The Persistent Dilemma of Preterm Delivery

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Overview

Preterm Birth
- Prevalence
- Etiology
Current Management Paradigms
- Prevention
- Therapeutics
Future strategies
- Placental targets
- Treatment of IAI
- Early vs. late PTB

Preterm Birth
Prevalence: 11.5% 2012, reduction last 6 years
450,000 births annually

Reductions across all ethnic categories

All Preterm and Late Preterm Births, as Percentage of All Births, 1990-2012

Figure 4. Preterm birth rates, by race and Hispanic origin of mother: United States, final 1990–2011 and preliminary 2012
Preterm Birth

**Prevalence:** Globally 15 million infants per year

**Etiology**

- **Births (thousands):**
  - Group A - Normal Distribution
  - Group B – IAI/Pathology

  Removed IAI from the OB distribution
  Analyzed distribution of remaining births
  Remaining births showed normal distribution

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**Observed U.S. Births 2005**

- gestational age (weeks)
- births (thousands)
Preterm Birth

Etiology

Early PTB – always pathologic

Late PTB – normal distribution of labor onset, non-pathologic

Late PTB and Postterm pregnancy are opposite ends of normal parturition spectrum

Preterm Birth

Late PTB

35-37 weeks gestation
~8% of pregnancies; ¼ of all PTB
Growing population
Impact is increasing
Neonatal risks
Healthcare costs
Maternal risks
ALPS trial

Preterm Birth

Current Management Paradigms: Prevention

IM 17-OHP: prior PTB 20-34 weeks
Vaginal Progesterone: CL < 25 mm
Cerclage: prior mid trimester losses, dilated cervix
Pessary: multifetal gestations
Preterm Birth
Current Management Paradigms: Prevention

17-OHP: Prior PTB 20-36 weeks [20-34]

![Graph showing comparison between placebo and 17-OHP](image)

Vaginal Progesterone: CL < 25 mm [15-24 mm]*
90-200 mg micronized progesterone
Begin at time of diagnosis
Continue through 36 weeks

*R Regardless of obstetric history

RCT: 17-OHP vs. vaginal progesterone for RPTB

Preterm Birth
Current Management Paradigms: Prevention

Cerclage:
History-indicated cerclage: 3 prior mid trimester losses or 2 with no live births; 12-14 wga

Ultrasound-indicated cerclage: cervical shortening < 25 mm in patient with prior PTB, subsequent shortening despite progesterone therapy; 16-24 wga

Physical-exam indicated cerclage: dilated cervix, any patient before 24 wga; consider amniocentesis

Bias - Shirodkar over McDonalds
Preterm Birth

Current Management Paradigms: Prevention

Pessary: multifetal gestations with premature cervical shortening

Not advocating for screening TVUS CL in multifetal gestations but if identified recommend pessary

Prevention of
Ascending infection - ? role for probiotics
Modulation of inflammatory pathway signaling
Premature cervical changes
Modulation of actin cytoskeletal signaling

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infection (n = 30)</th>
<th>No Infection (n = 140)</th>
<th>P value*</th>
<th>Area under receiver operating characteristic curve</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Acute-phase reactants</td>
<td></td>
<td></td>
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<tr>
<td>Alpha-1-acid glycoprotein</td>
<td>1908 ± 26</td>
<td>95 ± 26</td>
<td>&lt; .0001</td>
<td>0.85</td>
<td>0.79-0.96</td>
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<td>Alpha-1-antitrypsin</td>
<td>44.955 ± 3.6</td>
<td>10.504 ± 4.6</td>
<td>&lt; .0001</td>
<td>0.77</td>
<td>0.70-0.83</td>
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<td>Immunomodulators</td>
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<td>C-C chemokine ligand 7</td>
<td>2789 ± 16</td>
<td>268 ± 11</td>
<td>&lt; .0001</td>
<td>0.91</td>
<td>0.83-0.99</td>
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<tr>
<td>C-Reaction Protein</td>
<td>174 ± 20</td>
<td>38 ± 10</td>
<td>&lt; .0001</td>
<td>0.74</td>
<td>0.66-0.82</td>
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<td>Lysozyme</td>
<td>1510 ± 40</td>
<td>578 ± 63</td>
<td>&lt; .0001</td>
<td>0.94</td>
<td>0.86-0.99</td>
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<tr>
<td>Cystatin A</td>
<td>772 ± 28</td>
<td>498 ± 24</td>
<td>&lt; .0001</td>
<td>0.92</td>
<td>0.84-0.98</td>
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<tr>
<td>Matrix metalloproteinase-9</td>
<td>808 ± 82</td>
<td>132 ± 13</td>
<td>&lt; .0001</td>
<td>0.96</td>
<td>0.89-0.99</td>
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<tr>
<td>Neutrophil elastase</td>
<td>10 ± 34</td>
<td>2 ± 25</td>
<td>0.0001</td>
<td>0.96</td>
<td>0.89-0.99</td>
</tr>
</tbody>
</table>

