Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) Awardee Workshop

Executive Summary
February 15, 2022
Virtual

WELCOME AND OPENING REMARKS

Welcome and Overview
Janine Austin Clayton, M.D., FARVO, Director, Office of Research on Women's Health, NIH Maternal Mortality Task Force Co-Chair

Dr. Clayton welcomed the attendees. She noted that U.S. maternal mortality rates are rising, with homicide one of the leading causes of death during pregnancy and the postpartum period. Racial and ethnic minorities experience a disproportionately high percentage of pregnancy-related deaths. Addressing these health disparities will require integrative, multisystem research on the pre-pregnancy, pregnancy, and postpartum periods. This workshop highlights some of the fiscal year (FY) 2020 IMPROVE award recipients, who will share their preliminary results and identify gaps in maternal research.

Opening Remarks
Diana Bianchi, M.D., Director, NICHD, and NIH Maternal Mortality Task Force Co-Chair

Dr. Bianchi provided historical background, recalling that the congressional Black Maternal Health Caucus urged NIH to coordinate NIH-wide research to address health disparities in maternal health. This catalyzed the formation of the NIH Maternal Mortality Task Force, which provided the vision and impetus for IMPROVE. The success of the first IMPROVE research supplements in FY 2020 resulted in a doubling of the funding for FY 2021 to $13 million. The 22 new projects focus on the impact of COVID-19 on maternal health and the effect of structural racism and discrimination on maternal health outcomes in the context of COVID-19. The proposed FY 2022 congressional budget sets aside $30 million dollars for IMPROVE, which will permit non-supplemental funding.

CARDIOVASCULAR RISKS AND PREECLAMPSIA
Moderator
Gina S. Wei, M.D., M.P.H., National Heart, Lung, and Blood Institute (NHLBI), NIH

A Comorbidity-Based Screening Tool to Predict Severe Maternal Morbidity (SMM) at the Time of Delivery
Kathryn Johnson Gray, M.D., Ph.D., Harvard Medical School

This study aimed to enhance the obstetric comorbidity index (OB-CMI), a tool used to identify women at risk for SMM at delivery, by integrating it with data from the multi-ancestry LIFECODES pregnancy biobank. The enhanced OB-CMI was used to identify at-risk patients earlier in pregnancy, not waiting until delivery. Dr. Gray noted that changes that occur during pregnancy (particularly preeclampsia, gestational diabetes, and a body mass index [BMI] > 40) are important components for assessing at-risk patients. The investigators are also exploring how other sociodemographic factors (e.g., maternal race, ethnicity, insurance type, level of education, conception type) are related to the OB-CMI. Future research will look at whether genetic and biologic predictors of preeclampsia improve SMM risk predictions beyond the OB-CMI.

Severe Maternal Morbidity During Delivery Hospitalization Within an Integrated Healthcare System: Racial and Ethnic Disparities Related to Chronic Hypertension and Preeclampsia

Erica Pauline Gunderson, Ph.D., M.S., Kaiser Permanente Bernard J. Tyson School Of Medicine, Northern California Division of Research

This study evaluates the role of chronic hypertension (cHTN) and hypertensive disorders of pregnancy (HDP) in relation to SMM and racial and ethnic disparities, accounting for clinical, lifestyle, and social factors. Electronic health records (EHRs) from Kaiser Permanente Northern California were used to look at deliveries from 2009 to 2019 involving a singleton pregnancy (live or stillbirth) among women 18 to 45 years old with no serious disease. The two sub-cohorts in the analyses included women with prior cHTN (5.1%, *n* = 13,626) and a low-risk cohort composed of women with no cHTN and no history of preeclampsia (93.2%, *n* = 249,892). The study found that both cHTN and preeclampsia are related to higher risk of SMM during delivery hospitalization. Preeclampsia showed comparable high rates of SMM for groups with prior cHTN and without cHTN across all race and ethnicity groups. Native Hawaiian/Pacific Islander groups had the highest rates of SMM, followed by Black, Asian, and Hispanic groups, independent of age, obesity, smoking, and social factors. Identification and modification of SMM risk factors are crucial to eliminating maternal health disparities.

