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The effects of COVID-19 on pregnancy and implications for reproductive medicine

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COVID-19 was officially declared a pandemic in March 2020. Since then, our understanding of its effects on pregnancy have evolved rapidly. Emerging surveillance data and large cohort studies suggest that pregnancy is associated with an increased risk of intensive care unit hospitalization, invasive ventilation, and death. Pregnancies complicated by SARS-CoV-2 infection are associated with increased likelihood of cesarean delivery and preterm birth. Intrauterine transmission occurs, but seems to be rare. Critical gaps remain, and rigorous high-quality data are needed to better ascertain pregnancy risks and to inform antenatal and obstetrical management. (*Fertil Steril*® 2021;115:824–30. ©2020 by American Society for Reproductive Medicine.)

Key Words: COVID-19, SARS-CoV-2, pregnancy, obstetrics, perinatal transmission

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Since the first reported cases of coronavirus disease 2019 (COVID-19) in December 2019 and the official declaration of the outbreak as a pandemic by the World Health Organization (WHO) in March 2020 (1), there has been an explosion of cases and exponential growth in our understanding of the virulence, epidemiology, and clinical characteristics of this disease. In this review, we summarize and synthesize rapidly evolving knowledge regarding COVID-19 in pregnancy and reproductive medicine, as well as discuss critical gaps in the literature.

DISEASE SEVERITY AND CLINICAL COURSE IN PREGNANCY

Studies of pregnant people presenting for delivery have shown rates of SARS-CoV-2 infection in the United

States to range from ~2% to 20%, depending on the level of disease in the community studied (2–5). Although pregnant people have been shown to be at higher risk for severe complications from other respiratory pathogens (e.g., SARS-CoV-1, MERS-CoV, and influenza viruses) (6–8), initial data did not consistently show pregnant people to be at heightened risk for severe disease from COVID-19. In February 2020, the WHO-China Joint Mission issued a 40-page report that briefly (3 lines) mentioned an investigation of 147 pregnant persons whose risk of severe disease (8%) was not higher than that of the general population (9).

There were inconsistent findings from several other initial reports from China comparing small numbers of pregnant women with nonpregnant controls; some reports found an

increased risk of severe disease while others did not (10–14). Wei et al. compared 17 pregnant women to 26 reproductive-age nonpregnant controls with COVID-19 and found no adverse outcomes (intensive care unit [ICU] admission, mechanical ventilation, or cardiac, pulmonary, or renal complications) in either group (10). Cheng et al. compared hospitalized pregnant women (n = 31) with nonpregnant women aged 22–41 years (n = 80) and noted that pregnant women were less likely to require supplemental oxygen (6% vs. 44%; $P < .001$) and less likely to have severe COVID-19 (3% vs. 19%; $P = .002$), including decreased risk of ICU admission (11). Qiancheng et al. compared 28 pregnant women with 54 reproductive-age nonpregnant women and reported increased rates of hospitalization in pregnant women (25% vs. 0%; $P < .001$) but no difference in frequency of mechanical ventilation or death; the authors did not indicate whether hospitalization was due to maternal or obstetrical indications (12). Similarly, Wang et al. found no differences in COVID-19–related complications between pregnant (n = 30)

Received November 13, 2020; revised December 23, 2020; accepted December 29, 2020; published online January 1, 2021.

N.T.J. has nothing to disclose. S.A.R. has nothing to disclose. D.J.J. has nothing to disclose.

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Fertility and Sterility® Vol. 115, No. 4, April 2021 0015-0282/\$36.00

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<https://doi.org/10.1016/j.fertnstert.2020.12.032>

and nonpregnant ($n = 42$) women, and the median duration of hospitalization was lower in pregnant patients (14.5 vs. 17.0 days; $P = .01$) (13). Conversely, Liu et al. assessed outcomes in 21 pregnant women versus 19 age-matched nonpregnant controls and reported no difference in the frequency of ICU admission or mechanical ventilation (14). These studies were limited by their retrospective design and small sample sizes. In addition, there may have been some overlap in cases.

