Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Society for Maternal-Fetal Medicine Special Statement: COVID-19 research in pregnancy: progress and potential

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The COVID-19 global pandemic has broad implications for obstetrical care and perinatal outcomes. As we approach the 2-year mark into an unprecedented international pandemic, this review presents the progress and opportunities for research related to COVID-19 and pregnancy. Research is the basis for evidence-based clinical guidelines, and we aim to provide the structure and guidance for framing COVID-19–related obstetrical research. This structure will pertain not only to this pandemic but future ones as well.

Key words: COVID-19 pandemic, fetal outcomes, healthcare policy, maternal outcomes, neonatal outcomes, obstetrical research

Introduction

The perinatal health consequences of a global pandemic arise from numerous sources, including social and structural impacts (such as barriers in the access to care, stress, and financial burdens); the direct impact of viral illness on maternal, fetal, and neonatal outcomes; and the use of new therapeutics in pregnant individuals. The COVID-19 global pandemic has broad implications for obstetrical care and perinatal outcomes. However, the systems stressors created by the COVID-19 pandemic have also affected the rapid development and synthesis of research, which could guide healthcare policy, clinical decision-making, and basic and translational research regarding pregnancy and COVID-19. As we approach the 2-year mark into an unprecedented international pandemic, this review presents the progress and opportunities for research related to COVID-19 and pregnancy. Research is the basis for evidence-based clinical guidelines, and we aim to provide the structure and guidance for framing COVID-19-related obstetrical research. This structure will pertain not only to this pandemic but future ones as well.

Social-Structural Impacts of the COVID-19 Pandemic on Perinatal Outcomes and Research

Social, Environmental, and Economic Impacts

The tectonic social and economic shifts accompanying the global waves of the SARS-CoV-2/COVID-19 outbreaks created social fragility as a result of isolation, the illness or death of loved ones, stress of caring for dependents, and need for homeschooling, as well as financial instability caused by job loss and generalized economic recession. Additionally, stay-at-home orders and work-from-home arrangements diminished environmental pollutant production and may have changed the physical stress related to certain jobs. Notably, the impact of these stressors is distributed unequally by race and class in the United States because of the existing institutional and structural racism and classism that perpetuates the disparate access to resources for health and opportunity. It will take years to understand the full impact of the social, environmental, and economic changes created by stay-at-home orders, physical and social isolation, and job loss. Understanding the social structural changes related to the pandemic and their perinatal impacts is paramount for understanding the current pandemic, preparing for future events, and improving perinatal outcomes in normal circumstances (Figure 1).

Psychosocial and community stress and pregnancy outcomes

The relationship between acute and chronic stress and pregnancy outcomes is a subject of decades-long study; stress during pregnancy is associated with preterm birth, low birthweight, and other adverse pregnancy outcomes.[1,2] Similarly, researchers have linked chronic stress and an increased allostatic load to persistent racial inequities in adverse perinatal outcomes.[3–5] Although data are limited, the additional stress and isolation because of the COVID-19

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pandemic are likely to impact perinatal outcomes, including exacerbating racial, ethnic, and economic inequities. Exposure to disasters—whether natural or human-made—impacts maternal mental health, and the severity of the exposure predicts more severe mental health outcomes.[6]

Intimate partner violence (IPV) increases in frequency during pregnancy and is associated with adverse perinatal outcomes.[7] The complex layers of instability during the pandemic have contributed to an increase in IPV across the globe.[8] Stay-at-home mandates in many countries were associated with increased calls to authorities for assistance with IPV.[9] In other regions, reports of IPV decreased, which some have attributed to the inability of those experiencing violence to discreetly and safely connect with the services.[8] Economic independence is a key element in separating from an abusive partner, which is more difficult to achieve during a pandemic.

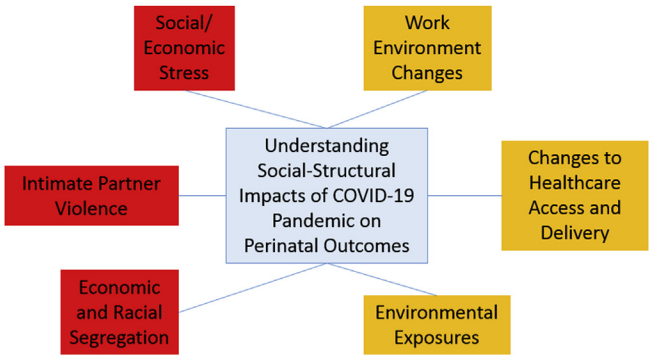
Like others working during the COVID-19 pandemic, pregnant individuals have experienced various changes in their work environments. Stressful working conditions (whether physical or emotional) have been implicated in adverse perinatal outcomes.[10] Work environment changes caused by COVID-19 may have both positive and negative impacts on work stress. A large survey of workplace changes related to COVID-19 and employee stress conducted at a large academic medical center revealed that workplace stress was higher than anticipated for most individuals.[11] However, some of this stress was mitigated by flexible work-from-home policies and transparent scheduling.

From a community perspective, COVID-19 hardships such as job loss, the proportion of COVID-19 infections and deaths, and business and school closures are not distributed evenly among neighborhoods or communities. Because of structural inequities, the impacts of the pandemic are concentrated in marginalized communities, which may, in turn, affect pregnancy outcomes. Economic and racial segregation are associated with low birthweight, small-for-gestational-age neonates, and preterm birth,[12,13] and these associations are most often attributed to chronic stress. These relationships may be further heightened because of the concentration of COVID-19 hardships in these same communities. For instance, in middle- and working-class Black communities, men are dying of COVID-19 at younger ages compared with White individuals.[14,15] The disproportionate loss of wage-earning, middle-aged Black individuals exacerbates the economic impact of the pandemic in these communities and may strain neighborhood recovery efforts.

