

Maternal Mental Health and Infant Development During the COVID-19 Pandemic

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IMPORTANCE The COVID-19 pandemic has prompted an unprecedented need to rapidly investigate the potential consequences for maternal mental health, infant and child development, and the mother-infant relationship.

OBSERVATIONS Globally, the mental health of pregnant and postpartum individuals has worsened during the pandemic regardless of infection status, and these concerning changes have disproportionately affected racial and ethnic minoritized people from underserved populations. Early indicators of infant neurobehavioral outcomes suggest that while in utero exposure to a maternal SARS-CoV-2 infection is likely negligible, limited data are available regarding the neurodevelopmental consequences for the generation of infants born during the pandemic. High maternal depression and grief during the COVID-19 pandemic are associated with lower levels of self-reported maternal-infant bonding. Yet nearly all published reports of child neurodevelopmental outcomes and dyadic functioning in the context of the pandemic rely on self-reported and parent-reported measures, which are subject to bias.

CONCLUSIONS AND RELEVANCE In the context of prior research, and considering the paucity of research on infant neurodevelopment following prenatal SARS-CoV-2 exposure and birth during the pandemic, robust scientific investigation is needed to detect indicators of compromised early outcomes that could inform widespread assessment and accessible intervention. We simultaneously caution against reflexive apprehension regarding the generation of children born during the COVID-19 pandemic.

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Over the first 2 years of the COVID-19 pandemic, significant efforts were made to study and characterize its mental health consequences for pregnant and postpartum individuals. Beyond the pandemic's profoundly unequal impact on underresourced and racial and ethnic minority communities,¹ many COVID-19-related stressors, including changes in medical care due to social distancing,^{2,3} financial strain,⁴ increased intimate partner violence,⁵ food insecurity,⁶ and loss of childcare,^{7,8} have disproportionately affected pregnant and postpartum individuals.⁹

Simultaneously, there have been global calls to action urging evaluation of the neurodevelopment of the generation of infants born during this crisis. Efforts have focused on assessing 2 hypothesized pathways of influence: The first purports that SARS-CoV-2 infection during pregnancy may alter neurodevelopment through vertical transmission of the virus.¹⁰⁻¹⁵ Despite this widely held hypothesis, there is a paucity of evidence to support vertical transmission of SARS-CoV-2 or associated effects of in utero viral exposure.¹⁶⁻¹⁹ The second pathway is based, in part, on the developmental origins of health and disease (DOHaD) framework. Specifically, maternal psychological experiences during pregnancy may confer infant neurodevelopmental risk through stress-based alterations in maternal biological processes that change the in utero environment and influence fetal development and future child functioning. In addition, stress-based changes in postpartum maternal behavior and mother-infant bonding are known to affect child outcomes.^{20,21}

With amplified hardship for pregnant individuals and those raising young children, especially among those from minoritized populations, and established pathways for intergenerational influences, identifying the pandemic's effects on this population, as well as on the bidirectional influences within the mother-child dyad, is essential for developing the public health agenda to mitigate potential adverse outcomes.

The goal of this Special Communication is 2-fold. First, we review the existing research on pandemic-related associations with mental health among pregnant and postpartum individuals, neurodevelopmental trajectories of infants and young children, and the mother-infant dyad. Second, we reflect on prior "natural experiments" and describe recommendations for future research aimed at assessing the potential influences of the pandemic on mothers and children across multiple dimensions to garner prospective, contemporaneous data on life circumstances affecting health across 2 generations.

