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Pregnancy and COVID-19: past, present and future

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Current evidence suggests that severe acute respiratory syndrome coronavirus 2 infection is associated with an increased incidence of adverse severe maternal and perinatal outcomes. However, vertical transmission is rare. The management of pregnant women with coronavirus disease 2019 (COVID-19) is similar to that of non-pregnant women, and effective treatments, including antiviral therapy, dexamethasone, and prophylactic anticoagulation should not be withheld during pregnancy.

During the early COVID-19 pandemic period, the management of pregnant women was often delayed until the polymerase chain reaction (PCR) results came out or due to close contact, even among those without symptoms. Out of concern for the spread of infection, cesarean sections were performed instead of vaginal birth, since infection could have led to an increase in maternal and neonatal morbidities. Additionally, if the maternal PCR test was positive, the neonate was quarantined, and despite infectivity decreasing 10 days after symptom onset. It is necessary to ease the strict measures of infection control in the field of obstetrics.

The presence or absence of maternal COVID-19 symptoms should be identified to stratify the risk, and vaginal delivery can be attempted in asymptomatic women with low infectivity. With more women being vaccinated safety data about vaccination is rapidly accumulating and no concerns have been detected. Globally, COVID-19 vaccines are recommended even during pregnancy. In order to prepare for future pandemics, it is necessary to apply lessons learned from this pandemic. Policymakers and healthcare leaders must determine efficient and effective strategies for preserving safe maternal care, even during an ongoing global emergency.

Keywords: Pregnancy; COVID-19; Severe acute respiratory syndrome coronavirus 2; Risk factors; Vertical infection transmission

Introduction

During the early phase of the coronavirus disease 2019 (COVID-19) pandemic, pregnant women faced uncertain maternal and perinatal risks associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1].

Compared with non-pregnant patients, the severity and susceptibility to infectious diseases during pregnancy is different because of immunological alterations induced by hormonal changes [2]. Estradiol in high concentrations during pregnancy enhances several aspects of innate immunity, whereas, progesterone produced by the placenta suppresses the maternal immune responses [2,3]. As pregnancy advances, the activity of T-cell, natural killer cell, and possibly B-cells decreases through the complex interplay between sex hormones and the immune system, which causes an increase in the severity of some infections in late pregnancy [2,4]. Similarly, with COVID-19, the prevalence of symptomatic and severe infections increases in the later stages of pregnancy [5-7]. Functional residual capacity, end-expiratory volume, and residual volume also decrease steadily due to diaphragmatic splinting and elevation by the gravid uterus. This results in a reduced total lung capacity and an inability to effectively clear pulmonary secretions [8]. Besides these immunological

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and physiological alterations, increased oxygen consumption and respiratory mucous membrane edema could potentially affect the severity and susceptibility to COVID-19 in pregnant women, increasing hypoxic compromise [9-12].

The optimal management of pregnant women with COVID-19 remains under debate because of concerns regarding its effect on neonates. In a global systematic review, meticulously observed increases in several adverse maternal and neonatal outcomes during the pandemic were noted compared to before it. These adverse outcomes resulted from the pandemic, its effects on the healthcare system and its direct impact on pregnancy. Initial data were not national representative samples, lacked appropriate comparison groups, and could not be adjusted for confounding factors, and thus, the results could be biased. The prevalence of SARS-CoV-2 infection among pregnant women is reportedly 3-20% with a broad spectrum of severity, ranging from asymptomatic to extremely severe cases [13,14].

Herein, we have reviewed the latest information on COVID-19 in pregnant women and adverse maternal and perinatal outcomes. Additionally, we discussed vaccine administration, management, and prenatal counseling regarding COVID-19 during pregnancy.

