

Impact of Comorbid COVID-19 and Substance Use During Pregnancy on Fetal and Infant Development Workshop

National Institute on Drug Abuse (NIDA) Brain Development Research Consortium

Virtual Meeting
Wednesday, July 20, 2022
10:00 a.m.–5:00 p.m. EDT

Background

The short- and potentially long-term effects of the COVID-19 pandemic cannot be overstated. Numerous underlying medical conditions, including pregnancy and recent pregnancy (defined as at least 42 days following the end of pregnancy), are associated with worse outcomes for those infected with SARS-CoV-2. In the short-term, SARS-CoV-2 infection among pregnant individuals increases their risk for severe illness leading to hospitalization, caesarean birth, and death. It also increases the risk for stillbirth, preterm birth, and poor fetal outcomes. The long-term impact of COVID-19 illness during and following recent pregnancy is still being determined. However, recent studies point to potential effects on neurodevelopment. Although efficacious vaccines have been developed that at the very least lessen severity for most individuals, vaccine hesitancy among pregnant individuals has been particularly high.

In addition to concerns about maternal COVID-19 illness, simply becoming pregnant and delivering during the pandemic is having a profound impact on families and their children. Social distancing, fears of children or personally becoming infected, economic burden, daycare and school closures are all examples of pandemic stressors that many have experienced and continue to endure. Moreover, for pregnant individuals, restrictions have meant changes to typical prenatal care as well as less real or perceived support during prenatal visits, delivery, and post-delivery. These factors have made pregnancy during the pandemic much different and arguably more stressful for most individuals compared to the pre-pandemic period. Data on maternal health during pregnancy and the neurodevelopment of infants born during the pandemic is emerging. Importantly, the reproducibility, persistence, and clinical meaningfulness of observed neurodevelopmental effects are to be determined.

Finally, the COVID-19 pandemic is occurring at a time when our nation is still grappling with the overlapping epidemic of opioid and other substance use disorders (SUD). Given these unique pandemic-related stressors, there are concerns that substance use may increase among pregnant individuals. Substance use during pregnancy is associated with poor outcomes for infants including miscarriage, preterm birth, and low birthweight. Fetal exposure to opioids, other substances, and alcohol can result in neonatal opioid withdrawal syndrome (NOWS), neonatal abstinence syndrome, and fetal alcohol spectrum disorders, respectively. Although research on substance use in pregnant individuals during the pandemic is ongoing, there is some evidence that substance use has increased among this population. Thus, the concern that

the pandemic may be exacerbating substance use among pregnant individuals is a major public health concern that could have a lasting impact on children born during the pandemic and exposed *in utero* to substances. The pandemic's short- and long-term effects on pregnant individuals merit continued attention. It will be important to assess whether the effects of COVID-19 infections, decreased social support, increased pandemic-related stress, worsened maternal mental health, and a possible increase in substance use on the COVID-19 generation are long lasting.

Virtual Meeting Description

On July 20, 2022, the NIDA Brain Development Research Consortium convened researchers and clinicians with expertise in SUD among pregnant women, fetal development, neonatology, maternal health, and pediatrics. The workshop aimed to review the state of the science in COVID-19 and substance use during pregnancy and their effects on fetal and infant development—with attention to research gaps and opportunities. The keynote address described gene-environment interactions that influence brain development and set the stage for four subsequent sessions and flash presentations. Presenters and panelists discussed the effects of COVID-19 infection (with attention to specific variants) on the developing fetus, pandemic stress on maternal health, and comorbid COVID-19 infection and/or pandemic stress and substance use on fetal outcomes and neurodevelopment. The pandemic has required clinicians to change care delivery and applied researchers to alter how they conduct their studies with human participants, which may offer lessons for future work. Presenters discussed innovations in remote data collection and telehealth born out of the pandemic.

Welcome and Introduction

Michelle Freund, Ph.D., Director, HEALthy Brain and Child Development Study (HBCD), Division of Extramural Research, NIDA

Dr. Freund welcomed participants to the meeting. She thanked speakers, panelists, and attendees, and expressed gratitude to Jessica McKlveen, Ph.D., and Da-Yu Wu, Ph.D., who organized the meeting.

Opening Remarks

Getting the Whole Picture About COVID-19

Janine Austin Clayton, M.D., FARVO, Director, Office of Research on Women's Health (ORWH), National Institutes of Health (NIH)

Dr. Clayton asserted that when it comes to sex and gender differences, what you do not know can hurt you. Many things—such as crash test dummies—are designed based on male bodies, leading to different patterns of injuries in women and men. Space suits were also designed for men. Health conditions can change in important ways over the life course of women (e.g., during pregnancy), yet this is often overlooked in research. Some medications only work in one

sex (e.g., some irritable bowel syndrome pharmacotherapies are effective in women but not men). Therefore, sex differences must be considered for all health-related issues.

Researchers have found that male immune pathways may elicit more severe immune responses, including in COVID-19. For example, autoantibodies against type 1 interferons underlie life-threatening COVID-19. The majority (94 percent) of patients with these antibodies were men. Studies suggest that men's poorer COVID-19 outcomes are related to sex differences in immune responses. For example, men with COVID-19 had higher levels of proinflammatory innate immune chemokines and cytokines than women. In contrast, women mounted more robust T cell activation during infection with SARS-CoV-2. Elevated levels of innate immune cytokines were associated with worse disease progression among women but not men. Findings of distinct mechanisms of COVID-19 disease progression between men and women provides a potential basis for sex-dependent approaches to prognosis, prevention, care, and therapy.

Pregnancy is a stress test that has lifelong effects. For example, women who experience preeclampsia (i.e., a severe hypertensive disorder of pregnancy) are at greater risk for hypertension and cardiovascular disease later in life. Social determinants of health—the conditions in the places where people live, learn, work, and play that affect a wide range of health and quality-of-life-risks and outcomes—influence maternal morbidity and mortality (MMM). In the United States, MMM has been increasing for the past 20 years. Prior to the COVID-19 pandemic, the United States had the highest rates of MMM among well-off countries. The pandemic highlighted preexisting disparities in MMM among women of color—particularly Black and American Indian/Alaska Native women. These disparities are related to access and quality of health care. Disparities in COVID-19 outcomes also occur among these populations, and although they were initially attributed to race, experts highlight the influence of social structure and environmental determinants of health. Race and ethnic group are more appropriately viewed as social constructs rather than medical risk factors.

Pregnant women (particularly women of color) infected with SARS-CoV-2 are more likely to be hospitalized, admitted to intensive care units (ICU) and intubated, receive oxygenation, and die. They are at higher risk of thrombotic events, preterm birth, and preeclampsia. Dr. Clayton emphasized that the MMM and COVID-19 crises present an opportunity to tackle intransigent disparities in maternal health. Applying a sex and gender lens is key to understanding COVID-19 and translating that knowledge into interventions. Such an approach is key to understanding transmissibility and pathogenicity, pathology, and predisposition to developing long COVID-19. Long COVID-19 (also called post-acute sequelae of COVID-19) is a condition marked by the continuation of symptoms—or the emergence of new ones—after recovery from acute COVID-19 illness. It will create opportunities for intervention and improve research in ways that will help account for future variants and vaccines, and enhance the efficacy of therapeutics.

Pandemic stress affects maternal health and child neurodevelopment. Becoming pregnant and delivering during the pandemic has a profound effect on families. Pandemic stressors include social distancing, fears of infection, economic burden, and daycare and school closures.

Additionally, pregnant women faced pandemic-related changes to prenatal care, and less support (real or perceived) during prenatal visits, delivery, and post-delivery. Importantly, health-related socioeconomic risks (HRSR)—such as food insecurity, housing instability, interpersonal violence, and difficulties with utilities and transportation—are linked with high rates of negative mental health outcomes. More than 40 percent of women had one or more pre-pandemic HRSR, and about half of women experienced incident or worsening HRSRs during the pandemic. The odds of negative mental health outcomes were two to three times higher among women with at least one incident or worsening HRSR. It will be important to apply lessons from the current and previous pandemics to understand how individuals with the least resources are affected. Dr. Clayton noted that, moving forward, the field needs more COVID-19 clinical trials that disaggregate results by sex. More research is needed on female-specific consequences of SARS-CoV-2 infection on pregnancy and immune system functioning.

Dr. Clayton thanked NIDA for its long-standing support for ORWH programs, such as the Specialized Centers of Research Excellence on Sex Differences and the Understudied, Underrepresented, and Underreported Administrative Supplements. NIDA has integrated the elucidation of sex/gender differences in the risk factors associated with SUD, its consequences, and treatment response in its mission. Sex and gender are also embedded in the HBCD Study and the Adolescent Brain Cognitive Development Study.

