
<td>PTB &lt; 33 wks</td>
<td>Vaginal progesterone 20 – 36 wks</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Grobman</td>
<td>657</td>
<td>PTB &lt; 37wks</td>
<td>17-OHP 16 - 36 wks</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Fonseca, NEJM 2007  
Hassan, Ultrasound Obstet Gynecol 2011  
Grobman, AJOG 2012
Maternal Serum Proteomics

- Secondary analysis of Preterm Prediction Study for validation of biomarker + novel proteomics for sPTB prediction
- Samples selected from 160 asymptomatic participants
  - 24 and 28 weeks – 40 spontaneous PTB, 40 term births
- 3 peptides from inter-alpha-trypsin inhibitor heavy chain (ITIH)-4 protein were significantly reduced in women having subsequent sPTB
- Predictive value at 28 weeks

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single ITIH-4 peptide</td>
<td>65%</td>
<td>82.5%</td>
</tr>
<tr>
<td>ITIH-4 peptides + 6 biomarkers</td>
<td>86.5%</td>
<td>80.6%</td>
</tr>
<tr>
<td>Cervix length ≤ 25mm</td>
<td>49.5%</td>
<td>86.8%</td>
</tr>
</tbody>
</table>

Esplin AJOG 2011
Iams, NEJM 1996
Proteomic Assessment of Preterm Birth (PAPR)

- Sera Prognostics, Inc.
- Observational cohort study n = 4000
- Proteomic profiles comparison of women who deliver preterm and term
- Inclusion Criteria – 18+ years of age, singleton gestation, no known fetal congenital anomalies
- Estimated Study Completion Date: April 2013
Summary

• Preterm birth is complex, multifactorial, and affected by host, societal, and environmental factors

• Despite intensive research efforts, our increased knowledge of the disease process and etiology has not translated into effective strategies for disease reduction

• Significant impact on prematurity prevention can only occur with advances in primary and secondary interventions
Integrated approach to research & implementation to promote healthy pregnancy & reduce PTB and stillbirth

Definitions & Discovery Science

- Descriptive epidemiology
- Standardized definitions
- Determinants of healthy pregnancy
- Pathway-specific pathophysiology

Develop Interventions

- Education
- Improved diagnostics
- Interventions relevant to context specific high-burden settings

Deliver Interventions

- Implementation and scale-up of proven Interventions
- Policy modification to promote interventions
- Evaluation

Improved understanding of determinants of healthy pregnancy and of risk factors and pathways for poor pregnancy outcomes are prerequisites to developing and implementing effective population-specific interventions and to promote rational health care policies. In turn, evaluation of effective interventions will further facilitate research into pathways, mechanisms, and identification of unique populations at risk.

One baby in ten is born premature. Worldwide.