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Health Sciences

Opportunities in Clinical Research to Reduce Maternal Morbidity and Mortality

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School of Medicine
Obstetrics, Gynecology and Reproductive Sciences

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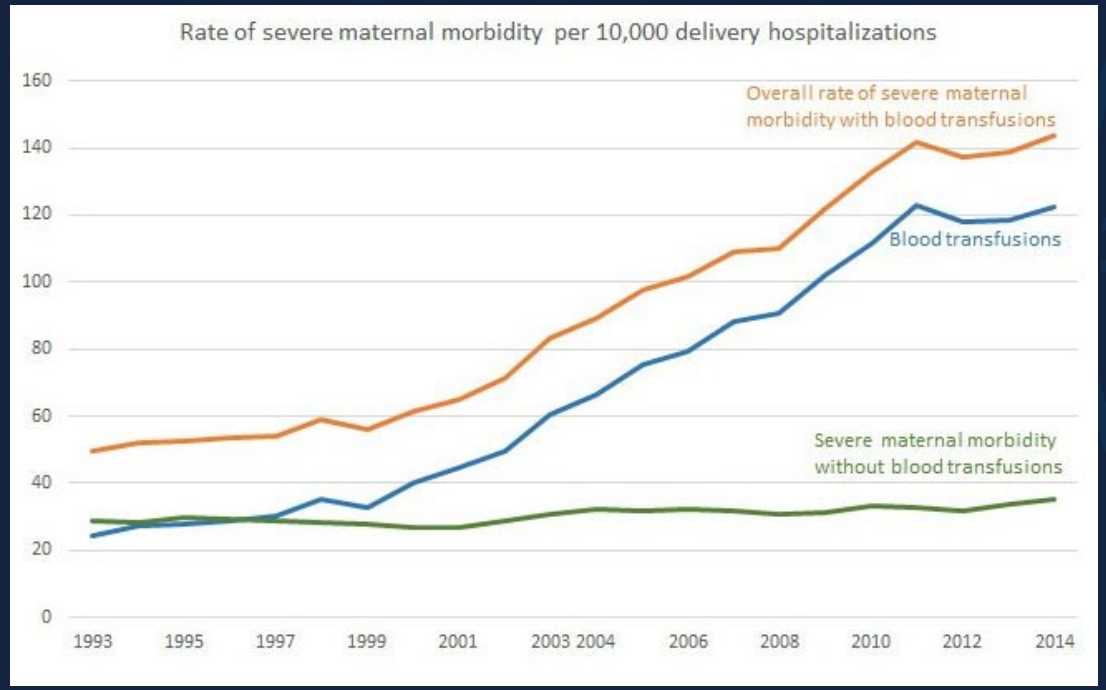
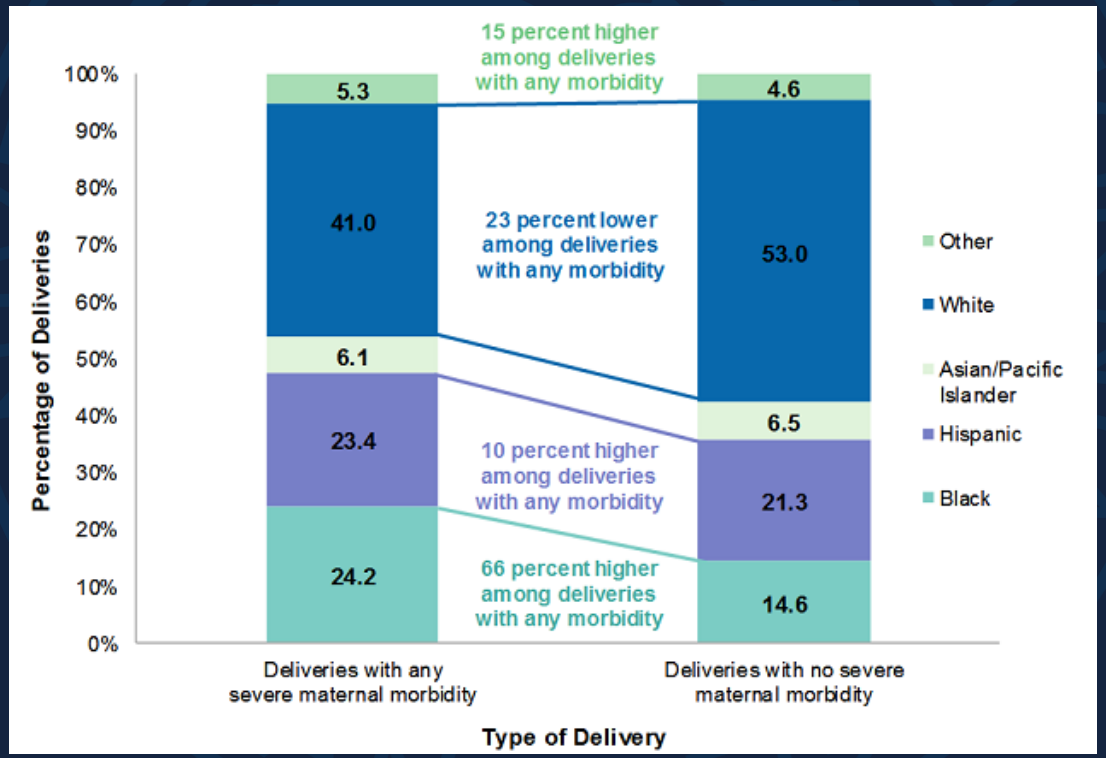
Maternal Morbidity and Disparities





