Advancing Drug Development for the Prevention of Spontaneous Preterm Birth

January 23 & 24th | 1:00 – 4:30 p.m. ET
Welcome & Introduction

Mark McClellan, MD, PhD
Director, Duke-Margolis Center for Health Policy
Meeting Agenda

January 23 (1:00 – 4:30 PM ET)
- Opening Remarks from FDA
- Current Understanding of Spontaneous Preterm Birth
- Ethical and Regulatory Considerations and Challenges Associated with the Development of Therapeutics for Prevention of Spontaneous Preterm Birth
- Impact of Preterm Birth on Families and Society

January 24 (1:00 – 4:30 PM ET)
- Opening Remarks and Summary of Day 1
- Assessing Efficacy and Safety in Clinical Programs for Therapeutics for Spontaneous Preterm Birth Prevention
- Dose-Finding and Clinical Trial Design Considerations
- Wrap-up with Workshop Moderators
Statement of Independence

• The Robert J. Margolis, MD, Center for Health Policy is part of Duke University, and as such it honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important issues.

• For more details on relevant institutional policies, please refer to the Duke Faculty Handbook, including the Code of Conduct and other policies and procedures. In addition, regarding positions on legislation and advocacy, Duke University policies are available at http://publicaffairs.duke.edu/government.
Virtual Meeting Reminders

• Attendees are encouraged to contribute throughout the meeting with questions in the Zoom Q&A function.
• This meeting is being recorded, and the recording and slide deck will be posted on the Duke-Margolis event page in the weeks following the meeting.
Opening Remarks from FDA

Robert Califf, U.S. Food and Drug Administration
Session 1: Current Understanding of Spontaneous Preterm Birth

Moderator: Kaveeta Vasisht, U.S. Food and Drug Administration
Session 1 Objective:

This session will highlight the impacts of spontaneous preterm birth and provide an overview of the epidemiology, etiologies, and pathophysiology of spontaneous preterm birth. There will be discussion of the current tools and methods used to predict spontaneous preterm birth and the progress made in recent years.
PRETERM BIRTHS IN THE UNITED STATES: TRENDS AND CHARACTERISTICS

Joyce Martin, M.P.H.
Team Lead, Perinatal Statistics and Research Team, Statistical Analysis and Surveillance Branch, Division of Vital Statistics, NCHS/CDC

Acknowledgment: Michelle Osterman M.H.S. Perinatal Statistics and Research Team, Statistical Analysis and Surveillance Branch, Division of Vital Statistics

Advancing Drug Development for the Prevention of Preterm Birth
February 23, 2024
METHODS
Methods

- Data derived from U.S. certificates of live birth (2003 revision)
- Collected via the National Vital Statistics System for the National Center for Health Statistics (NCHS)
- Includes information for essentially all US births
- Age, race and Hispanic origin of the mother is self-reported
- Medical information (e.g., gestational age, source of payment for the delivery, gestational hypertension) is derived from hospital medical records or reported directly by clinician
Methods

- Infant mortality data are from the NCHS linked birth/infant death files. This file links birth and death certificates of infant deaths under 1 year of age.

- Infant mortality data for 2022 are provisional.
Caveat

- Birth certificate data cannot adequately differentiate between spontaneous and nonspontaneous deliveries

- Accordingly, data for this presentation includes both spontaneous and nonspontaneous births.
Methods

- Reporting period:
  - 1989-2022
  - Primary focus is 2014 (the most recent low in the preterm rate) to 2022
- Data shown for singleton births when appropriate
- Preterm birth is defined as less than 37 completed weeks of gestation.
  - Extremely preterm = less than 28 weeks
  - Early preterm = 28-33 weeks
  - Late preterm = 34-36 weeks.
Methods

- Gestational age for 1989-2006 is based on the Date of the last normal menses (LMP)
  - Issues of data quality
- Gestational age for 2007–2022 is based the Obstetric estimate of gestation (OE)
- OE-based gestational age is missing from less than 1% of all records
  - Studies in 3 states during 2013-2019* found agreement between birth certificate and medical records within 2 weeks was high for each state.
  - Exact agreement ranged from moderate to high across the 3 states.

Methods

The OE is defined as:
The best obstetric estimate of the infant’s gestational age in completed week based on the clinician’s final estimate of gestation.

• Determined by the date of the last menstrual period if confirmed by early ultrasound.
Percent distribution of singleton births by gestational age, United States: 2022

- Extremely Preterm = 0.54%
- Early preterm = 1.52%
- Late preterm = 6.51%

- Full term = 57.11%
- Early term = 8.67%
- Preterm = 5.15%
Infant mortality by gestational age
Infant mortality rates by gestational age: United States: 2022*

*Provisional data. NOTE: Includes all pluralities.
Infant mortality rates for preterm births: United States: 2016 and 2022*

*Data for 2022 are provisional. NOTES: Includes all pluralities. All changes between 2016 and 2022 are significant at $p=0.05$
TRENDS IN PRETERM BIRTHS
Preterm birth rates, United States: 1981-2006

NOTES: LMP-based gestational age. Includes all pluralities

+36% (1981-2006)
+21% (1990-2006)
Singleton preterm births rates, United States: 1990 and 2006

1990: 9.70%
2006: 11.09%

+14%
(compared with +21% for all births)

NOTES: LMP-based gestational age.
Preterm birth rates, United States: 2006-2022

NOTES: OE-based gestational age; includes all pluralities.
Preterm birth rates, United States: 1981-2022

NOTE: Includes all pluralities
Preterm birth rates, all births and singletons only, United States: 1981-2022

NOTES: OE-based gestational age.
Percent distribution of singleton preterm births, United States: 2014 and 2022

NOTE: Increase at <28 weeks not significantly different at p <0.05
Singleton preterm births rates by maternal age, United States: 2014 and 2022

NOTE: Increases significant for all groups at $p = 0.05$
Singleton preterm birth rates by maternal race and Hispanic origin, United States: 1981-2022

NOTES: Race groups are non-Hispanic
DIFFERENCES IN PRETERM RATES BY VARIOUS CHARACTERISTICS
Preterm births rates by plurality, United States: 2022

- Singletons: 8.67%
- Twins: 61.27%
- Triplets/+: 98.99%
Singleton preterm births rates by maternal age, United States: 2022

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>8.85</td>
</tr>
<tr>
<td>20-29</td>
<td>7.49</td>
</tr>
<tr>
<td>30-39</td>
<td>7.65</td>
</tr>
<tr>
<td>40 and over</td>
<td>10.82</td>
</tr>
</tbody>
</table>
Preterm births rates by maternal race and Hispanic origin, United States: 2022

NOTE: Race groups are non-Hispanic. NHOPI is Other Pacific Islander; AIAN is American Indian and Alaskan Native. Includes all pluralities.
Singleton preterm birth rates by source of payment for the delivery, United States: 2022

NOTE: Other sources of payment include Indian health Service, CHAMPUS or TRICARE, other government (federal, state and local) or charity
Singleton preterm birth rates by various conditions, United States: 2022

- All singleton births: 8.67%
- Infertility therapies: 11.33%
- Smoked during pregnancy: 14.27%
- Gestational hypertension: 18.27%
- Prepregnancy hypertension: 20.86%
- Previous preterm birth: 27.08%
Preterm birth rates, by state: United States: 2022

U.S. percent was 10.38%; State range 8.18% (NH) to 14.80% (MS)

NOTE: Includes all pluralities.
Summary

- Infants born preterm are at greatly increased risk of death within the first year of life; risk declines with increasing gestational age until post-term.
- Preterm rates rose by more than 1/3 from 1989 to 2006; declined 8% from 2007-2014 but then rose 8% from 2014-2022.
- Large increases seen among all births and singleton births only.
- Recent increases (2014-2022) were among births:
  - At 28-33 and 34-36 weeks
  - All maternal age groups
  - For each of the largest race and Hispanic origin groups (White, Black, Hispanic).
Summary