Although early reports from the United States reported severe outcomes in pregnant women with COVID-19, many did not include an appropriate comparison group of nonpregnant women matched by age and underlying medical conditions (15–17). Later studies that included appropriate nonpregnant comparison groups suggested an emerging pattern of increased risk of disease severity in pregnancy. A national analysis of confirmed SARS-CoV-2 infection in all intensive care units in Sweden was one of the first studies to report increased morbidity in pregnancy. The authors compared pregnant with nonpregnant women aged 20–44 years and found an increased incidence of ICU admission in pregnant women (14.4 per 100,000 population [95% confidence interval (CI) 7.3–23.4]) compared with nonpregnant reproductive-aged women (2.5 per 100,000 [95% CI 1.8–3.5]); however, the authors could not differentiate between obstetric-related or disease-related indications for admission, nor were the data adjusted for underlying conditions (18). In a retrospective case-control study across four large hospitals in France and Belgium, Badr et al. compared 83 pregnant (>20 weeks' gestation) with 107 propensity score-matched nonpregnant controls and found that pregnant women were at increased risk of disease-related hospitalization (58.2% vs. 17.4%; $P < .001$), ICU admission (11.1% vs. 2.4%; $P = .02$), and invasive ventilation (10.2% vs. 1.7%; $P = .02$) (19).

The largest report suggesting heightened risk of disease severity in pregnancy was based on a review of laboratory-confirmed SARS-CoV-2 infections reported to the U.S. Centers for Disease Control and Prevention (CDC) from January to June 2020; the initial report found an increased risk of hospitalization, ICU admission, and mechanical ventilation, but not an increased risk of death (20). These data were recently updated through October 3, 2020, to include data from 23,434 symptomatic pregnant women compared with 386,028 symptomatic nonpregnant women aged 15–44 years with COVID-19. After adjusting for age, presence of underlying conditions, and race/ethnicity, pregnant women were significantly more likely to be admitted to an ICU (adjusted risk ratio [aRR] 3.0, 95% CI 2.6–3.4), require mechanical ventilation (aRR 2.9, 95% CI 2.2–3.8) or extracorporeal membrane oxygenation (aRR 2.4, 95% CI 1.5–4.0), and to die (aRR 1.7, 95% CI 1.2–2.4) compared with their nonpregnant counterparts. Although the study had several limitations, including missing pregnancy status in 65% of cases and potential reporting bias, with less severe cases likely underreported, these data suggest that pregnant women are at increased risk of severe disease compared with nonpregnant women of reproductive age (21). Several questions remain, including how the risk is modified by timing of the infection during pregnancy.

The clinical presentation and risk factors for severe disease in pregnant women are similar to those seen in nonpregnant reproductive-age women. Although the prevalence of various symptoms in pregnant compared with nonpregnant women varies in different reports (10, 14, 19, 22), a recent meta-analysis found that pregnant women were less likely to have fever and myalgia compared with nonpregnant women of reproductive age (23). However, large differences in clinical presentation have not been found. In one study, pregnant patients experienced a longer duration of symptoms, with 25% of women reporting persistent symptoms 8 weeks after symptom onset (22). Diagnostic findings also are similar, with pregnant patients with severe COVID as likely as nonpregnant patients to demonstrate abnormalities in laboratory values and radiographic findings (11, 14). Risk factors for severe disease in pregnant women appear to be similar to those seen in the general population and include obesity, hypertension, diabetes, and asthma (20, 24, 25). It is notable that approximately two-thirds of pregnant women with severe COVID-19 did not have an identified risk factor (23). A disproportionate percentage of COVID-19 hospitalizations in pregnancy, occurs in minority populations (20, 24, 25).

OBSTETRICAL COMPLICATIONS

Adverse maternal and obstetrical outcomes appear to occur more often among pregnancies complicated by COVID-19 than among unaffected pregnancies. Reports of SARS-CoV-2 infection in early gestation are scant and obstetrical outcomes have not been systematically reported. A few case reports have detailed outcomes in women with first- or second-trimester infection; pregnancy loss has been the primary reported outcome, although whether SARS-CoV-2 infection caused the pregnancy loss is unknown (26–28). In a case-control study that compared 100 cases of spontaneous abortion and 125 controls with ongoing pregnancies, no difference in the cumulative incidence of SARS-CoV-2 infection was seen (29).

Data from late second- and third-trimester pregnancies suggest an increased risk of adverse obstetrical outcomes associated with SARS-CoV-2 infection. Among Swedish women presenting in labor, SARS-CoV-2-positive women were matched by means of propensity scores with those testing negative; SARS-CoV-2-positive women were more likely than those testing negative to have preeclampsia (7.7% vs. 4.3%, prevalence ratio 1.84, 95% CI 1.0–3.4), although the finding was of borderline statistical significance. SARS-CoV-2-infected women were less likely to undergo labor induction (18.7% vs. 29.6%, prevalence ratio 0.64, 95% CI 0.45–0.90). Other maternal outcomes, such as postpartum hemorrhage and mode of delivery did not differ, nor was there any difference in neonatal outcomes including birth weight for gestational age, 5-minute Apgar score, and preterm birth (30).