CDC.gov

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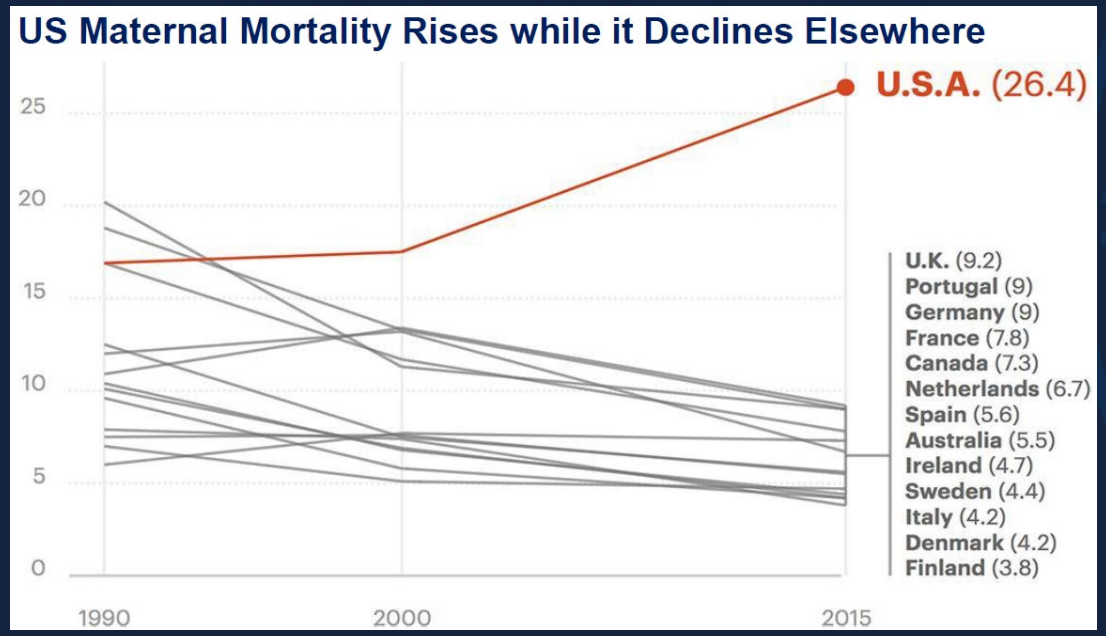
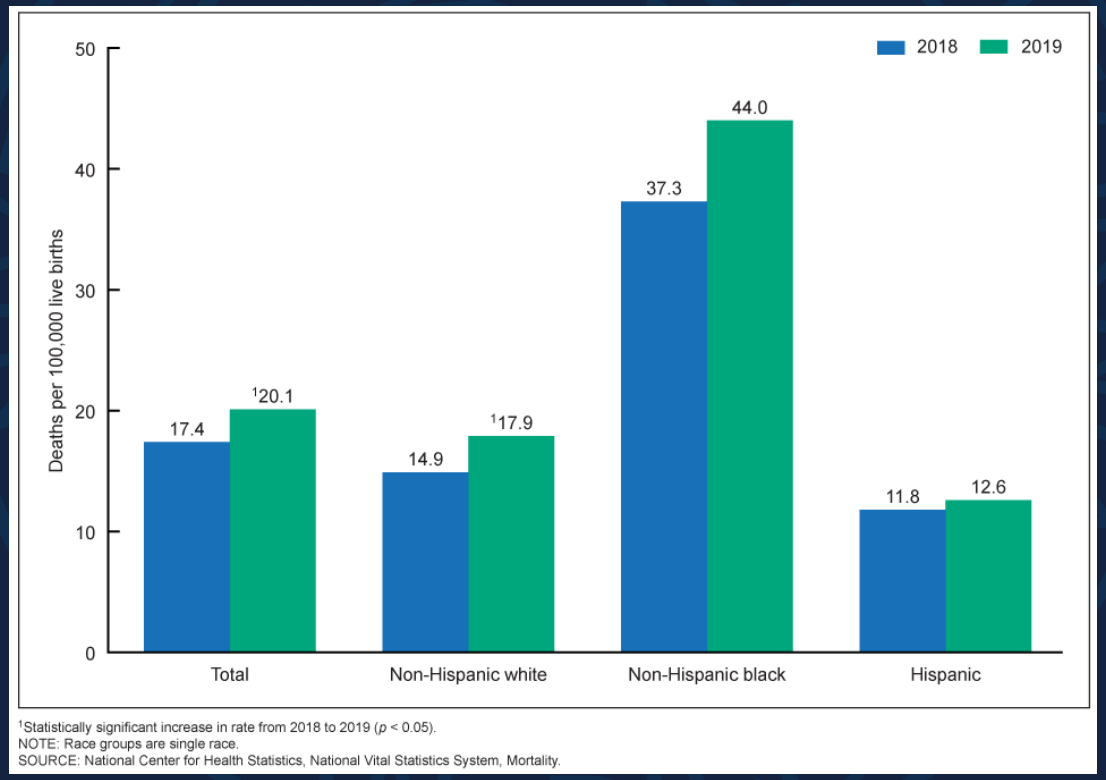
US Maternal Mortality and Disparities



