Low Birthweight/ Preterm Birth: Issues and Research Needs
Issues in LBW/Prematurity

- Increasing rates / Incidence
- Consequences
- Etiologies
- Risk Factors
- Markers
- Prevention strategies
- Research needs and focus
Preterm Delivery: A Public Health Priority

- 1 in 8 infants are born preterm
  - 476,000 preterm births each year
- Leading cause of hospitalization among pregnant women
- Leading cause of death among African-American infants
- Associated with developmental disabilities
US 1981-2002: Percent Preterm and LBW

- Preterm birth increased 29% since 1981
- LBW increased 15% since 1981

Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System

22% more twin births had PTD in 1996-7 than 1981-2

Martin et al, 2002
Disparity in preterm birth: race and ethnicity

Percent

1998  1999  2000  2001

American Indian/Alaska Native

Native Hawaiian/Other Pacific Islander

Black, Not Hispanic

White, Not Hispanic

Asian

Total Hispanic

SOURCE: National Vital Statistics System – Natality NCHS, CDC.
Leading Causes of Neonatal Mortality, 2001
(N / 100,000 live births)

- Preterm / LBW: 4,322
- Birth Defects: 3,875
- Maternal complications: 1,491
- Placenta / cord complications: 998
- RDS: 943

Table H. Deaths and percentage of total deaths for the 10 leading causes of neonatal and postneonatal deaths: United States, 2001

http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_09.pdf
Preterm Birth: Outcome

Accounts for:
- 1 out of 5 children with mental retardation
- 1 out of 3 children with vision impairment
- Almost half of children with cerebral palsy

---

N = 799

Bottoms, 1995
Preterm Birth: Long Term Outcome

For the baby:
- Increased risk for cardiovascular disease (MI, stroke, hypertension) as an adult
- Increased risk for diabetes as an adult
- Possible increase in cancer risk

For the mother:
- Increased risk for subsequent preterm delivery
Predictors of Preterm Birth

Importance of identification of markers

- To initiate risk-specific treatment
- To define a population and evaluate an intervention/therapy
- To learn mechanisms of preterm delivery
Risk factors for PTD

- Multiple gestation
- Previous preterm birth
- Uterine/cervical abnormalities
- Shortened cervical length
- African American race
- Age (<17, >35)

**Medical risk factors:**
- PROM
- Infections (UTI, vaginal infections, STD)
- High blood pressure
- Diabetes
- Clotting disorders (thrombophilia)
- Maternal weight (underweight or obesity)
- Short time period between pregnancies
- Certain birth defects
- Vaginal bleeding

**Lifestyle risk factors:**
- Late or no prenatal care
- Smoking
- Drinking alcohol
- Using illegal drugs
- Domestic violence
- Lack of social support
- High levels of stress
- Long working hours
- Low income
Women “at risk” for PTD

- Prior spontaneous PTD
- Multiple gestation
- Uterine anomaly
- Cervical incompetence
- Socioeconomic status
- Biochemical markers (e.g. FFN)
- Shortened cervical length
- Vaginal / cervical infections /inflammation

PTD risk based on prior pregnancy

Salama et al 1994
n=889
Risk Scoring Systems and PTD

- Low sensitivity, high false positive rates
- Majority of women who have PTD are from a low risk group
- Identification of high risk status has not led to improvement in outcome
- Importance of effective intervention for risk factor / marker
Categories of Preterm Births

- Spontaneous preterm labor (56%)
- Preterm premature rupture of the fetal membranes (20%)
- Preterm deliveries indicated for fetal or maternal reasons (22%)
Spontaneous Preterm Delivery: Mechanisms

- Uterine contractions
- Rupture of membranes
- Cervical ripening
- Cervical effacement
- Cervical dilation
- Infection
- Inflammation
- Cytokines, chemokines
Etiology of Spontaneous PTB

- Infection
- Other Pathologies
- No Pathology

Gestational Age
Infection and sPTD

- Evidence supports infection cause of PTD:
  - Clinical chorioamnionitis
  - Subclinical chorioamnionitis

Bacteria associated with prematurity

- Ureaplasma
- Mycoplasma
- Gardnerella
- Mobiluncus
- Peptostreptococcus
- Bacteroides
# Antibiotics: PTL & intact membranes

<table>
<thead>
<tr>
<th>Study</th>
<th>Antibiotic</th>
<th>N</th>
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<th>Improved Infant Outcome</th>
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<td>Erythromycin</td>
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<td>Romero, 1993</td>
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<td>Cox, 1995</td>
<td>Ampicillin / Amoxicillin</td>
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<td>Gordon, 1995</td>
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<td>Svare, 1997</td>
<td>Metronidazole / Ampicillin</td>
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<td>Oracle Trial</td>
<td>Erythromycin or Amoxicillin</td>
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</table>
Antibiotics & BV