Environmental exposures

As road and air travel decreased during the pandemic, air quality—measured by the amount of fine and coarse particulates and nitrous compounds present in the air—improved in some areas of the world.[16] The changes in air quality in the United States during the COVID-19 pandemic have been variable and appear related to population density and the timing and intensity of shelter-in-place mandates or business closures.[17,18] Fine particulates and other ambient pollutants have been implicated in an increased risk of preterm birth and other adverse outcomes.[19] However, as of the writing of this paper, there are no studies assessing the relationship between environmental pollution changes and adverse pregnancy outcomes during the COVID-19 pandemic.

FIGURE 1
Understanding the impacts of the COVID-19 pandemic on perinatal outcomes



This diagram depicts the intersection of contributors related to social (*red*) and structural (*yellow*) impacts of the COVID-19 pandemic on perinatal outcomes.

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Current areas of research

Given the complexity and interconnectedness of these macrosocial determinants of pregnancy outcomes, understanding the breadth and depth of the COVID-19 pandemic impact requires multidisciplinary efforts to bring the entire picture into focus and inform both the ongoing policies related to the pandemic and the preparation for future pandemics. Acknowledging the importance of the community and social determinants, the Eunice Kennedy Shiver National Institute of Child Health and Human Development's (NICHD) Gestational Research Assessments for COVID-19 (GRAVID) study[20]—a prospective observational study of over 200,000 women in 12 Maternal-Fetal Medicine Units (MFMU) Network centers—will include residential information in addition to standard medical record abstraction. This approach will permit researchers to understand the broader social and physical context of the pregnant individuals' experiences during the COVID-19 pandemic.

Areas for future research

Efforts to gather data about the psychosocial and macrosocial risk factors for poor pregnancy outcomes during the pandemic were understandably scattered and only rarely linked to adverse pregnancy outcomes because of low

numbers or the expense of follow-up. For instance, a survey on COVID-19–related anxiety in pregnancy did not collect data on pregnancy outcomes.[21] The most important areas of future inquiry in this arena include developing multi-institutional, multidisciplinary teams to accomplish large observational studies on the adverse pregnancy outcomes that we hope to measure. The GRAVID study will accomplish this objective for a subset of patients across the country and will be large enough to measure the maternal morbidity in addition to pregnancy outcomes such as preterm birth, stillbirth, and low birthweight. Perinatal research in this area would benefit greatly from partnerships with experts in other disciplines, including mental health experts, economists, sociologists, and geographers, to best represent and analyze complex macrosocial data.

Another opportunity for improved understanding is through observational studies that oversample smaller, at-risk populations. For example, Native and Indigenous peoples, especially those living on reservations in the United States, have been particularly devastated by the COVID-19 pandemic.[22] Structural inequity and broken treaty obligations have led to poor healthcare access, limited water and internet access, and transportation difficulties on Native reservation lands that exacerbate COVID-19 spread and worsen outcomes. Despite these difficulties, tribal leaders have developed rapid and resourceful responses based on the Native knowledge and community that may serve as learning opportunities for other systems.[23] However, large data gaps remain that hamper efforts to understand the scope of the problem or to disseminate knowledge. Developing partnerships with Tribal Epidemiology Centers and sovereign Native nations to highlight tribal knowledge (while preserving data sovereignty) around pregnancy and perinatal consequences of the pandemic among pregnant Native and Indigenous individuals would prove beneficial.

Alterations in Healthcare Access and Delivery

Current knowledge and ongoing research

Worldwide, changes of varying intensity occurred in healthcare delivery and access associated with shelter-in-place orders, including hospital capacity limitations and changes in healthcare delivery to limit disease transmission. Prenatal care, labor, and delivery occur over a relatively short period of weeks; therefore, changes in healthcare access may have a stronger impact during this compressed period. Diminished and altered access to healthcare is impacted by the macrosocial forces delineated in the prior section. An early modeling study funded by the Bill & Melinda Gates Foundation suggested that both maternal and child mortality were expected to increase in low- and middle-income countries with the COVID-19–related worsening of access to healthcare and malnutrition.[24] One prospective study in Nepal found a 50% decrease in "in-hospital births," and the authors surmise that pregnant individuals stopped presenting for care because of a fear of disease transmission in hospitals and a lack of public transportation because of lockdowns.[25] They also found an increase in perinatal mortality and preterm birth during the country's COVID-19 pandemic lockdown.[25] One study in the United Kingdom identified a higher rate of stillbirth during the pandemic period that was not associated with maternal SARS-CoV-2 infection as compared with a historic cohort,[26] which the authors speculate is associated with reduced prenatal care-seeking.[27] In contrast, other observational studies across Europe and the United States have identified a decrease in the preterm birth rate during the COVID-19 pandemic.[28,29] These conflicting findings highlight the need to assess not only access to healthcare but also to include the macrosocial impacts on preterm birth and perinatal mortality highlighted in the prior section.