Kassebaum, Lancet, 2016



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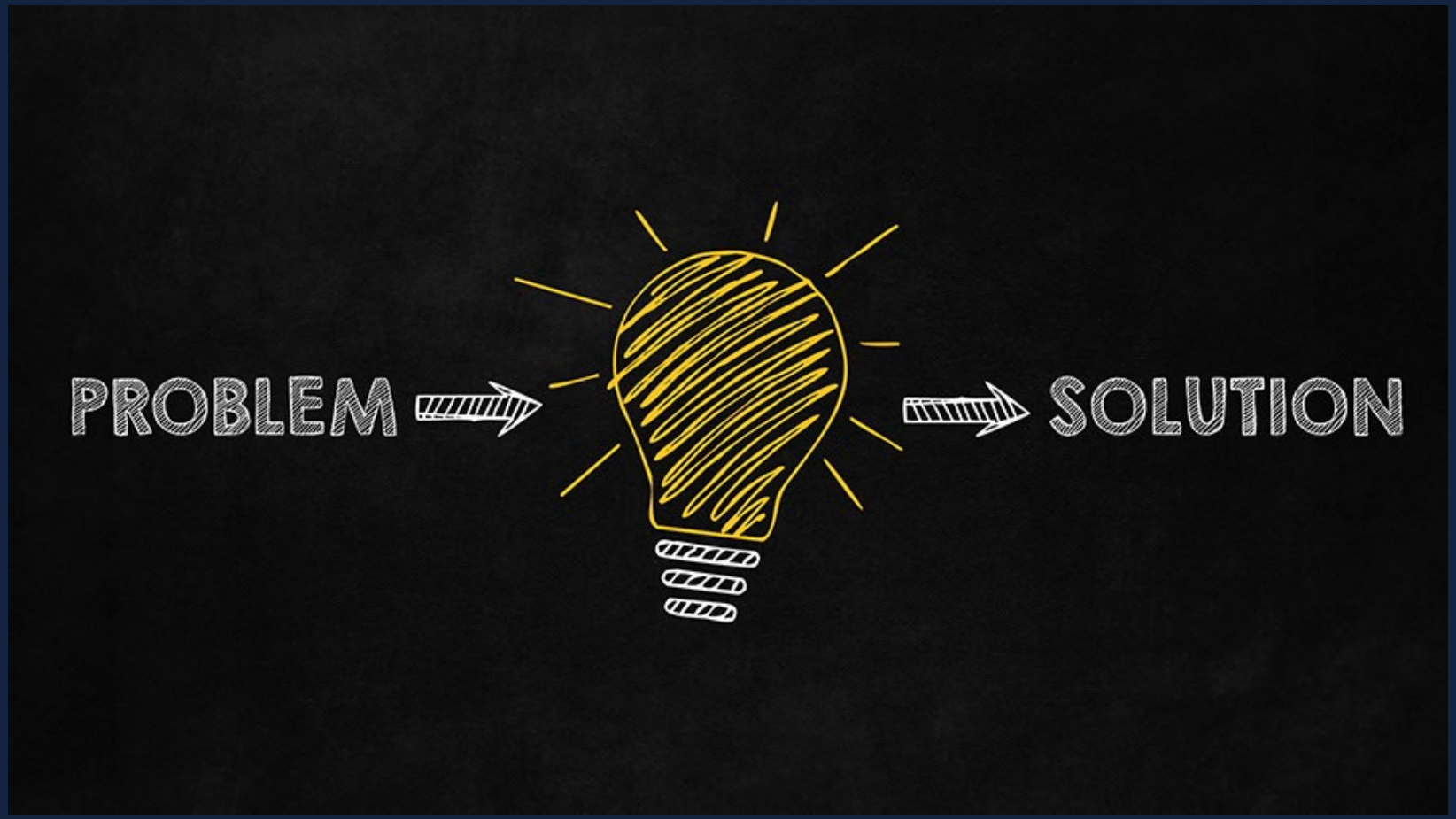
What do we do about it?



