Identifying and Reducing Preterm Births in Vulnerable Populations in LIC and HIC

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OPERA Meeting
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Global Progress to MDG 4 for child survival

3.1 million neonatal deaths, 40% of all under-five deaths

Preterm birth is now leading cause of neonatal and childhood death

As of 2013:
• *Single most important cause of* neonatal mortality *(34.1%)*
• *Leading cause of* U-5 *deaths* *(15.4%)*
Born Too Soon
The Global Action Report on Preterm Birth
EXECUTIVE SUMMARY
Preterm births: Where are the highest rates?

Of the 11 countries with highest rates, 9 are in Africa

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

US ranks 131st from top in rates and is among the highest 10 countries in numbers of preterm births
Born Too Soon: Main findings

1) 15 million babies are born too soon every year

2) Preterm birth rates are rising in most countries

3) Prevention of preterm birth must be accelerated

4) Many premature babies can be saved now with feasible care
Causes of Preterm Birth in Different Populations

1) LINC Factors associated with greater proportion of PTB in LIC/MIC

2) Known interventions more consistently applied in HIC

3) Other causes related to etiology of labor and preterm labor are unknown and studied mostly in HIC but should be applicable in LIC
Why is Preterm Birth Rate Higher in LIC than in HIC?

- Lifestyle
- Infection
- Nutrition
- Contraception
Why is Preterm Birth Rate Higher in LIC than in HIC?

- Lifestyle
- Infection
- Nutrition
- Contraception

- e.g. tobacco, alcohol, drugs, physical activity, diabetes, hypertension, asthma, thyroid disease, depression, violence

lifestyle+
Why is Preterm Birth Rate Higher in LIC than in HIC?

e.g. urinary tract, malaria, HIV, syphilis, bacterial vaginosis
Why is Preterm Birth Rate Higher in LIC than in HIC?

- Lifestyle
- Infection
- Nutrition
- Contraception

- Nutrition

e.g. underweight, obesity, anemia, folic acid, iron and other micronutrient deficiencies
Why is Preterm Birth Rate Higher in LIC than in HIC?

- Lifestyle
- Infection
- Nutrition
- Contraception

- e.g. age at pregnancy (adolescence, advanced), lack of spacing
Why is Preterm Birth Rate Higher in LIC than in HIC?

### Anemia During Pregnancy

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>% pregnant women/with anemia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigeria</td>
<td>66.7%</td>
</tr>
<tr>
<td>India</td>
<td>49.7%</td>
</tr>
<tr>
<td>Pakistan</td>
<td>39.1%</td>
</tr>
<tr>
<td>World</td>
<td>41.8%</td>
</tr>
</tbody>
</table>

* WHO Worldwide Prevalence of Anemia, 2008
Why is Preterm Birth Rate Higher in LIC than in HIC?

## Contraception and Pregnancy

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>Contraceptive Prevalence Rate (2008 - 12)</th>
<th>Adolescent Birth Rate (2008 - 12) Per 1000 15 - 19 year olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>55%</td>
<td>39</td>
</tr>
<tr>
<td>Nigeria</td>
<td>18%</td>
<td>113</td>
</tr>
<tr>
<td>Pakistan</td>
<td>27%</td>
<td>16</td>
</tr>
<tr>
<td>World</td>
<td>55%</td>
<td>49</td>
</tr>
</tbody>
</table>

**Contraceptive Prevalence Rate** = % of married women using any form of contraception  
**Adolescent Birth Rate** = # of births to 15-19 year olds per 1,000 15 - 19 year old girls
March of Dimes
Initiatives to reduce
Preterm Birth in LIC/MIC
The March of Dimes Global Network for Maternal Infant Health (GNMIH)
GNMIH projects 2015

Lebanon & Philippines
- Implement a workplace wellness program to improve maternal and neonatal outcomes
  - American University of Beirut, Lebanon
  - University of the Philippines, Manila

Malawi
- Improve prematurity prevention-related knowledge and practice of healthcare workers
  - Baylor College of Medicine & Texas Children’s Hospital
  - Kamuzu Central Hospital in Lilongwe, Malawi
Public-Private Partnership To Prevent Preterm Birth