Neurovascular Unit Dysfunction in Women with Severe Preeclampsia

Eliza Miller, M.D., M.S, Columbia University

This study investigates preeclampsia as related to the maternal neurovascular unit, to address the predominance of devastating maternal hemorrhagic strokes that occur in the first 2 weeks postpartum. The investigators developed and piloted two clinical protocols to prevent neurological SMM and maternal mortality, including postpartum stroke. The first protocol, which assessed providers' knowledge about warning signs of neurological SMM and maternal morbidity (MM), showed that providers would benefit from more information. To address this, the investigators and their collaborators developed a Maternal Stroke Prevention and Treatment manual. The second protocol was to develop and pilot a near-infrared spectroscopy (NIRS)–based bedside monitoring device to identify impaired cerebral autoregulation in women admitted to the hospital with postpartum preeclampsia. The investigators built a portable NIRS-

based cerebral oximetry monitor to identify perfusion problems in the maternal brain by continuous noninvasive blood pressure monitoring. Testing of the device for feasibility and tolerability based on participant feedback is ongoing.

Preconception Contributors to Severe Maternal Morbidity in Black and White Women
Janet Catov, Ph.D., M.S., University of Pittsburgh

This study examined the pre-pregnancy antecedents to SMM events and the associated racial disparities. The hypothesis was that poor cardiovascular health (CVH) and adverse psychosocial stress before pregnancy contribute to SMM and racial disparities. The study used data from the NHLBI Coronary Artery Risk Development in Young Adults (CARDIA) study to look at 1,392 women (51% Black) with 2,372 post-enrollment births for up to 1 year post-delivery. SMM was characterized using the CARDIA study criteria, which included delivery records and self-reported hospitalizations up to 1 year post-delivery. CVH and stress before pregnancy were assessed, along with self-reported adverse pregnancy outcomes. The study found that better pre-pregnancy CVH was associated with reduced risk of SMM in Black but not White women. Rates of pre-pregnancy stressful life events were higher in Black women than in White women and appeared to have a stronger but not statistically different association with SMM risk. Poor pre-pregnancy CVH was associated with risk of SMM in Black women, and pre-pregnancy stress was also linked to SMM.

IDENTIFICATION AND PREVENTION OF MATERNAL MORBIDITY AND MORTALITY RISK
Moderator
Sarah Yoon, Ph.D., RN, National Institute of Nursing Research, NIH

Maternal Obesity and SARS-CoV-2: Maternal Blood and Fetal Placental Immune Response
Andrea Goldberg Edlow, M.D., M.Sc., Harvard Medical School

Pregnant individuals with COVID-19 have a significantly increased risk for SMM and mortality. Obesity also increases the risk of SMM, but the underlying mechanisms are unclear. This study examined the impact of maternal obesity on cellular responses to SARS-CoV-2 across a spectrum of disease severity in pregnancy. This study isolated peripheral blood mononuclear cells and plasma from 74 SARS-CoV-2–positive individuals (31 with obesity), 36 SARS-CoV-2–negative controls (20 with obesity), and 26 nonpregnant SARS-CoV-2–positive women of reproductive age (13 with obesity). Participants were recruited before vaccines were available, so all were unvaccinated. Cytokine expression was quantified for monocytes and T cells and in maternal plasma. To determine how maternal obesity alters the maternal cellular (monocyte and T-cell) response to SARS-CoV-2, the investigators hypothesized that maternal obesity primes T-cells and monocytes toward an inflammatory phenotype, resulting in increased pre-inflammatory cytokine production in the setting of SARS-CoV-2. They found an increased pro-inflammatory potential of CD4$^+$ and CD8$^+$ T-cells in pregnancy with obesity, a finding that may help elucidate the increased risk for SMM.