- Preterm rates are highest:
  - Multiple births
  - Youngest and oldest mothers
  - Non-Hispanic Black and American Indian and Alaskan Native mothers
  - When Medicaid is the source of payment for the delivery
  - Pregnancies resulting from infertility therapies
  - Mother who smoked tobacco during pregnancy
  - Mothers with prepregnancy or gestational hypertension
  - Mothers with a previous preterm birth
  - In Mississippi, Alabama, Louisiana and D.C.
THANK YOU
jcm9@cdc.gov
Emre Seli, MD, Chief Scientific Officer of March of Dimes and Professor of Obstetrics, Gynecology, and Reproductive Sciences at Yale School of Medicine
State of Preterm Birth in the US

Relevance and complexity of the problem
Preterm birth rates across developed nations

- Denmark: 6.7
- Greece: 6.6
- Italy: 6.5
- Ireland: 6.4
- Slovakia: 6.3
- Norway: 6.0
- Sweden: 5.9
- Japan: 5.9
- Estonia: 5.7
- Lithuania: 5.7
- Finland: 5.5
- Croatia: 5.5
- Latvia: 5.3

Preterm birth rate (per 100 livebirths)
The U.S. remains among the most dangerous developed nations for childbirth.

5.6 million women live in areas with low access to maternity care

2 women will die from pregnancy-related causes today. And every day.

2 babies die every hour in the U.S.

Pregnancy-related deaths have doubled over the past 30 years.

2.2 million+ women live in maternity care deserts that have NO hospital offering obstetric care.

350,000+ babies are born to women living in counties with limited or no access to maternity care.
Maternal mortality* in the U.S. has nearly doubled since 2018.

Maternal mortality has nearly doubled since 2018, increasing from 17.4 deaths per 100,000 to 32.9 in 2021.

Maternal mortality rate (deaths per 100,000 live births) by race/ethnicity, 2018-2021

*Maternal mortality is the death of a woman while pregnant or within 42 days of termination of pregnancy, excluding those from accidental/incidental causes. (https://www.cdc.gov/nchs/maternal-mortality/evaluation.htm)

The U.S. preterm birth rate decreased in 2022 by less than 1%.

Preterm birth rate, United States, 2007-2022

Premature/preterm is less than 37 weeks of gestation. Preterm birth rate is defined as the percentage of live births born preterm.


Prepared by March of Dimes Perinatal Data Center, Oct 2023
Preterm Birth in the U.S.

THE FACTS

10.4% of births in U.S. are preterm

383,000 babies are born preterm annually in the U.S.

2X as likely to have a birth defect

Account for over 35% of infant deaths

$25.2+ Billion societal economic loss (medical, education, and productivity)

Developmental delays, neurological disorders, cerebral palsy, visual and hearing impairments, respiratory or intestinal insufficiency.
In the U.S., the preterm birth rate among babies born to Black birthing people is 1.5x higher than the rate among all other babies.

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Preterm Birth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>8.0</td>
</tr>
<tr>
<td>White</td>
<td>5.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>10.1</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>12.2</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>12.2</td>
</tr>
</tbody>
</table>

Many factors make birthing people more likely to have a preterm birth:

- **Smoking** (4.6% of all births): 15.2%
- **Hypertension** (2.6% of all births): 23.4%
- **Unhealthy weight** (5.3% of all births): 12.3%
- **Diabetes** (1.2% of all births): 28.8%
- **Previous preterm** (3.9% of all births): 30.0%
- **Carrying multiples** (3.2% of all births): 62.2%

The preterm birth rate was **10.4%** in 2022, a 1% decline from 2021, the highest rate in 10 years.

**Grade and Preterm Birth Rate**

- **A**: 2.7% or less
- **A-**: 2.8 to 8.1%
- **B+**: 8.2 to 10.5%
- **B**: 8.6 to 10.9%
- **B-**: 9.0 to 10.3%
- **C+**: 9.3 to 10.7%
- **C**: 9.7 to 10.1%
- **C-**: 10.1 to 10.5%
- **D+**: 10.4 to 10.8%
- **D**: 10.8 to 11.2%
- **D-**: 11.2 to 11.6%
- **F**: 11.6% or greater
MARCH OF DIMES
SOLUTIONS
RESEARCH AND DATA

• Prematurity Research Centers
• Research Center for Advancing Maternal Health Equity
• Maternity Care Desert Report
• Annual Report Card

PROGRAMS

• Supportive Pregnancy Care® Programs (group prenatal care)
• NICU Family Support®
• Mom & Baby Mobile Health Centers®

ADVOCACY

We have shaped national and state policies, such as:
• Preemie Act
• Paid Medical and Family Leave
• Protections for Pregnant Workers

EDUCATION

Accredited training and education for providers and families:
• Implicit Bias Training
• NICU Family Support®
• Consumer health education

STRATEGIC PARTNERSHIPS

We leverage strategic, equity-focused partnerships with public and private organizations at local and national levels
Gene expression related to premature birth
Maternal microbiome and immune response
Maternal-placental contributions to premature birth
Environmental factors and social determinants
Diagnostic biomarkers of preterm birth
Maternal comorbidities and preterm birth
Big data analysis
Drug repurposing
Comparison

Common funding mechanisms can unintentionally promote siloed work

- Publish-or-Perish
- Optimized for outputs
- Multiplicative Impact

The MOD network intentionally gathers researchers focused on finding a **solution** to preterm birth.

- Collaboration over Competition
- Optimized for outcomes
- Exponential Impact
Diagnosing and predicting risk of adverse outcomes helps us provide care where it’s needed most.

Harnessing the power of big data, electronic health records, and mass quantities of data, we search for the needle in the haystack. The signals we identify can lead to new studies, call out unknown correlated events, and zoom in on solutions faster than ever before.

Taking those data from our AI/ML models and other studies, we can begin to identify and quantify or stratify risk for things like preterm birth, preeclampsia, and other APOs.

This will lead to better care through earlier diagnosis and earlier, more personalized interventions.
Diagnostics can include signals from our microbiome.

MOD researchers are hard at work creating ways to characterize, identify, and create a profile of the vaginal microbiome at the bedside – providing earlier indication of risk for preterm birth.
Therapeutics can also take the form of new combinations of readily available and safe-for-pregnancy drugs that can help treat preeclampsia, preterm birth, and other poor outcomes.
And therapeutics can take the form of non-medical interventions.

Our researchers are testing ways to improve, bolster, or encourage the development of a healthy microbiota through supplementation of ‘good’ microbiome in those most at-risk.
It goes beyond working together.
We freely share data, samples, and knowledge with anyone interested in preterm birth.
RESEARCH AND DATA
• Prematurity Research Centers
• Research Center for Advancing Maternal Health Equity
• Maternity Care Desert Report
• Annual Report Card

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THANK YOU

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HEALTHY MOMS. STRONG BABIES.
Current Understanding of Spontaneous Preterm Birth

Michal A. Elovitz, MD
Inaugural Dean, Women’s Health Research
Founding Director, Women’s Biomedical Research Institute
Mount Sinai Professor of Women’s Health Research
Department of Obstetrics, Gynecology and Reproductive Sciences
Icahn School of Medicine
Disclosures

- Salary support from NICHD, NIAID and NINR
- Consultant with equity, MIRVIE
- Elovitzlab.org
- @docelovitz
The burden is enormous
“Current Understanding of Preterm Birth”

Where we have been
• No clear understanding of the biological drivers of sPTB
• “Lumping” of PTB has limited impact of translational research studies
• Assuming SPTB is ONE phenotype has hindered discovery & therapeutic development

Where we are & need to go
• Agnostic discovery of molecular drivers of preterm & term parturition
• Leveraging innovative techniques to reveal biology
• Focus on mucosal immunology, reproductive biology, epithelial biology, microbiology, tissue microenvironments
An accepted paradigm of the preterm birth
The failure of the current paradigm

Uterine Contractions

- Targeting uterine contractility
- Beta-mimetics
- Prostaglandin inhibitors
- Magnesium Sulfate
- Calcium channel blockers

Clinical trials targeting myometrial activity

NO BENEFIT
NO CHANGE IN PTB RATES

Uterine Infection

- Targeting uterine colonization b/t pregnancies

Clinical trials targeting uterine and vaginal infections

NO BENEFIT
NO CHANGE IN PTB RATES
Why did this paradigm fail?