Even as hospital systems struggled to respond to varying access challenges while diminishing disease transmission, alternative prenatal care models including telehealth, home blood pressure monitoring, and changes in antenatal visit timing, expanded rapidly.[30] Randomized trials of interspersing in-person antenatal visits with telehealth or remote services show equal rates of safety and similar or improved patient satisfaction for low-risk prenatal care compared with standard care.[31–33] However, the safety, efficacy, and patient tolerance of reduced-visit schedules and home monitoring using blood pressure cuffs and fetal Doppler monitors on a large scale are unknown.

Areas for future research

Because alterations in the availability or the delivery method of prenatal care may have benefits or risks both during and after the pandemic, research is necessary to determine the positive and negative effects of healthcare delivery changes including: (1) the differential impact of healthcare availability vs macrosocial changes (employment, environment, and psychosocial stress); (2) the equitable distribution of access to "COVID-safe" remote perinatal care access; (3) whether flexible and remote prenatal care options assuage psychosocial stress associated with the pandemic; and (4) the utility of interspersing remote monitoring and virtual prenatal care more widely even after the conclusion of the pandemic to increase prenatal care access more broadly.

Additionally, there is a need to survey access to and utilization of in-person and remote healthcare resources throughout the country in both urban and rural areas. Evaluation of payer databases (such as private health insurance, Kaiser, state Medicaid) linked to birth outcomes provides an avenue to investigate the differential utilization of telehealth vs in-person antenatal care visits and the relationship between patient demographics and perinatal outcomes. Concerns have been raised about inequitable access to telehealth care for patients without internet access, including rural, financially disadvantaged, homeless, and migrant patient populations.[34] A recent retrospective study of over 1000 rural US counties found that the loss of hospital-based obstetrical care was associated with

increases in both preterm births and out-of-hospital births.[35] Even before this pandemic, telemedicine has been studied as a means to improve healthcare access in rural areas. However, despite the potential benefits of telehealth, barriers continue to exist, including the cost of implementing such systems and technical issues such as broadband access.[36,37] Barriers to telehealth access and utilization are compounded by a general decline in access to obstetrical services in rural counties over the past decade[38] and highlights the importance of studying the impact of pandemic-related alternative healthcare models not just at a national level but also at regional levels in rural communities, migrant populations, and other vulnerable groups.

Clinical Studies on COVID-19 in Pregnancy

Susceptibility and Severity of COVID-19

Emerging novel strains of influenza and coronaviruses that cause severe respiratory disease[39–41] typically affect pregnant people disproportionately, in part because of the adaptive immunology and cardiopulmonary physiology of pregnancy.[42–47] Of note, the risks of morbidity with severe lower respiratory infections are not limited to maternal outcomes. Neonatal morbidity, including increased risks of preterm birth, fetal demise, and delivery of low birthweight infants, is associated with nearly all maternal severe lower respiratory viral infections.[39–42,47] Evaluating morbidity and mortality in pregnant vs nonpregnant adults is difficult because of inherent biases in reporting and publication. Data on whether pregnant women are more or less susceptible to severe COVID-19 disease remain mixed.[48–51] COVID-19 disease in pregnancy is associated with an increased risk of severe maternal and neonatal morbidity, including increased rates of preeclampsia, preterm birth, cesarean delivery, and low birthweight infants.[46,52–57] As the pandemic progresses, further data on the perinatal complications related to the trimester of infection should be evaluated. As we reach the midpoint of 2021, it is incumbent to understand horizontal (person-to-person) and vertical (mother-to-child) transmissibility and disease severity with the emerging SARS-CoV-2 variants and variant strains affecting individuals during pregnancy and the postpartum interval, especially among those who are not vaccinated.

The COVID-19 pandemic has laid bare the impact of structural and systemic racism on health outcomes. As in the nonpregnant population, COVID-19 has differentially affected Black and Hispanic pregnant individuals.[58,59] Data from the MFMU Network GRAVID study demonstrate that although the disease severity in pregnant individuals may not differ across racial groups, racial and ethnic minority groups are overrepresented among pregnant individuals who have tested positive for COVID-19.[60] This observation suggests that structural differences in access to healthcare resources and opportunities may drive increased infection rates among minority populations, leading to an increased burden of COVID-19 in these communities. Other socioeconomic factors contributing to an increased risk of perinatal COVID-19 disease were elucidated by a study conducted in New York City and include living with a higher number of individuals in the household, higher community unemployment rates, and living in larger residential units.[61]

The specter of implicit bias in healthcare delivery may also increase the likelihood of disparities in mortality or severe outcomes from COVID-19 infection. In addition, Black, Hispanic, and other individuals of color have disproportionately higher rates of hypertension, asthma, diabetes, obesity, and other chronic diseases at younger ages, which many attribute to the long-term health impacts of structural racism.[3,62] These increased rates of comorbidity are associated with increased COVID-19 severity and mortality at younger ages among Black and Hispanic individuals compared with Whites.[14,63] Mechanisms driving unexpectedly severe disease among healthier individuals are not yet elucidated; however, there is no biologically plausible reason why individuals of Black, Hispanic, or other minority racial or ethnic identities would develop more severe disease based solely on their race or ethnicity, as these are socially determined categories. A small number of studies in pregnant and nonpregnant individuals affected by the pandemic have highlighted the social construction of racial disparities,[61,64] but further work is needed to understand and dismantle the impacts of racism.