Randomized Clinical Trials

Pros

- The “gold standard”
- Limits bias in selection, direct comparison between 2 groups
- Can establish causation

Cons

- Strict inclusion criteria limits generalizability

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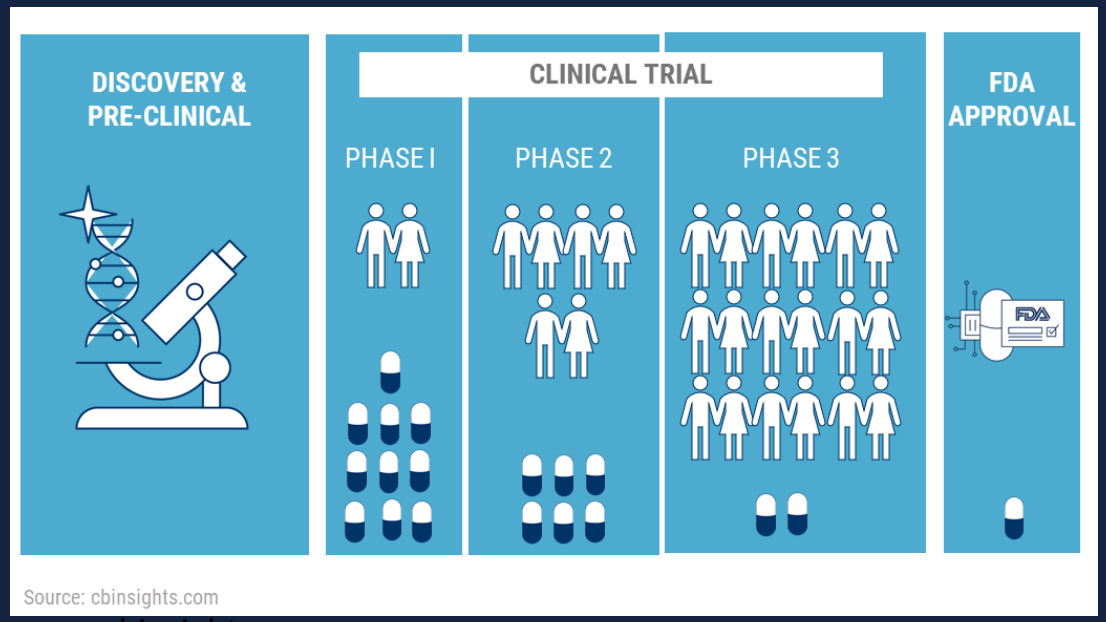
Clinical Trials and Pregnant People



Source: cbinsights.com

- 2 broad categories
  - Interventions to improve pregnancy outcomes
    - Preterm birth
    - Preeclampsia
    - Intrahepatic cholestasis of pregnancy
  - Interventions for common medical conditions that co-exist with pregnancy
    - Hypertension
    - Diabetes
    - COVID-19

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How do we perform clinical trials in obstetrics?

- Investigator initiated studies
  - NIH or other government funding
  - Industry
- NICHD MFMU
  - Only obstetric clinical trials research network

NICHD MFMU Origins

- Obstetrical management, especially for high-risk patient, had often adopted practices without objective evaluation