• Cervicovaginal epithelial barrier is not INERT
• Most vaginal microbes are non-motile. They cannot easily ascend into the uterine cavity
• The cervix is a biomechanical tissue that responds to load and stretch
• The immune response in the lower reproductive tract is much more complex than “pro- or anti” inflammatory and may not (likely does not) mimic functional immunity systemically or at the maternal-fetal interface
THE HUMAN MICROBIOME

Bacteria, fungi, and viruses outnumber human cells in the body by a factor of 10 to one. The microbes synthesize key nutrients, fend off pathogens, and impact everything from weight gain to perhaps even brain development. The Human Microbiome Project is doing a census of the microbes and sequencing the genomes of many. The total body count is vast, but it's believed over 1,000 different species live in and on the body.

25 SPECIES in the stomach include:
- Helicobacter pylori
- Streptococcus thermophilus

600+ SPECIES in the mouth, pharynx and respiratory system include:
- Streptococcus viridans
- Neisseria sicca
- Candida albicans
- Streptococcus salivarius

1,000 SPECIES in the skin include:
- Pityrosporum ovale
- Staphylococcus epidermidis
- Corynebacterium jeikeium
- Trichosporon
- Staphylococcus haemolyticus

500-1,000 SPECIES in the intestines include:
- Lactobacillus casei
- Lactobacillus reuteri
- Lactobacillus gasseri
- Escherichia coli
- Bacteroides fragilis
- Bacteroides thetaiotaomicron
- Lactobacillus rhamnosus
- Clostridium difficile

60 SPECIES in the urogenital tract include:
- Ureaplasma parvum
- Corynebacterium urealyticum

SOURCES: NATIONAL INSTITUTES OF HEALTH, SCIENTIFIC AMERICAN, HUMAN MICROBIOME PROJECT
The CV space as its own unique biological niche
Cervicovaginal Ecosystem

Reproductive Health

- Microbiota
- Mucus
- Epithelium
- Immune

Reproductive Risk

Cervix

Pelvic Floor
Is the vaginal microbiome associated with PTB?
<table>
<thead>
<tr>
<th>Author</th>
<th>Control (N)</th>
<th>Cases (N)</th>
<th>Study Design</th>
<th>Ethnic/Racial Diversity</th>
<th>SPTB</th>
<th>Characteristics of Microbiota associated PTB Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 Hyman</td>
<td>66</td>
<td>17</td>
<td>Longitudinal</td>
<td>Mixed ethnicity</td>
<td>No</td>
<td>Decreased diversity in white patients (n=7)</td>
</tr>
<tr>
<td>2014 Romero</td>
<td>72</td>
<td>18</td>
<td>Longitudinal</td>
<td>88% Black</td>
<td>Yes</td>
<td>CST IVB was present more (26.8%) in SPTB &gt; term (22.2%)</td>
</tr>
<tr>
<td>2014 Shiozaki</td>
<td>20</td>
<td>10</td>
<td>Cross sectional</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>2015 DiGiulio</td>
<td>34</td>
<td>15</td>
<td>Longitudinal</td>
<td>60% White</td>
<td>No</td>
<td>CST IV was inversely associated with gestational age: CST IV conferred a higher risk of PTB</td>
</tr>
<tr>
<td>2016 Subramaniam</td>
<td>20</td>
<td>20</td>
<td>Cross sectional</td>
<td>Mixed ethnicity</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>2016 Nelson</td>
<td>27</td>
<td>13</td>
<td>Cross-sectional</td>
<td>100% Black</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>2017 Stout</td>
<td>53</td>
<td>24</td>
<td>Longitudinal</td>
<td>69% Black</td>
<td>No</td>
<td>Decreased diversity between 1st and 2nd trimesters</td>
</tr>
<tr>
<td>2017 Kindinger</td>
<td>127</td>
<td>34</td>
<td>Cross sectional; Cerclage</td>
<td>65% White</td>
<td>No</td>
<td>L. iners</td>
</tr>
<tr>
<td>2017 Callahan</td>
<td>30 /55</td>
<td>9 /41</td>
<td>Longitudinal</td>
<td>56% White and Hispanic White; 81% Black</td>
<td>No</td>
<td>Subspecies clade of G. vaginalis in white women Decreased relative abundance of L. crispatus</td>
</tr>
</tbody>
</table>
Increasing bacterial abundance by specific anaerobes is associated with PTB at early gestational ages.
Complex interactions between microbial communities and the immune response are associated with risk of sPTB

Current Evidence on the Vaginal Microbiome & PTB

• Non-lactobacillus dominated microbial communities are associated with PTB (~1.5 fold) and with SPTB (~2 fold)

• Non-lactobacillus dominated microbial communities are more prevalent in Black reproductive-aged women

• Microbial composition alone (16s rRNA sequencing) is likely not sufficient to reveal the complexity of host-microbial interactions in the lower reproductive tract

• Environmental exposure and lived experiences impact vaginal microbiome

Elovitz MA, et al Nature Comm 2019  
Fettweis JM, Nature Med 2019  
Onyango S et al; Front Immunol. 2023
Anton, et al. Microbiome. 2022  
Anton L, et al Front Micro, 2018
Oyebode IH, Environ Res; 2023  
Burris HH, et al Am J OBGYN MFM 2024
Association does not mean causation
We are obligated to demonstrate that microbiome and/or host-microbial interactions are mechanistically involved in the pathogenesis of sPTB prior to developing/testing/offer therapeutics targeting the microbiome.
SPTB and Immunity: beyond the TH1/TH2 balance
Shifting Immunity over trimesters
An immune clock of human pregnancy


Term considered 33 weeks
Postpartum considered ‘normal immune mileu’
Inflammatory processes at the maternal-fetal interface are not the same in infection vs inflammation.

*Targeting one pathway would not work in all cases of sPTB.
Current Evidence on the role of immunity in sPTB

- Miles to go before we sleep…..
- TH1/TH2 paradigm is overly simplistic and unlikely to help identify those at risk or be a platform for therapeutic development
- Inflammation is a key feature of sPTB but how it starts and where to target it remains to be discovered
- Inflammatory process is complex and differs in the reproductive tract, maternal-fetal interface and in the fetus proper
Next Steps

• **Investment in science**
  • Understanding the biology that drives parturition
  • Team science must be mandated with scientists & clinicians involved

• Mandated phenotyping of PTB

• Proposed therapeutics in clinical trials must be based on **biological plausibility** that they target essential pathway involved in the pathogenesis of sPTB.
  • We must strive to do better in avoiding patient burden & misuse of limited resources
Current Funding:
- R01-HD098867
- R01-HD102318
- U19AI167899
- R01-AI145840
- R01-NR014784
- R01-NR014784-06S1

Current Team Members:
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- Yu Hasegawa, PhD
- Charuta Agashe
- Valerie Riis, MPH
- Liqhwa Ncube
- Fatoumata Barry
- Charlene Valdez
- Jennifer Young