The NICHD is participating in the National Institutes of Health Rapid Acceleration of Diagnostics (RADx-UP) program, which will employ a perinatal health lens to this ongoing work.[65] The RADx-UP program seeks to understand the factors associated with disproportionate rates in COVID-19 morbidity and mortality and reduce disparities for underserved and vulnerable populations that are disproportionately affected by, have the highest infection rates of, and are most at risk of complications or poor outcomes from COVID-19. In addition, the NICHD GRAVID study will collect information about the perinatal outcomes of pregnant women infected with SARS-CoV-2.[66] Internationally, the NICHD-funded Global Network is examining maternal and neonatal outcomes in women with and without perinatal SARS-CoV-2 infection across multiple sites in South Asia and Africa.[67] Each of these ongoing studies will contribute to our understanding of COVID-19 in pregnancy, both from the standpoint of individual responses to the disease and the social determinants of COVID-19 outcomes in pregnancy.

Perinatal Morbidity and Mortality Reporting

Although initial reports from China suggested a possible protective effect of pregnancy against COVID-19 morbidity and mortality, more recently published articles from other continents report equally or more severe disease and mortality in pregnant individuals than in nonpregnant individuals,[54,55,68–70] similar to past pandemics. Although the reason for the differences between the initial reports from China and subsequent reports from elsewhere in the world is currently unknown, several possible explanations have been proposed. First, it is anticipated that during any

pandemic, initial reporting via case series will be incomplete and subject to nonrandom selection bias. The assessment of epidemiologic characteristics including case-fatality ratios during a pandemic may be affected by right (Type I) censoring and ascertainment bias. Right censoring reflects poor outcomes that may occur outside the time to reporting interval and tends to underestimate morbidity or mortality; in contrast, ascertainment bias of poor outcomes tends to overestimate mortality. Mizumoto and Chowell[71] report that when an emerging pandemic overwhelms a healthcare system, an underestimation of the true disease burden and ascertainment bias occurs. In addition, large upper limit confidence intervals will always accompany small case series with zero mortality, leading to a false reassurance regarding the risk of death in early reporting. Because of this censoring bias (which is exacerbated in pregnancy and postpartum periods because of their inherently prolonged intervals), future research in subsequent pandemics should not quantify the risk or estimate mortality rates based on case reports or small series.

Addressing this issue will involve developing adequate global reporting mechanisms to rapidly collect, analyze, and disseminate information in the setting of emerging viral pandemics. Notably, every pandemic of the last 20 years has disproportionately affected pregnant people and fetuses. In the last 10 years, delays in recognizing the high fetal morbidity and mortality during the Zika virus infection outbreak and maternal morbidity and potentially the mortality during the H1N1 and SARS-CoV-2 pandemics have occurred. Moreover, given the disproportionate burden borne by vulnerable populations, early and rapid data collection is critically important to reduce the global impact. Highlighting this point is the recent international collaboration that has provided one of the largest perinatal morbidity and mortality evaluations of COVID-19 in pregnancy thus far.[54]

Therapeutic Trials

Current knowledge and ongoing research

General therapeutic approaches to the treatment of COVID-19 infection include immune modulators, antibody therapies, antiviral medications, steroids, and other immune suppressants. As in many disease states, randomized clinical trials that enroll pregnant subjects are severely lacking. A recently completed trial on dexamethasone to treat COVID-19 did not exclude pregnant subjects[72] but treated them with prednisolone instead of dexamethasone. However, the number of pregnant subjects included was too small to draw relevant pregnancy-specific conclusions. The ongoing RECOVERY trial in the United Kingdom, which is evaluating several therapeutics for COVID-19, does not exclude pregnant women. Two clinical trials (ClinicalTrials.gov Identifier: NCT04365231 and NCT04410562) are investigating hydroxycholoroquine interventions specifically for COVID-19 in pregnancy, but most of the hundreds of registered clinical trials for COVID-19 explicitly exclude pregnant subjects.