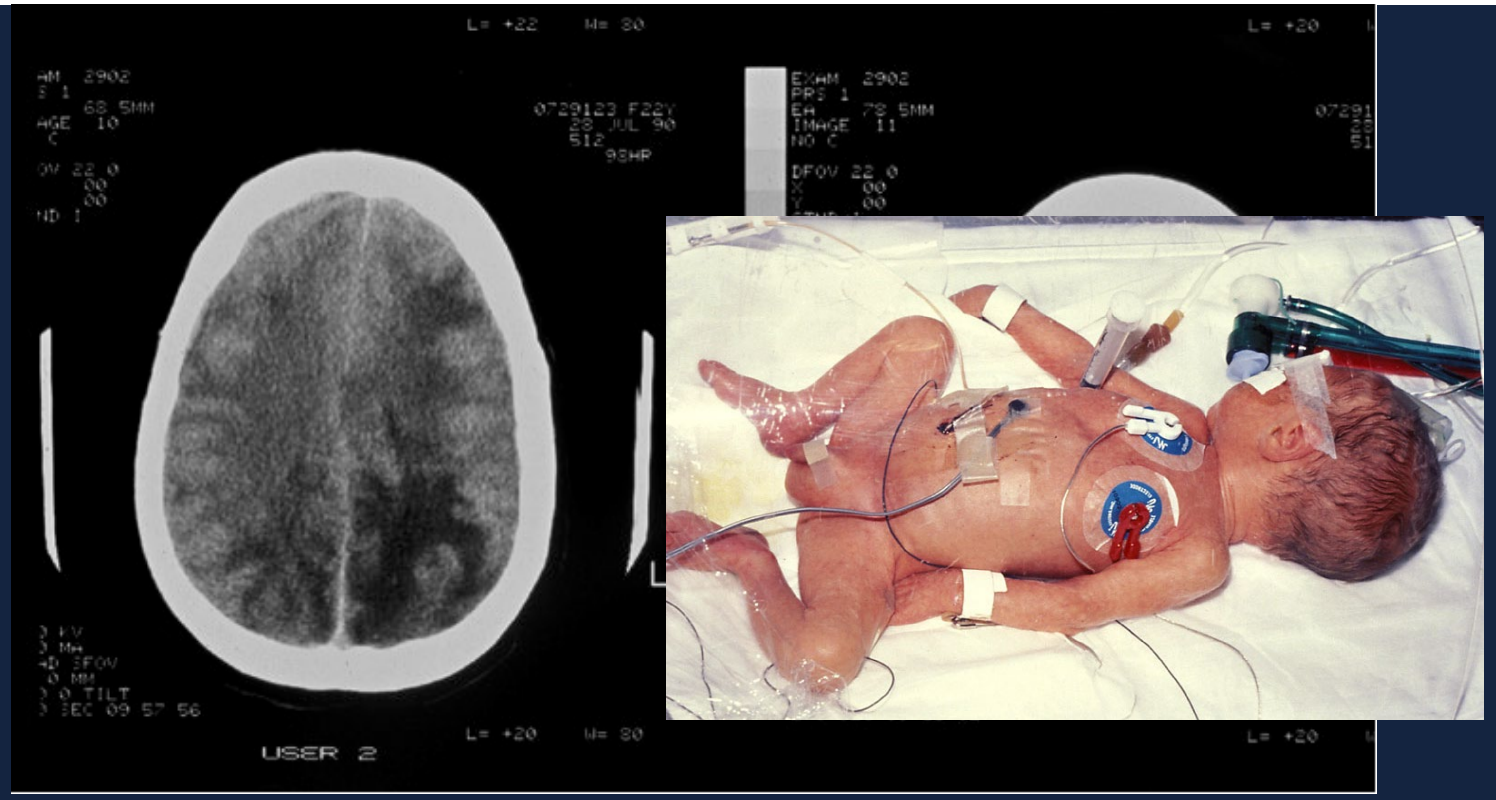
- To address the need for well-designed clinical trials in maternal fetal medicine, the NICHD established the MFMU Network in 1986

MFMU Network

- 12 University based academic medical centers
- ***ONLY*** federally funded obstetric clinical trials research network
- The MFMU Network conducts clinical studies to improve maternal, fetal and neonatal health with greatest priority given to randomized trials
- The aim is to:
  - **Reduce morbidity** to mom and baby, related to preterm birth, fetal growth abnormalities & maternal complications
  - **Address maternal mortality**
  - Provide rationale for evidence-based, cost-effective, obstetric practice

Pravastatin for the Prevention of Preeclampsia in High-Risk Women: A Pilot Study

Obstetric-Fetal Pharmacology Research Units (OPRU) Network
The National Institute of Child Health and Human Development



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Primary Research Question

- **What are the Pharmacokinetic properties and maternal and fetal safety profiles of pravastatin when used as a prophylactic daily treatment in pregnant women at high risk of preeclampsia?**