Remarks From NIDA's Director

Nora D. Volkow, M.D., Director, NIDA

Dr. Volkow commented that the world has changed dramatically. The COVID-19 pandemic continues, as the virus is mutating in unpredictable ways, accompanied by changes in society that affect everyone. However, some individuals have been more affected than others—especially those living in adverse socioeconomic environments. Pregnant and postpartum women can be among the most vulnerable individuals. Those who use drugs are often neglected despite the detrimental consequences for them and newborns. Stress increases drug taking and risk of relapse, including among women experiencing pandemic-related stressors. Homelessness increased during pandemic, with pregnant women at risk for this adverse situation, which elevates the likelihood of infection and COVID-19 illness. SARS-CoV-2 can be transmitted through the placenta to the fetus, although this is rare. Pregnant individuals who produce a strong immune response are more likely to experience long COVID, which also negatively affects the fetus.

Based on data from the 1918 influenza pandemic, scientists know that higher rates of psychiatric conditions (e.g., schizophrenia) occurred among the children of women who were infected during pregnancy. Maternal immune responses play a role in the manifestation of psychiatric disorders, including SUD, among these children. Strong immune responses damage multiple organs, including the brain. NIH-supported researchers aim to study the influence of maternal immune responses to SARS-CoV-2 in the HBCD Study. Long COVID is associated with vascular damage and other negative health consequences among women and likely the fetus (as the placenta is highly vascular). This is an important area of study.

Studies also report that children of women experiencing stress during the pandemic showed delayed development of white matter tracts in their brains. Researchers need tools to understand the mechanisms whereby social determinants of health negatively affect biological outcomes. Such effects seem to be cumulative, highlighting the importance of early intervention to prevent disadvantages among neonates of women who had COVID-19 during pregnancy. Collaboration and data sharing will be essential for advancing equitable research in this area.

Keynote Address

Gene-Environment Interactions Influence Brain Development: Endogenous-Exogenous Factors Across Developmental Time

Mark Scher, M.D., Emeritus Professor, Pediatrics and Neurology, Case Western Reserve University, University Hospitals Cleveland Medical Center, Rainbow Babies and Children's Hospital

Dr. Scher presented historical perspectives from-past NIH research projects that are relevant to the HBCD Study. The National Collaborative Perinatal Project (NCPP)—which studied 60,000 pregnancies and 58,000 children through age 8 years between 1959 and 1965—provided trimester-specific details of the mother-placenta-fetus (MPF) triad. This project facilitated the development of neonatology and maternal-fetal medicine, and contributed to the reduction in U.S. rates of maternal and infant mortality (which were high after the end of World War II). Lessons learned from the NCPP include that research in this area is expensive, longitudinal follow-up is difficult, interdisciplinary efforts are challenging, and societal conditions will change. The Maternal Health Practices and Child Development Studies conducted during the 1980s combined biological and behavioral teratology. These studies examined the effects of *in utero* exposure to alcohol, marijuana, and tobacco with 22 years of follow-up, such that intergenerational effects were determined. The forthcoming HBCD Study will compare the effects of exposure to opioids with other substances, as well as examine the changing societal influences affecting health and quality of life (e.g., COVID-19 pandemic). This important project will also study neurotherapeutics that combine preventive, rescue, and reparative strategies.

There are many endogenous and exogenous factors relevant to the COVID-19 pandemic and ongoing opioid crisis that influence the MPF triad. Maternal adaptation is seen before, during, and after pregnancy, as well as between pregnancies. Women adapt differently with each pregnancy to maintain the well-being of the MPF triad. Dr. Scher noted that the fetus is a semi-allogenic organism. He also stressed the importance of girls' reproductive health to later pregnancy. Between pregnancies, health must remain optimal to prepare the mother for the next pregnancy. Focusing on maternal health during all trimesters—including the three postpartum months—is crucial. Research is needed on the health of women (and disparities among different subgroups) across the life course, including beyond reproductive ages.

A dual approach to clinical decision-making maximizes accuracy and minimizes cognitive bias among practitioners. This approach can be applied to clinical care, medical education, and research. The first component is a horizontal approach, which looks at form and function (phenotype) across developmental time. The first thousand days—from conception to the second birthday—are crucial for neurodevelopment, as 80 percent of neuronal connectivity is laid down (and will go on to be permanent) during this period. The MPF triad plays a central role, of course. The second component is the vertical approach, which considers genetic influences through multiple system interactions during each developmental niche. Genetic networks interact with molecular, cellular, tissue, organ, and systems biology. The MPF triad also plays a central role here. Because biological systems are complex, women's health before, during, and after pregnancy and throughout life must be considered. The health of a girl will affect her reproductive system, any subsequent pregnancies and fetal brain development, and her health in later life.

Placental development and function are essential to the MPF triad. Placental changes (e.g., in its oxygen levels) across the three trimesters contribute to brain development. The placenta has many functions—including delivering oxygen and nutrition to the fetus, maternal-fetal signaling, waste removal, neurotransmitter synthesis, and inflammatory mediator production—and its health affects those of the mother and fetus. The balance of factors promotes a healthy or malformed fetal brain. Myriad environmental factors influence placental health, but this is highly complex to study. Endogenous factors include gene-environment influences on organ-specific outcomes across developmental time. Exogenous factors include environmental influences such as socioeconomic status, health care, pollutants, and legal and illicit substances.

Additionally, each pregnancy carries the risk of disease (pathogenic and nonpathogenic), which also affects fetal neurodevelopment and gene-environment interactions. Maternal immune activation (MIA) affects multiple systems and predates notochord formation. MIA's effects on neuronal precursor cell populations occurs within transient brain structures—with consequences to developing brain circuitries—and through multiple pathologic mechanisms. Ischemic placental disease during the second half of pregnancy also has negative effects on neurodevelopment and alters innate immune responses. Fetal inflammatory responses are complex, with multiple subtypes, and affect all organs (including the brain) and the immune system. Gene-environment interactions influence the MPF triad and child through shared placental genetic endowment between parents and the fetus and epigenetic effects. These interactions influence resilience and postnatally, may affect neonatal and childhood illnesses and expressions of neurological disorders. Many fetuses will be affected by multiple negative factors across developmental time, increasing their vulnerability for poorer brain health outcomes (e.g., schizophrenia and attention-deficit hyperactivity disorder).

The first half of pregnancy is particularly important in embryonic-fetal brain development, as this is the time when early transient neuronal structures (e.g., neural tube) and populations of neurons and glia are forming. If these structures and cell populations are abnormal from the mother's disease process transmitted through the placenta, neural migration and connectivity problems will occur. This includes the balance between excitatory and inhibitory elements of

the brain, which is a crucial influence on brain diseases expressed in childhood. Both exogenous and endogenous factors come into play. During the second half of pregnancy, the development of other fetal brain structures (e.g., the subplate zone, cortical plate, and cerebellar/hindbrain) predominates. At this time, the developing brain is sensory expectant and responds to both positive and negative environmental factors.

Postnatally, sensory input becomes emotionally mediated during the first 2 years of life. Genetic, epigenetic, environmental, sensory, and social inputs continue to affect the brain growth and development—with biological factors mediating and moderating physical and mental health outcomes. Time (e.g., critical or sensitive periods and timed neural plasticity) plays a crucial role. Important environmental factors include adverse childhood experiences (ACEs), poverty, racism, violence, access to resources, and responsive caregiving. Genetic and epigenetic susceptibility and fetal programming affect the response to stressors during early life and influence allostatic processes (e.g., neuroendocrine stress responsiveness, immune system, and sleep and circadian rhythms). Further influences on individual equilibrium include health behaviors and coping mechanisms, social support, and aging—with interactions occurring between adaptation and maladaptation processes.

Life course science and an interdisciplinary approach are required to understand these complex relationships and develop preventive strategies to improve public health. Dr. Scher concluded by commenting that NIH has developed a wealth of information across its Institutes, Centers, and Offices, which can facilitate an interdisciplinary approach to clinical decision-making, the education of biomedical scientists and clinicians, and research collaborations. Additionally, the field increasingly understands that transgenerational effects are crucial to human development and health (as shown by the opioid crisis).

