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COVID-19 in pregnancy: implications for fetal brain development

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The impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy on the developing fetal brain is poorly understood. Other antenatal infections such as influenza have been associated with adverse neurodevelopmental outcomes in offspring. Although vertical transmission has been rarely observed in SARS-CoV-2 to date, given the potential for profound maternal immune activation (MIA), impact on the developing fetal brain is likely. Here we review evidence that SARS-CoV-2 and other viral infections during pregnancy can result in maternal, placental, and fetal immune activation, and ultimately in offspring neurodevelopmental morbidity. Finally, we highlight the need for cellular models of fetal brain development to better understand potential short- and long-term impacts of maternal SARS-CoV-2 infection on the next generation.

Potential transgenerational impact of viral infections in pregnancy

Some viral infections acquired antenatally can have lasting, potentially devastating, impacts on the developing fetal brain. Those viruses that demonstrate neuroinvasion and neurotropism—that is, the ability to invade the blood–brain barrier and infect neurologic tissues, such as Zika virus or cytomegalovirus—can directly damage the developing fetal brain if transplacental transmission occurs [1,2]. Other infections that do not cross the placental barrier, including viral infections such as influenza, have also been consistently associated with adverse neurodevelopmental outcomes in offspring, primarily via mechanisms related to maternal, placental, and subsequent fetal brain immune activation [3–8]. Adverse neurodevelopmental outcomes observed following prenatal infection range from autism spectrum disorder (ASD), attention deficit hyperactivity disorder, and cognitive dysfunction, to anxiety, depression, and schizophrenia [3,4,7–13].

Past pandemics have provided a window into potential neurodevelopmental consequences in subsequent generations. For example, individuals who were fetuses during the 1957 influenza pandemic had an increased risk for being hospitalized for schizophrenia as adults [12]. The rubella pandemic of 1964 was associated with a 10–15-fold increase in ASD and schizophrenia in offspring [14]. In a cohort of more than 115,000 pregnancies, fevers in pregnancy were associated with an increased odds ratio of up to 3.1 for ASD [11].

The potential for neurodevelopmental morbidity in offspring exposed prenatally to SARS-CoV-2 is therefore of great concern. Given the large number of exposed individuals, even a modest increase in risk for adverse offspring neurodevelopment would still have a massive public health impact [15–20]. More than 59 million people in the United States and 300 million worldwide have been diagnosed with coronavirus disease 2019 (COVID-19)1, including over 155,000 pregnant women in the United States [21]. With approximately 140 million live births occurring annually worldwide1, and the prevalence of SARS-CoV-2 positivity in pregnant women as high as 15% in urban centers [22], the numbers of children exposed to maternal COVID-19 infection...
in utero worldwide could reach up to 20 million per year, particularly in the setting of low COVID-19 vaccine uptake in pregnant populations [23,24]. In fact, a 12-month follow-up of more than 7000 deliveries in a large hospital system, including more than 200 COVID-19-exposed pregnancies, suggested that prenatal SARS-CoV-2 infection is associated with an increased risk for offspring neurodevelopmental diagnoses [25].

There are multiple potential pathways by which a maternal infection with SARS-CoV-2 could impact the developing fetal brain [13,26–28]: (i) via MIA (see Glossary) during key neurodevelopmental windows in pregnancy; (ii) via direct fetal infection of neurologic tissues via transplacental transmission of virus; or (iii) via compromised placental function resulting in adverse pregnancy outcomes associated with an increased risk of neurologic injury (e.g., fetal growth restriction, preterm birth, abruption). In this review, we present emerging evidence regarding the impact of SARS-CoV-2 infection during pregnancy on offspring neurodevelopmental outcomes, explore potential mechanisms by which prenatal SARS-CoV-2 exposure might impact the developing fetal brain, and discuss virus and host factors that might influence risk. Lastly, we discuss the need for cellular models to best study the impact of SARS-CoV-2 on the developing brain, and to identify individuals most at risk for adverse outcomes who may benefit from early intervention or therapeutics.