ClinicalTrials.gov

NCT01717586

opru
Obstetric-Fetal Pharmacology Research Units Network

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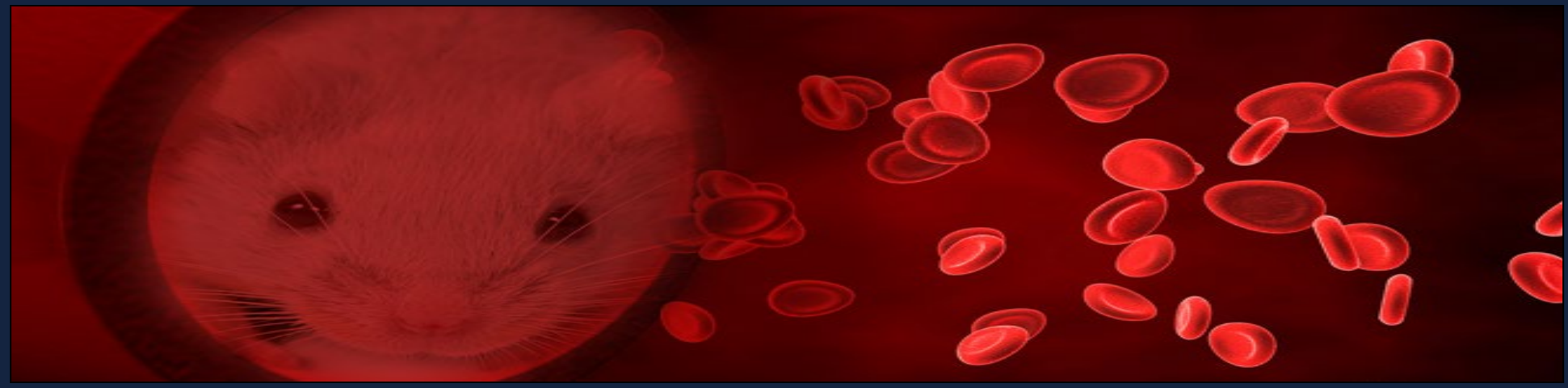
Results – Maternal Outcomes

	Placebo (N=10)	Pravastatin (N=10)
Preeclampsia	4 (40)	0
Mild	1	0
Severe features	3	0
GHTN	1	1
Highest BP mm Hg		
Systolic	152.4 ± 23.1	144.2 ± 18.4
Diastolic	96.8 ± 17.1	91.8 ± 16.1
GA at delivery, weeks	36.7 ± 2.1	37.7 ± 0.9
Indicated PTD < 37 wks	5 (50)	1 (10)
	RR 0.17, 95% CI (0.02-1.11)	
Length of hospital stay	4 [3 - 7]	3 [3 - 4]



A Randomized Controlled Trial of Pravastatin for the Prevention of Preeclampsia in High Risk Women

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

NIH National Heart, Lung, and Blood Institute

How the MFMU has changed lives

- The *Eunice Kennedy Shriver* NICHD is named after JFK's sister
- His first son, Patrick Bouvier, died of respiratory distress in 1963
  - He was 35 weeks

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antenatal Betamethasone for Women at Risk for Late Preterm Delivery

C. Gyamfi-Bannerman, E.A. Thom, S.C. Blackwell, A.T.N. Tita, U.M. Reddy, G.R. Saade, D.J. Rouse, D.S. McKenna, E.A.S. Clark, J.M. Thorp, Jr., E.K. Chien, A.M. Peaceman, R.S. Gibbs, G.K. Swamy, M.E. Norton, B.M. Casey, S.N. Caritis, J.E. Tolosa, Y. Sorokin, J.P. VanDorsten, and L. Jain, for the NICHD Maternal–Fetal Medicine Units Network*

Published April, 2016

Society for Maternal·Fetal Medicine

SMFM Statement

smfm.org

Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

A single course of betamethasone is recommended for pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.

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The importance of leveraging different study designs

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Top 3 Causes of Maternal Mortality