Pregnant women with COVID-19 are more likely to be delivered by means of cesarean section, but it is unclear whether the indication for the cesarean delivery was for worsening maternal status, other obstetrical indications, or

concern for perinatal transmission. U.S. cohort data suggest that cesarean rates are higher in pregnancies with SARS-CoV-2 infection compared with noninfected pregnancies, with rates higher with more severe disease. Among pregnant women who were universally tested at hospital admission for labor, Prabhu et al. found that SARS-CoV-2-positive women were more likely to undergo cesarean delivery than women testing negative (46.7% in symptomatic COVID-19, 45.5% in asymptomatic COVID-19, and 30.9% in women without COVID-19; $P=.044$) (31). Among 241 pregnancies in New York City with confirmed SARS-CoV-2 infection reported by Khoury et al., cesarean birth was more likely among those with severe (relative risk [RR] 1.6, 95% CI 1.1–2.3) and critical (RR 2.8, 95% CI 2.0–3.8) illness compared to the group with asymptomatic SARS-CoV-2 infection; cesarean delivery was not more common among women with mild illness (RR 1.0, 95% CI 0.67–1.6) (15). A high rate of cesarean deliveries (~60%) was observed among SARS-CoV-2-infected pregnancies in the United Kingdom (U.K.): 16% of all deliveries were for maternal indication due to SARS-CoV-2 and 44% for other indications (25).

Many, but not all, studies show an increased risk of preterm delivery among SARS-CoV-2-infected women. Khoury et al. reported a preterm birth rate of 15% compared with the overall U.S. population rate of 10% in 2019 (15). Using two different U.S. surveillance systems, Panagiotakopoulos et al. and Woodworth et al. reported preterm birth rates of 12.2% and 12.9%, respectively, which were elevated compared with historic rates of 8.9% and 10.2% (32, 33). DeLahoy et al. reported higher preterm birth rates in symptomatic compared with asymptomatic women (23% vs. 8%) using the COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) (24). Knight et al. also reported an elevated frequency of preterm births (25%). Eighty percent were considered to be iatrogenic: 48% due to maternal COVID-19, 14% due to fetal compromise, and 18% due to other obstetrical conditions (25).

Conversely, studies incorporating SARS-CoV-2-negative pregnant control subjects were equivocal or failed to find increased risk of preterm birth, but were limited by small sample size (30, 34). Although the study by Flaherman et al. did not find a difference in preterm birth rates in mothers with SARS-CoV-2 infection and uninfected pregnant controls, the mean gestational age at delivery decreased from 39 weeks in women with COVID-19 diagnosed >14 days before delivery to 37.5 weeks for those diagnosed <14 days before delivery ($P=.0009$). No difference in neonatal complications in infants born to infected mothers (low birth weight, difficulty breathing, apnea, or respiratory infection through 8 weeks of age) was observed (34).

An increased risk of stillbirth has been reported in one study. Panagiotakopoulos et al. found stillbirth prevalence (3.2%) to be more than four times higher among SARS-CoV-2-infected women than their baseline rate (0.6%) (32).

PERINATAL TRANSMISSION

Perinatal transmission of SARS-CoV-2 may occur during pregnancy (intrauterine) or during labor and delivery (intra-

partum). The high proportion of cesarean deliveries among SARS-CoV-2-infected mothers has limited our understanding of intrapartum transmission. Intrauterine transmission occurs when SARS-CoV-2 crosses the placenta to infect the fetus. Several authors have proposed criteria for intrauterine transmission (35–37). Although there are important differences in these proposed criteria, in general, evidence for intrauterine transmission requires three elements: 1) maternal infection, 2) early fetal exposure (in-utero), and 3) persistence of infection in the neonate after birth. Although a number of case reports are consistent with possible intrauterine transmission (38–40), the most compelling evidence to date of intrauterine transmission was reported by Vivanti et al., who described a 23-year-old nulliparous female at 35 weeks' gestation with severe COVID-19 who underwent cesarean delivery for fetal indications. Maternal nasopharyngeal, amniotic fluid, and placental swabs, as well as neonatal blood and respiratory tract samples all tested positive for SARS-CoV-2, with neonatal nasopharyngeal samples persistently positive for >24 hours of life (41). Data regarding possible intrauterine transmission during the first- and early second-trimester infections are extremely limited; most congenital infections have occurred following maternal infection late in gestation. The majority of neonates with possible intrauterine-acquired SARS-CoV-2 exhibit mild symptoms. It is unknown how often intrauterine transmission occurs, whether fetal/neonatal risks vary by trimester of infection, and how maternal disease severity and delivery mode affect transmission risks.