Associations of the COVID-19 Pandemic With Mental Health, Neurodevelopment, and the Mother-Infant Dyad

COVID-19-Related Disruptions and Maternal Mental Health

The COVID-19 pandemic has resulted in widespread disruptions in prenatal and postpartum care, including cancellations of prenatal

visits, shifts to virtual appointments, visitor restrictions during and after delivery, and postpartum mother-infant separation to avoid COVID-19 transmission from mother to infant. Two large studies found that such changes, in addition to the perceived risk of having had COVID-19 while pregnant and being a woman of color, were associated with elevated symptoms of depression, anxiety, preparedness stress, and perinatal infection stress.^{22,23} These pregnancy-specific changes and disruptions are superimposed on social determinants of health (SDOH) and on the longstanding racial and ethnic inequities in maternal mental health care.²⁴ A US survey distributed to pregnant women in April 2020 revealed substantially increased stress due to food insecurity (59.2%), job loss or changes to income (63.7%), loss of childcare (56.3%), and conflict between household members (37.5%).²⁵ Experiencing more COVID-19-related stressors was associated with a greater change in pre-pandemic vs postpandemic pregnancy-related anxiety. A similar change in self-reported anxiety, measured before and during the pandemic, was substantiated by a second smaller study.²⁶ As with many aspects of the COVID-19 pandemic, racial and ethnic disparities in health and well-being were intensified. For example, in 1 study, negative COVID-19 experiences were associated with greater risk for postpartum depression among Black women who experienced high levels of structural racism, but not among those who experienced low levels of structural racism.²⁷

A rapid review and meta-analysis of 46 studies conducted between December 2019 and February 2021 evaluated the worldwide prevalence of anxiety and depression among pregnant individuals during the pandemic.²⁸ The meta-analysis demonstrated that 25.6% of the pooled sample met a clinical cutoff for depression and 30.5% met a cutoff for anxiety based on self-report measures or determination by a clinician. Additional studies conducted in Canada and Italy have reported anxiety symptoms in 57% to 68% of pregnant respondents.^{29,30} Anxiety levels were highest among those who were in the first trimester of pregnancy during the initial wave of the pandemic in Italy compared with those in the second or third. A second Canadian study found that, compared with a historical sample of pregnant women surveyed prior to the COVID-19 pandemic, a cohort of pregnant women assessed during the pandemic reported higher levels of dissociative symptoms, posttraumatic stress disorder symptoms, and negative affect.³¹

Collectively, these studies provide converging evidence that COVID-19-related disruptions, some of which are layered on already existing hardship, have significantly compromised the mental health of pregnant and postpartum individuals. Notably, nearly all reports to date either exclude those with a current or prior SARS-CoV-2 infection or collapse across those with and without a SARS-CoV-2 infection, suggesting that the association of the pandemic with perinatal mental health is profound regardless of SARS-CoV-2 status.³² Decades of research indicates that maternal infection may also affect the child through pathways of direct viral insults to the developing fetus, maternal stress that can alter the in utero environment, and/or maternal mental health symptoms that may undermine optimal parenting.^{12,14,15}

Infant Neurodevelopment During the COVID-19 Pandemic

As the first infants born during the COVID-19 pandemic begin to reach critical developmental stages, there are ongoing efforts to evaluate neurobehavioral features that may have implications for future

development. We recently found that prenatal exposure to maternal SARS-CoV-2 infection vs no exposure is not associated with differences at 6 months of age on any of the subdomains of a parent-report assessment, the Ages & Stages Questionnaire (ASQ-3), regardless of maternal infection timing or severity. However, comparing the combined cohort of 6-month-old infants born during the pandemic (with and without in utero exposure to maternal SARS-CoV-2 infection) to a historical cohort of 6-month-old infants born at the same institution before the pandemic, pandemic-exposed infants had significantly lower scores on the gross motor, fine motor, and personal-social subdomains of the ASQ-3.³³ Moreover, infants born to mothers who were in their first trimester during the peak of the pandemic in New York City had the greatest decrements in scores on all 3 subdomains.