- Hemorrhage
- Preeclampsia
- Venous thromboembolism

1987

Top 3 Causes of Maternal Mortality

- Cardiovascular conditions
- Preeclampsia
- Venous thromboembolism

Top 3 Causes of Maternal Mortality

- Cardiovascular conditions
- Cardiomyopathy
- Venous thromboembolism

Top 3 Causes of Maternal Mortality

- Cardiovascular conditions
- Cardiomyopathy
- Sepsis

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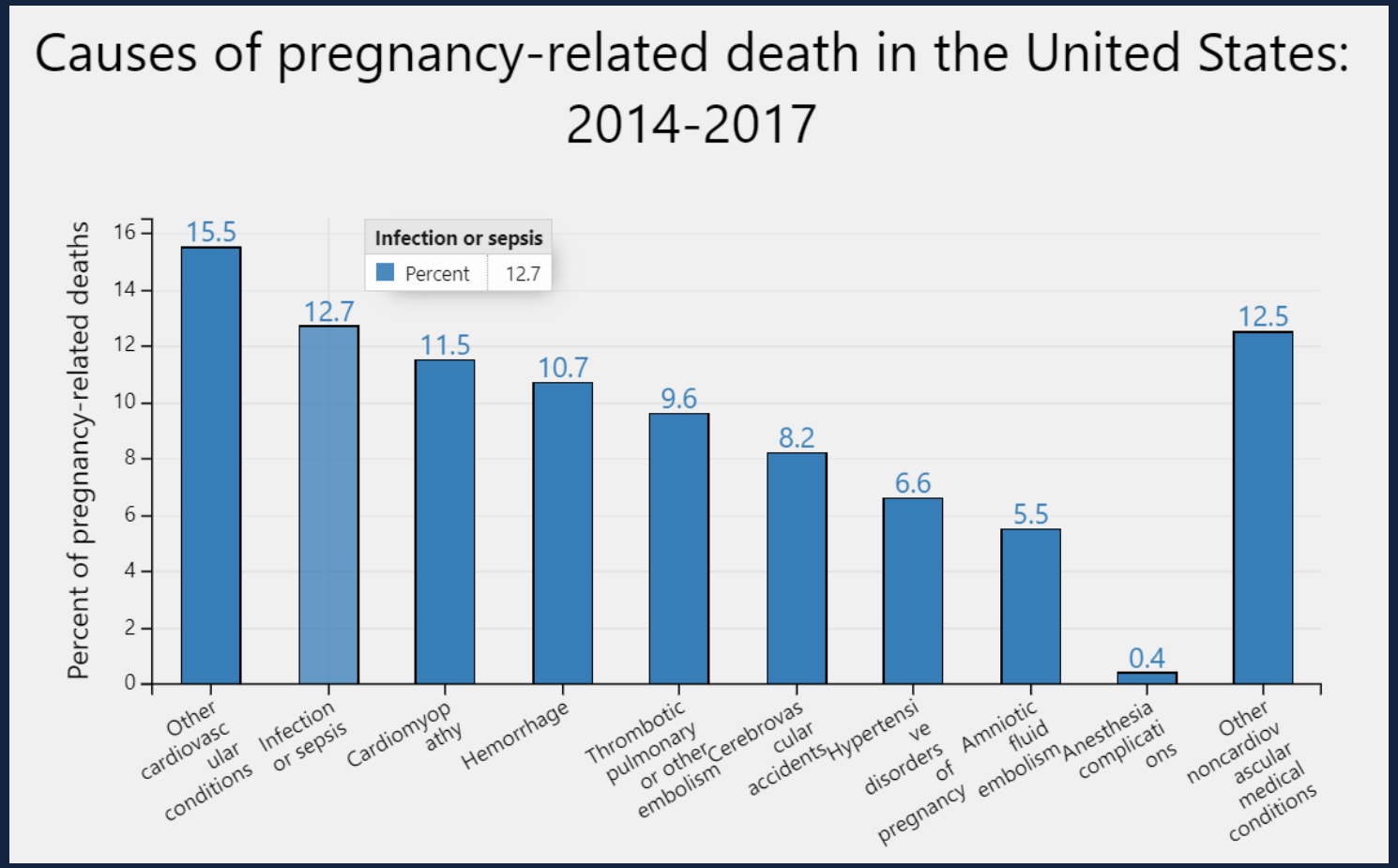
Pregnancy related deaths 2014-2017



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Pregnancy Complications in Nulliparous Women

Table 2 Frequency of perinatal outcomes according to maternal age group

Perinatal Outcomes	Total	Maternal Age Groups			*p*		
		< 35 years (a) (*n* = 471)	35–39 years (b) (*n* = 399)	≥40 years (c) (*n* = 87)	a vs.b	a vs. c	b vs. c
Gestational diabetes mellitus	101	27 (5.7)	57 (14.3)	15 (17.2)	< 0.001	< 0.001	0.041
Gestational hypertension	58	20 (4.2)	29 (7.2)	8 (9.2)	< 0.001	< 0.001	0.035
Pre-eclampsia	62	22 (4.6)	31 (7.7)	8 (9.2)	0.033	< 0.001	0.457
Ablatio placenta	7	2 (0.4)	4 (1.0)	1 (1.1)	0.073	0.051	0.865
Spontaneous preterm delivery before 34 weeks	83	39 (8.2)	36 (9.0)	7 (8.0)	0.469	0.754	0.601
Spontaneous late preterm delivery between 34 and 37 weeks of gestation	71	34 (7.2)	28 (7.0)	9 (10.3)	0.342	0.044	0.038
Prolonged rupture of membranes	41	21 (4.5)	16 (4.0)	4 (4.6)	0.780	0.913	0.612
Small for gestational age	80	21 (4.5)	48 (12.0)	11 (11.5)	< 0.001	< 0.001	0.560
Large for gestational age	21	7 (1.5)	12 (3.0)	2 (2.3)	0.072	0.134	0.411
Placenta previa	24	13 (2.8)	9 (2.2)	2 (2.3)	0.613	0.218	0.891
Post-term pregnancy	66	41 (8.7)	21 (5.3)	4 (4.6)	0.021	< 0.001	0.139
Operative vaginal delivery	16	9 (1.9)	6 (1.5)	1 (1.1)	0.451	0.112	0.207
Cesarean delivery	396	175 (37.1)	167 (41.8)	44 (50.5)	0.029	< 0.001	0.040