Session One: Impact of COVID Infection on the Developing Fetus

Known and Putative Impacts of Maternal SARS-CoV-2 Infection on the Placenta and Developing Fetus

Andrea Edlow, M.D., M.Sc., Division of Maternal-Fetal Medicine, Massachusetts General Hospital and Associate Professor, Harvard Medical School

One positive aspect of COVID-19 is that placental infection and vertical transmission to the fetus are rare (except for the Delta variant), despite the link between pregnancy and increased risk for severe illness. The vertical transmission rate for SARS-CoV-2 ranges from 1 to 3 percent, which is low relative to other viruses. This low rate seems to be associated with low viremia in maternal and cord blood among pregnant women as compared with nonpregnant patients. Additionally, placental patterns of ACE2/TMPRSS2 expression, which are negligible, may be protective. Dr. Edlow and colleagues identified physically distant expression of ACE2 and TMPRSS2 in the placenta, with weaker expression of TMPRSS2 relative to ACE2. Finally, Hofbauer cells do not appear to be involved in vertical transmission, as they do not express ACE2 and are not infected when placentas are infected with SARS-CoV-2. This characteristic contrasts with other viruses. However, the timing of infection during pregnancy matters. First

trimester patterns of ACE2/TMPRSS2 expression in the placenta may be more permissive of infection with SARS-CoV-2.

The viral variant also influences vertical transmission of SARS-CoV-2. The Delta variant was associated with increased maternal and neonatal risk. During the Delta epoch of COVID-19, proportions of severe-critical disease, ICU admissions, and rates of neonatal adverse outcomes (e.g., stillbirth) were higher than with previous variants. Limited data suggest that the Delta variant produced higher viral loads and increased risks of viremia and placental infection. In contrast, the Omicron variant was associated with greater incidence of infection, but less severe disease. For both Delta and Omicron, the majority (more than 90 percent) of infants infected with SARS-CoV-2 were born to unvaccinated mothers with non-severe disease.

Generally, transplacental transfer of maternal immunoglobulin G protects the neonate from infection. Dr. Edlow and her team were surprised when they observed reduced antibody-mediated protection against SARS-CoV-2 relative to other viruses (influenza and pertussis). Mothers with male fetuses have lower anti-SARS-CoV-2 antibody titers than those with female fetuses and transfer fewer antibodies to the male fetus. There is no effect of fetal sex on maternal influenza and pertussis antibodies. The researchers also observed exposure to MIA (which is linked with adverse neurodevelopment) and inflammation/immune activation at the maternal-fetal interface with SARS-CoV-2. Specifically, there was an upregulation of interferon-stimulated genes in addition to pro-inflammatory alterations (e.g., altered maternal T cells and macrophages and in Hofbauer cells in the placenta). Neonatal immune imprint after maternal SARS-CoV-2 also occurred. For example, there were pro-inflammatory cytokines in umbilical cord blood when mothers had recent/ongoing SARS-CoV-2. Maternal immune changes in SARS-CoV-2 included reduced CD4+ and CD8+ T cell fractions and monocyte exhaustion with increasing disease severity. Placental expression of interferon-stimulated genes (ISGs)—which play an important role in placental defense against viruses and other pathogens—was sexually dimorphic in SARS-CoV-2. ISGs were increased in male placentas and decreased in female placentas in mothers with SARS-CoV-2. Hofbauer cell density was increased in male placentas.

Dr. Edlow's team is using cord blood cells to model the effect of maternal SARS-CoV-2 infection on the fetal brain. The researchers created microglial-like cells from cord blood monocytes of both SARS-CoV-2-positive and SARS-CoV-2-negative women. Brain immune cells (microglia) modeled from cord blood of COVID-19-exposed neonates demonstrated altered synaptic pruning *in vitro*, suggesting that maternal infection is associated with altered synaptic pruning in some offspring. The researchers plan to link this model to offspring neurodevelopmental outcomes from electronic health records. Early data suggests possible neurodevelopmental impact of SARS-CoV-2 for the developing fetus, even in the absence of placental infection or vertical transmission. Prospective studies are needed to assess these relationships. Researchers need better methods are needed to identify at-risk infants and children. Cellular models show promise, but they need to be developed further.

Adverse Perinatal Outcomes with SARS-CoV-2 Infection

Torri Metz, M.D., M.S., Associate Professor, Maternal-Fetal Medicine, Vice-Chair for Research, Department of Obstetrics and Gynecology, University of Utah

Early in the pandemic, information was needed on how SARS-CoV-2 infection affects outcomes for mothers and neonates, and on the influence of pregnancy on the disease course of COVID-19. Taking a clinical perspective, Dr. Metz focused on how exposure to SARS-CoV-2 *in utero* affects neonates. As noted previously, pregnant people have a greater risk of COVID-19 severe illness. Investigators who work in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's Maternal-Fetal Medicine Units Network are conducting the Gestational Research Assessments for COVID-19 (GRAVID) study at 17 individual hospital sites across the United States. GRAVID is a retrospective cohort study of 14,104 pregnant or postpartum patients who delivered neonates between March and December 2020. The researchers compared primary outcomes—maternal death or serious morbidity from common pregnancy complications, including hypertensive disorders of pregnancy (HDP), postpartum hemorrhage, and infections other than SARS-CoV-2—between patients with and without SARS-CoV-2 who delivered on randomly selected dates. COVID-19 was associated with a higher risk of death or serious morbidity, which was driven by HDP and infections other than SARS-CoV-2. Maternal SARS-CoV-2 infection increased the risk of preterm birth and neonatal ICU admission. Adverse outcomes were seen among those with moderate or higher disease severity (except HDP).

The Post-Acute Sequelae of SARS-CoV-2 Infection (long COVID) and Pregnancy (PASC-PREG) project will be a 4-year observational study of individuals who have SARS-CoV-2 during pregnancy and their offspring. The researchers will assess neurologic, psychiatric, cardiac, respiratory, endocrinology, and reproductive outcomes. The study is important because the immune system is more tolerant during pregnancy, and pregnant people tend to have more severe viral illnesses. It is unclear how COVID-19 during pregnancy affects PASC. Additionally, the effects of COVID-19 on offspring are of interest because of possible maternal hypoxia and inflammatory responses and placental damage. A retrospective study linked infection with the Delta variant with stillbirths. In these cases, the placentas were positive for SARS-CoV-2. Massive perivillous fibrin deposition and chronic histiocytic intervillitis indicated placental insufficiency. A prospective cohort found that birth during the pandemic but not *in utero* exposure to SARS-CoV-2 was associated with differences in neurodevelopment at age 6 months. The findings of a retrospective cohort study suggest that maternal SARS-CoV-2 infection was associated with adverse effects on neurodevelopment. However, many questions remain, and the field needs ongoing high-quality research in this population.

Neuroplacentology: Placenta and the Developing Brain

Anna A. Penn, M.D., Ph.D., L. Stanley James Associate Professor of Pediatrics Director, Division of Neonatology, Columbia University

Dr. Penn coined the term neuroplacentology to describe the connection between the placenta and the developing brain in 2012. Anything that affects the placenta could potentially affect the developing brain. In addition to providing nourishment, the placenta actively shapes brain development. Functions of placenta include immune activation, stress regulation, growth and nutrition regulation, oxygenation perfusion, and hormone production. The placenta can be considered as “fetal armor,” but it can have “chinks” or points of vulnerability. For example, placental lesions are common in perinatal brain disorders (e.g., neonatal encephalopathy and infants with low Apgar scores and perinatal stroke).

The placenta is a critical neuroendocrine organ. It makes steroids, central nervous system peptides, including those in the hypothalamic-pituitary-adrenal axis. Some hormones that rise in late gestation are secreted by the placenta and cross the blood brain barrier. These show similar expression in mice and humans, allowing researchers to examine their effects experimentally in an animal model. Dr. Penn and colleagues have studied allopregnanolone (ALLO), a hormone that peaks at the end of gestation (when preterm birth occurs). ALLO regulates the GABA-A receptor—promoting cell proliferation, neurogenesis, and myelination, particularly in response to injury. Alterations in GABAergic tone are induced via placental dysfunction or placental transfer in infections (including SARS-CoV-2) and exposures to substance use or anesthetics. Dr. Penn and colleagues speculate that ALLO might be given as an intervention to ameliorate adverse neurodevelopmental effects of exposures (e.g., maternal SARS-CoV-2 or substances).

The team’s research using a novel transgenic mouse model (pIKO) for placental ALLO loss indicates that suppressing this hormone leads to anatomical, molecular, and behavioral alterations. Changes were seen in the cortex, cerebellum, and hippocampus. These changes are global, yet regional- and sex-specific. For example, placental ALLO loss impairs white matter development in the cerebellum. A structural analysis found that, as adults, males showed increased myelination in the cerebellum, whereas females showed decreased myelination in this brain structure. Therefore, a change in a single placental hormone can alter brain development. Notably, analysis of cerebellar tissue from term and preterm infants revealed a similar sexually dimorphic pattern in myelin. The clinical and developmental significance of this pattern is unclear, but the cerebellum is involved in repetitive motor tasks, social behavior, emotion, and attention. In addition to myelin alterations, male pIKO mice show reduced social interactions and increased stereotypies. These are autistic-like features—it would be an overstatement to say that pIKO models autism—that are male specific. Additionally, the myelin in male pIKO mice is not well functioning even though there is more of it. Cerebellar myelin-based protein (MBP) correlates with the autistic-like behaviors. Treatment with ALLO or muscimol during late gestation prevents cerebellar myelin and behavioral abnormalities and shifts MBP levels into the normal range.

