Review

Maternal-Fetal Medicine®

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Maternal and Perinatal Outcomes of SARS-CoV-2 and Variants in Pregnancy

Qiaoli Feng[1], Qianwen Cui[1], Zhansong Xiao[1], Zengyou Liu[2], Shangrong Fan[1,3,*]

Abstract

Pregnancy is a physiological state that predisposes women to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a disease that can cause adverse maternal and perinatal outcomes. The severity of coronavirus disease 2019 (COVID-19) disease is known to vary by viral strain; however, evidence for the effects of this virus in pregnant women has yet to be fully elucidated. In this review, we describe maternal and perinatal outcomes, vaccination, and vertical transmission, among pregnant women infected with the different SARS-CoV-2 variants identified to date. We also summarize existing evidence for maternal and perinatal outcomes in pregnant women with specific information relating to SARS-CoV-2 variants. Our analysis showed that Omicron infection was associated with fewer severe maternal and perinatal adverse outcomes while the Delta variant was associated with worse pregnancy outcomes. Maternal deaths arising from COVID-19 were found to be rare (<1.0%), irrespective of whether the virus was a wild-type strain or a variant. Severe maternal morbidity was more frequent for the Delta variant (10.3%), followed by the Alpha (4.7%), wild-type (4.5%), and Omicron (2.9%) variants. The rates of stillbirth were 0.8%, 4.1%, 3.1%, and 2.3%, respectively, in pregnancies infected with the wild-type strain, Alpha, Delta, and Omicron variants, respectively. Preterm birth and admission to neonatal intensive care units were more common for cases with the Delta infection (19.0% and 18.62%, respectively), while risks were similar for those infected with the wild-type (14.7% and 11.2%, respectively), Alpha (14.9% and 13.1%), and Omicron variants (13.2% and 13.8%, respectively). As COVID-19 remains a global pandemic, and new SARS-CoV-2 variants continue to emerge, research relating to the specific impact of new variants on pregnant women needs to be expanded.

Keywords: COVID-19; SARS-CoV-2; Variants; Pregnancy outcomes; Alpha; Delta; Omicron

Introduction

The coronavirus disease 2019 (COVID-19) pandemic was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has continued for three years, bringing huge challenges to health and economic systems worldwide. More than 641 million cases and 6.6 million deaths were reported as of December 2022.[1] Pregnancy is a unique status that is accompanied by alterations in immune function to protect the developing fetus; these changes may affect the clearance of infectious agents, especially viruses.[2] In addition, total lung capacity is reduced in pregnancy, thus increasing a woman's susceptibility to severe respiratory infections.[3] Therefore, the impact of COVID-19 on pregnant women and neonates is of significant interest globally. According to the body of published evidence, pregnancy does not increase susceptibility to SARS-CoV-2 infection but seems to worsen the clinical course of COVID-19 disease when compared with nonpregnant females of the same age. Pregnant patients have an increased risk of severe illness.[4–13] Figure 1 shows the systemic and respiratory disorders caused by SARS-CoV-2 infection[14] and the mechanisms of vertical transmission in pregnancy.[15,16]

SARS-CoV-2, the cause of COVID-19, can easily mutate over time, and several variant strains have been detected thus far. Considering the differential features of SARS-CoV-2 variants, understanding the potential impact of these variants on maternal and neonatal outcomes is vital if we are to better protect the health of both the mother and fetus. However, comparative reports based on predominant variants are limited. Although some national studies have tried to explore the clinical characteristics of pregnant women infected with different SARS-CoV-2 variants,[17–20] there is a lack of robust data at the global level to achieve broad and comprehensive agreement.

In this review, we discuss the severity of COVID-19 infection in pregnant women in relation to the predominance of different SARS-CoV-2 variants. We retrieved information from PubMed, Web of Science, and Medline databases up to the 10th of January 2023, using various search terms and relevant keywords, including SARS-CoV-2, 2019 coronavirus disease, COVID-19, variants, wild-type, Alpha, Beta, Gamma, Delta, Omicron, and pregnancy. We included observational studies in pregnant women with specific information on SARS-CoV-2 variants but excluded case reports. Individuals were identified to have a SARS-CoV-2 infection if they had a positive test result using polymerase chain reaction nucleic acid amplification testing. Because Beta and

[1]Department of Obstetrics and Gynecology, Peking University Shenzhen Hospital, Shenzhen 518036, China; [2]Department of Obstetrics and Gynecology, Huazhong University of Science and Technology Union Shenzhen Hospital, Shenzhen 518052, China; [3]Shenzhen Key Laboratory on Technology for Early Diagnosis of Major Gynecological Diseases, Shenzhen 518000, China.