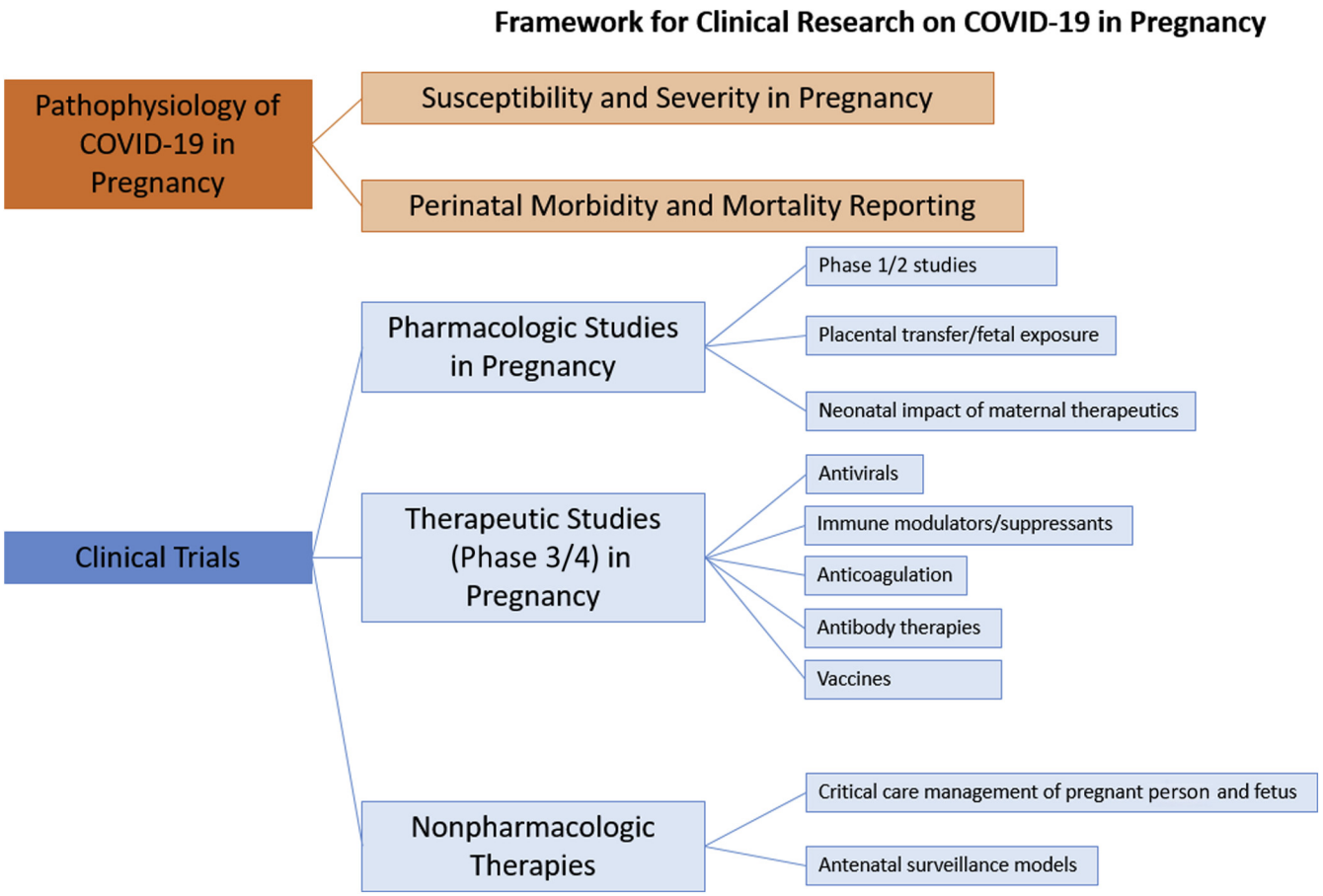
Areas for future clinical research

There is an abundant opportunity and need for clinical trials investigating therapeutics for COVID-19 in pregnancy. Figure 2 illustrates a framework for the needed clinical research efforts on COVID-19 in pregnancy. Although awaiting the inclusion of pregnant subjects in these trials, it should be noted that the absence of data is not equivalent to the presence of harm. Unless there is a known physiologic basis for an increased risk of harm (eg, a known teratogen), an intervention should not automatically be assumed to confer an increased risk because of pregnancy alone. Although the adaptive physiology of pregnancy increases the risk of morbidity and mortality from COVID-19 infection, these changes do not necessarily translate into disproportionate or unique risks of harm from therapies or vaccines for pregnant individuals or fetuses. The following discussion explores some unique considerations for the clinical trials of COVID-19 therapeutics and vaccines in pregnant individuals.

Phase 1/2 studies. In addition to safety and efficacy, phase 1/2 studies of COVID-19 therapeutics should include pregnancy-specific pharmacokinetics to understand how a drug's pharmacology could be altered during pregnancy. Pregnancy can substantially impact the pharmacokinetics of medications that are cleared renally or metabolized by certain hepatic cytochrome P450 enzymes that have increased activity in pregnancy.[73] Because pharmacokinetic studies can be time-intensive and expensive, other considerations include identifying intermediate biomarkers for therapeutic response to assess whether a similar response is achieved in pregnant compared with nonpregnant individuals. Additional safety considerations include studying placental transfer in animal or in vitro models and in vivo studies of cord blood and the neonate, whenever possible. For example, dexamethasone or betamethasone exhibits greater placental transfer and thus, greater fetal impact than prednisolone.

Phase 3/4 studies. The RECOVERY trial in the United Kingdom set a precedent by not excluding pregnant women, but few other studies have followed that lead. Clinical trials targeting pregnancy are severely lacking, and the inclusion of a small number of pregnant subjects in larger trials limits the pregnancy-specific interpretation of the risks, benefits, and adequate dosage. Pregnancy-specific studies are critical considering pregnancy-related disease modifications, including changes in immune activity, cardiovascular and respiratory physiology, coagulability, and inflammatory pathway activation. The lack of pregnancy-specific data could be easily rectified given that the therapies under study, such as the anticoagulants aspirin, heparin, or enoxaparin; anti-inflammatory drugs;

FIGURE 2
Suggested framework for categorizing required clinical research on COVID-19 in pregnancy



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and immunomodulators are already used frequently in pregnancy and have a reassuring safety profile.[74,75]

Multiple therapeutic areas should be studied specifically in pregnancy. The ideal regimen for anticoagulation in the setting of COVID-19 remains controversial.[76] This issue has not been studied in pregnancy,[77] a critical oversight given that the risks for thrombosis are inherently higher during pregnancy and the postpartum period. Furthermore, placental macro- or microthrombosis may be associated with preeclampsia and fetal growth restriction, which are additional outcomes that should be considered when studying the indications for and the timing of anticoagulation in the setting of COVID-19 in pregnancy. Another key area of interest is the management of critically ill pregnant patients. Maternal cardiopulmonary physiology and hematologic changes predispose pregnant people to hypoxemic respiratory failure and cardiopulmonary collapse. The COVID-19 pandemic highlights the uncertainty about the fetal effects of prolonged intubation, indications for delivery, and the applicability of therapies used to treat acute respiratory distress syndrome (ARDS) in nonpregnant people. For example, the feasibility, safety, and efficacy of prone positioning in pregnancy remain uncertain, although cases have been reported,[78,79] and the fetal effects and safe limits of permissive hypercapnia for ARDS management remain unclear.