Early evidence of adverse neurodevelopmental outcomes in children with prenatal exposure to SARS-CoV-2

Mounting evidence suggests that SARS-CoV-2 infection can cause both acute and chronic neurologic and psychiatric sequelae in adult and pediatric populations [29–34]. A recent study from the UK suggests that 3.8% of children hospitalized with COVID-19 experience a neurologic complication that also has long-term consequences, ranging from behavioral change, hallucinations, and encephalopathy, to status epilepticus, encephalitis, Guillain–Barré/acute demyelinating syndromes, chorea, and psychosis [35]. A persistent problem in interpreting these data is the paucity of studies with well-matched controls – for example, to understand whether these sequelae reflect direct effects of SARS-CoV-2, or simply the consequences of any severe illness requiring hospitalization. One early report using neurocognitive assessments suggested that the pattern of deficits in adults was nonspecific, consistent with other complicated hospitalizations [36]. Still, in aggregate, these results suggest at least the possibility that SARS-CoV-2 – whether via inflammation or immune-mediated mechanisms or via direct infection of the central nervous system – can have a lasting impact on the developed (and therefore likely also on the developing) brain.

Early signals of adverse neurodevelopmental outcomes at 3–6 months, 1 year, and 1.5 years in infants and children exposed to SARS-CoV-2 in utero, and/or born during the COVID-19 pandemic are emerging [37–41]. A longitudinal cohort study of 57 infants with prenatal exposure to SARS-CoV-2 in China identified deficits in the social–emotional domain of neurodevelopmental testing at 3 months of age [40]. A preliminary report of 298 infants born to women with SARS-CoV-2 infection during pregnancy found evidence of developmental delay in 10% of infants at 12 months of age, although neither study included a noninfected comparator group [41]. Another preliminary report of over 7000 infants born during the COVID-19 pandemic to both SARS-CoV-2 infected and noninfected mothers identified an association between maternal SARS-CoV-2 exposure and a neurodevelopmental diagnosis at 12 months [25]. Importantly, that study found that while the association between maternal SARS-CoV-2 exposure and offspring neurodevelopmental morbidity was enhanced by preterm delivery, the presence of a neurodevelopmental diagnosis was not entirely explained by prematurity, suggesting a more specific mechanism of effect than simply SARS-CoV-2 contributing to pregnancy complications. Whether a definitive connection exists between prenatal SARS-CoV-2 exposure and neurodevelopmental disorders in offspring is not yet known, in part because most children born to women infected in the first wave of the pandemic
are still too young for reliable diagnosis of many neurodevelopmental conditions. Despite the significant limitations of epidemiologic and clinical data sets in defining causality or mechanism, these preliminary data demonstrate the potential for prenatal SARS-CoV-2 exposure to impact early neurodevelopmental outcomes.

**MIA and placental immune activation in response to SARS-CoV-2 infection in pregnancy**

MIA is a primary link between maternal viral infection and offspring neurodevelopmental disorders. Convergent data from animal models have demonstrated that MIA, rather than a specific virus or bacterial infection, is likely the final common pathway by which most maternal infections confer offspring neurodevelopmental morbidity [42,43]. Rodent models of maternal influenza infection resulted in offspring behavioral phenotypes consistent with ASD and psychosis [54], but many of the same behavioral abnormalities were present when uninfected rodent mothers were injected with poly[I:C] [54], suggesting that MIA rather than any specific pathogen mediates the neurodevelopmental morbidity in offspring [53,55]. Immune cell populations, effector cytokines, and inflammatory markers critical in mediating abnormal offspring behavioral phenotypes in models of MIA include T helper 17 cells/interleukin (IL)-17α, IL-6, IL-1Rα, tumor necrosis factor-alpha (TNF-α), IL-10, C-reactive protein, and the complement system, among others [10,56–68]. Many of these same cytokines and inflammatory markers are also dysregulated in COVID-19 infection in the non-pregnant population [69–76].