A similar analysis from China comparing 6- and 12-month-old infants growing up during the pandemic with a historical cohort found that those developing in the pandemic environment scored significantly lower on fine motor and communication subdomains of the ASQ-3 at 12 months but not at 6 months of age.³⁴ When stratified by birth order, these differences remained significant only for the firstborn, suggesting a potential buffering effect of siblings during quarantine or improved coping strategies among experienced parents. In contrast with our report, none of the infants in the pandemic group were exposed in utero because they were born before its onset. A study of maternal psychological distress during the pandemic and infant brain development revealed associations between prenatal distress and changes in infants' white matter microstructure, as well as functional connectivity between the right amygdala and right superior orbitofrontal cortex and between the right amygdala and inferior frontal gyrus.³⁵ Taken together, these data suggest both prenatal and postnatal associations between the pandemic and neurodevelopment. However, it is important to note the paucity of research on this topic to date.

Relational Health of the Mother-Infant Dyad During the COVID-19 Pandemic

Accumulating evidence points to the mother-infant dyad as a unit necessitating its own assessment with bidirectional influences through epigenetic, behavioral, and psycho-social engagement during a time of robust brain plasticity in both mother and infant.^{36,37} Sensitive and synchronous maternal behavior promotes affiliative and reciprocal behaviors in the infant, which in turn reinforce the functioning of the dyad.³⁷ Simultaneously, qualities in the infant can elicit or reinforce different parenting approaches.³⁸ In the context of a pandemic during which there is both increased prevalence of maternal distress and evidence of altered infant neurobehavior, there is a need to understand the pandemic's association with the bidirectional influences between the mother and infant and the overall well-being of the dyadic relationship.

Reports of COVID-19-related psychological distress leading to disruptions in dyadic relational health are emerging. High maternal depression and grief during the COVID-19 pandemic were associated with lower levels of self-reported maternal-infant bonding, though somewhat counterintuitively, higher levels of COVID-19-specific health worries were associated with greater bonding, and there was no association between anxiety and bonding.³⁹ Results from the MOM-COPE cohort study revealed that higher perinatal maternal anxiety at delivery was associated with poorer self-reported

mother-infant bonding and higher infant *SLC6A4* methylation.^{40,41} Lower mother-infant bonding and higher *SLC6A4* methylation were associated with maternal reports of reduced infant regulatory capacity, including cuddliness, orienting, low-intensity pleasure, and soothability and maternal parenting stress, and the quality of mother-infant bonding mediated the association between maternal anxiety and infants' 3-month regulatory capacity.

In another report, individuals who delivered during vs those who delivered before the pandemic endorsed greater acute stress during and immediately after childbirth, with higher stress mediating the association between giving birth and higher childbirth post-traumatic stress disorder symptoms, lower maternal-reported ratings of infant bonding, and lower ratings of self-reported maternal attachment.⁴² In a study of infants born to mothers with a SARS-CoV-2 infection during pregnancy, the number of days of mother-infant separation, which may disrupt the early mother-infant relationship, was inversely associated with 3-month-old infant scores on maternal reports of communication, gross motor, and personal-social subdomains of the ASQ-3.⁴³

Of note, a comparison of 2 cohorts of postpartum women seeking treatment for postpartum depression either before or during the pandemic demonstrated higher rates and severity of postpartum depression and anxiety during the pandemic.⁴⁴ However, the 2 cohorts did not differ in mother-infant bonding, suggesting a protective effect of treatment-seeking behavior. Thus, with the exception of treatment-seeking mothers, higher perinatal maternal depression and anxiety but not COVID-19 health concerns are associated with reduced mother-infant bonding, which in turn is associated with qualities of infant temperament and neurodevelopment.

The COVID-19 Pandemic in Context: Prior Research and Recommendations for Future Directions

Before the COVID-19 pandemic, studies of neurodevelopmental effects of in utero viral exposure primarily focused on direct action of the virus on brain development and behavior without considering the influence of increased maternal prenatal stress. Influenza, rubella, poliovirus, herpes simplex virus, and HIV during pregnancy are associated with psychotic disorders in adulthood⁴⁵ and early studies of Zika virus have demonstrated language deficits in childhood.⁴⁶ Most relevant to SARS-CoV-2, there are few documented cases of SARS-CoV-1 and Middle East respiratory syndrome infection during pregnancy and consequently limited information on child neurodevelopmental outcomes.⁴⁵