The idea that placental hormones may be used to protect the developing brain in cases of fetal exposure to opioids or SARS-CoV-2 could be tested. The U.S. Food and Drug Administration (FDA) has approved brexanolone (a medication that modulates the GABA-A receptor) for the treatment of postpartum depression. Dr. Penn suggested that a medication that has well-established safety could be evaluated for neurodevelopment protective effects.

Panel Discussion

Are the current limitations to researchers' understanding of the MPF triad mostly technical?

Dr. Scher: The limitations are both scientific and political. There are new fetal surveillance tools that are open to all, even individuals from populations that experience health disparities. Well-meaning doctors perform various diagnostic tests in each trimester during pregnancy as part of fetal surveillance. Yet, the field does not have tests that are specific enough to detect problems in all organ systems. We need diagnostic tools that look at the placenta and the developing brain in a trimester-specific manner, as well as tests based on all omics areas (e.g., genomics, transcriptomics, proteomics, and metabolomics). Other major issues are funding and access to care. The American College of Obstetricians and Gynecologists is working to increase standards, but maternal levels of care are not adequate in my view. An interdisciplinary discussion is needed to improve diagnostic tools during pregnancy, and NIDA has a role to play.

As the pandemic continues, what can pregnant women do to protect themselves from SARS-CoV-2?

Dr. Metz: The general guidance of social distancing, masking, and vaccination all apply to pregnant women. The viral variants create a moving target and present challenges. The severity of COVID-19 seems to depend on the particular variant. Because the Delta epoch was fairly short in duration, the protective measures generated for it were never implemented. A challenge in protecting pregnant women from COVID-19 is vaccine hesitancy among this population.

Dr. Edlow: We know that vaccination prevents severe COVID-19 disease, which most likely helps reduce the risks for negative fetal outcomes. The vaccine is the primary tool of protection. COVID-19 research must be coupled with public health and social changes to reduce infection. Most clinical populations have been infected with Omicron. Social determinants of health (e.g., maternal stress, food insecurity, and structural racism) add to individual risk factors for pregnant women. A major challenge is that the infrastructure for public health is inadequate in the United States. Improving the system requires investment and political will.

Dr. Penn: Women who are vaccinated during pregnancy transmit antibodies to their offspring, which helps with newborn protection several months after delivery. Therefore, maternal vaccination is important for protecting the health of children in the long term. It is also crucial that children receive a COVID-19 vaccination at age 6 months (the FDA has now approved Pfizer and Moderna vaccines for this age group), but we have a long way to go to convince families.

We also need new tools to study the placenta, placental changes, and pathology. The field needs placentas from as many pregnant people (with and without COVID-19) as possible, but this is expensive and time consuming.

Session Two: Impact of Pandemic Stress on Maternal Health and Neurodevelopment of Children Born During the Pandemic

Pandemic-Related Stress and Maternal Mental Health

Courtney Townsel, M.D., M.Sc., Assistant Professor, Maternal Fetal Medicine, University of Michigan

During the first year of the COVID-19 pandemic, the global prevalence of anxiety and depression increased by 25 percent. This increase was related to social isolation resulting from the pandemic, constraints on people's ability to work, inability to seek support from loved ones, and minimal engagement with communities. Women reported greater effects of pandemic-related stress than men. Other groups disproportionately affected by pandemic-related stress included people with preexisting physical health conditions. Individuals with preexisting mental health disorders who became infected were more likely to experience severe outcomes than those without these conditions. Outpatient mental health services were often disrupted during the pandemic, decreasing access to essential care. Pandemic-related stress, associated worries, and mental health effects were also highly prevalent—with some gender and racial/ethnic disparities.

Pandemic-related stress during pregnancy is important because prenatal stress and anxiety are well-established risk factors for preterm birth, macrosomia, and infant health problems and may have long-lasting effects on the offspring. The prevalence of perinatal anxiety was already high prior to COVID-19 (about 21 to 25 percent) and increased during the pandemic. Perinatal depression symptoms also increased during the pandemic. These elevations are, in part, related to changes in maternal care (e.g., cancellation of prenatal appointments and whether and how many support people could attend the birth). Vaccine hesitancy—delaying or declining vaccination—is high among pregnant women and those trying to conceive compared with other women of reproductive age. One study found that Black individuals had a fourfold increased likelihood of delaying or declining COVID-19 vaccines. Disparities in maternal mortality continue and were worsened during the pandemic.

Protective structures and strategies to alleviate stress in maternity care can be put into place. Proactive outreach, social support, childbirth education, and updated parenting resources (information on what to expect during labor and delivery) may help alleviate maternal stress. The disruptions in mental health care access during the pandemic have been, in part, mitigated by a shift toward telehealth services. However, limitations include inadequate infrastructure and preexisting inequalities. Several educational campaigns have been implemented to provide pregnant women with information on COVID-19 vaccination, as a great deal of pandemic-related stress was related to misinformation.

Born During the Pandemic: Neurodevelopmental Consequences for the COVID-19 Generation
Dani Dumitriu, M.D., Ph.D., Assistant Professor, Department of Pediatrics, Columbia University

Dr. Dumitriu spoke from the perspective of a neuroscientist and pediatrician, who worked on rodent models of stress and resilience prior to the pandemic. She emphasized the importance of intervening during the first 2 years of life to counter stress and other negative exposures. Research indicates that breastfeeding, sleep hygiene, face-to-face interaction, and bonding with a caregiver all improve neurodevelopment. In contrast, toxic stress and parental stress during early development have a negative impact on neurodevelopment. Any experience that occurs during pregnancy can be embedded into a child's health via prenatal programming—representing the developmental origins of health and disease.

The COVID-19 Mother Baby Outcomes (COMBO) Study at Columbia University uses a collaborative approach to understand the effects of both SARS-CoV-2 infections and the pandemic on the developing fetus, future child health, and future maternal health. The outcomes being studied span domains known to be affected by other prenatal infections and insults—such as fetal growth, risk of child asthma, neurodevelopment, maternal mental health, and mother-infant bonding. In January 2021, COMBO partnered with the Centers for Disease Control and Prevention's Epidemiology of SARS-CoV-2 in Pregnancy and Infancy (ESPI) Study to characterize SARS-CoV-2 infection during and up to 6 months after pregnancy. The ESPI COMBO focuses on cases up to 6 months in age, and the main COMBO study continues to follow dyads after the 6-month milestone. The study is both longitudinal and cross-sectional, as participants may enter at any point. COMBO involves more than 100 researchers and 1,300 mother-child dyads. Dr. Dumitriu reviewed the potential pathways for the neurodevelopmental consequences of *in utero* exposure to SARS-CoV-2 and/or the pandemic. She briefly discussed the results of a comparison between a historical cohort and the COMBO study for parent reports and objective observations of child neurodevelopment.

Lessons Learned on What to Expect When You're Expecting in a Pandemic
Jamie Lo, M.D., Department of Obstetrics and Gynecology, Oregon Health & Science University

Dr. Lo stressed the importance of differentiating the effects of SARS-CoV-2 infection with being affected by the pandemic. There has been an increase in maternal deaths during the pandemic due to limited access to prenatal care, increased stress, and a lack of social support available before and after delivery. In the United States, maternal death rates—which were already higher than those in peer countries—rose about 33 percent during the pandemic. The pandemic offers a number of lessons and suggests actions to address multiple problems in women's health.

It is clear that the health care system does not adequately address sexual and reproductive health—and this problem was exacerbated by the pandemic. For example, some states classified abortion as a non-essential service during the pandemic. Generally, policies did not loosen restrictions on medication abortions monitored via telehealth. Many women had

problems obtaining contraception during stay-at-home orders. In Dr. Lo's view, these issues suggest that we need to treat sexual and reproductive health care as essential care and oppose efforts to restrict women's access to legal sexual and reproductive health services. She suggested that policies allow telemedicine coverage for medication abortion and promote access to mail-order abortion. It is also important to ensure viability of the medication supply chain for contraceptive drugs and devices, medication abortion, and other sexual-reproductive-health drugs.

The pandemic also highlighted that gaps in maternal care in the United States are widening. Underlying reasons for this include a lack of diversity in the health care workforce, discrimination in health care, limited homebirth education and mental health services, and gaps in postpartum care. Dr. Lo suggested that this problem could be addressed by transforming maternity care to make prenatal care, childbirth, postpartum care, and motherhood safer and more holistic. She commented that it would also be helpful to promote the role of doulas and full-scope practice for certified nurse midwives as a way to enhance diversity in the health care workforce. Finally, awareness for maternal mental health services should be increased.