Immune activation at the maternal–fetal interface and in fetal cord blood has been observed in prenatal SARS-CoV-2 infection

Although the immune and inflammatory response to SARS-CoV-2 in pregnancy is only beginning to be characterized, early data show a proinflammatory cytokine phenotype in pregnant women with active SARS-CoV-2, with interferon-gamma (IFN-γ), IL-1β, and IL-6 most implicated, particularly in cases of severe COVID-19 disease [77,78]. Several studies have demonstrated the potential for maternal SARS-CoV-2 infection to stimulate an intense placental immune and inflammatory response [79–81], both in the presence (rare) [81] and absence (more common) [80,82,83] of direct SARS-CoV-2 infection of the placenta. Substantial infiltration of maternal immune cells into the placenta has been observed in cases of severe maternal COVID-19 disease, adverse neonatal outcomes, and heavy placental SARS-CoV-2 viral burden [81]. In addition, maternal SARS-CoV-2 infection is associated with hyperplasia and/or increased density of fetal placental macrophages or Hofbauer cells, typically in the absence of Hofbauer cell infection [80,84]. In placentas without evidence of direct SARS-CoV-2 infection, transcriptomic analysis has demonstrated upregulation of inflammatory pathways of maternal decidual natural killer and T cells and upregulation of interferon-stimulated genes (ISGs) in placental villous tissue [79,80]. Notable sex differences have been observed in the placental immune response to maternal SARS-CoV-2 [80], which suggests that sex plays an important role in fetal and offspring vulnerability to maternal SARS-CoV-2 infection.

Increased cord blood cytokine levels and altered cord blood immune cell profiles including increased proportion of natural killer cells, Vδ2+ γδ T cells, and regulatory T cells have been observed in maternal SARS-CoV-2 infection in the absence of fetal infection [85,86], pointing to the potential for MIA itself to generate a proinflammatory fetal response. Single-cell RNA sequencing of cord blood mononuclear cells demonstrates a significant impact of maternal SARS-CoV-2 on cord blood monocyte programs, with ISGs upregulated in CD14+ and CD16+ monocytes [87].
Importantly, observed fetal immune imprinting to date has been nonspecific to SARS-CoV-2, occurring in the absence of vertical transmission [86,87].

How can maternal and placental immune activation and inflammation impact the developing fetal brain?

Several candidate mechanisms have been proposed in models of MIA which may apply to maternal SARS-CoV-2 infection as well (Figure 1).

(i) MIA is associated with rapid induction of immune (e.g., type I–III IFN pathways) and proinflammatory responses (e.g., TNF-α, IL-6, IL-1β) in the placenta and the developing fetal brain,
particularly in the setting of activation via Toll-like receptor (TLR) 7/8 signaling pathways, and to a lesser extent for immune activation via TLR3/TLR4 signaling pathways [42,88–91].

(ii) Dysregulated placental serotonin signaling, as the placenta is the primary source of serotonin for the developing fetal brain [92,93]. Both maternal and placental immune activation and inflammation alter placental serotonin signaling, which in turn influences fetal brain development via impaired synaptogenesis, neuronal migration, and axonal targeting [93–97].

(iii) Maternal and placental immune activation are also associated with other alterations in fetal brain neurotransmitter signaling, including the dopaminergic, cholinergic, GABAergic, glutamatergic, and melanocortinergic systems (the latter mediated primarily by dysregulated leptin signaling) that influence fetal brain development and future risk for conditions such as schizophrenia, addiction, and disordered eating [49,98–103].

(iv) Maternal and placental immune activation are associated with placental and fetal brain mitochondrial dysfunction, oxidative stress, and disrupted protein homeostasis [88,91,104,105]. The maternal and offspring gut microbiome may also be important modifiers of the impact of MIA on the developing brain and offspring outcomes [56,105,106].