HEALTH DISPARITIES

The COVID-19 pandemic has emphasized the contribution of structural racism and social determinants to health inequities. Similar to data from the general population, SARS-CoV-2 infection and disease severity have been higher in pregnant women who were racial/ethnic minorities, uninsured, low income, or from neighborhoods with low income, high crowding, or increased density. These findings have been seen in different U.S. locations (42, 43) and internationally (25, 44). COVID-19 has the potential to worsen existing disparities in maternal and infant mortality (45, 46).

INDIRECT EFFECTS OF PANDEMIC MITIGATION EFFORTS

In addition to direct effects of SARS-CoV-2 on infected pregnant women, the effects of pandemic mitigation efforts on uninfected pregnant women also need to be considered.

Effect of Lockdown on Preterm Birth

Data from several studies suggest declines in preterm birth during the lockdown period (47–49). In Denmark, the prevalence of extreme prematurity (≤ 27 wk 6 d) was significantly lower during the lockdown period than during the same time period in previous years (odds ratio 0.09, 95% CI 0.01–0.40) (47). Using quasi-experimental methods in the Netherlands, Been et al. demonstrated reduction in preterm birth across gestational age strata, but it was

statistically significant only for gestational age of 32 to 36 weeks 6 days (48). Similarly, Philip et al. found a 73% reduction ($P=.022$) in the rate of very low birth weight (<1,500 g) infants during the lockdown period in Ireland compared with data from the preceding two decades (49). The authors did not determine whether the reductions were due to differences in spontaneous versus indicated preterm birth. The mechanism responsible for the reduction in preterm births is unknown; further study of these findings could lead to identification of measures to reduce preterm birth.

Data on rates of stillbirth during the pandemic from the U.K. and from Nepal tell a different story (50, 51). The study from the U.K. showed a significantly higher incidence of stillbirth during the pandemic period (9.3/1,000 births) than during the pre-pandemic period (2.4/1,000 births) (difference 6.9/1,000 births, 95% CI 1.8–12.0; $P=.01$) (50). Similarly, data from Nepal showed an increased risk of stillbirth during the lockdown (21/1,000 births) compared with before the lockdown (14/1,000 total births; $P=.0002$) (51). Whether these findings were due to direct effects of COVID-19 or an indirect effect associated with changes in health care attendance or delivery is unknown.

Maternal Psychologic Impact

Reports have demonstrated worsening of maternal mental health status and increased isolation during pregnancy and the postpartum period related to the pandemic. A cross-sectional study of postpartum depression in a setting with universal prenatal depression screening demonstrated increased rates of depressive symptoms after the pandemic declaration (29.6%) compared with before (26.0%; $P=.02$) (52). Higher levels of pandemic-related stress in pregnant women were associated with abuse history, chronic illness, income loss due to the pandemic, perceived risk of having had COVID-19, alterations to prenatal appointments, high-risk pregnancy, and being a woman of color (53). The pandemic's effects on maternal mental health and well-being, partner bonding (given restrictions in visitor policies and labor personnel), and long-term familial well-being will need to be explored (52, 54).

Health System Changes

The COVID-19 pandemic and associated mitigation efforts have had significant effects on health care systems. Shifts in health care delivery toward emergency preparedness and response might have led to reduction in other health services, which could have deleterious downstream effects in reproductive health (e.g., increase in unplanned pregnancies, increased sexually transmitted infections, decreased prenatal care attendance, and increased maternal and infant mortality) (55). Several reports have documented potentially deleterious effects related to reduced health care seeking behaviors, including reduced prenatal care utilization and hospitalizations (56–59).

However, the response to COVID-19 has also brought about innovations around health system delivery

including the widespread rapid implementation of telehealth. A randomized controlled trial conducted in the U.S. before the pandemic demonstrated that a model of prenatal care that reduced the number of in-person prenatal visits and incorporated home monitoring and virtual care was associated with high acceptability, reduced pregnancy-related stress, and similar perceived quality compared with usual care (60). However, telehealth services had not been commonly used in obstetrics before the pandemic. During the pandemic, the CDC recommended optimizing use of telehealth services and the federal government improved access to telehealth services. In addition, the American College of Obstetricians and Gynecologists published recommendations for telehealth use in February 2020. Models of prenatal care that reduce in-person visits and increase telehealth visits were rapidly integrated into many health care systems. In addition to potentially reducing the risk of exposure in the health care setting, models such as this found high patient satisfaction (61). In addition, this has the capacity to improve access, attendance, and utilization of pregnancy services to those previously unable to access care. In this way, health systems are capitalizing on health information technologies and mobile health platforms to improve access, especially to those in remote or resource-limited settings.