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- Andrea Edlow, MD; MGH
- Doug Lauffenburger, PhD; MIT
- Boris Juelg, MD; Harvard
- Jose Clemente, PhD; Sinai
- Jeremiah Faith, PhD; Sinai
- Miriam Merad, MD, PhD; Sinai
- Heather Burris, MD, MPH, PENN
- Louis Soslowsky, PhD; PENN
- Kate O’Neill, MD, MTR; PENN
- Susan Khalil, MD, MS; Sinai
- Sing Sing Way, MD, PhD; Cinn
Session 1: Current Understanding of Spontaneous Preterm Birth

**Moderator:** Kaveeta Vasisht, U.S. Food and Drug Administration

**Speakers:**
- Joyce Martin, Centers for Disease Control and Prevention
- Emre Seli, March of Dimes
- Michal Elovitz, Mount Sinai, Icahn School of Medicine
Session 2: Ethical and Regulatory Considerations and Challenges Associated with the Development of Therapeutics for Prevention of Spontaneous Preterm Birth

Moderator: Christine Nguyen, U.S. Food & Drug Administration
Session 2 Objective:

Experts will provide an overview of regulatory considerations, including the process of evaluating efficacy and safety of investigational products. The experts will discuss the ethical considerations used in clinical trials and the challenges to develop therapies for preterm birth.
Food and Drug Administration
The Duke Margolis Center for Health Policy

Advancing Drug Development for the Prevention of Spontaneous Preterm Birth

January 23-24, 2024
Regulatory Considerations for Development of Therapeutics for Prevention of Spontaneous Preterm Birth

January 23, 2024

Christina Chang, MD, MPH
Director, Division of Urology, Obstetrics and Gynecology
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Overview

• General considerations for clinical development programs
• Development programs enrolling pregnant persons, including for prevention of preterm birth (PTB)
• FDA’s review of marketing applications
General Considerations for Clinical Development Programs
Goal of Clinical Development

**Chemistry, Manufacturing, & Controls**
21 CFR 312.23(a)(7)
- To assure identity, strength, quality, and purity of the drug substance and drug product

**Non-Clinical**
21 CFR 312.23(a)(8)
- To assure that it is reasonably safe to conduct the proposed clinical investigations.

**Clinical**
21 CFR 314.126
- The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.
- Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs.
Developing Drugs for Use in Pregnant Women
Only 9 Drugs Ever Approved and Marketed for Obstetrical Indications (First Box)

<table>
<thead>
<tr>
<th>Drugs Approved Specifically for Obstetrical Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Methylergonovine maleate (Methergine)</td>
</tr>
<tr>
<td>• Oxytocin (Syntocinon nasal spray and Pitocin for injection)</td>
</tr>
<tr>
<td>• Ritodrine (Yutopar)—no longer marketed</td>
</tr>
<tr>
<td>• Dinoprostone (Prepidil and Cervidil)</td>
</tr>
<tr>
<td>• Magnesium sulfate</td>
</tr>
<tr>
<td>• Doxylamine succinate and pyridoxine hydrochloride (Diclegis)</td>
</tr>
<tr>
<td>• Hydroxyprogesterone caproate (Makena)—now withdrawn</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Drugs Prescribed for Approved Indications, Used in Pregnancy</th>
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<tbody>
<tr>
<td>• Antiseizure medications</td>
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<tr>
<td>• Antihypertensive medications</td>
</tr>
<tr>
<td>• Beta-adrenergic inhalers for asthma</td>
</tr>
<tr>
<td>• Antibiotics</td>
</tr>
<tr>
<td>• Glucocorticoids for autoimmune diseases</td>
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<table>
<thead>
<tr>
<th>Approved Drugs Prescribed in Pregnancy for Unapproved Uses in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antenatal steroids to enhance fetal lung maturity</td>
</tr>
<tr>
<td>• Indomethacin to stop preterm labor</td>
</tr>
</tbody>
</table>

Prescription Drugs Used in Pregnancy

• About 70% of pregnant persons are prescribed one or more drugs* during pregnancy (excluding over-the-counter vitamins and minerals)

• Ways FDA-approved drugs may be used during pregnancy:
  – pregnancy-related condition (approved or “on-label” use)
  – medical indication (approved or “on-label” use)
  – unapproved use (“off-label” use)

*For the purpose of this presentation, the word “drug” refers to both small molecules and biologics.

Physiologic Changes in Pregnancy Affect PK/PD Parameters

**Absorption**
- Nausea/vomiting in early pregnancy
- Rise in progesterone → delayed gastric emptying and prolonged gastric transit time

**Distribution**
- 30-50% increase in cardiac output, starting in 1st trimester
- 40-50% increase in blood volume by 3rd trimester
- Decreased albumin (diminished protein-binding)

**Metabolism**
- Changes in activities of CYP450 enzymes (e.g., ↑ CYP2A6, ↓ CYP 1A2)

**Excretion**
- Increased renal blood flow; 50% increase in glomerular filtration rate
- Increased clearance of renally-excreted drugs

If a Drug Candidate is Under Consideration for Obstetrics-Related Indication

Is it an FDA-approved product?

Yes
- Nonclinical toxicology data are available
- Clinical experience in non-pregnant women may be available
- Pregnancy exposure registry may be available to support safety
- Are there PK data to ensure adequate systemic exposure in pregnancy?

No
- Are nonclinical reproductive and developmental toxicity studies complete/adequate?
- Are there concerning findings in these nonclinical studies?
- Are there effective alternative therapies?
- Risk/benefit consideration for mother and fetus?
Prevention of Spontaneous Preterm Birth
Preterm Birth Is a Significant Public Health Concern

• PTB - delivery prior to 37 weeks of gestation
  – 10% of all births
  – 8% singleton pregnancies¹

• Clinical condition: Neonatal mortality, significant morbidity and long-term physical and developmental impairment from PTB

• High unmet need: No approved therapies for reducing risk of neonatal morbidity/mortality from PTB

**Study Population and Study Objective**

- Is the study population well-defined?
- What is the intended use of the drug?
  - Primary prevention
  - Secondary prevention
GA at Delivery as Surrogate Endpoint:
Uncertain Drug-Induced Prolongation of Pregnancy Improves Neonatal Outcomes

- Etiology of PTB, drug MOA poorly understood
- Sufficient evidence indicating later age of GA of *spontaneous* delivery correlates with improved neonatal outcomes
- No robust evidence indicating *drug-induced* prolongation of pregnancy correlates with same improved neonatal outcomes at the same GA of spontaneous delivery

- Subclinical Infection?
- Subclinical uteroplacental insufficiency?
- Fetal reasons?
- Other reasons for which it is better to deliver than remain in utero?
Efficacy Measurements

• **Clinical Endpoint for Full Approval**: Neonatal mortality/morbidity from prematurity (how the neonate feels, functions, or survives)

• **Surrogate Endpoint for Accelerated Approval (AA)**: Gestational age (GA) of delivery used as a proxy measure for neonatal health
  – Reducing the risk of delivery < X weeks gestation, in and of itself, is not clinically relevant without a reduction in adverse neonatal outcomes associated with PTB

*GA at delivery has been referred to as an "intermediate clinical endpoint." Neither surrogate endpoint that reasonable predicts clinical effect nor intermediate clinical endpoint are direct measures of clinical benefit of interest; they support AA, not traditional, approval.*
FDA’s Review of Marketing Applications
Considerations for Regulatory Decisions

• FDA provides guidance to drug sponsors, evaluates their data, then decides if the drug can be approved. Criteria for approval:
  – Substantial evidence of effectiveness
  – Benefits outweigh the risks

• FDA ensures manufacturing processes of drugs are adequate to preserve the drugs’ quality and purity

• The labeling is not false nor misleading

• FDA monitors the safety of drugs post-approval
Substantial Evidence of Effectiveness

• Must be established pre-approval

• Requires “adequate and well-controlled investigations”
  – Generally interpreted as ≥ two adequate and well-controlled trials
  – Two trials reduce the likelihood of chance or bias
  – Under certain circumstances, FDA can accept evidence from a single multi-center trial if appropriate, or a single trial plus confirmatory evidence

• Drug doesn’t have to be better than or as good as another approved drug
Structured Framework for Benefit-Risk Assessment

• FDA uses a structured assessment of the data, uncertainties, and conclusions with regard to:
  – Analysis of the condition
  – Current treatment options
  – Benefit
  – Risks and risk management

• Conclusions regarding benefit-risk
Types of Approval

• For traditional approval, the drug must establish benefit by improving how patients feel, function, or survive.