MIA models have pointed to aberrant programming of fetal microglia and dysregulation of cytokine networks as key mechanisms underlying abnormal fetal brain development, with microglia primed toward a proinflammatory phenotype and altered synaptic pruning implicated in offspring morbidity [59,107–110]. Given the extent of synapse formation and pruning that occurs in fetal and neonatal life [111–114], developmental microglial function represents a critical target for investigation to better understand the impact of SARS-CoV-2-driven immune activation on the developing fetal brain. MIA has also been associated with abnormalities of offspring neural progenitor cell proliferation; impaired neuronal migration; alterations in neuronal density and perineuronal nets; altered dendrite structure, synaptogenesis, and synaptic function and plasticity; and changes in interhemispheric and corticolimbic connectivity [49,66,105,115]. Thus, in utero exposure to SARS-CoV-2-related MIA may be associated with altered development of multiple brain cell types and functions, with the timing of the insult, presence or absence of other exposures, and intrinsic fetal characteristics such as fetal sex or genetic susceptibility dictating fetal resilience or vulnerability.

Transplacental transmission of SARS-CoV-2 and direct fetal infection: uncommon in observations to date

Transplacental transmission of virus capable of infecting neural tissue can have lasting and devastating consequences on the developing fetal brain. A key factor in understanding potential fetal infection risk is whether maternally acquired SARS-CoV-2 can transmit across the placenta, the primary physiological and immunological barrier preventing viral transmission from the maternal to fetal circulation [116–118]. The preponderance of evidence to date suggests that adverse neurodevelopmental effects of SARS-CoV-2 infection, at least with the ancestral strain and strains preceding the B.1.617.2 (Delta) variant, are more likely to occur via maternal and placental immune activation and downstream impact on the developing fetal brain, rather than via direct fetal infection with SARS-CoV-2 in utero [28,119]. Population-level data suggest that rates of SARS-CoV-2 positivity among newborns in SARS-CoV-2-exposed pregnancies range from 1% to 3% [83,120–124], with placental infection being a relatively rare event. One meta-analysis of case reports and case series estimated the rate of placental infection as 7% [125], although prospective studies have identified even lower rates of placental infection [83,84,126,127]. Protective mechanisms against placental infection include low rates of maternal SARS-CoV-2 viremia, preserved immune defenses at the syncytiotrophoblast border, and the lack of coordinated expression of molecules required for SARS-CoV-2 attachment and entry (ACE2 and TMPRSS2) into the syncytiotrophoblast [80,83,128]. Evidence supporting fetal infection – that is, documented viral particles in the sterile amniotic space or fetal tissue – has been limited to case reports [129].
Consistent with the observed low rate of placental infection and vertical transmission, data are now available from completed pregnancies exposed to SARS-CoV-2 during all developmental windows (first through third trimesters). To date, no characteristic congenital syndrome has emerged after prenatal SARS-CoV-2 exposure that would suggest direct fetal infection [122,123,130,131]. Prenatal neuroimaging studies in pregnant cohorts have similarly failed to identify evidence of grossly visible fetal intracranial pathology associated with maternal SARS-CoV-2 infection, though the small number of women included with severe or critical illness versus mild disease may limit generalizability of these findings [132,133]. All these data point to maternal and placental immune activation and consequent fetal neuroimmune activation as primary drivers of neurodevelopmental morbidity in SARS-CoV-2-exposed offspring, rather than direct placental and fetal brain infection as has been observed with Zika virus or maternal cytomegalovirus infection [1,2].

Potential vulnerability of the fetal brain to SARS-CoV-2 infection
Despite the aforementioned observational data against direct fetal infection as a major mechanism of risk to the developing fetal brain, animal and cellular models have demonstrated the potential for SARS-CoV-2 to directly infect fetal brain tissue, should the placental barrier be broached. A comprehensive analysis of fetal brain sequencing data from publicly available data sets identified low expression of canonical spike (S) protein interactors ACE2 and TMPRSS2, but high expression of novel S protein interactors throughout gestation, with highest expression occurring in the second and third trimesters, suggestive of increased vulnerability during this window of gestation [134]. Limited evidence from adult human and animal models suggest that the SARS-CoV-2 virus can bypass or disrupt the blood–brain barrier and gain access to neurological tissue [135–137]. Models using cerebral organoids with proteomic signatures similar to fetal brain tissue [138] have provided evidence of SARS-CoV-2 capability of neuroinvasion and neurotropism for the choroid plexus, cortical neurons, and glial cells [137,139–141]. Taken together, these data raise the possibility that neurodevelopment at the cellular level could be directly impacted by prenatal infection with SARS-CoV-2, if viral particles gain access to the fetal circulation.