CRITICAL GAPS AND PRIORITY RESEARCH AREAS

As we continually learn more about COVID-19 in pregnancy and the implications for reproductive medicine, critical gaps remain. Ideally, to better understand the effects of pregnancy on COVID-19, studies would compare pregnant persons with COVID-19 with appropriately matched nonpregnant persons with COVID-19. To better understand the effects of COVID-19 on pregnancy outcomes, studies would compare pregnant persons with COVID-19 with appropriately matched pregnant persons without COVID-19. Unfortunately, many studies have not included appropriate comparison groups.

To date, evidenced-based data to guide preventive and therapeutic interventions for the management of COVID-19 in pregnancy are lacking. A systematic review of ongoing COVID-19 therapeutic clinical trials listed at [ClinicalTrials.gov](https://www.clinicaltrials.gov) through June 29, 2020, demonstrated that pregnancy was an exclusion criterion for many studies of therapeutics for COVID-19 (e.g., 69% of chloroquine/hydroxychloroquine, 80% of lopinavir/ritonavir, and 48% of convalescent plasma studies), despite use of these medications and knowledge about their safety profiles during pregnancy for other clinical indications (62). Until such data are available, a sensible approach that balances the strength of available data, disease severity, and the maternal, fetal, and neonatal implications is required (63).

Although pregnancy should not be an exclusion for patients otherwise eligible for therapeutic and preventive interventions, better data are needed to inform pregnancy-specific effectiveness, risks, and benefits. For example, prone positioning has been demonstrated to reduce severity of lung injury and mortality in patients with moderate to severe disease (64, 65). Modified prone positioning is feasible in late gestation (66), but its effectiveness has not been established

and whether this is an acceptable alternative that mitigates poor outcomes is not known. Similarly, remdesivir and tocilizumab have safely been administered in pregnancy outside of clinical trials (67, 68) but these data are difficult to assess given lack of clear criteria for administration, difficulty to establish therapeutic efficacy, and inability to provide pregnancy-specific guidance for administration and monitoring.

Similarly, at the time of writing there are more than 130 candidate vaccines under development, 11 vaccines are in phase 3 clinical trials, and at least one vaccine has preliminarily demonstrated clinical efficacy in preventing SARS-CoV-2 infection. (<https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html>). National organizations have called for the prioritization of pregnant women in vaccine trials, yet as of October 19, 2020, all but one of 39 COVID-19 vaccine trials recruiting adults aged 18–45 years listed pregnancy/breastfeeding as an exclusion criterion (phase I/II trial NCT04568031). A seminal report from the National Academy of Medicine Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies highlighted the extent to which the interests of women were underrepresented in biomedical research efforts and the harms associated with their inadequate inclusion in the research agenda (69). The PREVENT working group, a joint collaboration of experts across academia, industry, and government, expanded this guidance to focus specifically on pregnant women and vaccination. In “Pregnant Women and Vaccines Against Emerging Epidemic Threats: Ethics Guidance for Preparedness, Research, and Response,” they call for the “presumptive inclusion of pregnant women” and to “normalize the position that pregnant women are to be included in vaccine deployment programs and vaccine research and development. With inclusion of pregnant women as the default position, the burden of proof, both scientific and ethical, falls on those who want to argue for their exclusion.” The authors provided 22 concrete recommendations for ethically responsible, socially just, and respectful inclusion of the interests of pregnant women in the development and deployment of vaccines against emerging pathogens (70).

CONCLUSION

Our understanding of COVID-19 has evolved rapidly. Pregnancy appears to be an independent risk factor for severe COVID-19-associated complications. Severe COVID-19 in pregnancy is associated with increased rates of cesarean delivery and preterm birth. Efforts to make evidence-based recommendations regarding care of pregnant women and their newborns are hampered by the paucity of rigorous high-quality data. Improved reporting systems are needed to inform new standards in maternal care. Until such data are available, we must harness lessons learned from other infectious outbreaks, such as the importance of fostering research, public health surveillance, synthesizing and integrating rapidly evolving research into clinical practice, and mitigating disease transmission whenever possible.

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