• For accelerated approval, the drug needs to show an effect on an endpoint reasonably likely to predict clinical benefit (e.g., radiographic shrinkage of certain cancers is reasonably likely to predict an improvement in overall survival).
Accelerated Approval

- Reserved for drugs that treat serious conditions and provide meaningful benefit over existing therapy
- These drugs must still meet the same standards for effectiveness and safety as a traditional approval
- The applicant must conduct postmarketing trial(s) to confirm the anticipated clinical benefit
- FDA can withdraw the drug or indication for certain reasons, such as not conducting the confirmatory trial or failure to verify clinical benefit
Resources

- Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biologic Products
- Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence
- Benefit-Risk Assessment for New Drug and Biological Products
- Draft Guidance for Industry: Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials
- Health and Human Services (HHS) Human Subject Protection regulations, including pregnant women
- Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)
- Investigational New Drug (IND) Application | FDA
Ethical Considerations for Clinical Trials for the Prevention of Preterm Birth

Anne Drapkin Lyerly, MD, MA
Professor, Department of Social Medicine
Research Professor, Department of Obstetrics and Gynecology
Toward a Paradigm of Inclusion

2009

Second Wave Initiative
Toward the Responsible Inclusion of Pregnant Women in Medical Research

Highlighted harms of exclusion, research as ethical imperative

2013

PHASES
Pregnancy + HIV/AIDS: Seeking Equitable Study
Guidance launched July 2020

2017

PREVENT
Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies


2021

PREPARE
PRomoting Equity for Pregnant Adolescents in REsearch

Pregnancy-specific evidence: a critical need

Dosing that reflects physiologic changes of pregnancy

Without it: Undertreatment or toxicity

Fetal Safety that establishes likelihood of birth defects and longer-term impacts

Without it: Exposure to inappropriate or unknown risk

Maternal Outcomes that predict the impact of treatment on maternal health

Without it: Exposure to inappropriate or unknown risk
Excluding pregnant persons from research does not eliminate risk; rather it shifts risk to the clinical setting where it expands.
“Inclusion of pregnant women and lactating women in clinical trials is essential, unless there are compelling scientific reasons for their exclusion.”
PRGLAC, 2018
Ethical Foundations

Protection from intervention-related risks

Access to the benefits of new technologies

Respect for pregnant people’s own health
Is false hope any hope at all?

-Anjali Kaimal, MD, MAS

New York Times, March 7 2023
The *Janus face* of risk in pregnancy

**PREGNANCY**

- Notice dangers of intervention without due regard for harms of non-intervention
- Reticence to use medications to treat chronic/emergent health conditions in pregnant person
- “Better safe than sorry”

**BIRTH**

- Notice dangers of non-intervention without due regard for burdens of intervention
- Persistent use of interventions (e.g., EFM) even if they are unproven or harmful
- “Just in case”


Image adapted from Greta Carmen, “Janus”
Distinctive **characteristics** of pregnancy-specific (obstetrical) conditions

**Non-pregnancy-specific**
- e.g.: asthma, depression, RA
- On-label
- +/- investigational drug
- Pregnancy-specific safety/dosing

**Pregnancy-specific (obstetrical)**
- e.g., pre-term birth, pre-eclampsia
- Off-label
- +/- investigational
- Efficacy is also unknown
Distinctive ethical considerations for research addressing pregnancy-specific (obstetrical) conditions

- Balancing **risks and benefits** – acceptable risk may be lower when efficacy is unknown
- Achieving **clinical equipoise** – may be easier to establish, but more difficult to convince clinicians and patients that it exists
- Ensuring **equitable study** of maternal outcomes for interventions that tend to focus on improving fetal/neonatal health
- Setting **research priorities** – most pregnancy-specific conditions lack FDA approved intervention, making pregnancy an “off label condition” and reinforcing need for evidence
Conclusions

- Broad recognition that research in pregnancy is an *ethical imperative*
  - Pregnant people deserve *protection, access, and respect*

- Pregnancy-specific interventions raise *different challenges*:
  - Risk distortions affect assessment of *risks and benefits and equipoise*, and (lack of) attention to *maternal outcomes*

- Prospect of false hope, absence of evidence-based interventions emphasize *high priority* for research on pregnancy-specific (obstetrical) conditions
Acknowledgment and disclosures

• Work from the PHASES/PREPARE Projects were supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award number R01AI108368. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

• Dr. Lyerly has received support from UCB Biosciences and 3D Communications
Development of Therapeutics for Prevention of sPTB: The Challenges

George Saade, MD
EVMS Foundation Chair for Women’s Health
Associate Dean for Women’s Health
Professor and Chair, EVMS Obstetrics and Gynecology
Eastern Virginia Medical School
The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy

J Scaffidi,^a BW Mol,b,c JA Keelander


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<th>Registry URL</th>
<th>All trials in registry</th>
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The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy

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Therapeutics for Tertiary Prevention (Tocolytics)

- Ritodrine (withdrawn 1998)
- Atosiban (not approved)
- GSK (halted)
- Ebopripant (OBE022, returned to XOMA)
Therapeutics for Primary and Secondary Prevention

New medicines for spontaneous preterm birth prevention and preterm labour management: landscape analysis of the medicine development pipeline

Annie R. A. McDougall1*, Roxanne Hastie2, Maya Goldstein3, Andrew Tuttle3, Anne Ammerdown4, A. Metin Gümüşozlu5 and Joshua P. Vogel13

(A) Phase III Candidate name
Omega-3 fatty acids
Aspirin
Progesterone, natural, micronized (vaginal/topical)
Pravastatin
Pentaerythrityl tetranitrate
Zishen Yutai Pill
Probiotic Lactobacilli
Vitamin D
Mapping the translational science policy ‘valley of death’

Eric M Meslin, Alessandro Blasimme and Anne Cambon-Thomsen

Adapted from: Canadian Institutes of Health, (2011)
Mapping the translational science policy ‘valley of death’

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Basic Biomedical Research

Clinical Science and Knowledge

Clinical Practice and Health Decision Making

Adapted from: Canadian Institutes of Health, (2011)
Why is this Bridge so Elusive?