To determine how SARS-CoV-2 affects the fetal placental macrophage (Hofbauer cell) single-cell

transcriptome, the investigators hypothesized that even in the absence of placental infection, maternal SARS-CoV-2 infection alters the Hofbauer cell transcriptome. They found that COVID-19 was associated with a distinct fetal placental macrophage signature, with more than 1,400 differentially expressed genes in Hofbauer cells. The significant impact of maternal COVID-19 on fetal placental macrophages suggests fetal immune effects even in the absence of vertical transmission.

LINK MOMS: Addressing Maternal Morbidity and Mortality in Community Health Centers
Sadia Haider, M.D., M.P.H., Rush University, and Rachel Caskey, M.D., MAPP, University of Illinois at Chicago

Timely access to care could be a critical preventive measure for SMM and maternal mortality. This study uses a population-based approach to identify the clinical, social, economic, and behavioral factors associated with adverse outcomes for pregnant and postpartum people. The goal is to create a LINK MOMS registry to identify at-risk people and facilitate earlier access to care. The Health Catalyst Population Builder EHR-based platform was used to identify patients meeting the criteria for specific conditions that could result in poor maternal health outcomes. Some of the key variables for identifying people at risk for SMM and maternal mortality were gestational diabetes, depression, multiple gestations, smoking, maternal age, domestic violence, and hypertension. Nearly 3,000 patients have been identified as being positive for at least one variable and have been included in the registry. Validation of the registry's accuracy in identifying at-risk people is in progress. The registry will be tested in community heath centers and the findings used to facilitate successful implementation in clinical care settings.

Is Maternal Risk-Appropriate Care Associated with Decreased Severe Maternal Morbidity for Abnormal Placentation? Preliminary Results of a Mixed Methods Study
Kimberly Gregory, M.D., M.P.H., Cedars-Sinai Department of Obstetrics and Gynecology

Placental disorders contribute significantly to maternal morbidity and mortality. This study aimed to identify the policies and procedures in place at high-volume "accreta centers of excellence" (i.e., ≥ 6 placenta accreta cases per year) in California over a 2-year period to determine the protocols, services, and procedures routinely used, as recommended in the literature for centers of excellence. Structured interviews with the chief of obstetrics or a named designee were conducted at 20 out of 29 of the hospitals, all of which had a higher proportion of patients with abnormal placental disorders and higher rates of SMM than other California hospitals did. The investigators found consistency across hospitals in the use of multidisciplinary teams, arterial lines, massive transfusion protocols, and a designated surgical team. There was little consistency in the disciplines represented on the multidisciplinary teams and in the use of magnetic resonance imaging, central lines, ureteral stents, cystoscopy, interventional radiology, preoperative plans for going directly to a cesarean hysterectomy, or formal debriefing after the procedure. The number of physicians on the accreta teams ranged from 1 to 15. The investigators concluded that given the contribution of placental disorders and hemorrhage to SMM, more detailed information is needed to determine which policies and procedures should be universal for optimum outcomes across all sites. Dr. Gregory suggested

stratifying hospitals by policies and procedures and evaluating maternal SMM outcomes both by including and excluding hysterectomy and transfusions. Excluding hysterectomy and transfusions would likely provide a better metric of SMM for abnormal placental conditions.

STRUCTURAL AND SYSTEMATIC CONTRIBUTORS TO MATERNAL MORBIDITY AND MORTALITY

Moderator
Jennifer Alvidrez, Ph.D., Office of Disease Prevention, NIH

Affordable Care Act (ACA) Medicaid Expansion and Maternal Morbidity
Pinka Chatterji, Ph.D., the University at Albany