Globally, a significant decline in maternal mental health occurred during the pandemic—with 43 percent of women reporting posttraumatic stress, 31 percent anxiety/depression, and 53 percent loneliness. The COVID-19 pandemic hit communities of color hardest, compounded by longstanding health inequalities caused by systemic racism. Systems and organizations that provide perinatal care and social services to individuals with low incomes were stretched thin, perpetuating maternal health inequities. To address this issue, Dr. Lo recommended improved data collection efforts and data systems for tracking maternal/infant outcomes by race, ethnicity, and other characteristics for increasing accountability.

Telehealth can enhance the standard of care and improve maternal morbidity and mortality, as well as address rural-urban health disparities in maternal care. However, she cautioned that inequities in access to technology and high-speed Internet are potential barriers. Dr. Lo suggested increasing efforts to finance and support telemedicine in pregnancy and expanding the scope of permitted and reimbursed maternal telehealth benefits. Several prenatal care programs are using telemedicine and find that patient satisfaction increased or remained unchanged, with no difference in other outcomes. Other health care facilities are providing telemedicine specialist consultations for women with high-risk pregnancies. Expansion of telehealth for perinatal care would help safeguard maternal health during other emergencies in the future. The pandemic within the pandemic is the increase in intimate partner violence in the COVID-19 era. To address this problem, Dr. Lo commented that efforts to provide access to support, refuge, and medical care need to be strengthened and expanded.

COVID-19 has exposed major gaps in public health and health care systems. Dr. Lo suggested that this could be addressed by increasing federal funding of the state Title V Maternal and Child Health block grant, which has been underfunded for years, in her view. It would also be helpful to increase the wages and benefits of the maternal and child health workforce and to develop initiatives to address preparedness and response for maternal and child health prior to

the onset of disasters. Continued social and health policy changes—including Medicaid reforms—are needed to make widespread improvements in health coverage to improve greater access to care for individuals before, during, and after pregnancy. Dr. Lo suggested that continued efforts to support policies that address fair pay, paid leave, and sick days, and supplemental incomes are needed. She remarked that increasing postpartum Medicaid coverage, presumptive eligibility, and income limits for pregnant individuals would facilitate such efforts. Additionally, expanding Medicaid coverage under the Affordable Care Act, broadening telehealth coverage and reimbursement, and increasing access to Medicaid Family Planning Programs would be positive policy changes in her view.

Finally, Dr. Lo noted that COVID-19 brings the concept that quality maternal health care requires employing multiple strategies that address different levels of underlying challenges to the forefront. Actions include designating maternal care as essential and disseminating appropriate protocols at the national level. Facilities that offer maternal health care might enact risk reduction strategies, with districts leveraging technological adaptations to increase access to care. At the community level, mobilization and advocacy efforts could be leveraged to combat fear.

Panel Discussion

Moriah Thomason, Ph.D., New York University

Julie Croff, Ph.D., M.P.H., Oklahoma State University

Laura Stroud, Ph.D., Brown University

Mishka Terplan, M.D., M.P.H., Friends Research Institute

What will facilitate the study of the pandemic's effects on children?

Dr. Thomason: International collaborations that share data will generate large cohort studies that could examine the dose effects of stress on child outcomes. Such efforts would need to be funded.

We know that there has been a dramatic increase in substance use disorder among pregnant women. Are there any studies on pregnant women infected with SARS-CoV-2 that compare those with and without substance use disorder?

Dr. Dumitriu: It is not easy for researchers to obtain expedited clearance from Institutional Review Boards to include questions on substance use for the pregnant populations. Some studies might have a few questions on substance use that could be analyzed.

Dr. Lo: I believe there may be an upcoming published article on this topic, there is not much data otherwise. It would make sense if substance use and COVID-19 had additive effects.

From a research and policy perspective, “stress” is nonspecific. How are we defining stress and how should be measure it?

Dr. Townsel: This is a good question, as there are many constructs (e.g., allostatic load and perceived discrimination) under the umbrella of stress. The question highlights the importance of engaging social scientists, conducting multidisciplinary research, and applying other frameworks in clinical studies. Investigators must engage patients early in the process, especially consulting participants when developing research questions to address issues of importance to them. As vaccine education information was disseminated, gaps in vaccine hesitancy closed. Effectiveness and harms important to everyone, so those concerns must be addressed.

Dr. Dumitriu: In our work, we have seen that it is important not to generalize—that is, assume that the pandemic was always stressful for all women. Some mothers had positive pandemic experiences. The direction of differences in mothers’ lived experiences during the pandemic by race/ethnicity are not always intuitive. Another positive trend during the pandemic was that children and pregnant women did not contract other viruses (e.g., influenza).

Dr. Croff: My team has also found positive themes for women, both those who are at high and low risk for substance use disorder, during the pandemic. Some of the positive experiences—such as developing new hobbies, spending more time with family, increasing outdoor activities, and having a smaller but deeper social network—might be incorporated into recommendations for improving maternal and child health.

What is the major area for future research?

Dr. Dumitriu: Long-term follow-up of mothers and children in cohort studies.

Does the HBCD Study incorporate COVID-19 exposure?

Dr. Freund: We plan to ask whether mothers and infants were COVID-19 positive or negative in questionnaires.

Session Three: Impact of Comorbid COVID-19 Infection and/or Pandemic Stress and Substance Use on Fetal Outcomes and Neurodevelopment

Intersection of COVID-19 and Opioid Use in Pregnancy: Effects on Fetal and Infant Development

Elisha Wachman, M.D., Associate Professor, Department of Pediatrics, Director of Pediatric Academic Research, Boston University School of Medicine/Boston Medical Center

Dr. Wachman noted that the effects of prenatal opioid exposure combined with COVID-19 on the developing have not been studied and represent uncharted territory. Prenatal opioid

exposure is linked with many adverse outcomes for children—including fetal growth restriction, impaired brain growth, preterm birth, NOWS, risk for possible neurodevelopmental impairment, and increased likelihood of SUDs in adulthood. Research from animal models indicate that opioids directly act on endogenous opioid receptor signaling pathways, which has developmental consequences (e.g., disturbed myelination and altered interneuron development and migration). Functionally, *in utero* opioid exposure can impair development of locomotor activity and sensorineural milestones.

Human studies using structural magnetic resonance imaging (MRI) find overall smaller volumes in neonatal and fetal brain after opioid exposure, while functional MRIs show altered sensory connectivity. Research on long-term outcomes consistently finds altered behavioral outcomes, executive functioning, sensory processing, socioemotional problems, and visual diagnoses among individuals with prenatal opioid exposure. Importantly, medications for opioid use disorder normalized effects on sensory connectivity, and prospective studies show that they shifted developmental scores into the normal range. However, studies in this area have limitations—including that they are underpowered, do not account for covariates and confounders, are usually retrospective, have an inappropriate control group, and do not account for socioeconomic factors.

Maternal stress also affects the long-term outcomes of infants. Prenatal stress is associated with intrauterine growth restriction, preterm birth, lower birth parameters, alterations in Neonatal ICU Network Neurobehavioral Scale profiles, fetal and neonatal MRI changes, and lower motor and cognitive scores on the Bayley Scale of Infant Development. Stress may be transmitted from mother to infant through several mechanisms—including cortisol, epigenetic alterations, and neuroimmune effects. Stress can be assessed by measuring cortisol via maternal and infant hair samples. Research by Dr. Wachman and colleagues found that levels of cortisol in maternal hair was associated with severity of NOWS and that infant hair cortisol levels increased over the first 2 months after birth. Opioid use disorder can produce epigenetic alternations in non-pregnant individuals. Maternal psychosocial stress and substances can cause epigenetic modifications, which are associated with infant neurobehavior and long-term outcomes. Opioid-exposed infants who showed more epigenetic changes in the mu-opioid receptor gene (*OPRM1*) also had more severe NOWS. Opioid-exposed infants also demonstrated differential methylation patterns in genes related to synaptic transmission. Animal research indicates that *in utero* opioid exposure negatively affects the maturation of the neuro-immune system and the trajectory of central nervous system development. Specifically, opioid-exposed animals showed higher baseline concentrations of inflammatory cytokines than those that were not exposed. Opioid exposed animals also hyper-secreted pro-inflammatory cytokines when given immunological challenges.