Proposal: March of Dimes and MDG Health Alliance seek to halve global preterm birth rates over a five-year period

By: Engaging various governmental, private sector and civil society partners

Target factors: Lifestyle, Infection, Nutrition, Contraception (LINC)

Initial focus: India, Nigeria, Pakistan

- India, Nigeria and Pakistan account for 33% of all preterm births and 50% of all deaths from preterm birth

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>India</td>
<td>3,500,000</td>
<td>326,496</td>
</tr>
<tr>
<td>Nigeria</td>
<td>770,000</td>
<td>85,715</td>
</tr>
<tr>
<td>Pakistan</td>
<td>750,000</td>
<td>69,054</td>
</tr>
<tr>
<td>Total</td>
<td>5,020,000</td>
<td>481,265</td>
</tr>
<tr>
<td>World</td>
<td>15,000,000</td>
<td>965,102</td>
</tr>
</tbody>
</table>

% World 33  50
Scientific/Molecular Explanations for PTB

- **LINC identifies** associations, but not causation at biologic level
- HIC focuses more on known interventions and finding yet unknown causes of PTB
- Spacing and smoking common to both LIC and HIC; difference in ethnicities persist in both LIC and HIC
Transdisciplinary Research Areas

Infants delivered at 37 completed weeks of gestation per 100 births rose from 1990 to 2006. Declines were observed, however, from 2008 to 2009 among late-preterm infants (at 34–36 weeks), from 8.77% to 8.66% and early preterm (34 weeks), from 3.56% to 3.51% (Table 4). The total preterm rate declined significantly among births to non-Hispanic white (from 11.14% to 10.92%), and Hispanic (from 12.10% to 11.97%) infants (Table 4).

Low Birth Weight

The low birth weight (LBW) (2500 g) rate was 8.16% in 2009, essentially unchanged from the 2008 rate of 8.18% (Table 4). The percentage of infants born LBW had increased fairly steadily since the mid-1980s (6.2% in 1984), but began to decline in 2006. Rates of very low birth weight (1500 g) were stable, 1.45% for 2009. The small observed changes in the LBW rates from 2008 to 2009 among the 3 largest race and Hispanic origin groups were not statistically significant (Table 4).

Over the past several decades, national LBW levels have been influenced by the rise in the rate of multiple births; more than one-half of these infants weigh 2500 g at birth. A rise in LBW was also observed between 1990 and 2006 for singleton deliveries. The birth weight distribution has changed markedly since 1990 for all births as well as for singletons only. During 1990–2009, the percentage of infants weighing 3500 g increased, whereas births at higher weights have decreased. The reasons for this shift toward lower birth weights are not fully understood, but may include obstetric intervention earlier in pregnancy, older maternal age, and increased use of infertility therapies.

Infant Mortality

In 2009 a total of 26,531 infant deaths were reported in the United States according to preliminary data. The IMR was 6.42 infant deaths per 1000 live births, a figure significantly lower (by 3%) than the 2008 rate of 6.61. The NMR for 2009 was 4.19, also significantly lower than the 2008 NMR of 4.29 neonatal deaths per 1000 live births.


FIGURE 3 Infant, neonatal, and postneonatal mortality rates by race and Hispanic origin of mother, United States, 2007. Includes persons of Hispanic and non-Hispanic origin. Note: Neonatal is <28 days and postneonatal is 28 days to 1 year. See Mathews et al. Source: CDC/NCHS, National Vital Statistics System.
Interventions Applicable in HIC Differ from Those in LIC
Evidence Based Prevention in HIC

1. Eliminate early elective deliveries (HBWW)
2. Progesterone for prior PTB
3. Fewer embryos transferred per cycle (Assisted Reproductive Technologies)
4. Cerclage when indicated
5. Eliminate maternal smoking
Preventing Preterm Births in HIC

• Lancet 2013 (Chang, et al.) (Gates, MOD, NICHD, WHO) reported 5% rate reduction applying all proved interventions (9.6 to 9.1% in 39 VHHDI).

• In High Resource countries often we do not know how to prevent preterm birth - especially 24-34 weeks.