Finally, the rapidly emerging SARS-CoV-2 vaccines must be addressed. Vaccine trials in pregnancy have begun (ClinicalTrials.gov Identifier: NCT04765384 and NCT04754594), and initial vaccination reports in pregnancy are emerging.[80–84] The ethics of a placebo-controlled vaccine trial in pregnancy when vaccines are available widely albeit still under an emergency authorization for a condition that has pregnancy-specific morbidity and mortality are questionable. However, pregnancy-specific studies are key, as shown by the studies of other vaccines (influenza, pertussis) in pregnancy that have yielded information about the timing of administration to optimize both maternal and neonatal immunity.[85,86] The specific areas of interest include: (1) strength and durability of immune response in pregnant people; (2) strength and durability of passive immunity in neonates via placental transfer and

breastmilk; (3) reduction in maternal and neonatal COVID-19 disease burden with vaccination; and (4) use of registries to evaluate the safety of vaccines during pregnancy and breastfeeding. Additionally, future trials to examine variant strain protection with vaccine "boosters" should be designed to include gravidae.

When including pregnant subjects in future clinical research, the following approaches may yield more rapid results while addressing ethical concerns. Rather than stagger placebo-controlled vaccine trials (or other therapeutic trials) in nonpregnant adults and then in pregnant individuals, we suggest including pregnant patients in the studies of therapies without evidence of maternal or fetal harm in preclinical studies. This approach allows rapidly emerging, novel, life-saving therapies to be approved with data available on pregnancy. For therapies already approved in nonpregnant adults, focused studies in pregnancy are also important; however, single-arm or dual active-arm studies are preferable to avoid withholding potentially life-saving therapy. Finally, the US Food and Drug Administration (FDA) has recognized the harm of excluding pregnant patients from research, acknowledging that "the frequent lack of information based on clinical data often leaves the healthcare provider and patient reluctant to treat the underlying condition, which in some cases may result in more harm to the woman and the fetus than if she had been treated." In addition to declaring that "development of accessible treatment options for the pregnant population is a significant public health issue,"[87] the FDA also provides basic guidance for the inclusion of pregnant patients in research.

Translational Research

Current Knowledge

SARS-CoV-2 pathophysiology

One reason that the severity of COVID-19 disease was initially underestimated in pregnancy is likely related to the challenges in classifying the distinct pathophysiology of the disease. The general effects of symptomatic SARS-CoV-2 infection (which functionally defines COVID-19 disease) are now appreciated to fall into 3 key categories: respiratory,[88] cardiopulmonary,[89] and systemic inflammation with or without sepsis or vasculitis (including the so-called "cytokine storm").[90,91]

Maternal immune response

Although it is frequently stated that pregnant women are "immunosuppressed," such assumptions are incorrect.[43] Rather, human pregnancy represents highly adaptive immunity, including the competency of B-cell-mediated humoral, innate, and T-cell–mediated immune responses that allow the pregnant person to become tolerant to the fetus yet remain immunocompetent to ward off pathogens.[43] There are emerging studies on both the maternal immune response and the vertical transmission of immunity.[92–95]

A profound cytokine storm leading to sepsis or a vasculitis-like response, which is the systemic inflammatory response identified with SARS-CoV-2, has now been well-documented.[90,91] In general, the most consistent pattern of this cytokine storm involves the upregulation of 3 general classes of cytokines and chemokines: (1) interferon-gamma–induced proteins (eg, interferon-gamma–induced protein-10); (2) monocyte chemotactic proteins (MCPs) and macrophage inflammatory proteins (MIPs; eg, MCP-3 and MIP1); and (3) interleukins (ILs) and interleukin receptor antagonists or agonists (eg, IL-1Ra, IL-1, and IL-10).