SARS-CoV-2 variants of concern and potential fetal risk
A key caveat in interpreting the available data is that observations primarily reflect the effects of ancestral viral strains, while less is known about placental and fetal effects of recent variants of concern, in particular the Delta and Omicron variants. It is plausible that mutations associated with enhanced immune escape or transmissibility could impact the risk for transplacental infection. Unfortunately, detecting anything other than a large or abrupt increase in vertical transmission will require the accumulation of data over time.

Prenatal SARS-CoV-2 variant exposure and placental impact
Recent evidence showing a near twofold increased risk of stillbirth associated with maternal SARS-CoV-2 infection, with a greater magnitude of association during the Delta-predominant period of the COVID-19 pandemic [142], has raised concerns that the SARS-CoV-2 virus itself might be directly responsible for adverse pregnancy outcomes [129]. Of critical importance is whether Delta-variant SARS-CoV-2 infection may differentially affect either (i) placental function or (ii) the integrity of the placental barrier to infection and thus the susceptibility for vertical transmission and/or more direct effects on the developing fetal brain.

As previously noted, the emergence of new strains complicates generalizations about SARS-CoV-2 mechanisms of risk. Delta variant infections have been linked to higher viral loads [143] and an increased risk of hospitalizations [144] in non-pregnant individuals compared with prior variants, as well as increased severity of maternal disease in pregnancy [145–147]. Delta spike
P681R mutation may also affect virulence and tissue tropism by enhanced S protein cleavability by furin [148,149], a transmembrane serine protease that is widely expressed by both the placental syncytiotrophoblast [150,151] and fetal brain tissue [134]. Although a characteristic histopathological signature associated with maternal SARS-CoV-2 infection was not clearly identified with the ancestral strain [83,84,152,153], SARS-CoV-2 placentitis – the triad of histiocytic intervillitis, perivillous fibrin, and villous trophoblastic necrosis in the setting of SARS-CoV-2 infection – has emerged as a histopathological entity observed in association with both Alpha- and Delta-variant maternal SARS-CoV-2 infections, and has been linked to poor pregnancy outcomes including stillbirth in case reports [154,168]. Although definitive evidence linking Delta-variant SARS-CoV-2 placentitis to increased risk for fetal infection is lacking to date, these observations suggest the biological possibility that prenatal Delta-variant SARS-CoV-2 could lead to global placental dysfunction, and breach of the placental immune barrier.

**SARS-CoV-2-associated preterm birth and neurodevelopmental risk**

Prenatal SARS-CoV-2 exposure may also impact offspring neurodevelopment by contributing directly to adverse pregnancy outcomes. Indeed, SARS-CoV-2 infection acquired during pregnancy is associated with an increased risk of preeclampsia and preterm birth [25,122,155–158], outcomes which have independently been associated with offspring neurodevelopmental risk [159,160]. The association between SARS-CoV-2 and preterm birth complicates studies of neurodevelopment, because it impacts the ability to understand specificity of virus-associated risk. If the mechanism of action of SARS-CoV-2 is simply to cause maternal illness that, in more severe cases, contributes to preterm delivery, then full-term offspring should not experience elevated rates of neurodevelopmental sequelae, and efforts to investigate specific viral effects are unlikely to be necessary. By contrast, if this is not the case, it is critically important to understand the additive, or multiplicative, effect of the virus itself when preterm delivery occurs in the setting of or following maternal SARS-CoV-2 infection.

To date, only one study has addressed this question [25] and found that maternal infection was still associated with a greater risk for 12-month neurodevelopmental adverse outcomes after adjustment for preterm delivery. When analysis was limited to full-term deliveries, the magnitude of risk was diminished, and the 95% confidence interval included no effect, but risk in numeric terms remained substantial. While preliminary, this highlights the importance of well-controlled follow-up studies that evaluate the impact of gestational age at delivery.