• Limited interest from industry
• Limited governmental funding
• Limited infrastructure
• Limited expertise
Overall Challenges

• Small market:
  • Short duration of treatment
  • Few eligible

• Fetal effects
  • Difficult to ascertain (multiple organs, ascertainment methods, long term)
  • Post-market responsibility

• Clinical endpoint
  • Choice (e.g. single vs composite, early vs late)
  • Competing and conflicting (e.g. maternal vs fetal, early vs late)
Specific Challenges

• Choice of intervention
  • Mechanisms
  • Limitations of animal models
• Trial eligibility
• Impact of clinical care
• Comparator
  • FDA approved vs off-label use
• Establishing safety
• Outcomes
  • Noisy outcomes (clinical judgment, combination of APOs)
  • Low frequency outcomes
Suggested Solutions

• Funding
  • Mechanistic studies, in-vitro and in-vivo models
  • Infrastructure
  • Clinical trial
  • Multi-countries

• Help for non-industry
  • Support for IDE and regulatory approvals

• Consensus on clinical endpoints and on safety

• Consider novel trial design
  • Adaptive designs
  • Desirability of Outcome Ranking (DOOR) outcomes
  • Bayesian analysis

• Streamline process
Orphan Drug Act (ODA)

• Financial benefit and incentives to offset small market

• Disease affects <200,000 patients per year
  • Sickle cell disease
  • Cystic fibrosis
  • Early PTB <34 weeks’ (100,000/yr) but not PTB <37 weeks’ (300,000/yr)
Orphan Drug Act (ODA)

• Financial benefit and incentives to offset small market

• Disease affects <200,000 patients per year
  • Sickle cell disease
  • Cystic fibrosis
  • Early PTB <34 weeks’ (100,000/yr) but not PTB <37 weeks’ (300,000/yr)
Useful Approval Paths

• Fast Track
• Breakthrough Therapy
• Accelerated Approval
• Priority Review
Accelerated Approval

• Serious condition with unmet needs

• Long disease course or long duration to definite outcome
  • Child outcome but not immediate neonatal outcome

• Approval based on either
  • Surrogate endpoint (marker that predicts clinical benefit)
  • Intermediate clinical endpoint (therapeutic effect considered reasonably likely to predict clinical benefit)

• Post-approval studies needed (e.g. confirm finding or endpoint)
Incentives & Return on Investment
BPCA Legislation

On-Patent
- Pharmaceutical Companies’ Drug Studies
- Pediatric Division Oversight

Off-Patent
- Prioritization
- Clinical Trials
- Training
Paediatric Regulation

The Paediatric Regulation came into force in the European Union (EU) on 26 January 2007. Its objective is to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0 to 17 years.
Gordian Knot
Seemingly intractable problem solved by unexpectedly direct, novel, rule-bending, decisive, and simple approach that removes the perceived constraints
CANCER MOONSHOT

INITIATIVES 2017–2022

OVER 70 CONSORTIUMS OR PROGRAMS

OVER 240 RESEARCH PROJECTS
50 years ago, Nixon gave the U.S. a 'Christmas present,' launching the war on cancer

DECEMBER 23, 2021 - 1:25 PM ET

By Gabrielle Emanuel
A Pregnancy Moonshot is Needed
Session 2: Ethical and Regulatory Considerations and Challenges Associated with the Development of Therapeutics for Prevention of Spontaneous Preterm Birth

Moderator: Christine Nguyen, U.S. Food and Drug Administration

Speakers:

• Christina Chang, U.S. Food and Drug Administration
• Anne Lyerly, UNC School of Medicine
• George Saade, Eastern Virginia Medical School
Break – 10 minutes

We will have a brief break and return at 3:25 pm.
Session 3: Impact of Preterm Birth on Families and Society

Moderator: Sarahn M. Wheeler, Duke University School of Medicine
Session 3 Objective:

This patient-focused session will discuss the short- and long-term challenges of caring for infants and children born preterm from the voices of parents and experienced clinicians, nurses, caregivers, and social workers.
Session 3 Panelists

Deb Discenza
PreemieWorld Foundation, Inc.

Jennifer Degl
Maternal and Infant Health Advocate, Author

Ashley Randolph-Cooley
GLO Preemies

Wakako Eklund
Pediatrix Medical Group

JaNeen Cross
Howard University School of Social Work
Closing Remarks

Mark McClellan, MD, PhD
Director, Duke-Margolis Center for Health Policy
Closing Remarks

Mark McClellan, MD, PhD
Director, Duke-Margolis Center for Health Policy
Thank You!

Contact Us

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Advancing Drug Development for the Prevention of Spontaneous Preterm Birth

January 23 & 24th | 1:00 – 4:30 p.m. ET
Opening Remarks and Summary of Day 1

Nancy Allen LaPointe, PharmaD, MHS
Faculty Fellow, Duke-Margolis Center for Health Policy
Agenda

January 23 (1:00 – 4:30 PM ET)

• Opening Remarks from FDA
• Current Understanding of Spontaneous Preterm Birth
• Ethical and Regulatory Considerations and Challenges Associated with the Development of Therapeutics for Prevention of Spontaneous Preterm Birth
• Impact of Preterm Birth on Families and Society

January 24 (1:00 – 4:30 PM ET)

• Opening Remarks and Summary of Day 1
• Assessing Efficacy and Safety in Clinical Programs for Therapeutics for Spontaneous Preterm Birth Prevention
• Dose-Finding and Clinical Trial Design Considerations
• Wrap-up with Workshop Moderators
Session 4: Assessing Efficacy and Safety in Clinical Programs for Therapeutics for Spontaneous Preterm Birth Prevention

Moderator: Lynne Yao, U.S. Food and Drug Administration
Session 4 Objective:

Experts will discuss the efficacy and safety assessments used in clinical programs as well as opportunities to improve and address the challenges within these programs. The discussion will consider how researchers can identify clinically relevant neonatal outcomes.
Session 4 Panelists

Mark Hudak
University of Florida
College of Medicine

Tamorah Lewis
University of Toronto

Anjali Kaimal
University of South Florida

Christina Chang
U.S. Food and Drug Administration

An Massaro
U.S. Food and Drug Administration

Robert Nelson
Johnson & Johnson
Break – 15 minutes

We will have a brief break and return at 2:35 pm.
Session 5: Dose-Finding and Clinical Trial Design Considerations

Moderator: Michal Elovitz, Ichan School of Medicine at Mount Sanai
Session 5 Objective:

Field experts will discuss the importance of identifying a target drug for development and the data needed to support clinical trials for both novel and approved products, emphasizing consideration of different study populations and control groups in clinical trials. They will also discuss dose finding while considering physiologic changes in pregnancy and drug metabolism.
Nonclinical Safety Assessment of Pharmaceutical Products to be Administered During Pregnancy

Duke Margolis Workshop

Advancing Drug Development for the Prevention of Spontaneous Preterm Birth

January 23-24, 2024

Kimberly Hatfield, PhD

U.S. FDA, CDER, Office of New Drugs
Division of Pharmacology/Toxicology – Rare Diseases, Pediatrics, Urology and Reproductive Medicine
~ supporting the Division of Urology, Obstetrics and Gynecology
Objectives

Explain the content and characteristics of nonclinical studies that are conducted to predict the safety of a pharmaceutical product to a developing human in the prenatal period.
Why Conduct Nonclinical Toxicity Studies?

Animal studies to evaluate drug toxicity are mandated
• 1962 Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act (FD&C Act)
  • Response to thalidomide tragedies
  • Demonstration of both the safety and efficacy of marketed drugs
• 21 CFR 312.23(a)(8) – animal toxicology necessary to support first in human clinical trials

Regulations and guidance for how and when to conduct nonclinical studies have been developed over many years
• International guidance (ICH; International Council for Harmonization)
• FDA Guidance (https://www.fda.gov/regulatory-information/search-fda-guidance-documents)

Reproductive/developmental toxicity studies are one part of the total nonclinical assessment of a drug product.
What Do Reproductive and Developmental Toxicity Studies Measure?

Reproductive toxicity
- Structural and functional alterations that affect reproductive competence in sexually mature males and females
  - Male and female fertility
  - Parturition (labor and delivery)
  - Lactation

Developmental toxicity
- Adverse effects on the developing organism (teratogenicity)
  - Mortality
  - Alterations to growth
  - Structural abnormalities
  - Functional impairment
How Do We Evaluate Reproductive & Developmental Toxicity?

• Repeat dose toxicology studies
  • Histopathology evaluation of the reproductive organs
  • Evaluation of estrous/menstrual cycle (extended time in any one stage?)