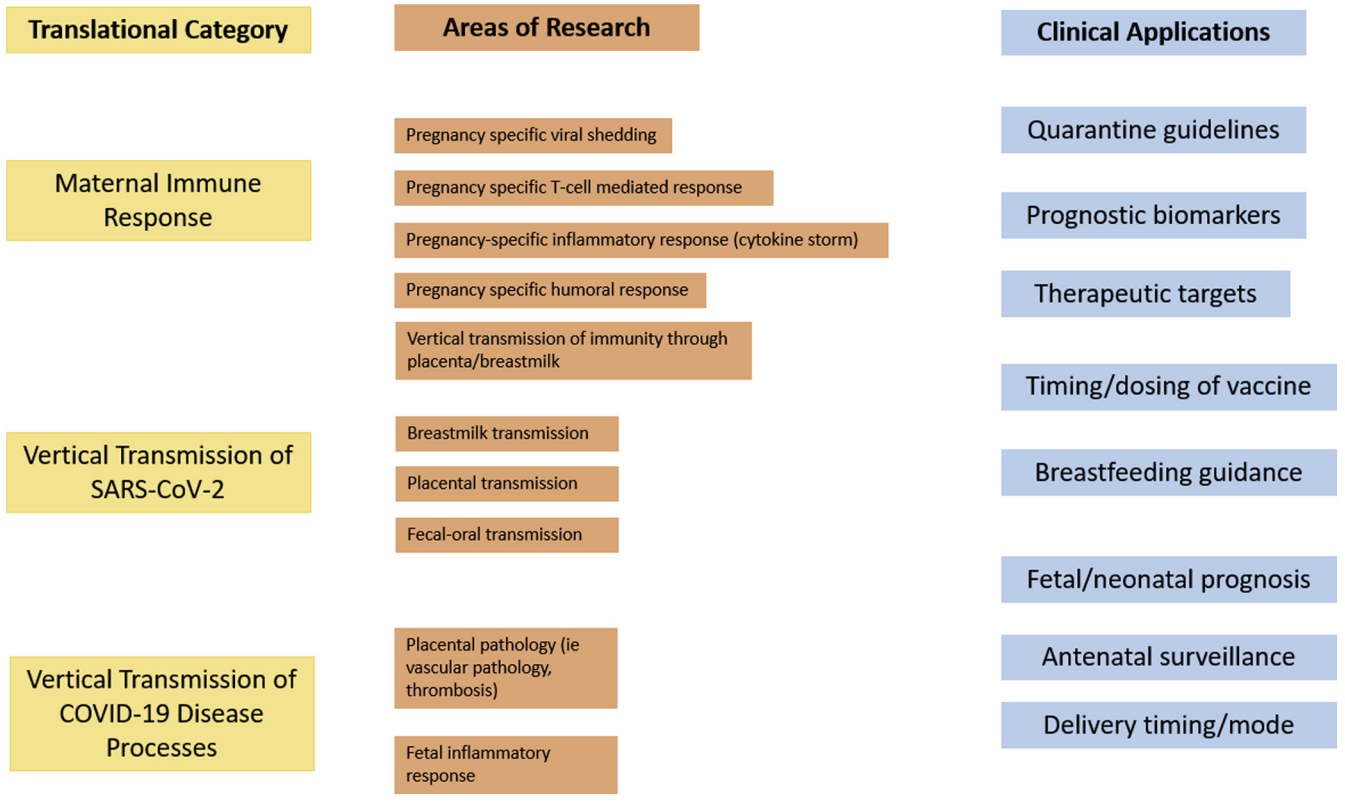
Placental pathology and vertical transmission

To date, it remains unclear how often the true vertical transmission of a live virus from a pregnant person to a fetus occurs. There are consistent reports of adverse perinatal and neonatal outcomes reported among pregnant women with SARS-CoV-2 infection and COVID-19 moderate and severe disease including preterm birth, stillbirth, intrauterine fetal demise (IUFD), neonatal death,[78,96–99] and placental pathologic findings related to SARS-CoV-2 exposure.[100–102] These outcomes are consistent with reports of adverse perinatal outcomes of stillbirth, IUFD, fetal growth restriction, and placental abruption seen with SARS-CoV-1 in 2003 and MERS-CoV in 2012. Understanding the mechanisms by which these viruses gain entry into cells may help elucidate how they could be vertically transmitted.

SARS-CoV-1 (the viral pathogen responsible for the SARS epidemic in 2003) and SARS-CoV-2 are both enveloped virions containing a single positive-strand RNA genome belonging to the *Betacoronavirus* genus of the *Coronaviridae* family. SARS-CoV-2 uses the same angiotensin-converting enzyme 2 (ACE2) as its putative cell entry host receptor as SARS-CoV-1 and bears 80% to 85% nucleotide homology to SARS-CoV-1.[103] Although both SARS-CoV-1 and CoV-2 bind ACE2 via the viral surface spike glycoprotein (S protein, 76% protein identity), potential differences in the role of specific serine and cysteine proteases in the cleavage of the S protein for priming for enhanced cell entry may exist between these 2 viruses.[103–105]

When considering the potential for vertical transmission, both the placenta and the stool or meconium may be of importance, because a less-lethal common *Coronaviridae* (229E) genus is known to be transplacentally transmitted. However, whether it uses the same or different cell entry receptors as SARS-CoV-2 (eg, ACE2) is unknown.[106,107] Moreover, although ACE2 mRNA is more highly expressed in human placental syncytiotrophoblasts early in gestation and the ACE protein localizes to fetal endothelium, the placental expression of the host proteases (such as transmembrane protease serine 2 [TMPRSS2] and others) necessary for the cleavage of the S protein and receptor priming is unknown and has generally only been described in lung and airway cells or their progenitors.[108] As a result, whether the necessary and sufficient host molecular machinery to enable the efficient transplacental vertical transmission and subsequent fetal infection is present or absent in the second- or third-trimester human placenta remains

FIGURE 3
Areas of translational research on SARS-CoV-2 in pregnancy and clinical implications



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controversial.[109,110] However, most high-quality studies consistently report the placental detection of SARS-CoV-2 virus, which may or may not portend clinically meaningful fetal infections detectable in the liveborn neonate.[100,101,110–122]

Regarding fecal-oral transmission, SARS-CoV-2 RNA has been found in the stool samples of people infected with the virus, some of whom tested negative from respiratory samples. Additionally, immunofluorescence visualization of biopsy specimens is consistent with viral uptake in the glandular cells of the gastric, duodenal, and rectal epithelia.[123–125] These findings raise concern for the possibility of fecal-oral transmission, which would have potential implications in obstetrical practice and risk of vertical transmission in pregnant patients who were known to harbor infectious virions in their stool or vagina at the time of vaginal delivery. However, infectious SARS-CoV-2 virion load in the stool or vagina is not known, and the demonstration of fecal-oral transmission remains purely speculative at this juncture.