• But PTB rates 5.5% in Sweden and 4.5% in Intergrowth cohort of low risk women.
How Low Can the Preterm Birth Rate Go Without More Discoveries?

• Axiom: We do not know the explanation for labor or early preterm births

• We must learn what causes early preterm birth if successful treatment is to be devised

• Therefore, focus is on prevention / discoveries
Etiology of Preterm Birth

- Inflammation, infection; cytokines that respond to infections or trauma
- Micro-organisms in the reproductive tract (microbiome)
- Genes governing gestational length and onset of labor
Etiology of Preterm Birth

• Sociodemographic disparities, environmental factors and biological basis

• Signals that initiate labor (fetal, maternal)

• Anatomical changes in uterus, cervix or placenta
A Transdisciplinary Network

1. march of dimes®
   prematurity research center
   at Stanford University

2. march of dimes®
   prematurity research center
   Ohio Collaborative

3. march of dimes®
   prematurity research center
   at Washington University in St. Louis

4. march of dimes®
   prematurity research center
   at The University of Pennsylvania

Final center to be announced later this year
1. Microbiome and Preterm Birth
   - Per organ and per gestational week
2. Placental Transcriptome
   - Fetal cell free DNA and RNA in maternal blood
3. Data Coordination Center
   - Overlay results of different thematic data sources (multivariate) from all Centers
Microorganisms in the Reproductive Tract

Gestational age at delivery:
- <238 days (34 weeks)
- 240-253 days
- >260 days (37 weeks)
Themes

1. Cervical Photoacoustic Endoscopy
   - To observe changes in the cervix

2. 3-D Electromyometrial Imaging
   - To localize uterine contraction initiators

3. Chrono-disruption and Preterm Birth
   - To evaluate one explanation underlying sociodemographic disparities
Electrocardiographic Imaging to Identify Cardiac Pacemakers

A: Electrical Sensing
B: CT Imaging

= Pacemaker Localization
Electromyometrial Imaging (EMMI) to identify Uterine Pacemakers

Electrical Sensing + MRI = Localization
Genetics and Preterm Birth

• Heritability 30% (maternal only)
• Genes found in whole genome family linkage studies
  – FSHR (Finnish)
  – IGF1R (Finnish)
  – COL5A2 (Norwegian)
  – SERPINB2 (Mexican)

All protein-coding genes
Surprises from GWAS Studies

- Inadequate number of genes found to explain known heritability
- Significant “hits” have usually been in gene “desert” region (non-coding)
- Where are the (hidden) genes?
Location in Genome of Significant Whole Genome Associations

- **Protein Coding** (7%)
- **Untranslated Exonic** (2%)
- **Intronic** (41%)
- **Intergenic** (50%)
Regulation of Protein-Coding Genes

- Genetics
  - Gene regulatory element (chromatin accessible)
  - Long range interactions
- Environment
  - Histone modifications
  - Transcription Factors
- Tissue specificity
  - DNA methylation and hydroxymethylation
  - RNA polymerase
  - mRNA
  - miRNA
  - lincRNA
Could quantitative changes in regulatory genes provide biologic (molecular) explanation for persisting deleterious transgenerational effects of disparities in vulnerable populations?
Are advances made in HIC transportable to more vulnerable populations?
Transporting HIC Advances to LIC

Efficacy “proved” in HIC and portability validated

Implementation in LIC

Low efficacy may be observed
Potential Explanations for Lack of Efficacy in LIC

- Different genetic pool
- Differences or increase in confounding environmental factors (toxicants; gene-environment interaction)
- Unanticipated implementation problems
Resolving the Low LIC Efficacy

Efficacy low in LIC

Return to HIC for explanations
Value of 360° to HIC

1. HIC learns why efficacy is lower in LIC

2. Lessons learned become applicable to minorities residing in their own (HIC) country
Conclusions

1) Explanations and associations for PTB differ quantitatively between LIC and HIC; resources and high-tech laboratory approaches usually possible only in HIC

2) Operational efficacy in both LIC and HIC requires HIC–LIC collaboration (feedback loop)

3) Lessons learned in LIC will help lower PTB-rate in vulnerable populations residing in HIC