Mechanism of maternal influence of COVID-19

SARS-CoV-2 infection in pregnant women can lead to a variety of consequences, ranging from asymptomatic cases to critical diseases, which is similar to infections in non-pregnant women [15-18]. The World Health Organization reported that approximately 80% of COVID-19 infections during pregnancy are mild or asymptomatic, 15% are severe and require supplemental oxygen, and 5% are critical, requiring mechanical ventilation [19]. However, other studies suggest that 40-45% of the infected population [20], or even only 20% [21], remain asymptomatic. Lee et al. [22] reported that 13.6% of the infected pregnant population in South Korea was asymptomatic. Preliminary data suggests that infection with the delta variant during pregnancy may be associated with a higher risk of placental dysfunction and fetal compromise than the previous alpha and omicron variants [22,23].

Although most pregnant women with SARS-CoV-2 experience mild disease and recover, 1 in 11 develop a severe or critical disease, 1 in 10 are hospitalized specifically due to a COVID-19 concern, 1 in 30 are admitted to the intensive care unit (ICU) for respiratory concerns, 1 in 60 are mechanically ventilated, and 1 in 80 die, suggesting an increased risk of hospitalization and an elevated case-fatality rate among pregnant women compared to non-pregnant women of a similar age [24]. Shortness of breath reportedly occurs in 18% of patients with COVID-19 [12]. Physiological dyspnea, due to increased maternal oxygen demands from a heightened metabolism, gestational anemia, and fetal oxygen consumption is common in pregnancy and must be distinguished from pathological breathlessness.

Compared to non-pregnant women, pregnant women are three times more likely to be admitted to an ICU, 2.9 times more likely to require invasive ventilation, and 1.7 times more likely to die [25]. A Canadian surveillance study and Norwegian population level analysis also showed that the risk of hospitalization and ICU admission was significantly higher among pregnant women with COVID-19 than among non-pregnant women in the reproductive-age group [26,27].

The pandemic and its effects on the healthcare system could have also caused adverse maternal morbidities. In South Korea, where COVID-19 was controlled relatively well without any lockdowns or medical health system collapse, most pregnant women with COVID-19 were less likely to manifest symptoms and showed less severe disease progression [22].

Older age and underlying medical conditions are associated with an increased risk of moderate-to-severe or critical COVID-19 illness among pregnant women. This information can be used for targeted public health messaging to help pregnant women understand their risk of moderate-to-severe or critical COVID-19 illness [28,29]. The risk factors for severe disease are similar between pregnant and non-pregnant women [18,30], and include obesity, older age, and underlying medical conditions such as chronic lung disease, chronic hypertension, and pre-gestational diabetes.

Possible complications of COVID-19 in mothers

Most studies, except one, have reported that COVID-19 infection during pregnancy is associated with a higher rate of preterm birth [27,31-34]. National data in the United King-

dom and United States (US) registries of pregnancies with COVID-19 suggest that pregnant women should be counseled that SARS-CoV-2 infection increases the risk of preterm delivery [35]. Fever, hypoxemia, and severe respiratory disease increases the risk of preterm labor and premature rupture of membranes. Initial data showed that >90% of hospitalized mothers with COVID-19 had pneumonia, and preterm birth was the most common adverse pregnancy outcome. Additionally, infection-induced hypoxemia was poorly tolerated by the fetus and frequently stimulated preterm labor after mid-pregnancy [33]. Overall, preterm birth rates were higher in pregnant women with COVID-19 than in those without COVID-19 in the US (7.2% vs. 5.8% in Jering et al. [36], 12.9% vs. 10.1% in a national rate [37,38], and 14.8% vs. 10.2% in Katz et al. [39]; respectively).

A limitation of several studies was that they did not distinguish between spontaneous and iatrogenic preterm births. Although this hypothesis is unproven, several third-trimester cases were delivered by planned cesarean sections because of a bias catalyzed by the belief that management of severe maternal respiratory disease would improve after delivery. Whether preterm birth is associated only with severe or critical SARS-CoV-2 infection remains controversial. Some studies have asserted that an increase in preterm births appears to be limited to women with severe or critical diseases [24,40,41]; underlying comorbidities also likely play a role.

