Worldwide market for preterm birth diagnostics and therapeutics

Edward Evantash, MD, FACOG, Medical Director, VP Medical Affairs, Hologic Inc.
1. Preterm Birth: what we know and what we don’t
2. Global Market
3. Opportunities for investment
4. Factors for commercial success

Agenda
01

Preterm birth
Global burden of preterm birth

11 countries with preterm birth rates over 15% by rank:

1. Malawi
2. Congo
3. Comoros
4. Zimbabwe
5. Equatorial Guinea
6. Mozambique
7. Gabon
8. Pakistan
9. Indonesia
10. Mauritania
11. Botswana

Preterm birth rate, year 2010:
- <10%
- 10-<15%
- 15% or more
- Data not available
- Not applicable


Note: rates by country are available on the accompanying wall chart.
Not applicable- non WHO Members State
Preterm birth is major cause of morbidity and mortality

15M
preterm births every year

1.1M
deaths from preterm birth complications

75%
deaths that could be prevented

What we know about preterm birth

• Risk factors are poor predictors
  – 70% of pregnancies with risk factors deliver at term
  – 50% of preterm births are first time pregnancies
  – Majority of preterm births are to women with no identifiable risk factors

• Preterm contractions are a poor indicator of preterm labor

• Limited diagnostics and therapeutics exist today

• Goals to reduce preterm birth have been set by numerous organizations and little has been achieved in terms of reductions
  – In a review of 65 countries, only 3 showed a reduction in preterm birth trends from 1990-2010

Current clinical management

Symptomatic Labor

– Too late for prevent preterm birth
– Objective is to maximize maternal and neonatal outcomes
  » Steroids for fetal lung maturation
  » Tocolytics to provide time for steroid administration
  » MgSO4 for neuro-protection
  » Antibiotics on suspected infection to reduce neonatal sepsis

Asymptomatic High-Risk Management

– Early gestation appears to be optimal time to prevent PTB
  » 17-hydroxyprogesterone caproate for prior sPTB
  » Vaginal progesterone for short cervix
  » Cervical cerclage for prior short cervix

Most clinical management not activated until a woman has symptoms
Causes & 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

- Uterine Contractions
- Cervical Change
- Preterm PROM

- Preterm Birth

Opportunities for investment
Worldwide market potential

Total pregnancies
135 Million

Total pregnancies in developed regions
14.3 Million

High risk pregnancies*
7.2 Million

Pregnancies presenting with symptoms of preterm labor*
2.86 Million

* (developed regions)

Opportunities

Best potential for pharma to prevent preterm birth is early in gestation

- Drugs which target preterm labor have not been effective in reducing preterm birth rate

- While not able to prevent preterm birth if targeted to women in preterm labor, these drugs should focus on improving neonatal outcomes (RDS, sepsis, intraventricular hemorrhage, etc)

Accurate prediction early in gestation of those who will deliver preterm

1. Allows for early intervention
2. Allows for better targeting of interventions
3. Allows for re-evaluation of effectiveness of interventions
   - Wrong conclusion may have been considered in the past due to poor study group selection
What is used today

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prior Preterm Birth</th>
<th>Short Cervix</th>
<th>Other High-Risk</th>
<th>Nulliparous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>17P</td>
<td>Vaginal progesterone</td>
<td>Nothing</td>
<td>Nothing</td>
</tr>
<tr>
<td>Tocolytics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
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- Opportunity exists to develop therapeutics and companion diagnostics for a large segment of the market
Looking ahead: areas of opportunity

**Cervical Shortening**
- Can progesterone work better if supplemented prior to shortening?
- New target population for cerclage

**Stretch Mechanisms**
- New research identifying pathways (e.g. connexin 43)
- New opportunity for drug action

**Microbiome**
- Oral, placental and vaginal microbiomes under investigation
- Targeted therapies to correct dysbiosis (e.g. OmniBiome Therapeutics, Inc)
Looking ahead: areas of opportunity

Inflammation and Infection:

**Dx**
- Identification of pregnancies with infection or inflammation
- Non-invasive

**?**
- Causes 30% of PTB
- Reduce neonatal sepsis

**Tx**
- Antibiotics may be effective, study needed
- Need agents that attenuate inflammatory cascade
**Clinical Trials**

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Therapeutics</th>
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<tbody>
<tr>
<td>• Need to demonstrate impact on clinical benefit, not simply accuracy of test</td>
<td>• Selection of appropriate patient population is key</td>
</tr>
<tr>
<td>• Multiple step approach: identification of sub-population at risk for preterm birth, then intervention studies to show benefit</td>
<td>• Numerous etiologies for preterm birth, unlikely that a single drug works for all</td>
</tr>
<tr>
<td>• Need to gather data on healthcare cost and impact; necessary for reimbursement and test adoption</td>
<td>• May need companion diagnostics to better target pharma agents</td>
</tr>
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• Internationally, some countries are now requiring regulatory approval in the country of manufacture
Regulatory Process

- Need to address safety, not only efficacy
- Regulatory hurdles OUS are getting stricter and more attention is being paid to the clinical benefit of the diagnostic or therapeutic

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Therapeutic</th>
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<tbody>
<tr>
<td>Specimen collection</td>
<td>Formulation and delivery</td>
</tr>
<tr>
<td>Device interaction with patient</td>
<td>Dosage, bioavailability, bioequivalence</td>
</tr>
<tr>
<td>Accuracy of test result</td>
<td>(measures drug release into system)</td>
</tr>
<tr>
<td>Misinterpretation/misuse of test result</td>
<td>Safety evaluation continues beyond market release (e.g. Makena)</td>
</tr>
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</table>
Adoption of new technologies

- Regulatory approval of a drug or device does not guarantee the medical community will adopt the technology.

- In addition to safety and efficacy data required for regulatory approvals, companies must:
  - Demonstrate cost savings
  - Demonstrate clinical benefit that describes a change in management or outcomes
  - Generate “local” data to demonstrate results remain the same in various populations
  - Obtain adequate reimbursement
  - Inclusion in Society and National guidelines