U.S. SMM rates have been rising in recent years. There is growing evidence that preconception health is an important factor in determining pregnancy and childbirth outcomes. In 2014, Medicaid income thresholds were expanded to include more low-income adults, including those without minor children. Expansions were adopted by a majority of states. This study looked at whether Medicaid expansion was associated with maternal health outcomes and behaviors among women ages 21 to 55 and whether there were differential effects based on maternal age, particularly for older mothers (≥ 35 years old), who are at an elevated risk for maternal morbidity and mortality. Data were gathered from birth certificates and state-level SMM rates. The investigators found that after Medicaid expansion, there was a significant increase in identified health problems before and during pregnancy in mothers in the expansion states in 2014 and 2015, but these numbers declined from 2016 to 2018. Medicaid expansion also appeared to be associated with an increase in health problems during delivery for both younger and older mothers, but these levels remained high for older mothers while decreasing over the years for younger mothers. No effects of Medicaid expansion were seen on state SMM levels, and the study did not find consistent effects of the Medicaid expansions on maternal health behaviors, including the use of prenatal care.

Mitigating the Impact of Implicit Bias on Maternal Morbidity and Mortality for African American Women
Gwendolyn Norman, Ph.D., M.P.H., Wayne State University, and Sarah Blake, Ph.D., M.A., Emory University

Healthcare providers' attitudes and behaviors have been identified as factors that contribute to health disparities. Unrecognized bias against racial and ethnic minorities might significantly affect communication and receipt of care, particularly as related to patient–provider interactions, provider treatment decisions, patients' adherence to treatment, and health outcomes. This research is a collaborative effort between Environmental influences on Child Health Outcomes (ECHO) cohorts in Detroit, Michigan, and Atlanta, Georgia, to interview African American women and their healthcare providers to identify barriers and facilitators to equitable and respectful delivery and postpartum care for Black women, then to develop strategies for a culture of respectful care and cultural humility for building patient trust, increasing meaningful provider communication, thereby reducing disparities in adverse maternal outcomes. Preliminary interview results indicate that providers both recognize that

Black women experience stress due to racism and acknowledge that implicit bias might play a role in their care of Black patients. The data will be used to develop a toolkit of specific strategies for mothers to use to counter negative interactions and obtain patient-centered, respectful care.

A Public Health Exposome Approach to Maternal Mortality
Emily Harville, Ph.D., Tulane University School of Public Health and Tropical Medicine

As part of a parent grant to identify social contexts (e.g., structural racism, violence, income inequality) that increase risk for pregnancy-related mortality (PRM) and pregnancy-associated homicide, this study aimed to develop models incorporating individual- and environment-level predictors of maternal mortality for the United States as a whole and in Louisiana specifically, using an exposome-wide computational approach. The investigators extracted relevant variables from five domains of the Public Health Exposome (PHE): social, health and healthcare, policy (e.g., government programs), natural (e.g., climate, weather), and built (e.g., land use, transportation). They hypothesized that exposure to all these domains over time affects the risk of death during pregnancy and the postpartum period and that differential exposures to this exposome produce maternal population health inequities. The PHE variables found to be direct upstream predictors of maternal mortality rates at the county level were overall years of potential life lost, lack of physical activity, and extreme heat (i.e., heat index of 105°F). Other indicators of PRM were poverty, smoking, and inadequate access to food. The study concluded that contextual factors, such as poverty, that predict general health also predict maternal mortality and that maternal mortality correlates with overall population health and disability. These are not separate issues.

Understanding Maternal Vitamin D Deficiency in Rural Pregnant Women in South Carolina
Carol L. Wagner, M.D., Medical University of South Carolina

Underrepresented minorities, including African Americans, are at greatest risk of vitamin D deficiency and have the highest risk of maternal complications. Several studies suggest that vitamin D supplementation started early in pregnancy and sustained throughout reduces the risk of preeclampsia, preterm birth, gestational diabetes, and Cesarean section. This study was designed to better understand maternal and healthcare professionals' attitudes and beliefs about vitamin D deficiency during pregnancy in rural South Carolina. The investigators used EHRs to track baseline vitamin D deficiency in 822 pregnant women, most of them African American, to document the severity of the problem, rates of treatment, and pregnancy outcomes. The investigators found that 11% of the infants were preterm (i.e., born before 37 weeks). Vitamin D status was measured in only 8.4% of the women; of that group, 57% met the criterion for deficiency. In this cohort of very at-risk women, only 9.1% were prescribed vitamin D supplementation. Patients who were interviewed were unaware of the deficiency and of the link between vitamin D deficiency and adverse pregnancy outcomes. Physicians cited conflicting data about when to prescribe vitamin D and noted patients' lack of compliance even with taking prenatal vitamins. Access to care was also a factor: Less than 50% of the women had access to perinatal services within a 30-mile drive of their homes, and more than 10% had to