Foundational knowledge about the role of maternal stress in shaping infant brain development and behavior has been gained through "natural experiments" studying previous pandemics, periods of famine, natural disasters, and war. Perhaps most famously, the Dutch Hunger Winter of 1944-1945 was a period of extreme famine and presumed stress in the Netherlands. Fetal exposure to maternal famine resulted in increased risk of schizophrenia in adulthood⁴⁷ but not disorders of childhood, hypothesized as a direct effect of inadequate nutrition. Project Ice Storm, which assessed child development after a severe storm in Canada, reports that in utero exposure to objective but not subjective maternal stress is associated with lower language and cognitive abilities.⁴⁸ A study

of infants in utero during Hurricane Katrina found that greater maternal posttraumatic stress disorder symptoms, postpartum depression, and hostility as measured by a self-assessment of symptoms of psychopathology (though not hurricane-related stressors) were associated with maternal report of difficult infant temperament.⁴⁹

Similar to prior natural experiment research, COVID-19 studies to date have either focused on the effect of viral exposure or the effect of maternal stress on child outcomes. Critically, many studies are not designed to disentangle the effects of the virus from those of the pandemic environment, including levels of maternal stress. For example, as indicated, many studies do not stratify their sample based on maternal SARS-CoV-2 status, collapsing across participants with and without an infection. The gestational timing of the infection and/or the maternal stress experience, as well as the severity of maternal disease symptoms, also are infrequently considered.

Clinics and hospitals such as the Columbia University Irving Medical Center/NewYork-Presbyterian Hospital, which introduced universal SARS-CoV-2 nasopharyngeal polymerase chain reaction and SARS-CoV-2 serological testing on admission for delivery, can enable researchers to determine potential associations with prenatal SARS-CoV-2 exposure and to disentangle infection-related effects from stress effects. Recognizing that this degree of information may not be available to all researchers, we encourage researchers to conduct prospective studies involving regular SARS-CoV-2 testing and tracking. When this is not possible, infection status and history could be obtained through electronic health records along with participant interviews to determine the specific timing and severity of an infection. Further, to identify the association with maternal psychological and socioeconomic stress, especially in the context of SDOH factors, it is important to go beyond a standard battery of self-reported mood questionnaires; the COVID-19 and Perinatal Experiences (COPE) survey, which was developed by the COVID Generation (COVGEN) Research Alliance,⁵⁰ includes items pertaining to COVID-19-specific psychological and socioeconomic stressors, including changes in access to food, job security, housing stability and safety, and other SDOH stressors.

As many institutions faced suspension of in-person research activities, self-reported and parent-reported measures have been the primary source of outcome data for nearly all published reports of child neurodevelopmental outcomes and dyadic functioning in the context of the pandemic, including our own. Self-reported and parent-reported measures are subject to bias, and we have previously purported that parent-reported measures of child development may be more a reflection of parental perception than of development per se.³³ Methods using direct observation of the child's functioning and mother-infant dyad are preferable. We strongly encourage researchers to modify existing paradigms and assessment protocols to allow for remote data acquisition from the participant's home, which confers the unique benefit of data collection in a highly naturalistic setting.⁵¹

Three primary goals should be considered when developing such protocols: (1) prioritizing safety of the participants and researchers, (2) optimizing data quality through pilot assessments and clear instructions for participants, and (3) minimizing participant burden by providing organized and simplified study materials.⁵² Following these principles, our ongoing COVID-19 Mother Baby Outcomes (COMBO) initiative³³ administers a modified version of

the Developmental Assessment of Young Child, Second Edition (DAYC-2), an observer-based assessment of infant neurodevelopment, through a Zoom session at 6 to 12 months of age. Caregivers are mailed a kit with items needed for the evaluation so that all assessments are standardized. During the administration of the DAYC-2, study staff administer items in 1 of 3 ways: (1) through direct observation of spontaneous behavior, (2) by asking the caregiver if the infant demonstrates a specific behavior, or (3) through instructing the caregiver to prompt a behavior. To assess the quality of the mother-infant dyadic relationship at 4 to 6 months of age, we remotely conduct novel paradigms (eg, a mask face experiment modeled after the Face-to-Face Still-Face Paradigm⁵³) and standard paradigms (eg, observed mother-infant interactions^{54,55}) aimed at assessing maternal behavior and sensitivity, child responsiveness, and the relationship quality of the mother-infant dyad.

