Advances in preterm birth prevention: Impact on PPROM management

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Outline

• Overview Preterm birth
  – Focus on PTL and PPROM
    • Differences in clinical phenotype

• Latest advances in treatment/diagnostics
  – Focus on progesterone therapy
  – Diagnosis of subclinical infection
Preterm Birth

- PPROM 25%
- Preterm labor 45%
Spontaneous Preterm Birth: A Syndrome?

- PTL, PPROM, and preterm cervical effacement and dilation without labor
  - One syndrome with multiple etiologies?
  - Multiple syndromes with distinct etiologies?
Categorize

Spontaneous Preterm Birth

• Based on presentation NOT mechanism

• SPTB occurs as clinical presentation of
  – Infection
  – Vascular insult
  – Uterine overdistension
  – Stress or other pathologic processes

• Syndrome with no diagnostic test/treatment
Preterm Labor—ADAPTIVE

• PTL is an *adaptive* mechanism of host defense
  – Eliminate fetus from hostile environment

• Treatments aimed at common terminal pathway and not mechanism of disease-inducing activation will not be effective

Spontaneous Preterm Birth

- PPROM <18-24 hours latency
- PTL and delivery
PPROM and Neonatal Death

- California Perinatal Quality Care Collaborative
- 17,501 neonates at 24 - 34 weeks gestations
- No PPROM vs recent PPROM vs prolonged PPROM
- 24-26 wks prolonged PPROM associated with decreased mortality
  - (18% vs 31%; OR 1.79; CI 1.25 – 2.56)
- Membrane rupture not associated with increased neonatal mortality

Blumenfeld et al, Obstetrics & Gynecology: December 2010
Extreme PPROM

• 1,437 PTD at 23-27 wks; 236(16.4%) complicated by PPROM
• PPROM higher rate of chorioamnionitis
  – (33.8 vs. 17.0%; P < 0.001)
• PPROM higher neonatal death at 23-24 wks
  – (70.0 vs. 54.8%; P = 0.013)
• PPROM and chorioamnionitis significant after adjusting for GA and gender
  – (OR = 3.32; 95% CI 2.43–4.51, P < 0.001)

Newman et al; Archives of Gynecol and Obstet,2009
Neonatal Outcomes in PPROM

• Uncomplicated PPROM (n=488) vs SPTL (n=1465) 28-34 wks

• PPROM increased risk for
  – Composite neonatal morbidity (53.7% vs 42.0%; \( P < .001 \))
  – Mortality (1.6% vs 0.0%; \( P < .001 \))
  – Respiratory morbidity (32.8% vs 26.4%; \( P = .006 \))

• Adverse outcome more likely
  – Latency period >7 days, oligohydramnios, male fetus, nulliparity

• Prematurity-related morbidity in PPROM cannot be extrapolated from PTDs

Nir Melamed et al, Presented at SMFM 2010, Chicago
Hypothesized Mechanisms

- Cervical change
- Uterine Contractility
- Decidual activation
Cervical Changes

- Regulation of ECM composed of collagen, elastin, and fibronectin

- Cervical ripening is result of:
  - decreased collagen content
  - increased collagen solubility
  - increased collagenolytic activity
Cervical Changes

• Influx of inflammatory cells into the cervical stroma
  – Cytokines/prostaglandins affect ECM metabolism
  – Influenced by estrogen and progesterone

• Cervical changes are gradual over weeks

• PTB often preceded by cervical ripening
Cervical Changes

Progesterone

ECM Remodeling

Cervical Ripening
Funnelling

Preterm labor
Uterine Contractility

• Change from uncoordinated contractures to coordinated contractions
  – produce increase intrauterine pressure

• Oxytocin important regulator of contractility
  – produced by decidua and hypothalamus (endocrine and paracrine)
Uterine Contractility

- Gap junction formation and the expression of gap junction protein connexin 43
  - Similar in term and preterm labor

- **Progesterone**, estrogen and prostaglandins implicated in gap junction formation and expression of connexin 43
Decidual Membrane Activation

- PPROM membranes
  - Decreased collagen types I, III, and V
- Structural ECM implicated in tensile strength of the membranes
Inflammation and Membrane Destruction

- TNFα and IL1β induce collagen remodeling and apoptosis
- Apoptosis correlates directly with FM physical weakness
- FM undergo remodeling resulting in weaken

Kumar, Moore; Biol of Reprod, 2006
Destruction of Chorion Cells

• Apoptosis in chorion increased with chorioamnionitis (Murtha, Infect Dis OB/GYN, 2002; George, Am J Perinat, 2008)

• Chorion layer thinned in PPROM (Fortner abstract #16, SMFM)
Recent Advances

• Progesterone as a therapeutic tool for at risk individuals

• Advances in molecular identification of organisms
Progesterone’s Role in Pregnancy

• Maintains uterine quiescent

• Functional progesterone withdrawal prior to labor
  – changes in PR-A/PR-B expression

• Progesterone is an anti-inflammatory agent
  – Inhibits NFκB which inhibits COX 2 and prostaglandin production
Decidual Activation

Progestosterone

FM Remodeling

Progestosterone

PPROM

PTL

Uterine Contractility

Progestosterone

ECM Degradation

Progestosterone
And now for something completely different!

Identifying mechanisms resulting in SPTB
Is Subclinical Infection an etiology of PTB?