drive 100 miles or more for care. Education for both patients and providers about vitamin D supplementation is needed.

Medicaid Expansion and Postpartum Health
Claire E. Margerison, Ph.D., M.P.H., Michigan State University

In 2014, the ACA allowed states to expand Medicaid to all adults with incomes below 138% of the federal poverty level. Thirty-eight states and the District of Columbia have since enacted Medicaid expansion. This study examined the impact of Medicaid expansion on postpartum insurance coverage, mental health, and pregnancy-associated mortality. The study used two datasets: the Pregnancy Risk Assessment Monitoring System (PRAMS) to obtain self-reported Medicare coverage and postpartum depressive symptoms, and U.S. vital statistics data (i.e., death certificates), to assess pregnancy-associated mortality. Although Medicaid expansion likely increased Medicaid coverage in the postpartum period, the investigators found that there was no impact of Medicaid expansion on postpartum depressive symptoms and no statistically significant associations between Medicaid expansion and pregnancy-associated mortality during pregnancy, within 42 days postpartum, or in the later postpartum period. There was also no significant impact of Medicaid expansion on rates of pregnancy-associated mortality among Hispanic, non-Hispanic Black, or non-Hispanic White people. Medicaid expansion did appear to be associated with a reduction in pregnancy-associated mortality among non-Hispanic Black patients, a finding that requires further study. The investigators concluded that insurance coverage alone is likely necessary but insufficient to reduce racial and ethnic disparities in postpartum morbidity or mortality.

MENTAL AND BEHAVIORAL HEALTH

Moderator
Lauren Hill, Ph.D., National Institute of Mental Health, NIH

Severe Maternal Morbidity (SMM) in Commercially Insured Individuals
Kara Zivin, Ph.D., M.S., M.A., M.F.A., University of Michigan

The study focused on SMM in all delivering women who were continuously enrolled 1 year before and 1 year after delivery. The investigators compared delivery-related early and late postpartum SMM among individuals in the United States with commercial insurance from 2016 to 2017. Blood transfusions were separated from other forms of maternal morbidity in the analysis because of the prevalence of SMM related to blood transfusions. The researchers found that the leading causes of SMM during delivery were blood transfusion, hysterectomy, eclampsia, heart failure or arrest, and acute kidney failure. In the periods from discharge to 42 days postpartum and from 43 days to 365 days postpartum, additional causes of SMM included sepsis and adult respiratory distress syndrome. The investigators also compared SMM with and without blood transfusions across these same time periods, broken out by race and ethnicity (i.e., White, Asian, Black, Hispanic, unknown) and by the presence of perinatal mood and anxiety disorders (PMADs). Black individuals had the highest rates of SMM and PMADs across all three periods, both with or without the inclusion of blood transfusion data.

Leveraging Technology to Improve Screening, Brief Intervention, and Referral to Treatment (SBIRT) for Pregnant and Postpartum Persons
Constance Guille, M.D., Medical University of South Carolina