Preterm Birth

Network 4: Extracellular matrix proteins – cytoskeletal, cell movement, cell assembly

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Preterm Birth
Current Management Paradigms: Therapeutics

Tocolysis:
Indomethacin 24-28 weeks
MgSO4: 24-32 weeks
Calcium channel blockers: 24-34 weeks
Oxytocin receptor antagonists

- **Indomethacin 24-28**: 50-100 mg load, then 25 mg q 4-6 hrs PO/PR
- **MgSO4 24-32**: 6 gm load, then 2 gm/hr
- **Ca Channel Blockers 24-34**: 10-20 mg PO q4-6 hrs
- **Indomethacin 24-28** and **MgSO4 28-32** and **Ca 32-34**

Preterm Birth
Current Management Paradigms: Therapeutics

Neuroprotection MgSO4: 24-32 weeks
Reduction in cerebral palsy
Protocol from NICHD trial recommended in the U.S.

- Load 6 gm then 2 gm/hr continuous
- If delivery not imminent in 12 hours the D/C
- Restart when PTL restarts at 2 gm/hr
- Repeat loading dose if > 6 hours from D/C

Future strategies

- Placental targets
- Treatment of IAI
- Early/Late PTB

Preterm Birth
Placental targets

- Functional MRI – placental modeling, flow, adaptation
- Microbubble infusion – measure flow, delivery of therapeutic targets
  - Modulation of -
    - innate immune response
    - apoptosis
Preterm Birth

Placental targets

Placental villous hypermaturity (PVH) in late PTB – common finding in idiopathic PTB

Late PTB: analysis of 82 placentas: acute chorioamnionitis 40%, other 22%, idiopathic PTB 38%

Frequency of PVH in idiopathic PTB 84%
Similar to cases with IUGR or preeclampsia 89%
Chorioamnionitis 30%, p<0.001


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Treatment of IAI: treating *U. parvum* in rhesus model of IAI with maternal IV Azithromycin therapy

Waited until after PTL/IAI clinically evident (6-8 days after inoculation); sterilized AF within 4 days

Grigsby PL, AJOG 207(6) 2012

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Treatment of IAI in humans pregnancies:

Eradication of *Ureaplasma urealyticum* from the amniotic fluid with transplacental antibiotic treatment

Erythro, amp, gent, clinda x 6 days

Successful treatment of preterm labour by eradication of *Ureaplasma urealyticum* with erythromycin

Erythro x 10 days

Antibiotic treatment of intra-amniotic infection with *Ureaplasma urealyticum*. A case report and literature review

Erythro x 7 days, fluoroquinolone and clinda x 10 days

Romero RR et al, AJOG 166(2) 1992

Mazor M et al, Arch Gyn Obstet 253(4) 1993

Smorgick N et al, Fetal Diag Ther 22(2) 2007

Grigsby PL et al, AJOG 207(6) 2012
Preterm Birth

Clinical treatment of IAI/PTL limited by
- Lack of large well designed trials
- Necessity to perform amniocentesis
- Inability to determine chronicity of IAI

*Need for noninvasive markers or subclinical infection

Preterm Birth

Proteins related to premature or failed initiation of labor

The concept is not novel in medicine:

Endocrinology (thyroid, diabetes)
- TSH
- Hypothyroidism

Hematology (platelets, clotting factors)
- Factor VIII
- Hemophilia
- Thrombophilia (stroke)

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Challenges of proteomics in late PTB

- Findings on pooled samples may not apply to individual cases
- Misidentification of proteins is possible
- Cost and time of analysis
- Need to reproduce findings/validate on separate, large cohorts
Preterm Birth

Clouseau’s postulate

Limitation – always get results

You may get the right answer, but are you asking the right question?

Need to ask the right question, in the right way

Importance of validation studies