- RCT metronidazole + BV with hx prior sPTD
  PTD 18% v 39%, p<.05  Morales et al 1994

- RCT metronidazole + erythromycin in high risk women, +BV
  PTD 23% v 37%, p<.001  Hauth et al 1994
NICHD: MFMU BV/TV Trial

- **Aim:** To establish whether metronidazole therapy will reduce the risk of PTD in women with asymptomatic bacterial vaginosis or trichomonas vaginalis
- **Design:** double-masked, placebo-controlled trial
- **Eligibility criteria:** <24 wks, BV or TV positive
- **Intervention:** Four doses of 2g metronidazole or placebo
- **Primary outcome:** delivery at < 37 weeks’
- **Sample:** BV: 1900 pregnant women (950/group) TV: 1900 pregnant women (950/group)

Rates of Preterm Birth

Asymptomatic BV

<table>
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Asymptomatic TV

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</tr>
<tr>
<td>Metronidazole</td>
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</table>

PTD

BV/TV trials

- TV trial stopped by DSMC after interim analysis found increased PTD in metronidazole group
- Effectiveness of treatment
  - BV: 78% negative for BV
  - TV: 93% negative for trichonomiasis

BV/TV trials: Conclusions

- Treatment of asymptomatic
  - BV does not reduce PTD or adverse perinatal outcomes
  - TV increased the risk of PTD

Results from these trials changed the practice of indiscriminate use of antibiotics in pregnancy

Fetal Fibronectin (FFN)

- Membrane protein localized to area between fetus and mother
- Role in implantation and placentation
- When detected in cervical or vaginal secretions of asymptomatic women is associated with >50-fold increased risk in PTD<28wks
- Intrauterine infection may disrupt fetal membranes and result in release of FFN

Antibiotics for FFN+ to prevent PTD

- **Aim:** To establish whether metronidazole therapy will reduce the risk of PTD in FFN+ women
- **Design:** double-masked, placebo-controlled trial
- **Eligibility criteria:** FFN+ at 21-25 wks
- **Intervention:** 10 day course metronidazole and erythromycin or placebo
- **Primary outcome:** delivery at < 37 weeks’
- **Sample:** 715 pregnant women
- **Findings:** No improvement in sPTD or nn outcome

Andrews et al, Obstet Gynecol 2003
Infection, Antibiotics and PTD

- Infection with intact membranes: No
- +BV, high-risk women: Yes
- +BV, low risk women: No
- +TV: No
- +FFN: No

Antibiotics Helpful
Home Uterine Contraction Monitoring to Prevent Preterm Delivery

- 2422 insured, at-risk women
- Intervention: weekly phone call, daily phone call, or HUCM system
- HUCM & Daily Call groups: higher Rx
- No changes in PTD, birthweight, cx dilation

Dyson et al  NEJM 1998
The HUAM Prediction Study

- Blinded monitoring of Women w/ Risk of PTD
  - Contraction frequency was related to risk of PTD
  - Contractions predicted PTD poorly
    - Sensitivity = 9.3% for ≥ 4 Contractions / hr
    - PPV = 26.7% to predict birth < 35 weeks
- Contractions are common in pregnancy
- Increased frequency in women who will have PTD is too small to be clinically useful
- Contractions occur late in process

Iams et al  NEJM 2002
Shortened cervix

Mechanism of Effacement:

Relative Risk of SPTD < 35 wks by % of cervical length at 24 wks

Iams et al, NEJM 1996
Cervical length

- Follows a Bell curve
- Risk of PTD increases as cervical length decreases across entire range of length
- Cervical changes are same at all GA

Limited studies available to determine effectiveness of Cerclage to prevent PTD in women with PTD

Berghella et al AJOG 1999
Althuisius et al AJOG 2000
Rust et al AJOG 2001
Newman et al AJOG 2002
Cerclage: Meta-Analysis & Reviews

- Owen et al *AJOG* 2003:
  - “Results are inconclusive”
- Odibo et al *Ob Gyn Survey* 2003:
  - “Trend toward less PTD but not NN mortality”
- Bachmann et al *Acta Obstet Gynecol* 2003:
  - “Significant reduction in PTD < 34 weeks”
- Belej-Rak et al *AJOG* 2003r
  - “No support for cerclage to reduce PTD”

To *et al, Lancet* 2004; 363:1849-53
RCT of 253 women with CL <15 mm: cerclage vs none
  No difference PTD <33 wks (22% vs 26%, p=0.4)
Progesterone