• Reproductive/developmental toxicology study designs
  • Fertility and early embryonic development (FEED)
  • Embryofetal development (EFD)
  • Pre- and postnatal development (PPND)
Reproductive/Developmental Toxicity Study Design

The reproductive/development cycle is defined by 4 biological phases and is separated into 3 dosing segments:

- Fertility and Early Embryonic Development (FEED)
- Embryofetal Development (EFD)
- Maturation
- Preweaning
- Weaning
- Mating
- Gestation
- Pre- and Postnatal Development (PPND)
- Implantation
- Parturition
Embryofetal Development (EFD)

Important for drugs that could be used during pregnancy

Evaluated in 2 species: a rodent (usually rat) and non-rodent (usually rabbit)
Dosing occurs from implantation through organogenesis/closure of hard palate

N = at least 16 pregnant females / dose group

- Average litter size of 6 (rabbit) – 12 (rat) → large numbers of offspring to evaluate
  - necessary for level of statistical power
  - to be assured any findings are increased above natural background
Embryofetal Development (EFD) Endpoints Assessed

**Maternal health endpoints:**
- Body weight changes
- Evaluation of general toxicity to organ systems relative to nonpregnant females

**Embryofetal development and other pregnancy parameters:**
- Gravid uterine weight
- # fetuses
- Pre- and post-implantation embryofetal loss
- Gross evaluation of the placenta

**Fetal health endpoints:**
- Altered growth
- Body weight
- Gross evaluation of external, visceral, and skeletal development
Pre- & Postnatal Development (PPND)

Important for drugs that could be used during pregnancy, or for those administered during lactation

Evaluated in 1 species: usually rat
Dosing occurs from implantation through end of lactation
One male and one female offspring per litter selected for rearing to adulthood and mating (reproductive competence)

N = at least 16 pregnant females / dose group
Pre- & Postnatal Development (PPND)
Endpoints Assessed

Maternal health and maintenance of pregnancy during treatment:
  • Body weight changes
  • Duration of pregnancy
  • Pregnancy (whole litter) loss
  • Live/dead offspring at birth

Offspring (F1 generation) exposed in utero or via lactation:
  • Body weight
  • Pre-/post-weaning survival and growth
  • Sexual maturation
  • Fertility (reproductive capacity)
  • Physical development
  • Sensory function/reflexes
  • Behavior, learning, memory

Offspring (F2 generation) not exposed
  • External exam
  • Survival to PND 4-7
Timing of Nonclinical Studies

What nonclinical data do we have before evaluating reproductive/developmental toxicity?

1) Mechanism of action, receptor & organ targets (indication)
2) Absorption / Distribution / Metabolism / Excretion (ADME)
   How long does the drug stay in the circulation?
   Does the drug break down to active or toxic metabolites?
3) General toxicity in non-pregnant animals
   What are the target organs? What are safe doses?
   Does it affect reproductive organs?
4) Genotoxicity
   Is the drug a mutagen? Can it damage DNA?
Timing of Reproductive Toxicity Studies – During the IND

**Traditional clinical trial**

*males, postmenopausal individuals, and/or individuals of child bearing potential (with pregnancy testing and contraceptive use):*

- General toxicity studies with reproductive organ assessments
- FEED & EFD studies
- PPND studies
Timing of Reproductive Toxicity Studies – During the IND

Clinical trial for a pregnancy-specific indication
OR
Clinical trial enrolling pregnant individuals
(treatment population is actively pregnant individuals)

ALL reproductive studies (FEED, EFD, PPND),
general toxicity, and genotoxicity
COMPLETE
before pregnant individuals are enrolled

IND Phase 1
IND Phase 2
IND Phase 3
NDA

Phase 1 generally enrolls non-pregnant subjects
Phase 2-3 generally enrolls pregnant subjects
How Do We Extrapolate Animal Findings to Humans?

Repeat Dose, EFD and PPND studies will yield a value for the *dose that produces no toxicity in animals*

**NOAEL – No Adverse Effect Level**

The NOAEL is compared to the recommended human dose:

\[
\frac{\text{NOAEL}}{\text{therapeutic dose in humans}} = \text{Multiple of Exposure (MOE)}
\]

The larger the MOE number → the safer the drug

The MOE and the totality of safety information about the drug are used to guide dosing decisions and communicate risk.
Animal Data Guides Risk Assessment

Animal data informs human risk when very limited or no human data are available.

- If **NEGATIVE**, animal data can support further clinical testing
- If **POSITIVE**, animal data can help define a safe human dose range

**LIMITATIONS**

- Clinical trials can be rejected or modified if:
  - Animal data show potential harm to the fetus that cannot be detected until birth (*non-monitorable toxicity*)
  - Exposure to the fetus cannot be determined
  - Risk / benefit is unfavorable
Decision Process –
Proposed Clinical Trial in Pregnant Individuals

Review team integrates **ALL** information – from **BOTH** nonclinical and clinical studies

- Are animal findings relevant to humans?
- Can we estimate fetal drug exposure?
  - How much compared to the mother? Which trimester(s)?
  - Could the fetal brain be exposed?
  - Could adverse effects occur in the fetus more than the mother?

**It all comes down to **BENEFIT** vs **RISK**

- How serious is the indication for the mother? For the fetus?
- Is the benefit certain? Is the population that would benefit well-defined?
- If the drug is toxic to the fetus, is it monitorable? Is it reversible?
- If the mother is NOT treated, will her condition be a risk to her fetus?

Reproductive / developmental toxicity studies in animals provide essential information for the clinician to make a treatment decision and to inform the patient of risk
Reference to Guidance

- ICH-S5(R3) - Detection of Toxicity to Reproduction for Human Pharmaceuticals (Feb 2020)
- Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (July 2020)
- Reproductive and Developmental Toxicities -- Integrating Study Results to Assess Concerns (Sept 2011)
- ICH-M3(R2) - Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (Jan 2010)
- ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (May 2012)


FDA Guidance: https://www.fda.gov/regulatory-information/search-fda-guidance-documents
Dose Finding Considerations for Prevention of Preterm Birth

Doanh (Donny) Tran, PhD
Office of Clinical Pharmacology
Office of Translational Science
Disclaimer

• The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.
Outline

• Introduction to 3 Phases of drug development
• General recommendations on dose finding studies
• Effect of pregnancy on pharmacokinetics (PK)
• Potential implication on dose finding for prevention of preterm birth
General Drug Development Phases

**PHASE 1**
- Single ascending dose and multiple ascending dose studies to assess PK, safety and tolerability
- Studies evaluating effects of intrinsic and extrinsic factors and drug interactions
- For a repurposed drug, may rely on clinical pharmacology findings from prior studies as appropriate
  - Often PK in pregnancy is not available and would need to be evaluated

**PHASE 2**
- Proof of concept studies
- Dose finding studies
  - Important to find optimal dose to confirm in Phase 3

**PHASE 3**
- Large clinical safety and efficacy trials
Phase 2 Dose Finding

• Sponsor should conduct a Phase 2 dose finding study to help select doses for Phase 3
• Identifying the most optimal dose to take into Phase 3 is critical to ensure best chance of success
  – Too high of a dose can lead to unacceptable toxicity
  – Too low of a dose risk not showing efficacy
• The dose(s) selected for further study in Phase 3 should be supported by robust scientific justification.
Dose Finding Study Considerations

• Phase 2 dose finding study should include a range of doses to allow analysis of dose- and/or exposure-response
  – Recommend at least 2 dose levels in addition to placebo control
  – The dose levels should have adequate separation to avoid the risk of being at the plateau of exposure-response relationship curve
  – For drugs with high PK variability, a greater spread of doses should be considered
  – Wide range of dose may also be needed in cases where there are not good pharmacologic endpoints or biomarkers to provide guidance on what dose is needed

• Should discuss with FDA to gather recommendations for potential improvements

• Modelling and simulation should be conducted to predict dose and dosing interval that provide best risk/benefit balance for evaluation in Phase 3
Dose Finding Study Design

**Parallel Study**
- Randomization to several fixed dose groups
- Placebo inclusion is desired (unless not ethical)
- Most likely to be applicable for study of prevention of preterm birth

**Cross-over study**
- Randomized cross-over of several dose levels
- Good when there is rapid drug effects with treatment and rapid return to baseline after removal of treatment
- May not be applicable for prevention of preterm birth, unless there is a rapidly responding biomarker is identified

**Titration Study**
- Forced or titrated to a response
- Cannot distinguish response due to increased dose vs. response due to increased time on therapy or cumulative dose effect

See ICH E4 – Dose Response Information to Support Drug Registration
Effect of Pregnancy on PK

- Oral drug absorption may change due to presence of nausea and vomiting, increased gastric pH, prolonged gastric emptying, and prolonged small bowel transit time.
- Distribution may change due to increased plasma volume, increased body weight, increased body fat, decreased plasma albumin, etc.
- Metabolism and excretion may change due to changes in the activity of metabolizing enzymes, increased hepatic blood flow, increased renal blood flow, and increased glomerular filtration rate.