Ongoing Research

Several studies are ongoing in this arena. Figure 3 provides a conceptual framework for both current studies and those that are needed in the future. Pregnancy CoRonavIrus Outcomes RegIsTrY study (PRIORITY), an observational cohort study of pregnant patients who were tested for COVID-19 and had a positive test result, has ancillary studies examining the vertical transmission of immunity and disease processes by collecting samples at delivery, including placenta and cord blood. The intramural branch of the NICHD (Perinatology Research Branch) is investing in translational studies of COVID-19 in pregnancy, which include understanding the biology of SARS-CoV-2, its effects on the placenta and lung tissue, and the mechanisms that lead to severe symptoms and death among older people and those with underlying health conditions (https://www.nichd.nih.gov/research/supported/COVID).

The NICHD is also participating in the RADx-UP initiative that aims to identify the biomarkers and tools to improve the diagnostic strategies for COVID-19 and predict the severity of COVID-19 disease in pregnant people and children.

Areas for Future Research

Prognostic biomarkers

Another specific area of need in COVID-19–related research is the identification of prognostic markers in pregnancy. Cellular and cytokine studies in COVID-19 have

shown rapid induction of antibody-producing cells and follicular T-helper cells during infection,[126] and SARS-CoV-2–specific cluster of diffentiation (CD), CD4+ and CD8+ T cells have been identified in convalescent patients.[127] Lymphocytopenia has been observed,[128] especially a reduction in CD4+ and CD8+ T cells, and it is predictive of COVID-19 progression.[129] In systemic cytokine responses, studies report that high levels of several cytokines associated with COVID-19, including IL-6 and IL-8, are associated with COVID-19,[129,130]suggesting that proinflammatory mediators contribute to disease severity. Notably, both the mild and severe forms of the disease result in changes in the levels of circulating cytokines and chemokines.[131]

To date, the effects of COVID-19–related cytokine responses (including the association with disease severity and the latency to delivery) on pregnancy are unknown. A maternal inflammatory response can lead to a fetal inflammatory response syndrome. Prior research suggests that increased levels of IL-6 are associated with preterm birth,[132] fetal growth restriction,[133] and fetal inflammatory response syndrome,[134] all of which are associated with adverse short- and long-term neonatal outcomes. These associations highlight the link between cellular/innate immunity and maternal and perinatal (fetal or neonatal) health.

Other biomarkers of interest identified in nonpregnant populations should be studied specifically in pregnancy because many of these markers are altered during pregnancy and labor. These biomarkers include inflammatory markers such as IL-6, C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase[135,136]; hematologic parameters including platelet count and activity and d-dimer levels[137]; and immunologic markers such as T-cell cytology.[129]

Characterization of the COVID-19 disease process

Although there have been many publications on the clinical course of COVID-19 in pregnancy, there are limited data on the immunological disease process. Research is needed to compare the variability in the viral burden and shedding in pregnant vs nonpregnant individuals; to determine whether the natural shift in immunity in pregnancy impacts the immune response in pregnant vs nonpregnant people; and track the time course of development and durability of antibodies during pregnancy, including transmission in cord blood and breast milk.

Placental pathology and disease transmission

A significant need remains for research into the incidence and mechanism of maternal-fetal disease transmission, especially in light of maternal vaccination and monoclonal antibody therapies. There are additional considerations about the role of the placenta in mediating or modulating both the viral burden and maternal disease. It is known that the placenta plays a role in the timing of onset and the severity of preeclampsia. Hosier and colleagues recently published a case of second-trimester symptomatic COVID-19 complicated by severe preeclampsia and placental abruption.[138] These investigators showed that SARS-CoV-2 localized predominantly to syncytiotrophoblasts at the maternal-fetal interface. However, distinct from the preeclampsia placental histopathology in the absence of COVID-19 disease, a dense macrophage infiltrate without vasculopathy was also identified. Other investigators also have shown an association between SARS-CoV-2 infection and both preeclampsia and fetal growth restriction.[49,139] Future research delineating the role of placental pathology independent of ACE2-receptor–mediated effects is an opportunity to interrogate novel mechanisms.

Impact of maternal disease on the fetus and neonate

Although vertical transmission appears to be rare, there are limited data on the impact of maternal disease on the fetus and the neonate, including the effects of a potentially prolonged inflammatory state, hypoxia, and thrombotic disease. These maternal conditions can impact fetal developmental pathways with long-term outcomes that have not yet been elucidated, including alterations in stress pathways, fetal inflammatory response syndrome, and epigenetic changes.

Conclusion

The COVID-19 pandemic has created a need for research into several key areas that pertain to pregnancy and maternal/fetal health from a population health level to a basic science level. The pandemic has highlighted how personal, social, environmental, and workplace changes may impact pregnancy, healthcare provision, and perinatal outcomes. The rapid advance of therapeutics for the treatment and prevention of COVID-19 has been admirable, but there remains a lag in the inclusion of pregnant populations and studies specifically on treatment and prevention of pregnancy-related complications. We have yet to fully understand the impact of SARS-CoV-2 on the maternal/fetal unit, including the immune and inflammatory response in pregnancy and the role of the placenta and placental pathology in perinatal outcomes and vertical transmission. We applaud the projects that are underway to explore these areas and highlight the gaps in current knowledge for future work. Such research is critical if we are to appreciate the current pandemic and prepare for future pandemics.

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