• Steroid hormone
• Progesterone is a small hydrophobic molecule.
• Diffuses freely through the plasma membrane of all cells
• In target cells, (endometrium)
  • becomes tightly bound to a cytoplasmic protein the progesterone receptor
• the complex of receptor-hormone moves into nucleus
• binds to a progesterone response element (a specific sequence of DNA in the promoters of certain genes that is needed to turn those genes on/off). The complex of progesterone with its receptor forms a transcription factor.
Actions of Progesterone on the Myometrium

- Decreases conduction of contractions
- Increases threshold for stimulation
- Decreases spontaneous activity
- Decreases number of oxytocin receptors
- Prevents formation of gap junctions
Early Trials of Progesterone

Johnson JWC. *NEJM* 1975;293:675-680
- 43 patients (recur Ab or PTD)
- Rx: 17P or placebo
- 41% of placebo group delivered <36 wks
- 100% of treated group delivered >36 wks

- 168 pregnant women in the military
- Rx: 17P or placebo
- Low birth weight infants:
  - 7.5% in treated subjects
  - 9.0% in placebo subjects
Meta-analysis of 17P in pregnancy

- 5 trials: high risk women with 17P
- Pooled analysis of results showed:
  - Reduction in rates of preterm birth
    Odds ratio 0.50, 95% CI: 0.30-0.85
  - Reduction in rates of low birthweight
    Odds ratio 0.46, 95% CI: 0.27-0.80

Keirse MJNC. *Brit J Obstet Gynecol* 1990;97:149
Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study

- University of Sao Paulo Medical School, Brazil
- RCT double-blind, placebo controlled
- 1996-2001
- Rx: daily Progesterone (100 mg) vs placebo as vaginal suppository from 24 – 34 wks

Da Fonseca et al
AJOG 2003;188:419-24
Methods

- 157 high risk singleton pregnancies, 15(9.5%) lost to follow-up;
  - Prior sPTD (avg 33 wks)
  - Prophylactic cervical cerclage
  - Uterine malformation

- Analyzed remaining 142
  - 70 placebo
  - 72 progesterone

Da Fonseca et al
AJOG 2003;188:419-24
Characteristics

- Qualifying delivery (wks) 33.3 33.4
- Maternal age (yrs) 27.6 26.8
- Caucasian 68% 71%
- Risk Factor
  - Prior PTD 90% 97%
  - Uterine malformation 5.6% 1.4%
  - Incompetent cervix 4.1% 1.4%
Rates of Preterm Birth

- <37 weeks: P<0.03
- <34 weeks: P<0.002
- PTL: NS

Da Fonseca et al
AJOG 2003;188:419-24
Uterine contraction frequency
1 hr monitoring/wk

UC/hr

Placebo

Progesterone

P<0.004

Gestational age (wk)

Da Fonseca et al
AJOG 2003;188:419-24
Findings

- Progesterone
  - prevented preterm delivery in women with prior PTD, especially <34 wk
  - reduced the frequency of uterine contractions

Da Fonseca et al
AJOG 2003;188:419-24
Progesterone trial for the prevention of preterm delivery in high-risk women

NICHD Maternal Fetal Medicine Units Network

Meis et al, NEJM, 2003
NICHD: MFMU Progesterone Trial

- **Aim:** To establish if weekly progesterone injections in women with prior spontaneous preterm delivery (sPTD) reduces the risk of PTD
- **Design:** double-masked, placebo-controlled trial
- **Eligibility criteria:** singleton pregnancy 16-20 wks with documented previous sPTD
- **Intervention:** progesterone or placebo
- **Primary outcome:** delivery at < 37 weeks’
- **Sample:** 463 pregnant women

19 Centers enrolled women with:

- Documented history of spontaneous preterm birth at 20⁰ to 36⁶ weeks’ gestation in a previous pregnancy
- Gestational age at entry of 15-20³ weeks confirmed by ultrasound
- Singleton gestation, with no major fetal anomalies

Randomization & follow-up

- Given a trial injection of the placebo inert oil, and asked to return in 1 week
- At next visit, (160 - 206 wks) randomly assigned by a central randomization scheme, to receive injection of 250 mg 17P or a placebo inert oil
- The women returned for weekly injections of 17P or placebo until 37 weeks or delivery

Review by Data and Safety Monitoring Committee

- Interim analysis was performed after 351 subjects had delivered
- Analysis showed positive effect for the primary outcome
- Enrollment of new subjects was halted when 463 subjects randomized

Screening & Randomization

- 2980 women screened
  - 1941 ineligible
  - 1039 eligible
    - 576 refused consent or declined after trial injection
    - 463 randomized
      - 310 17-P
      - 163 placebo
Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>17-P</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Qualifying delivery (wks)</td>
<td>30.5</td>
<td>31.3</td>
</tr>
<tr>
<td>Maternal age (yrs)</td>
<td>26.0</td>
<td>26.5</td>
</tr>
<tr>
<td>Married</td>
<td>51%</td>
<td>46%</td>
</tr>
<tr>
<td>African American</td>
<td>59%</td>
<td>58%</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>26.9</td>
<td>25.9</td>
</tr>
<tr>
<td>Smoking</td>
<td>22%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Progesterone: Rates of Preterm Birth