In short, PK may be affected in pregnancy. Impact may be seen in the first trimester with larger impact in later trimesters.

Kazma et al. (2020), PMID: 32026239; Hazenberg et al. (2021), PMID: 33548055; Chaphekar, Caritis, and Venkataramanan (2020), PMID: 33205432
Characterizing PK in Pregnancy

• PK and safety should be characterized in non-pregnant subjects before proceeding to dosing in pregnant subjects.

• As our target patient population is pregnant people, PK should be characterized for the period in which the drug will be administered (e.g., 1st, 2nd, and 3rd trimester)

• PK can be collected in a clinical study of pregnant people being treated for prevention of preterm birth

• A separate PK study could be conducted in pregnant individuals if the risk to the patient and the fetus is minimal*

Dose Finding for Prevention of Preterm Birth

• Drug dosing likely spans all three trimester of pregnancy
  – Dose may need to be adjusted as pregnancy progresses to maintain the target drug concentration
  – Opportunity for longitudinal study design where PK (and applicable PD) can be captured in the same individual over the course of pregnancy
• Parallel dose design is likely needed if endpoint is delivery
• Not clear if there are PD endpoints which shows rapid response and could predict clinical efficacy
Summary

- **Dose-response** or **concentration-response** information is critical to select an optimal dose for Phase 3.
- A **dose finding study** is recommended to help guide dose selection.
- PK may be **altered** during pregnancy and needs to be considered.
- A **parallel study design** may be useful for dose finding studies for prevention of preterm birth.
U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY
Session 5: Dose-Finding and Clinical Trial Design Considerations

Moderator: Michal Elovitz, Mount Sinai, Icahn School of Medicine

Panelists:

- Kimberly Hatfield, U.S. Food and Drug Administration
- Doanh (Donny) Tran, U.S. Food and Drug Administration
- Kevin Prohaska, U.S. Food and Drug Administration
- Steve Caritis, University of Pittsburgh Medical Center
- Kelle Moley, Ferring Pharmaceuticals
The Dosing Regimen for 17-hydroxyprogesterone caproate was suboptimal
Lessons for Future Pharmacotherapy for Pregnant Women

Steve Caritis, MD
Prerna Vijay DODEJA MS,
Shringi SHARMA PhD,
Raman VENKATARAMANAN PhD
Sources of Data Presented

1. Maternal Fetal Medicine Units Network (MFMU)
   Relationship between 17-alpha hydroxyprogesterone caproate concentration and spontaneous preterm birth.

2. Obstetrical-Fetal Pharmacology Research Units (OPRU)
   Pharmacology and placental transport of 17-hydroxyprogesterone caproate in singleton gestation.

3. Obstetrical-Fetal Pharmacology Research Centers
   Relationship between plasma concentration of 17-hydroxyprogesterone caproate and gestational age at preterm delivery.
Relationship Between 17-OHPC Concentration and sPTB

Rate of sPTB According to 17-OHPC concentration Quartile

K-M Survival According to Plasma 17-OHPC Concentration Q1 vs Q2-4

Relationship between 17-alpha hydroxyprogesterone caproate concentration and spontaneous preterm birth
Probability of sPTB According to 17-OHPC Concentration

\[ P = 0.04 \]
### Logistic Regression Relating Various Plasma Concentration Threshold of 17-OHPC to Risk of sPTB at <37, <35 and <33 Weeks

<table>
<thead>
<tr>
<th>Concentration threshold</th>
<th>sPTB (&lt;37 wks) OR (95% CI)</th>
<th>sPTB (&lt;35 wks) OR (95% CI)</th>
<th>sPTB (&lt;33 wks) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6 ng/ml (27/295)</td>
<td>0.9 (0.2-3.6)</td>
<td>1.4 (0.3-5.8)</td>
<td>1.5 (0.3-8.1)</td>
</tr>
<tr>
<td>≤ 7 ng/ml (49/295)</td>
<td>1.7 (0.6-4.6)</td>
<td>2.4 (0.8-7.3)</td>
<td>1.8 (0.5-6.9)</td>
</tr>
<tr>
<td>≤ 8 ng/ml (74/295)</td>
<td><strong>2.4 (1.0-5.9)</strong></td>
<td><strong>2.8 (1.0-7.7)</strong></td>
<td><strong>3.6 (1.0-12.3)</strong></td>
</tr>
<tr>
<td>≤ 9 ng/ml (113/295)</td>
<td>3.0 (1.2-7.1)</td>
<td>2.3 (0.8-6.4)</td>
<td>3.2 (0.9-11.7)</td>
</tr>
<tr>
<td>≤ 10 ng/ml (154/295)</td>
<td>3.1 (1.2-8.2)</td>
<td>2.0 (0.7-5.9)</td>
<td>2.7 (0.6-11.0)</td>
</tr>
<tr>
<td>≤ 12 ng/ml (212/295)</td>
<td>3.1 (0.8-11.9)</td>
<td>1.5 (0.3-6.7)</td>
<td>3.0 (0.3-27.9)</td>
</tr>
</tbody>
</table>

Adjusted for time from enrollment to blood sample, number of prior sPTBs and cervical length.
Simulated 17-OHPC Concentrations Based on Half-Life

- Q1 T1/2 11.5d
- Median T 1/2 14 d
- Q3 T1/2 17.2 d

Simulated Trough Concentrations Depicting the Impact of Loading Dose on Time to Reach and Sustain 9 ng/ml Target

Median $t_{1/2}$ 1-14 Days and SS 11 ng/ml

- **500 mg load*2**
- **500 mg dose*1**
- **250 mg - no load**

17-OHPC- ng/ml vs. Weeks After 1st Injection
Session 5 Panelists

Kim Hatfield
U.S. Food and Drug Administration

Doanh (Donny) Tran
U.S. Food and Drug Administration

Kevin Prohaska
U.S. Food and Drug Administration

Steve Caritis
University of Pittsburgh Medical Center

Kelle Moley
Ferring Pharmaceuticals
Wrap-up with Workshop Moderators

Moderator: Nancy Allen LaPointe, Duke Margolis Center for Health Policy
Wrap-Up Session Objective:

Panel members will discuss the key takeaways from each session and provide next steps in advancing drug development for the prevention of preterm birth.
Wrap-up Panelists

Christina Chang
U.S. Food and Drug Administration

Christine Nguyen
U.S. Food and Drug Administration

JaNeen Cross
Howard University School of Social Work

Lynne Yao
U.S. Food and Drug Administration

Michal Elovitz
Ichon School of Medicine at Mount Sinai
Closing Remarks

Nancy Allen LaPointe, PharmaD, MHS
Faculty Fellow, Duke-Margolis Center for Health Policy
Thank You!

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