**The role of cellular models in understanding mechanisms of risk to the fetal brain**

To date, efforts to understand MIA have largely focused on either large-scale human epidemiologic studies or human biological materials, which may indicate risk but are vulnerable to confounding, and animal models of disease, which allow more complete experimental control but may not recapitulate key elements of brain development. Cellular models can bridge these two investigative forms, particularly models that make use of primary human cells that may retain epigenomic effects of environment and infection. For example, in a prior work, patient-derived microglia-like cells differentiated from peripheral blood monocyte precursors demonstrated abnormal phagocytosis of synaptic materials, providing a potential mechanism of disease for schizophrenia or related disorders [161]. More recently, these protocols have been adapted to generate microglia-like cells from umbilical cord blood [162], providing a more direct means of characterizing the impact of in utero exposures for a specific individual. Another emerging strategy utilizes Hofbauer cells, fetal placental macrophages which may be isolated from the placenta after delivery and cultured [116]. An advantage of these cells is that, like microglia, they are yolk sac-derived, and thus may closely mimic the exposures and developmental processes of brain microglia [163].
Multiple published protocols also enable the generation of microglia-like cells from iPSCs. A limitation of this approach, compared with the prior two, is that generation of iPSCs entails disruption of the epigenome, prohibiting epigenomic investigations [164]. Alternatively, an advantage is that iPSCs can be expanded, banked, and used for large-scale experiments or screens. Regardless of source, such models provide an opportunity to conduct mechanistic studies in human cells to understand SARS-CoV-2-mediated effects.

Concluding remarks
The data presented here demonstrate the potential for maternal SARS-CoV-2 infection to drive maternal, placental, and fetal immune activation, and thus the potential for adverse fetal neurodevelopmental programming. Future studies will need to evaluate whether the feto-placental immune responses observed in maternal SARS-CoV-2 infection are associated with longer-term neurodevelopmental and neuropsychiatric morbidity in offspring. While the majority of available data are for third trimester infections or active infection at the time of delivery, the implications of infection earlier in gestation on offspring outcomes will be critical to a holistic understanding of risk. An important observation is that immune activation need not impact only fully differentiated cells – indeed, by impacting yolk sac-derived precursor cells, an early (e.g., first trimester) insult may still impact brain development via the microglial progenitor pool [165–167]. Thus, it is critical to understand not only direct/immediate effects on cells, but also persistent effects, as a putative mediator of neurodevelopmental consequences. How the timing of infection, variant strain, fetal sex, other prenatal exposures (e.g., maternal cardiometabolic conditions, substance use, stress, environmental or medication exposures, other infections in pregnancy), and perinatal/postnatal exposures (e.g., subsequent infant or child infection with SARS-CoV-2, breastfeeding status) intersect to impact offspring neurodevelopment will be important to a comprehensive understanding of the potential lasting impact of the COVID-19 pandemic on the next generation (Clinician’s corner and see Outstanding questions).

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Declaration of interests
The authors report no conflicts of interest.

Resources
https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100
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Outstanding questions
What will neurodevelopmental outcomes be in children exposed to prenatal SARS-CoV-2 infection at age 2 years and beyond?
Does trimester of maternal infection impact offspring neurodevelopmental outcomes?
Does prenatal SARS-CoV-2 infection that results in placental infection and/or vertical transmission have a differential (e.g., more severe) impact on offspring neurodevelopmental outcomes? Large, population-level studies will be needed to answer this question given the relative rarity of placental infection and vertical transmission.

How do variant strain and severity of maternal illness impact offspring neurodevelopmental risk?
What is the impact of fetal sex on offspring neurodevelopmental risk?
How do other pre- and perinatal exposures, and the postnatal environment, interact with prenatal SARS-CoV-2 infection to impact offspring neurodevelopmental risk?

How can cellular models be leveraged to understand neurodevelopmental risk at the individual level and guide precision interventions and/or therapeutics?
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