Prenatal COVID-19 exposure might influence infant development through several mechanisms—including vertical transmission, functional reprogramming of innate immune cells in the fetal brain, epigenetic changes in key genes for brain development, and alterations in synaptic pruning within the brain. COVID-19 can generate inflammation via a cytokine storm, which causes more severe disease in pregnant women and increases the risk for preterm birth

and pregnancy complications. The Mothers and Infants Affected by Signs and Symptoms of COVID-19 Study found elevated IL-6 in mothers and infants, along with the cytokine storm and altered neonatal gut immune function and neurodevelopmental outcomes. Mothers and infants in this prospective cohort study also had elevated IP-10, along with cytokine storm, inflammatory chemokines, leukocyte chemotaxis, cellular apoptosis, and inhibition of vascular growth. These elevated immune factors were associated with pregnancy complications. Mothers and infants also showed elevated IL-8, along with cytokine storm and altered developmental outcomes. Women in this study had been infected with SARS-CoV-2 during various trimesters, and researchers found that those who had the virus early in pregnancy had higher inflammatory markers at delivery. Generally, there are links between antenatal inflammation and long-term infant outcomes. Neonatal brain injury among preterm infants is associated with increased levels of TNF- α , IL-6, IL-8, and IL-1 β . Maternal infections increase the risk for neurodevelopmental disorders, such as autism spectrum disorders and schizophrenia.

Pandemic-related stress also influences outcomes—such as worse maternal mental health, increased maternal stress and depression, impaired maternal-infant attachment, altered birth outcomes, and heightened risk for neurodevelopmental impairment. A retrospective study found increased odds of a neurodevelopmental diagnosis during the first 12 months in a group of infants who had been COVID-19 exposed. However, prospective studies of 6–12-month-old infants found no differences between those who had been exposed to COVID-19 compared with controls. A comparison of pandemic-era infants and historical controls observed worse developmental outcomes for the COVID-19-exposed group.

There is little information on the intersection of COVID-19 and opioid exposure during pregnancy and infant outcomes. However, there are higher rates of COVID-19 among those with SUDs. The pandemic has also increased intimate partner violence, depression, anxiety, and stress while decreasing access to support resources. The pandemic has also been accompanied by an increase in overdoses and non-prescribed use of opioids, and an elevated risk for preterm delivery and adverse neonatal outcomes. The intersection of COVID-19 and opioid exposure during pregnancy may influence infant and long-term outcomes among children through effects on inflammation, altered immune function, stress, and epigenetics. With multiple variables—including maternal stress, prenatal opioid exposure, co-exposures, environmental factors, COVID-19 inflammation, infant sex, demographics, and prematurity—possibly influencing outcomes, it is complicated to isolate causes.

Research on treating NOWS indicates that non-pharmacologic care (e.g., rooming in, breastfeeding, and parental presence) positively affects infant outcomes—decreasing pharmacologic treatment rates and lengths of hospital stays by 50 percent. Such interventions may also improve outcomes for children prenatally co-exposed to COVID-19 and opioids. Researchers also need to study the effects of COVID-19 vaccines and treatment, as well as medications to treat opioid use disorder, on the outcomes of these children. Research is also needed on the mechanisms underlying the combined effects of prenatal COVID-19 and opioid exposure and their long-term outcomes. Animal and translational studies are needed, as well as work to identify modifiable factors for possible intervention.

Impact of COVID-19 on Healthcare Utilization and Outcomes Among Pregnant Persons With Substance Use Disorders

Elizabeth Krans, M.D., M.Sc., Assistant Professor, Department of Obstetrics and Gynecology and Reproductive Sciences, Magee Women's Health Research Institute, University of Pittsburgh

As a health services researcher, Dr. Krans focused on the significant detrimental influence that COVID-19 had on access to treatment of SUDs and overdose prevention. There has been a spike in overdose death rates since the pandemic—a 28.5 percent increase as of April 2021 compared with the prior 12-month period. Fentanyl (and other synthetic opioids) is a main driver of overdose deaths, but psychostimulants (cocaine and methamphetamine) also contribute. With social distancing and disruptions in services, more patients use drugs alone, face increased barriers to treatment, and experience increased psychosocial stressors (e.g., unemployment and IPV). Other factors likely contribute to increasing overdose deaths, including changes in the drug supply and disruption to harm reduction measures.

Alcohol use increased in the general population during the pandemic, but elevations in consumption and severity of alcohol use disorder were greater among women compared with men. There was also a 25 percent increase in cannabis use among pregnant women in California during the pandemic. A Canadian study conducted between April and September 2020 found that stress related to financial difficulties was associated with an increase in cannabis and tobacco use. In the general population, substance use increases the risk of COVID-19 morbidity (e.g., stroke, heart attacks, arrhythmia, chronic lung disease, and asthma) and worse COVID-19 outcomes, even when co-morbidities are taken into account.

Pregnant women with opioid or stimulant use disorder have an increased risk of severe maternal morbidity. Medications for opioid use disorder does not decrease the risk, although they do lower the likelihood of overdose. Data from the INTERCOVID Multinational Cohort Study of pregnant women with and without SARS-CoV-2 infection found that individuals with a SUD received COVID-19 screening tests less frequently, but they were diagnosed at higher rates compared with those without. COVID-related hospitalizations were also higher among pregnant women with a SUD compared with those without (36 percent versus 8 percent, respectively).

The pandemic altered care for SUDs in several ways. For example, restrictions were eased to allow take-home methadone doses and telemedicine prescribing of controlled substances. The liberalization of methadone dosing was associated with fewer patients who overdosed and discontinued treatment. However, appointment access was severely restricting, including for new patients. A prospective observational trial of pregnant women who received opioid use disorder treatment with buprenorphine by telemedicine or in person found no differences in treatment retention. Another study found a reduction in no-show rates when comparing the change from in-person to hybrid approach to treating substance disorder among pregnant women. However, pregnant women who use opioids face barriers to accessing treatment, as several programs—especially those in rural areas—stopped taking patients during the pandemic. There is also COVID-19 vaccine hesitancy among the general population of people

with SUDs. In Dr. Krans's view, the current challenge is to sustain, identify, and adopt COVID-related innovations for health care deliver and to increase efforts to address the vulnerability and instability that places individuals at risk when major life disruptions (e.g., a pandemic) occur. She stressed the importance of intervention research that examines within group rather than between group differences.

Panel Discussion

Do you think the policy changes to the buprenorphine waiver and to allow take-home methadone will continue?

Dr. Krans: Observed daily dosing of methadone is a punitive restriction, and we now have data supporting take-home doses. There is no reason to tie the dosing process to medication rather than the individual. The data on take-home dosing indicate that we need to rethink observed dosing and other aspects of care beyond the pandemic.

Has there been any follow-up on vaccine hesitancy among people with substance use disorder?

Dr. Krans: I am unaware of any follow-up data. In my program, most patients have had COVID-19 and do not want to get vaccinated.

Is there an effect of ACEs on the stress response among pregnant women with substance use disorder?

Dr. Wachman: People with substance use disorder have a very high prevalence of ACEs. Over time, chronic stressors can blunt the stress response. However, researchers have studied acute stress more, so we do not know the effect on childhood chronic stress over the life course.

Please comment on the mother's trauma history and the transmission of stress to the next generation?

Dr. Wachman: Maternal history of trauma is known to affect attachment and parenting, and the ability to respond to an infant is the biggest influence on child-parent interaction.

Dr. Krans: Trauma has a major effect on substance use disorder patients. Trauma is often an ongoing process with cumulative effects, which makes it complex to understand.

How do the pandemic and child welfare involvement interact?

Dr. Wachman: This would be an interesting area for research. In my team's study, parents had custody.

Dr. Krans: The threat and fear of child separation among women with substance use disorder is a stressor that could be studied and shows that it can be difficult to isolate stress-related factors.

Can cortisol measures distinguish maternal stress during pregnancy and childrearing?

Dr. Wachman: Large cohorts are needed to disentangle these effects.

Session Four: Innovations in Remote Data Collection and Telehealth Born Out of the Pandemic

Innovative Methods for Remote Assessment of Neurobehavioral Development

Hannah Gustafsson, Ph.D., Assistant Professor, Department of Psychiatry, Oregon Health & Sciences University

Dr. Gustafsson reviewed how she and her team developed remote data collection procedures for the Prenatal Environment and Child Health (PEACH) Study and the COVID-19 and Perinatal Experiences (COPE) Study. The PEACH Study was in progress when the pandemic was declared, so the initial goal was to translate existing in-laboratory assessments (i.e., questionnaires, behavioral assessments, and biospecimen collection) to remote settings. Questionnaires were completed via RedCap, behavioral assessments conducted via video conference software, and biospecimens collected by participants and shipped to the laboratory overnight in insulated coolers. These methods were later applied to the COPE Study.