* Corresponding author: Shangrong Fan, Department of Obstetrics and Gynecology, Peking University Shenzhen Hospital, Shenzhen 518036, China. E-mail: fanshangrong@163.com.

Maternal-Fetal Medicine (2023) 5:2

Received: 15 January 2023 / Accepted: 15 February 2023

First online publication: 27 March 2023

http://dx.doi.org/10.1097/FM9.0000000000000189.

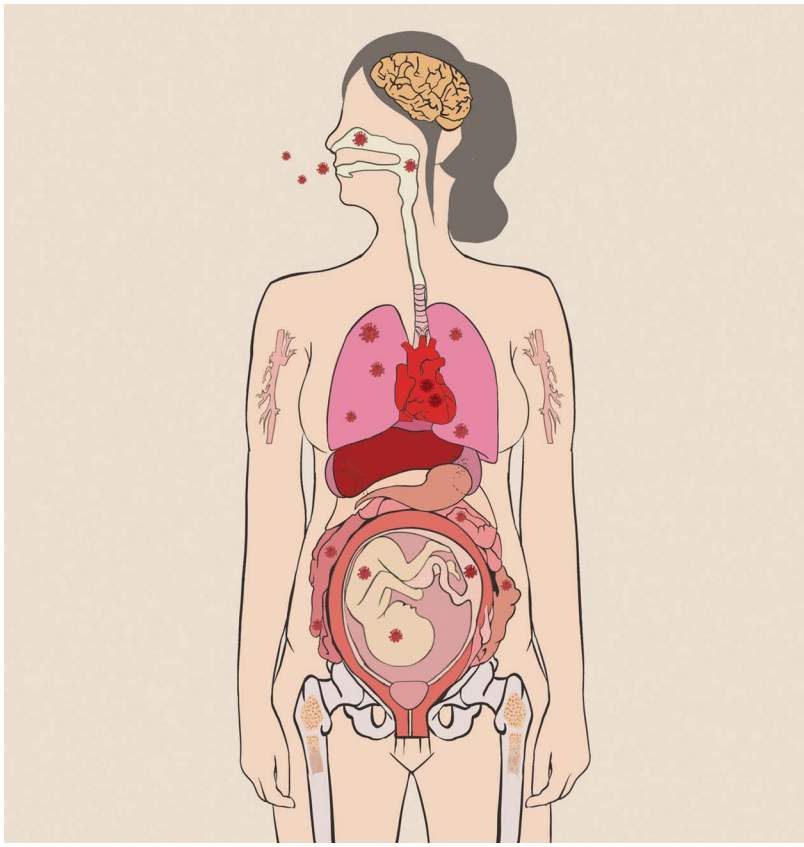

Figure 1. Systemic and respiratory disorders caused by SARS-CoV-2 infection and possible vertical transmission in pregnancy. The virus is transmitted via respiratory droplets and aerosols from person to person and then binds to nasal epithelial cells in the upper respiratory tract. After local replication and propagation of the virus, along with the infection of ciliated cells in the conducting airways, the virus migrates from the nasal epithelium to the upper respiratory tract. As a result of the involvement of the upper airways and systemic immune response, along with the release of inflammatory cytokines, the disease manifests with symptoms of fever, malaise, dry cough and even severe pneumonia, as well as myocarditis, gastroenteritis, or placentitis, in some cases. The diagnosis of COVID-19 is made by direct detection of SARS-CoV-2 RNA by nucleic acid amplification tests or by the detection of viral protein with an antigen test. The vertical transmission of SARS-CoV-2 infection from women to the fetus through the placenta is rare but possible. Adapted from Fan *et al.*[14] COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Gamma variants are not globally dominant and have been rarely classified in previous studies, the included research was mainly based on the wild-type, Alpha, Delta, and Omicron variants.