PPROM or PTL or Both?
Uncultivated Bacteria
Etiology of Inflammation

• AF from 46 PTB and 16 controls (term and genetic amnio)

• No DNA amplified in controls

• Bacterial DNA all (16/16) of culture +; (9/16) additional species

• 17% (5/30) of the culture - samples

Yiping et al, J of Clin Micro, January 2009
Uncultivated Bacteria  
Etiology of Inflammation

• 2/3 detected by PCR not isolated by culture
  – *Fusobacterium nucleatum, Leptotrichia (Sneathia) spp., Bergeyella sp., Peptostreptococcus sp., Bacteroides spp., Clostridiales*

• PCR + had elevated AF IL-6, histological chorioamnionitis, funisitis and neonatal early-onset sepsis

Yiping et al, J of Clin Micro, January 2009
Microbes and PPROM Inflammation

- PCR identified more species than culture (44 vs 14 species) included uncultivated taxa

- PCR positivity associated with lower BW, higher RDS and NEC rates

Di Guilio et al, Amer J of Reprod Immun, July 2010
Commercial Break
Global Alliance to Prevent Prematurity and Stillbirth (GAPPS)

• GAPPS’ Mission is to Improve Birth Outcomes Worldwide by leading a collaborative, global effort to increase awareness and accelerate innovative research and interventions that will improve maternal, newborn and child health outcomes around the world.
GAPPS: Born Too Soon

- Aspects of preterm birth
- Priorities for action based on national, regional and global estimates
- Care before and between pregnancy
- Care during pregnancy and childbirth
- Care for the preterm baby
GAPPS

• Strategic investments in innovation and research are required to accelerate progress
  – Goal to cut preterm birth rate in half by 2025
• Inequalities in survival rates around the world are stark:
  – 50% of babies born at 24 wks survive in high-income countries
  – 50% of babies born at 32 wks die in low income settings
From our widely accessible specimen repository to targeted global advocacy efforts, GAPPS projects are shifting the paradigm for prematurity and stillbirth.
The preterm birth syndrome: a prototype phenotypic classification

Jose Villar, MD, MSc, MPH, FRCOG, Aris T. Papageorghiou, MBChB, MRCOG, Hannah E. Knight, MSc, Michael G. Gravett, MD, Jay Iams, MD, Sarah A. Waller, MD, Michael Kramer, MD, Jennifer F. Culhane, PhD, MPH, Fernando C. Barros, PhD, Agustín Conde-Aguero, MD, MPH, Zulfiqar A. Bhutta, MBBS, FRCP, FRCPCH, FCPS, PhD, Robert L. Goldenberg, MD

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GAPPS

Prototypic Phenotype Classification

• Classification based on clinical phenotypes defined by characteristics of
  – mother, fetus, placenta, signs of parturition or pathway to delivery

• Risk factors and mode of delivery are not included

• Does not force any preterm birth into a predefined phenotype
  – allows all relevant conditions to be part of the phenotype

• Classification system will improve understanding of cause and improve surveillance across populations
GAPPS-
Prototypic Phenotype Classification

5 components in a preterm birth phenotype:
1. Maternal conditions that are present before presentation for delivery
2. Fetal conditions that are present before presentation for delivery
3. Placental pathologic conditions
4. Signs of the initiation of parturition
5. Pathway to delivery
GAPPS-
Prototypic Phenotype Classification

**Significant Maternal Conditions**
- Extraterine Infection
- Clinical Chorioamnionitis
- Maternal Trauma
- Worsening Maternal Disease
- Uterine Rupture
- Pre-Eclampsia/Eclampsia

**Significant Fetal Conditions**
- IUGD
- IUGR
- Abnormal FHR/BPP
- Infection/Fetal Inflammatory Response Syndrome
- Fetal Anomaly
- Alloimmune Fetal Anemia
- Polyhydramnios
- Multiple Fetuses
  - a) Twin-Twin Transfusion Syndrome
  - b) demise of fetus in multiple pregnancy

**Placental Pathologic Conditions**
- Histological Chorioamnionitis
- Placental Abruption
- Placenta Previa
- Other Placental Abnormalities

**Signs of Initiation of Parturition**
- No Evidence of Initiation Parturition
- Evidence of Initiation of Parturition
  - Cervical Shortening
  - PPROM
  - Regular Contractions
  - Cervical Dilatation
  - Bleeding
  - Unknown Initiation

**Pathway to Delivery**
- Caregiver Initiated
  - Clinically Mandated
  - Clinically Discretionary
  - Iatrogenic or No Discernable Reason
  - Pregnancy Termination
  - No Documented Clinical Indication

- Spontaneous
  - Regular Contractions
  - Augmented

**Birth**
- 16 to < 38+6 Weeks
**Maternal conditions**
- Extrauterine Infection
- Clinical Chorioamnionitis
- Maternal Trauma
- Uterine Rupture
- Preeclampsia/Eclampsia

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## GAPPS-Prototypic Phenotype Classification

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**Birth >16 to <38+6 weeks**
Summary

• Spontaneous preterm birth is a syndrome composed of multiple phenotypes
  – Need to separate for research

• Progesterone role in preterm birth prevention
  – Why does it work?

• Molecular techniques for identification of microbial invasion
  – Insights into etiology of preterm birth
Questions?