Another study found an increased risk of preterm birth among all pregnant women with COVID-19 compared to those without COVID-19 [32]. The fact that higher maternal stress is associated with preterm birth should be considered in situations where the maternity service may change during the pandemic [42]. According to Chmielewska, the overall incidence of preterm births before 37 weeks of gestation did not significantly change in pandemic (relative risk [RR], 0.94; 95% confidence interval [CI], 0.87-1.02); however, the incidence of preterm births were lower in high-income countries (RR, 0.91; 95% CI, 0.84-0.99), where spontaneous preterm births are already low, which indicated that preterm birth during the pandemic was associated with healthcare system collapse [43]. There is an urgent need to prioritize safe, accessible, and equitable maternity care within the strategic response to the pandemic and in future health crises.

COVID-19 infection is also associated with a higher rate of cesarean delivery [33,44,45]. A large cohort study in the US reported that the overall rates of cesarean delivery were generally similar or modestly higher in pregnant women with COVID-19 than in those without COVID-19 [38]. This elevated risk was primarily due to an increase in medically indicated preterm cesarean deliveries; only symptomatic patients with SARS-CoV-2 required cesarean deliveries because of lower utilization of labor analgesia [39].

During the early pandemic period in South Korea, it was difficult to secure the transfer of infected mothers from the delivery room to the operating room when an emergency cesarean section was required. Additionally, there were concerns about transmitting the infections to medical staff and newborns. Therefore, most mothers underwent cesarean section with a shorter delivery time, which seemed to reduce the possibility of medical staff being infected. Given accumulating evidence regarding infection route, it is necessary to discuss the appropriate delivery mode for pregnant women with COVID-19.

Pregnant women with SARS-CoV-2 infection reportedly have higher rates of preeclampsia [35,46], although this was not observed in a Canadian national research using Canadian COVID-19 in pregnancy surveillance-preg [27]. Further, among pregnant women, severe COVID-19 is associated with preeclampsia, gestational diabetes, and low birth weight compared to mild COVID-19 in review article on the early phase of pandemic [32].

Placental infection and transmission of COVID-19 to the fetus and neonate

Placental infection and vertical transmission

It is important to determine whether SARS-CoV-2 can cross the placenta and cause direct adverse effects on the fetus, as has been observed with other severe pathogens (e.g., *Trephonema pallidum*, rubella virus, cytomegalovirus, Zika virus). Although the overall rate of congenital SARS-CoV-2 infections is <2% of maternal infections [47], only a few well-documented cases of probable in utero transmissions have been reported [48,49]. A systematic review of 47 studies found that vertical transmission was confirmed in only 0.3% of the patients, was probable in 0.5%, and was possible in 1.8% [50].

Several factors may explain the rarity of vertical transmission. For intrauterine transmission of a viral pathogen, the pathogen needs to reach and cross the placenta [51]; how-

ever, SARS-CoV-2 infection is not associated with high levels of viremia [52,53]. In utero transmission of infection typically occurs via a hematogenous route and sometimes can ascend via the genital tract. Viremia rates in patients with COVID-19 appear to be higher in patients with severe disease, possibly with the delta variant and in transient disease [22]. No evidence of transplacental infection has been identified to date. However, the virus has been identified in a few neonates, suggesting that, though rare, the ascending route of infection and intrapartum transmission from contact with vaginal secretions are responsible [23,48,49].

Despite the placentas testing positive for SARS-CoV-2, very few newborns manifest virus-induced diseases. The protective effects of the placental barrier against viral infections remain a mystery [54]. In a 2022 systematic review, maternal risk factors for mother-to-child transmission included severe COVID-19, death, admission to an ICU, and postnatal infection; moreover, the severity of maternal COVID-19 appears to be associated with SARS-CoV-2 positivity in the offspring [47]. These results can guide and enhance prenatal counseling for women about COVID-19 during pregnancy. However, the results should be interpreted with caution in view of the limited number of included cases [33].