One in five women will experience maternal mental health and substance use problems during pregnancy and after delivery. The U.S. Maternal Mortality Review Committees reported that one in nine maternal deaths are due to mental health conditions and that 100% of these deaths are preventable. Although professional organizations recommend screening pregnant and postpartum women for mental health, doing a brief intervention, then referring them to treatment (i.e., the SBIRT model), nationally only one in eight women will be screened, and Black people are less likely to be screened or access treatment than White people. This study, called Listening to Women (LTW), was designed to leverage technology to overcome barriers to SBIRT. Women who came in for prenatal care were monitored for anxiety, substance use, and intimate partner violence by replying to questions using phone text messaging, either in the office or at home. Women who screened positive for these problems were contacted by a remote care coordinator who provided a brief intervention by devising a plan for addressing the woman's social and mental health needs and helping her get into treatment. The LTW system, which was piloted in a large obstetrics practice, compared women enrolled in LTW with standard of care (i.e., in-person SBIRT) and found that those enrolled in LTW were 1.5 times more likely to be referred to treatment and five times more likely to go into treatment. Black women were less likely than White women to screen positive for anxiety with LTW screening than with in-person screening. However, Black women were significantly less likely to make it to treatment with in-person screening, in contrast with LTW screening. During post-study interviews conducted with predominantly Black women who had used LTW, respondents said that LTW was user-friendly and not time-consuming. They were comfortable with the text method, especially when assured of confidentiality. They liked being able to express themselves in private, without being seen or judged in person, and appreciated the convenience of being contacted by a care coordinator to help them navigate complex mental healthcare services. Future modifications to LTW will include emphasizing the system's privacy, instituting more patient–provider concurrence in terms of race, and addressing the areas of stigma and distrust that are barriers to receiving care.

Postpartum Opioid-Related Mortality in Medicaid Patients
Elizabeth Suarez, Ph.D., Harvard Medical School

Opioid overdose accounts for up to 10% of pregnancy-associated deaths. Women with opioid use disorders (OUDs) may also be particularly vulnerable to other causes of death in the postpartum period. These deaths have not been well characterized. This study sought to describe the timing and risk factors for postpartum maternal deaths (between delivery and 1 year postpartum) attributable to opioid overdose and to describe the timing and causes of postpartum maternal deaths unrelated to overdose in women with OUDs. Data were obtained from the Medicaid Analytic eXtract (MAX) from 2006 to 2013 and the National Death Index (NDI) from 2007 to 2013. The linked MAX-NDI data identified 1,393 pregnancies with death from delivery to 1 year postpartum (102 women with OUDs) and 4,970,668 pregnancies

without death (48,800 women with OUD)s. In looking at all pregnant women, White pregnant women were found to be at highest risk for opioid overdose death. Other risk factors included maternal morbidity (e.g., obstetric, mental health), substance use disorders other than those involving opioids, opioid dispensing during pregnancy and in the postpartum period, numerous emergency department visits, and high postpartum use of healthcare. Risk factors for pregnant women with OUDs were similar, with the exception of maternal morbidity, which was not strongly associated. There was a strong predictive negative association of the use of opioid agonist therapy (OAT) in pregnancy and postpartum, with fewer deaths among those receiving treatment with buprenorphine and methadone. The study showed that the incidence of death in the year following delivery is 6 times higher in women with OUDs than in women in the general population, regardless of cause. OAT was strongly associated with a decreased risk of opioid overdose death. The fact that women who died of opioid overdoses had frequent contact with the healthcare system between delivery and death suggests potential avenues of intervention.

CONCLUSION AND THANKS
Courtney F. Aklin, Ph.D., Acting Associate Deputy Director, NIH, and NIH Maternal Mortality Task Force Co-Chair

Dr. Aklin said this workshop should serve as an urgent reminder about the importance of IMPROVE and how much work remains to be done. Healthcare providers will benefit from a better understanding of how to look for signs of distress in their patients, and everyone must look for new targets for research, including the role of healthcare coverage at the local and national level and the promise of new digital technologies. Significantly reducing maternal deaths, particularly among Black and American Indian/Alaska Native women, is one of the aspirational goals for the NIH strategic plan for 2021–2025. The Maternal Mortality Task Force will continue to play a leadership role in encouraging research on maternal health and maternal health disparities.

Drs. Aklin, Clayton, and Bianchi thanked the awardees, task force members, attendees, and staff for an incredible workshop that provided a strong platform for expanding the effort.