To determine the feasibility of remote infant behavioral assessment, the research team asked experts to rate the adaptability of various tasks and conducted some pilot testing using various Internet capable devices in an iterative process. The team selected the following tasks to use for remote infant behavioral assessment: Arm Restraint Task, Still Face Paradigm, Caregiver-Child Interaction Task, Do/Don't Tasks, Object Permanence Task, Snack Delay Task, and Visual Attention Task. The Visual Attention Task for infants was delivered via computer, with data analysis of eye-tracking software.

Adapting tasks to remote contexts involved trade-offs and challenges. However, the limited camera angles were not as large an issue as the researchers expected. Asking experts to identify the most essential information to capture helped the team to collect high-quality data on infants. To standardize stimuli, the researchers mailed or provided no-contact drop-off of supplies. Most participants had access to an Internet-capable devices, but if not loaned equipment was provided via no-contact drop-off. To promote the success of remote infant behavior assessment, Dr. Gustafsson suggested preparing caregivers (e.g., email a list of common household items and images of the task flow) and communicating clearly throughout the visit. Staff training is also important, particularly on the features of video conference software, ideal camera angles, and appropriate deviations.

For pre- and postnatal biospecimen collection, the researchers assessed feasibility and sample integrity. They determined the comfort of participants collecting biospecimens and explored different devices for optimizing collection methods. The biospecimen collection kit comprised an insulated cooler shipped overnight on ice packs or delivered without contact. Kits were received and processed immediately and inspected for temperature and spillage. Requiring participants to collect samples from themselves can be challenging without another individual (e.g., hair samples). Some types of sampling can be intimidating for some participants. To facilitate the process, the researchers developed detailed instructions and unboxing videos for participants and offered video conferencing consultations and information about mailing options. When kits were returned, the majority (more than 99 percent) were usable.

Researchers at New York University have developed rubrics for infant behavior data quality. Dr. Gustafsson's team used these rubrics to code the data. The rubrics emphasize the visibility of the child/caregiver, interruptions, and parental adherence to instructions. Inter-rater reliability for Still Face, Object Permanence, and Snack Delay tasks were good, with less than 1 percent of the data deemed to be not codable.

Development and Testing of Virtual HOME Inventory

Leeann Whiteside-Mansell, Ed.D., Professor, Department of Family and Preventive Medicine, University of Arkansas for Medical Sciences

Home Observation for Measurement of the Environment (HOME) is a widely used assessment of parent-child interactions and home environments. It has been used in many large child development projects and intervention programs across the world, and will be used in the HBCD Study. There are more than 270 publications on HOME, which was developed by Robert Bradley, Ph.D. The HOME Inventory assesses multiple dimensions of children's home life. The infant-toddler HOME has 45 items clustered into six dimensions, which are assessed in a free-form (conversational) visit ("What is your typical day like?"). However, the scoring of the HOME Inventory is rigid. The six dimensions are: (1) responsivity, (2) acceptance, (3) organization, (4) learning materials, (5) involvement, and (6) variety. The research team's first goal was to examine the functioning of the original 45 items. Dr. Whiteside-Mansell showed photographs from remote assessment, providing examples of scoring in the different dimensions under various conditions (e.g., the number of children in the home and device used for the visit). Almost all caregivers had Internet access and a device to participate in interactive remote interviews. Mothers with smartphones often showed the visitor around the house so they could see the child's play area.

During in-person and virtual HOME visits for children ages 3 to 36 months, the team collected data on 52 pairs across the two sites. The researchers found that only 3 percent of participants found connecting for the virtual call difficult. Parents liked both forms of the visits—with a 50-50 split between those who preferred in person and virtual. Of the six dimensions, only one was scored differently between in-person and virtual visits. The total HOME scores were similar across contexts. The team is conducting a detailed analysis of item-level data for four items.

In conclusion, virtual data collection with the HOME requires important and additional logistical instructions for data collectors and parents. For example, parents need to know the best type of device and how to use the device to generate video. Visitors need to be able to set up the call without problems, support parents in using the technology and moving the visit to different rooms, and remember to take the time for the visit to become comfortable. Overall, data collected in each context is comparable. Although the researchers had expected that many observable items would be difficult to assess, this was not the case. In-home visitors struggled to see more of the house because of COVID-19. Most parents were comfortable taking the device/video on a tour of the house and outside.

Panel Discussion

In data analysis, do you use an algorithm to adjust for differences between parents and in parent-child relationships?

Dr. Whiteside-Mansell: We assess item-level test-retest reliability using the in-home visit as the standard. We examine items that are non-concordant, looking at whether the variation is random (within 5 percent) or skewed (greater than 5 percent). Although the visitors vary, the questions are standard. The order of the in-person and virtual visits does not affect HOME scores.

What are some lessons learned from participant-centered research design that could be applied to telemedicine?

Dr. Gustafsson: My team and I underestimated what aspects of assessment could be translated to remote data collection—and I think this lesson extends to telemedicine. For example, parents were able to collect blood from their infants using a small device without problems and cut their own hair for samples. We originally perceived more risks to remote data collection than there actually were. Some participants subsequently moved out of state but have been retained in the study because we are able to collect data remotely. Participants are capable of greater adherence than we thought. The pandemic offers researchers an opportunity to rethink data collection methods.

Dr. Whiteside-Mansell: Initially, my team made the mistake of focusing on facilitating remote visits from the perspective of the parent and child rather than the interviewers. Although they had been trained, our interviewers had never conducted a home visit, so we needed to boost their comfort level with being more naturalistic (as opposed to simply completing a form).

What demographic challenges might affect accessibility to remote data collection?

Dr. Whiteside-Mansell: Arkansas is rural, and many people have Wi-Fi challenges. Our study did not reach the most rural families, which is a concern. Having participants coming into the laboratory or deploying data collectors into homes has also caused problems (e.g., 2-hour drives only to find no one at home). One approach is to attend to participant demographics and address barriers.

Flash Talks

Cognitive and Socioemotional Development in Infants Exposed to COVID-19 in Utero: A Moderating Role of Prenatal Psychosocial Stress

Denise Werchan, Ph.D., Postdoctoral Researcher, Department of Child and Adolescent Psychiatry, New York University NYU Langone Health

Concerns about the effects of the COVID-19 pandemic on pregnant women and infants include maternal stress exposure (e.g., mood and anxiety disorders), which may influence social, emotional, and behavioral adverse developmental outcomes. Dr. Werchan stressed the importance of examining the combined effects of prenatal infection and pandemic-related stress on infant neurodevelopment. About one third of the women reported being COVID-19 positive during pregnancy.

The COPE Study examines the experiences of pregnant women and new mothers during the height of the pandemic in New York City—measuring prenatal outcomes and following up 6 and 12 months after delivery. The researchers focused on infant visual attention at age 6 months because it is a behavioral model for early neurodevelopment, emerges in first months of infancy and shows rapid change, and varies in development among individuals. Importantly, infant visual attention predicts cognitive and socioemotional function, as well as risk for neurodevelopmental disorders (e.g., autism). The team measured this outcome objectively via a remote video conference platform, and Dr. Werchan developed a novel system for remote eye-tracking anywhere in the world. Coding of infant visual attention is automated, and gaze patterns and shifts can be analyzed. At 12 months, they assessed neurodevelopmental risk by asking parents to report infant social and emotional function via a survey.

The team found that the interaction of maternal psychosocial stress and a prenatal maternal COVID-19 diagnosis were strongly linked with individual differences in infant visual attention. Higher levels of prenatal psychosocial stress in the setting of maternal COVID-19 were linked with less efficient infant visual attention at age 6 months. These infant attention scores—but not a COVID-19 diagnosis or prenatal stress alone—predicted socioemotional development and risk for neurodevelopmental disorder at age 12 months when maternal mood/anxiety and socioeconomic status were taken into account. Prenatal COVID-19 infection alone was not associated with infant outcomes.

Multiple-Modality Approach in Evaluating the Effects of the COVID-19 Pandemic on Pregnant and Postpartum Women in a Well-Characterized Cohort

Sharon Ruyak, Ph.D., RN, Assistant Professor, College of Nursing, University of New Mexico

Dr. Ruyak described how she and her colleagues evaluated maternal pandemic-related stress within an ongoing prospective cohort study (ENRICH-2). They incorporated intense repeated sampling of substance use and emotional well-being by ecological momentary assessment (EMA), as well as physiological data (e.g., heart rate and heart rate variability [HRV] and sleep).

The ENRICH-2 cohorts study focuses on identifying neurobehavioral deficits related to prenatal alcohol exposure early in life. For the supplementary investigation on COVID-19, a subset of patients who were either pregnant or in the postpartum period were enrolled from the larger cohort study. Participants provided information on their levels of pandemic-related stress, sleep quality, emotional regulation, substance use, and attachment during telephone interviews. Subsequently, EMA measured substance use three times daily and a wearable device assessed HRV and sleep for 2 weeks.

