International Federation of Gynecology and Obstetrics
FIGO/March of Dimes Working Group for Preterm Birth Prevention

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IDENTIFYING RISK FACTORS AND CAUSES OF PRETERM BIRTH
Preterm Birth Rates

1) 15 million babies are born too soon every year

2) Worldwide yearly rates up to >15%; 1.1 million deaths mostly in Low/Middle Income Countries (LMIC)

3) 5 – 10% preterm birth rate in high income countries (HIC), varying widely country to country
Evidence Based Prevention (2012)

1. Eliminate Early Elective Deliveries (<39 weeks)
2. Progesterone given a previous PTB
3. Better ART practices (fewer embryos transferred per cycle)
4. Cervical cerclage when increased
5. Eliminate maternal smoking
Preventing Preterm Births

• If compliance existed for all evidence-based interventions (2012) the PTB reduction would only be 0.5%: 9.6% to 9.1%

• Even in High Resource countries, we can few preterm births – especially 24-34 weeks can be prevented

• But there are differences amount countries
  — PTB rates 5.5% in Sweden versus 7.8% in U.K. and 9.2% in Germany

Lancet 2013; 381:223-24
Other Preventive Measures (2016)

- Pregnancy Spacing (Delivery-conception interval > 18 months) Biological explanation provided in 2015: altered vaginal microbiome after delivery


- Vaginal progesterone for short cervical length (FIGO)
- Aspirin for pre-eclampsia
FIGO/March of Dimes (MOD) Memorandum of Agreement (2014)

- Committee member exchanges to assure transparency
- Symposia on PTB at FIGO triennial Congress (Vancouver 2015) and at FIGO regional meetings
- Generate Good Practice documents for Prevention of Preterm Birth
- Share MOD basic discoveries, translation, and implementation strategies
- Translate good practice globally
Other Preventive Measures (2016)
Intra-Country Analysis to Characterize Outcomes by Practice Patterns

- Largest study and first cross-country study: 4.1M births with individual-level data from four countries and one comparator US state
  - **Czech Republic**: National Registry of Reproduction Health - Mothers at Childbirth and Newborns: 1.3M
  - **New Zealand**: National Maternity Collection maintained by the New Zealand Ministry of Health: 247K
  - **Slovenia**: Slovenian National Perinatal Information System maintained by the Slovenian National Institute of Public Health: 175K
  - **Sweden**: Swedish Medical Birth Register maintained by the Swedish National Board of Health and Welfare complemented by data from Statistics Sweden: 1.1M
  - **California**: vital statistics linked birth/death file from the California Department of Health Services: 1.3M

PLOS One, 2016
Individual Patient Data (Country Analysis)

- Identify **individual** significant risk factors (prior preterm birth, preeclampsia)

- Identify most significant **single** risk factor among those overlapping (low education, low socioeconomic status)

- Identify risk factors with lower odds ratios that are nonetheless highly prevalent and having greater **population** impact (nulliparity, male sex)
FIGO Working Group Multivariate Analysis: Preterm Birth Odds Ratios

18 reports on 20 factors

- Prior PTB
- Hypertension / Preeclampsia
- Diabetes
- Maternal Age
- BMI
- Prenatal Care
- Education
- Poverty

High Individual Risk
Lower Population Prevalence

Low Individual Risk
Higher Population Prevalence
Waterfall Analysis – Determining How Much Known Risk Factor(s) Explain PTB Rate: Best Practice vs Population Rate

PTB Rate (%)
- Best
- Observed

Unknown (Sex)
Policy & Public health (Tobacco)
Clinical Practice (Early Induction)

Risk Factors
## Preterm Birth Individual Odds Ratio (FIGO)

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<th>Slovenia</th>
<th>Sweden</th>
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Predicting PTB
By Risk Factor Combinations

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• Determine which healthcare sector should be assigned responsibility to lower PTB rate: provider, public health/government, research
PTB Per Risk Factors