Transmission during breast feeding

Most SARS-CoV-2 infections identified in infants after birth are caused by exposure to infected caregivers. However, data on the safety of breastfeeding by SARS-CoV-2-infected mothers are reassuring. Replication-competent SARS-CoV-2 has not been detected in breastmilk [55]. An observational cohort of 116 SARS-CoV2-infected mothers reported consistent use of surgical masks, hand hygiene, and breast cleansing; all mothers safely breastfed without SARS-CoV-2 transmission [56]. The possible risk of transmission must be weighed against the known benefits of mother-infant bonding and the minimal risk of severe infant illnesses. Most guidelines support newborns rooming in with their infected mother, particularly when the mother is afebrile and asymptomatic [57,58].

Possible complications of COVID-19 in newborns

Most newborns of SARS-CoV-2-positive mothers are uninfected and in good condition at birth [24]. Neonatal morbidity (e.g., the need for mechanical ventilation) has largely been related to preterm birth and adverse uterine environments resulting from critical maternal COVID-19 [31,59-61]. Severe respiratory compromise from COVID-19 could result in maternal hypoxia, which could negatively affect neonatal outcomes. Neonatal adverse outcomes are thought to result from maternal hypoxemia rather than from a direct effect of the pathogen. Guan et al. [12] reported that fetal complications of COVID-19 include miscarriage (2%) and intrauterine growth restriction (intrauterine growth restriction [IUGR]; 10%). Lokken et al. [24] suggested that neonates born to mothers with severe or critical COVID-19 at the time of delivery were more likely to have low birth weight (<2,500 g) and be admitted to the neonatal intensive care unit for fetal indications than those born to women with mild COVID-19 or having recovered from COVID-19 [24].

As previously mentioned, vertical transmission of SARS-CoV-2 infection is very rare [50]. However, maternal hypoxemia is known to develop in 8-20% of pregnant women infected with SARS-CoV-2, which could be associated with adverse neonatal outcomes [27,30]. Protracted maternal respiratory compromise increases the risk of IUGR; it drives the release of potent vasoconstrictors such as endothelin-1 and hypoxia-inducible factor, resulting in placental hypoperfusion and fetal hypoxia [62]. Theoretically, fetal hypoxia can cause IUGR and low birth weight, and is associated with prematurity and infant mortality [63,64]. Exposure without infection of the placenta in pregnant women with COVID-19 is associated with either maternal [65] or fetal [66] vascular malperfusion.

Early data suggests that maternal COVID-19 is not associated with an increased prevalence of IUGR [33,67]. However, perinatal outcome data when the infection is acquired in early pregnancy are limited. Any condition that results in prolonged maternal hypoxia or placental dysfunction places the fetus at risk of IUGR. Emerging data suggests an association between COVID-19 in pregnancy and stillbirth; however, early studies were unable to adjust for potential confounders [28,29].

DeSisto et al. [68] reported that American women with COVID-19, with over 1.2 million deliveries and over 8,000 stillbirths were at an increased risk of stillbirth compared to women without COVID-19. The magnitude of this association was higher during the period of delta variant predominance than during the pre-delta period [68]. In other countries, such as India, a rise in stillbirths was attributed to disruptions in maternal care and supportive services such as

food and micronutrient supplementation during the pandemic [69].

According to Jacoby et al. [29], the upper limit of the CI of 13.4% for miscarriage among pregnant women in the first trimester in a longitudinal US cohort was reassuring because it was not significantly higher than the expected miscarriage rate without viral infections. These results can guide the counseling of women infected with SARS-CoV-2 early in pregnancy that the frequency of miscarriage does not increase above baseline due to infection [29,37]. Further, the frequency of congenital anomalies in women with COVID-19 reportedly did not increase above the pre-pandemic baseline either [37,70].

Management of SARS-CoV-2 infection during pregnancy

The therapeutic management of pregnant women with COVID-19 should be the same as that of non-pregnant patients, except for molupiravir. The use of molnupiravir is not recommended in pregnant women unless there are no other options and the need for therapy is clearly indicated. The therapeutic management of pregnant women with COVID-19 based on disease severity is summarized in Table 1 [61].