Data are presented as n (%)

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Gaps in current approach

- Developing centers with infrastructure to enroll pregnant women (of all risk levels) to answer pertinent research questions
- Levering EHRs to gather and analyze data on a general, large-scale population of pregnant individuals
- Identifying and addressing barriers to research in under-represented groups
- Leveraging implementation science to study proven interventions in groups where the outcomes can be improved

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Need Alternatives to Diversify Research Opportunities

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Opportunities: Maternal Morbidity and Mortality

- Continues to increase
- Single OB research network with limited funding
- Need more research networks focusing on pregnancy complications
  - MFMU: investigator initiated
  - Additional future research networks: RFA rapid response and study implementation
- Need infrastructure for nimble response to priority research areas

Opportunities: Clinical Research in Community Settings

Integrating Research into Community Practice — Toward Increased Diversity in Clinical Trials

Janet Woodcock, M.D., Richardae Araojo, Pharm.D., Twyla Thompson, Pharm.D., and Gary A. Puckrein, Ph.D.

Woodcock et al, NEJM, 10.2.2021

- Engaging community clinicians in research
  - Offering training, mentorship and access
- Levering these relationships to enroll a more diverse population in clinical trials
- “Lack of trial access is a particularly problematic barrier for both clinicians and patients.”

Opportunities: Expanding traditional mechanisms to allow for follow-up

- Traditional R01 funding for clinical trials provides 5 years to study a pregnancy intervention and outcomes related to that intervention
  - Does not allow for long-term infant follow-up
  - Does not allow for maternal follow-up, particularly beyond 6-weeks postpartum
- Need to study the life-course that is the continuum of pregnancy, postpartum, fetal programming, infant and childhood outcomes, subsequent pregnancy
  - Maintaining prospective cohorts
  - Incorporating detailed pregnancy questions into ongoing pediatric cohorts

Opportunities: Moving beyond the RCT

- Considering multilevel clinical trials
- Affect at least two levels of influence—for example, the patient and the health care provider
- Usually includes community input
- Economies of scale to study interventions on target population
- Cons: allow for interactions, makes interpretation of which intervention is leading to the effect more challenging

Opportunities: Including Pregnant People in non-Obstetric Clinical Trials

- Prototype: Exclusion of pregnant individual in the COVID trials
- September 29, 2021—CDC Urgent Health Advisory: recommending vaccination of pregnant people
  - 22 of 161 deaths from COVID in pregnancy occurred in August (13.7%)
- Chronic medical conditions and pre-existing conditions are related to maternal morbidity
- Interventions to mitigate chronic medical conditions are not studied in pregnant people

Opportunities: Inclusion in Clinical Trials

- NIH requires that women and underrepresented groups are included in clinical trials
- "women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, *unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate* with respect to the health of the subjects or the purpose of the research"
- Exclusion of women, children, gender, race must be justified
- **Exclusion of pregnancy needs no justification**

Opportunities: Studying non-obstetric interventions in pregnancy

- Once inclusion of pregnant people should be considered, non-pregnancy interventions would be studied in pregnancy
  - Behavioral interventions
  - Mental health
  - Technology
- Reduces the need to replicate findings in pregnant populations
- Is the ethically correct solution

Opportunities: Leveraging EHR data

- Pregnancy data generated copiously in the EHR
- Coordination of this effort at the national level
- Common variables; variable dictionary
- Epidemiologic data to identify morbidities, outcomes of newly introduced interventions, and implementation barriers
- Collect data on underrepresented groups and those less likely to be involved in clinical trials
  - Access and/or desire

Conclusions

- Numerous opportunities to study maternal morbidity and mortality
- Need to move beyond single clinical research network in obstetrics
- Need to allow for follow-up and life course evaluations in current time-limited mechanisms
- Need to leverage EHR data
- NEED to justify exclusion of pregnant people in ALL clinical trials

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