Previous PTB and Preeclampsia: 1 and 2 only
Categorization of Risk Factors by Interventions

**Research**
- Prior PTB
- Smoking
- Early Induction

**Policy and Public Health**
- 22 – 23%

**Clinical Practice**
- 5 – 6%

Examples
Preterm Birth: Swedish Best Practice v Population

Sweden

Research 71%
Policy and Public Health 22-23%
Clinical Practice 5-6%

PTB rate (%)

Base-Nulli- Male Previous Precl- Educa-Smoking Age BMI Employ- DBTS- HPTN- HPTN- DBTS- Previous ART Total
line parous baby PTB amnesia tion

2.13 0.30 0.23 0.09 0.39 0.11 0.12 0.15 -0.14 0.03 0.00 0.00 -0.01 0.11 0.05 4.97

*
Take Home Messages:

- Unexplained knowledge gap exists between best practice PTB rates and population PTB rates

- Not explained by sociodemographic or known clinical risk factors
Causes of Preterm Birth:

• 2/3 of all preterm births are associated with risk factors lacking a known biological basis

• These risk factors are not amenable to changes in clinical practice or public health / policy
Next Steps: Working Group for Preterm Birth (PTB) Prevention

• Apply lessons learned in High Income Countries to Middle Income Countries

• Generate robust predictive models for PTB based on available risk factors

• Integrate Working Group results with biological studies into initiation of labor (March of Dimes Prematurity Research Centers)
March of Dimes
Prematurity Research Centers

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

5. March of Dimes®
   Prematurity Research Center
   UChicago • Northwestern • Duke
What Initiates Labor?

- Genetic factors
- Dysfunctional energy metabolism (mother and fetus) – mitochondria, diet
- Inflammatory / Infectious etiologies
- Fetal or maternal signals that initiate labor
- Anatomic changes in uterus, cervix or placenta
Strategies for Elucidating What Initiates Labor and Preterm Labor

- March of Dimes Prematurity Research Centers: Investigators not previously in preterm birth research

- Diverse team of multi-specialty physician investigators, engineers, physicists, geneticists, genomicists, social scientists, epidemiologists

- Big-data informatics: multiple-layer analysis to integrate biological findings with environmental and sociodemographic factors
Examples of Fundamental Investigations Undertaken to Explain How Pregnancy is Maintained and Labor Initiated
What Genetic Factors Could Influence Labor?

- 30% heritability. Recurrence risk up to 30%
- Protein-coding genes governing inflammation, gestational length, onset of labor
- Mitochondrial genes governing bioenergetics (nutrition and diet)
- Regulatory genes and networks could if disturbed be plausible explanations for inter-generational persistence of sociodemographic disparities (stress; racism)
Why Determine Genes Affecting Preterm Birth?

- Causative coding gene = potential therapeutic strategy including pharmaceutical agents: e.g., hyper-active ion-channel myometrial gene could be inhibited

- At risk prediction and aggressive prevention therapy for at risk cohorts

- Minimize exposure to deleterious agents for at risk cohorts

- After expression of regulatory genes susceptible to stress
What is the microbiome?

- Microbiome commensal microorganisms living within the human body
- Colonize all “exposed” tissues (oral, respiratory, digestive, skin, uro-genital)
- 10 times more organisms than human cells; 100 times more DNA
Lack of Lactobacillus (CST 4) Observed in Preterm Birth (Reproductive Tract)

DiGiulio, Callahan, McMurdie, et al., PNAS, 2015
How are Uterine Contractions Initiated and Proceed Voluntarily

- Where are uterine pacemakers?
- Locate pacemakers using the same strategy by which cardiologists locate foci of cardiac arrhythmias.
- Aberrant pacemaker activity could be altered to preterm birth
Electromyometrial Imaging (EMMI) to identify Uterine Pacemakers

Electrical Sensing + MRI = Localization