Our study sample is socioeconomically diverse, and thus far we have found that mothers across the socioeconomic spectrum have been able to participate in the remote assessments. Remote assessments enable participants with fewer resources, who may have felt compelled to complete in-person assessments for compensation despite concerns about viral exposure, to receive the benefits of participation safely and autonomously, further reducing potential bias in the sample.⁵² In some geographic regions, it may be necessary to provide participants with mobile hotspots to ensure high-quality data collection.

Further, we note that most prior natural experiments and longitudinal studies of prenatal programming have not previously measured brain function in infants (there is a recent exception³⁵). The inclusion of neuroimaging may allow for early detection of compromised neurobehavioral outcomes. Such neuroimaging would further substantiate DOHaD science. Additionally, prior natural experiments have not measured brain function in mother-infant dyads to understand how brain function in one might be associated with the functioning of the other. In a subsample of participants in our COMBO initiative, including 50 dyads with maternal prenatal SARS-CoV-2 infection and 50 unexposed case-matched (by sex and gestational age) dyads, we are conducting functional magnetic resonance imaging studies on mothers and infants independently to examine the functional connectivity of socioemotional (fronto-limbic) circuits within the first year of life.

We hypothesize that pandemic-related stress will be associated with altered connectivity in both mother and infant, which will result in variation in caregiving behavior and dyad functioning. With these data, we will be able to evaluate associations between population-level, objective COVID-19-related stressors, including socioeconomic disruptions (as well as viral exposure), and brain functioning, as well as mental health outcomes in mothers and children. These

multidimensional and innovative research strategies may identify early signals of the pandemic's effect and contribute to rapid implementation of public health measures to ameliorate or prevent long-term effects.

Caveats to COVID-19 Research Findings

As with all research, it is essential to acknowledge limitations in methodologies and other cautionary issues. One concern is sample representativeness. Who is being enrolled in COVID-19-related initiatives focused on pregnant individuals and their infants? Those who are most affected by the pandemic and eager to share their experiences and/or in need of the monetary compensation? Or are the people most affected being missed because they are too distressed and/or time constrained to engage in research or lacking reliable Wi-Fi for remote data collection? As already described, much of the child outcomes to date are based on maternal report, such that the mother is the source of the independent and dependent variables, a concerning study design. How much is the stressful pandemic experience negatively biasing her assessment of her child? Disentangling long-standing SDOH factors from pandemic effects will necessitate rigorous attention. Furthermore, pandemic-related decrements in development must be identified as early as possible to garner public health resources for intervention.

Mechanisms of resiliency should also be identified. Despite the extreme hardships brought on by the pandemic, societal changes such as working from home and having increased time with family may have ameliorated the negative effects of pandemic-related stressors. Researchers must proceed cautiously, ensuring that any findings of adverse outcomes are rigorously replicated, that moderating factors in outcomes are identified, and that an entire generation of children is not prejudged as compromised in their neurobehavioral functioning.

Conclusions

The COVID-19 pandemic has upended lives, and it continues to ravage the world. It has a disproportionate reach into already disadvantaged communities, particularly underresourced and racial and ethnic minoritized individuals. The association between the pandemic and the mother-child dyad is largely unknown, necessitating careful research tracking of outcomes to develop rapid clinical translation to address potential enduring consequences for maternal mental health and children's development. Detecting the pandemic's early neurobehavioral effects on mothers and the next generation will provide insights into intervention strategies and contribute significantly to DOHaD and stress science.

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