Vaccine

As mentioned previously, even though the incidence of severe maternal complications of COVID-19 infection is low in pregnant women, it has been reported to be higher than in non-pregnant women of the same age, as reflected by factors such as ICU admission and the need for mechanical ventilation. In this way, the SARS-CoV-2 infection in pregnant women appears to be more severe, and so pregnant women were included early in the COVID-19 vaccination target.

Breastfeeding does not influence vaccination timing [71]. Vaccination-induced maternal SARS-CoV-2 antibodies pass into the breast milk and appear to offer passive protection to infants [72,73].

COVID-19 mRNA vaccines generate robust immune responses in the plasma and milk of lactating women without any reported severe adverse events [28]. Vaccines lower the risk of infection and severe disease and improved treatments for COVID-19 lower the risk of progression; thus, indications for delivery are reduced, which in turn reduce prematurity [41]. An adjusted hazard ratio of 0.22 (95% CI 0.11-0.43) for SARS-CoV-2 infection with BNT162b2 vaccination versus non-vaccination was reported in a large registry of 15,060 pregnant women in Israel [74]. Vaccination decreases the risk of progression to severe or critical COVID-19 and the need for hospital and ICU admissions in pregnant women [75,76].

In a study including 122 pregnant women (gestational age, 35-41 weeks), COVID-19 mRNA vaccines induced a transplacental antibody transfer detectable in cord blood as early as 16 days after the first dose [77].

No safety concerns were detected in the vaccine safety monitoring systems for people who received an mRNA COVID-19 vaccine late in pregnancy or for their babies [78-82]. An mRNA COVID-19 vaccine did not increase the risk of miscarriage in pregnant women who received the vaccine just before or during early pregnancy (<20 weeks) [78-80,83]. Administration of the mRNA COVID-19 vaccine during pregnancy was not associated with an increased risk of complications, including preterm birth, stillbirth, bacterial infection of the placenta, and excessive maternal blood loss after birth [80,83,84]. Furthermore, administration of COVID-19 vaccine before and during the first trimester was not associated with an increased risk of detectable birth defects [84].

Implementing evidence-based COVID-19 prevention strategies, including vaccination before or during pregnancy, is critical for reducing the impact of COVID-19 on stillbirths [68].

Choice of vaccine

An mRNA vaccine (e.g., Pfizer/BioNTech, Moderna) or a recombinant protein subunit adjuvant-vaccine (e.g., Novavax) is preferred over a vector-based vaccine (e.g., Janssen/Johnson & Johnson) for administration. All three COVID-19 vaccines currently available can be administered to pregnant or lactating women, with no preference for the vaccine type. Although the safety data in pregnancy are rapidly accumulating and no concerns have been detected, additional information about birth outcomes, particularly among women vaccinated earlier in pregnancy, is needed [14].

Table 1. Therapeutic management of pregnant women with COVID-19 based on disease severity[a)]

Disease severity	Recommendations for antiviral or immunomodulator therapy	
	Situation	Recommendations
Does not require hospitalization or supplemental oxygen	All patients	Ritonavir-boosted nirmatrelvir (paxlovid)
Hospitalized for reasons other than COVID-19	All patients	Ritonavir-boosted nirmatrelvir (paxlovid)
		Remdesivir
Hospitalized but does not require oxygen supplementation	All patients	Remdesivir
Hospitalized and requires conventional oxygen	Patients who require minimal conventional oxygen	Remdesivir
	Most patients	Dexamethasone plus remdesivir
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add PO baricitinib or IV tocilizumab to 1 of the options above
Hospitalized and requires HFNC oxygen or NIV	Most patients	Promptly start 1 of the following, if not already initiated: dexamethasone plus PO baricitinibf, dexamethasone plus IV tocilizumab
		If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained: dexamethasone
		Add remdesivir to 1 of the options above
Hospitalized and requires MV or ECMO	Most patietns	Promptly start 1 of the following, if not already initiated: dexamethasone plus PO baricitinib, dexamethasone plus IV tocilizumab
		If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained: dexamethasone

COVID-19, coronavirus disease 2019; PO, per os; IV, intravenous; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; NIH, National Institute of Health.