Progesterone Results: Ethnic Group

Effectiveness of Progesterone

- 5-6 women with a previous sPTB would need to be treated to prevent one birth <37 weeks

- 12 women with a previous sPTB birth would need to be treated to prevent one birth <32 weeks

Progesterone prevents neonatal complications

Compliance and Side Effects

- Compliance with the weekly injections was excellent

- 91.5% of the women received their injections at the scheduled time

- Side effects were minor and were similar in the 17P and placebo groups

Progesterone prevents recurrent preterm delivery

- Weekly injections of progesterone prevented recurrent preterm birth and improved the neonatal outcome for pregnancies at risk
- Effective in preventing very early as well as later preterm birth
- Effective in both African American and Non-African American women

ACOG Committee Opinion: Use of Progesterone to Reduce Preterm Birth

- Recent studies support progesterone supplementation reduces PTD in select group of women (prior sPTD < 37 wks)
- Further studies are needed to evaluate the use of progesterone in patients with other high-risk conditions (multiple gestation, short cervical length, positive FFN)
- Recommend restricting progesterone use to prevent PTD for women with prior sPTD

Obstet Gynecol 2003;102:1115-6
Putting it all together

Should women “at risk” be started on progesterone?

- PTD etiologies: heterogeneous
- Limited (if any) ability to predict PTD
- Many women “at risk”
  - Demographic characteristics
  - Behavioral factors
  - Obstetric history
- Certainly not all will benefit from progesterone
Should women “at risk” be started on progesterone?

- Prior to da Fonseca and Meis trials – no evidence based research supporting preventative treatment for women to prevent PTD
- Overall, limited data available for at risk conditions
- There is evidence to support progesterone treatment for women with prior sPTD
Women “at risk” for PTD

**Prior spontaneous PTD**
- Multiple gestation
- Uterine anomaly
- Cervical incompetence
- Socioeconomic status
- Biochemical markers (e.g. FFN)
- Shortened cervical length
- Vaginal / cervical infections /inflammation

**Medical risk factors:**
- PROM
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- Short time period between pregnancies
- Certain birth defects
- Vaginal bleeding

**Lifestyle risk factors:**
- Late or no prenatal care
- Smoking
- Drinking alcohol
- Using illegal drugs
- Domestic violence
- Lack of social support
- High levels of stress
- Long working hours
- Low income
Prior spontaneous PTD
- Only one risk factor
- Small % of all PTD

Major initiatives into:
- Understanding the cause(s)
- Methods of prevention and treatment in pregnant women
- Optimal management/treatment of neonates
Major Research Advances

- Markers, management and prevention of PTD
  - Markers: history, FFN, cervical length
  - Management: antenatal steroids, antibiotics & PPROM
  - Prevention: Progesterone

- Management of preterm neonate
  - Inhaled nitric oxide
  - Optimal nutrition for preterm neonate
Prematurity/LBW Research needs:

- **Major focus:**
  - Prevention
  - Treatment
  - Management of preterm neonates

- **Mechanisms:**
  - Researcher initiated grants
  - Targeted requests
  - NIH Multicenter Networks
  - Education

Mechanism
Pathophysiology
Genetics
Disparity
NICHD Networks

• High risk pregnancies: PTD/LBW prevention and management
• Management of the preterm and LBW neonate
• Long term outcome of prematurity and LBW
LBW/Prematurity: Research Needs

- Investigator initiated grants
- Trials in NICHD clinical networks
  - Identify markers
  - Identify treatment
  - Identify preventative therapies
  - Identify optimal management
- Long-term follow-up
- National Children’s Study
Long term study of environmental influences on children’s health and development

Children’s Health Act, 2000 authorized NICHD Director to collaboratively “…conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children’s health and development”

Follow 100,000 children during prenatal development, birth, childhood into adulthood

Would allow major scientific initiatives to gain understanding, management and treatment of preterm birth
Prematurity Prevention: A Public Health Priority

- 1 in 8 infants are born preterm (476,000 preterm births / year)
- Leading cause of neonatal death
- Major cause of long-term morbidity
- Impacts adult health
LBW/Prematurity Prevention

To reduce:
- LBW, Preterm labor and delivery
- Risk of pregnancy related deaths and complications related to pregnancy
- Infant mortality caused by LBW/prematurity

Critical need for:
- Answers to major research questions
- Clinical trials and longitudinal data
- Long term follow-up
The goal: healthy children and mothers…