Most participants reported that they experienced greater stress or worse mental health during the pandemic. About 20 percent of participants (most of whom were postpartum) said they drank more than usual during the pandemic. About 12 percent of participants said they used marijuana more than usual during the pandemic. HRV measures were lower when participants reported alcohol use via EMA, which may indicate changes in autonomic nervous system function, poorer self-regulatory ability, and lower resilience.

The preliminary conclusions from the research are that COVID-19 was associated with substantial disruption in daily life and dysregulation in self-reported psychological health among pregnant and postpartum women. The pandemic was also associated with an increased risk in alcohol and marijuana use among pregnant and postpartum women. Additionally, alcohol use may be associated with lower HRV in pregnant and postpartum women. The next steps for the researchers include examining the relationships among EMA measures, reports of emotion regulation, and substance use.

Pregnancy During the COVID-19 Pandemic (PdP) Study: Relationships Between Prenatal Mental Health and Infant Brain Structure and Function

Kathryn Manning, Ph.D., Postdoctoral Research Fellow, Developmental Neuroimaging Lab, Department of Radiology, University of Calgary, Child and Adolescent Imaging Research Program, Alberta Children's Hospital Research Institute

The developing brain is susceptible to changes during pregnancy and in early childhood. Prenatal psychological distress (including anxiety and depression) can cause an increase of circulating cortisol through dysregulation of the maternal hypothalamic-pituitary-adrenal (HPA) axis. Combined with mild hypoxia, this may affect the structure of the developing fetal brain as well as behavior.

The PdP Study is a nationwide project that recruited more than 11,000 pregnant women across Canada to respond to surveys about their mental health and social support experiences during the COVID-19 pandemic. The preliminary results indicate that women had symptoms of anxiety and depression that were three- to four-fold higher than normal (i.e., compared with pre-pandemic times and with the general population). The researchers hypothesize that these experiences may have long-term effects on their children. The team also found a strong relationship between the quality of partner support and levels of maternal prenatal distress (i.e., lower stress with greater support) after controlling for maternal education, household income, and race.

Dr. Manning and colleagues focused on imaging a subset of PdP infants born during the pandemic whose mothers reported on their mental health and social support during pregnancy. The researchers used diffusion tensor imaging and resting-state functional MRI to examine infant brains while they slept naturally. The results suggested that infant brain white matter microstructural measures were related with prenatal maternal distress. Higher prenatal maternal distress was related to a relatively more mature amygdala-prefrontal white matter microstructure. Amygdala functional connectivity and relationships with prenatal distress were mediated by social support. The infants of mothers who reported lower social support—but not those with higher support—showed a relationship between prenatal distress and functional connectivity brain measures.

In conclusion, the relatively premature infant white matter microstructure was significantly related to higher levels of reported maternal prenatal distress. The quality of social support appears to buffer the relationship between prenatal maternal distress and infant brain amygdala functional connectivity. The findings highlight the need for online or in-person interventions to support quality relationships during pregnancy.

Leveraging Qualitative Research and Technology to Improve Screening and Treatment of Perinatal Substance Use Disorders

*Constance Guille, M.D., Director of the Women's Reproductive Behavioral Health Division,
Professor, Department of Psychiatry and Obstetrics/Gynecology, Medical University of
South Carolina*

Dr. Guille described research that used focus groups and aimed to create a website for obstetric providers and women with peripartum SUDs. Qualitative research findings from women with peripartum SUDs indicated that although they recognized that the website could offer information, the most important factor to them was a good relationship with a trusted clinician. Obstetric providers found the website content helpful, but they felt they would not use it. Instead, they needed to improve their screening and referral process. In light of this feedback, the researchers reconsidered the next steps in the context of literature describing barriers to effective screening and referral to treatment for pregnant women who use substances.

The research team developed the Listening to Women and Pregnant and Postpartum People (LTWP) program, a text-message-based screening system. Women entering routine prenatal care are told that perinatal mental health problems and substance use are common and that to ensure the best care possible, they could be monitored throughout pregnancy and in the first postpartum year. Women who enrolled by text immediately received mental health and SUD screenings to complete on their phone. Screening results are sent to a remote care coordinator (masters' degree in clinical social work) who developed a care plan and referral to treatment (telemedicine offered). The coordinator also discusses screening results with the care team.

A pilot study compared LTWP with the standard of care (i.e., in-person Screening, Brief Intervention, and Referral to Treatment) in a large outpatient prenatal practice. Compared with

women in the standard of care condition, those who participated in LTWP were more likely to be screened, screen positive, be referred to treatment, and receive treatment. Looking at the results by race, Black women who were screened in person were less likely to receive treatment than White patients. This difference was not seen in the LTWP group. The researchers have completed interviews of Black women with peripartum SUDs to obtain more feedback on the LTWP system and are now conducting a pilot randomized-controlled trial to compare the program with the standard of care.

Panel Discussion

From the perspective of researchers and participants in clinical studies, what elements do you think will be permanently changed by the pandemic?

Dr. Croff: I think we need to ensure that flexibilities that are more common because of the pandemic do not become stressors. For example, snow days used to be flexible time for families, but now everyone works or goes to school remotely.

Dr. Manning: Prior to the pandemic, many people were living under extreme stress every day, but it was not obvious. The pandemic has highlighted these disparities and groups who need help the most.

Dr. Werchan: Remote participation in research may help improve recruitment of individuals from groups not typically represented in studies (overcoming barriers such as a lack of transportation). Researchers should include tasks that participants can perform on their smartphones, as more people with less socioeconomic status have these devices.

Dr. Guille: Telemedicine is convenient for patients and gives providers insights into home life. But patients engage in positive behavioral activations when they visit the clinic (e.g., personal presentation and getting out of the house), so we need to consider what interactions should be remote.

What have been your experiences using wearables in research projects?

Dr. Ruyak: Our study did not use research-grade wearable devices, so we had some problems. Women in the study wore the wearable devices, which moved and did not collect the data we wanted. However, participants find these devices easy to work with. EMA devices collect a great deal of granular within person data, which can be important for tracking substance use and autonomic nervous system regulation—enabling just-in-time intervention. A negative aspect of EMA devices is that researchers must follow up in person on missing data. EMAs are flexible, allowing researchers to ask any type of questions via multiple presentation options.

How were research staff members affected by the pandemic?

Dr. Thomason: When circumstances changed, many staff members' living arrangements were altered. The declaration of the pandemic was a discrete, formal event, but there has been nothing to mark moving forward. I believe this is needed so people do not drift.

Dr. Manning: I work with younger students, who were more affected by the pandemic as they were trying to balance the demands of online courses with research. In science, maintaining motivation is difficult without in-person interaction to discuss ideas and study results.

Is pandemic-related fatigue related to uncertainty? How can we distinguish uncertainty from stress and social isolation?

Dr. Manning: A Canada-wide study of pregnant women's mental health trajectories throughout the pandemic might offer a way to quantify uncertainty, as they experienced limitations on who could be allowed in the delivery room.

Dr. Croff: One might be able to capture uncertainty by examining the differences between first and later pregnancies, as women who have given birth before know what to expect.

Dr. Terplan: I have been considering vaccine hesitancy and medical mistrust among pregnant women with a[n] SUD. Currently, there is mutual mistrust between patients and providers. In my view, patient mistrust is legitimate because so many women have experienced historical trauma and discrimination. Mistrust on behalf of providers is misplaced and based on prejudice, as they assume patients lie about or do not disclose substance use. Research and clinical contexts should provide a safe place to disclose substance use. The responsibility to create such contexts lies with researchers and clinicians. Telehealth visits make drug testing more difficult and have forced providers to think differently.

For the HBCD Study, women will provide urine specimens, and the data will be sent to a central repository. Women will be assured that the researchers will not share the results, but how can researchers make specimen collection more palatable to participants who feel mistrust?

Dr. Terplan: Establishing an alliance with patients is crucial to building trust. Historically, urine tests have been used as a tool for punishment, but they could be used for positive purposes. Making people aware that they have the right to refuse testing and emphasizing that submitting samples is voluntary are important to keeping patients engaged. Discussing patients' concerns about testing can help researchers and clinicians establish an alliance with them.

Dr. Krans: Pregnant women are more willing to provide samples for drug testing if the results will not be in their electronic health records.

Dr. Terplan: A general comment is that exposure to the SARS-CoV-2 virus and the effects of the pandemic both affect pregnant women and are important considerations for prenatal exposure

to substances and subsequent development. The data presented at this meeting suggest that we need to be more specific about stress and social structures and study how they translate into biological events.

Closing Remarks

Dr. Freund and Dr. Wu thanked presenters and panelists for a rich discussion. They thanked participants for their time and attention.