[a)]Modified from NIH COVID-19 treatment guidelines [71].

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Timing

We recommend that unvaccinated women planning for pregnancy, pregnant or recently pregnant women obtain the full vaccination course at the earliest, regardless of the gestational age or breastfeeding status. Booster injections are advised when they are eligible for it. A bivalent mRNA COVID-19 vaccine is recommended for the booster [85].

Primary vaccine administration earlier rather than later in gestation provides the most maternal benefit; it reduces the maternal risk of COVID-19-related hospitalization, death, and pregnancy complications. Although fetal and newborn antibody levels appear to be higher with primary vaccination later in pregnancy [86], this potential benefit does not outweigh the overall pregnancy (maternal, fetal, and newborn) benefits of early vaccination, or account for the effects of booster doses when eligible [87].

COVID-19 vaccines may be administered at the same time as other vaccines, such as influenza and Tdap, which are routinely administered in pregnancy. An interval between vaccinations is unnecessary, and anti-D immunoglobin does not interfere with the immune response to vaccines. Thus, the timing of administration for prevention of alloimmunization is based on standard clinical protocols.

Conclusion

The collapse of the healthcare system in the early days of the COVID-19 pandemic led to avoidable deaths in both mothers and babies. However, based on current evidence, healthcare providers can counsel pregnant women that SARS-CoV-2 infection does not increase the incidence of severe adverse maternal and perinatal outcomes and that vertical transmission is rare. Additionally, they should recommend COVID-19 vaccination to women planning for pregnancy and even in those who are already pregnant.

The clinical management of pregnant women with COVID-19 is similar to that of non-pregnant women, and effective treatments should not be withheld [61]. Antiviral therapy, dexamethasone, and prophylactic anticoagulation are recommended for SARS-CoV-2 infection management [60].

In the early days of the COVID-19 pandemic, the management of pregnant women was often delayed until the PCR result came out or due to the risk of close contact, even in those without symptoms. Out of concern for the spread of infection, cesarean sections were performed instead of vaginal birth since infection could have led to an increase in maternal and neonatal morbidities. Additionally, the neonate was quarantined if the maternal PCR test was positive, despite infectivity decreasing 10 days after symptom onset. It is necessary to ease the strict measures of infection control in the field of obstetrics. Most of all, we should prepare novel protocols reflecting the latest trends for obstetric and neonatal practice for more efficient management of pregnant women with COVID-19.

Patients with SARS-CoV-2 infection who deliver by cesarean section face a higher risk of complications, such as infection, bleeding, and thromboembolic evens, than those who deliver vaginally [88,89]. If pregnant women in labor have a positive PCR test for COVID-19, the presence or absence of maternal SARS-CoV-2 symptoms should be identified to stratify the risk. Vaginal delivery can be attempted in asymptomatic women with low infectivity. Further research is needed to determine if potential barriers are needed at the time of delivery.

Safety data about vaccination in pregnancy is rapidly accumulating, with more women being vaccinated and no safety concerns have been detected despite the large number of pregnant women being vaccinated. Globally, the recommended COVID-19 vaccine, and numerous other vaccines, have been proven to be safe and effective in preventing COVID-19 in pregnant women [72,78,90,91].

Most experts believe that the SARS-CoV-2 infection is likely to become endemic [92]. Thus, data on the effects of SARS-CoV-2 infection during pregnancy are being constantly collected. It is also necessary to apply the lessons learned from this pandemic to improve our preparations and responses to new infections that may occur in the future. Policymakers and healthcare leaders should determine effective and robust strategies for preserving safe maternal care, even during ongoing global emergencies.

Conflict of interest

None.

Ethical approval

This research does not need ethics approval.

Patient consent

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