SARS-CoV-2 and variants

SARS-CoV-2 is the RNA virus that causes COVID-19.[14] The host receptor for cell entry is the angiotensin-converting enzyme 2 receptor, which is found mostly in alveolar epithelial and stromal cells.[21] Various mutations have been observed in the SARS-CoV-2 genome over time; these arise naturally through viral replication and may affect important pathogenic components of the virus, such as the receptor-binding domain of the spike protein.[22] Mutation of the spike proteins has been demonstrated to enhance the receptor binding affinity of these proteins in host cells and reduce affinity for binding to neutralizing antibodies, thus leading to an increased risk of viral transmission and ineffective immune responses.[23]

Of these variants, some are associated with increased transmissibility, severity, or possible immune evasion and are also known as "variants of concern"; these were responsible for several waves of infection during the COVID-19 pandemic. Alpha (B.1.1.7 lineage), Beta (B.1.351 lineage), Gamma (P.1 lineage), Delta (B.1.617.2 lineage), and Omicron (B.1.1.529 lineage), named by the Virus Evolution Working Group of the World Health Organization, are the most common variants reported in the existing literature.[24] The Alpha variant was identified in the United Kingdom in late 2020 and spread at least 50% faster than earlier circulating strains.[25–28] Around the same time, the Beta variant was detected in South Africa. Another highly transmissible variant (Gamma) was tracked to the Amazonas state in Brazil, although the Beta and Gamma variants did not become globally dominant variants. The Alpha variant was associated with an increased risk of hospitalization and mortality, as indicated by evidence when compared with other lineages.[29] In the spring of 2021, the Delta variant from India, which was approximately 60% more transmissible than the Alpha variant,[30] took over as the predominant variant and spread worldwide. Compared with Alpha, the Delta variant was shown to double the risk of hospital admission[31]; this may have resulted from the high viral load of the Delta variant.[32,33] The currently circulating variant of concern, Omicron, which originated in South Africa, has an increased transmissibility rate of more than 105% compared with Delta[34] and has accounted for the vast majority of

global COVID-19 cases since late 2021. Although Omicron is more prone to immune escape, its replication in the upper and lower respiratory tracts, along with its pathogenicity, are markedly attenuated when compared with the wild-type strain and other variants.[35] Figure 2 describes the timeline of the predominant SARS-CoV-2 variants.

Maternal outcomes

Asymptomatic cases are common in individuals with laboratory-confirmed SARS-CoV-2 infection, ranging from 54% to 95% in pregnant women.[4,36] Although the symptoms and signs of COVID-19 during pregnancy generally seem to be similar to those in nonpregnant individuals,[5,37] pregnant women infected with SARS-CoV-2 are more prone to experience critical illness and require intensive care unit (ICU) admission and mechanical ventilation support than nonpregnant women of reproductive age,[4–11,38] especially in pregnancies with comorbidities, obesity, and advanced maternal age.[39,40] Figure 3 shows a chest computed tomography (CT) image of a severe case of COVID-19 in a pregnant woman before and after extracorporeal membrane oxygenation (ECMO) treatment. Global data have also revealed the poorer outcomes of pregnancies during the COVID-19 pandemic with increasing maternal mortality, stillbirths, preeclampsia, and preterm births.[41–46] Therefore, pregnant women are recognized as a high-risk subgroup for COVID-19 infection, with the need for high-level supportive care.

With subsequent waves of COVID-19 predominated by new variants, the pattern in pregnant women is observed to have changed when compared with that documented for the wild or original virus, with increasing risk of infection, complications, requirement for hospitalization, intensive care management, and even invasive oxygenation, on account of acute severe respiratory failure.[47–50] A national population-based prospective cohort study, featuring data from 315 Italian maternity hospitals, reported a significant increase in severe COVID-19 illness during the Alpha-variant period (n = 2550) when compared with the wild-type period (n = 756), with a 3.24-fold higher odds (95% confidence interval (*CI*), 1.99–5.28) for needing ventilatory support and/or ICU admission.[51] Similar figures were reported in the United Kingdom (UK) during the second wave of the pandemic.[47,48] The Delta variant seems to be far more transmissible and is associated with increased disease severity than previous strains.[52–54] A multicenter prospective cohort study reported by Adhikari *et al.*,[52] featuring 1515 pregnant women, described increased COVID-19–related morbidity during a period of Delta predomination, especially in populations with lower vaccine acceptance. Later, a publication from the Centers for Disease Control and Prevention that included 116,958 pregnancies with symptomatic SARS-CoV-2 infection reported that pregnant women during the Delta period had a higher risk of ICU admission (adjusted risk ratio [*aRR*], 1.41; 95% *CI*, 1.17–1.69), receiving invasive ventilation or ECMO (a*RR*, 1.83; 95% *CI*, 1.26–2.65), and maternal death (a*RR*: 3.33; 95% *CI*, 2.48–4.46), than those during the pre-Delta period.[17] Similar findings were demonstrated by data from the UK obstetric surveillance system national cohort including a total of 4436 hospitalized pregnant women with symptoms of confirmed SARS-CoV-2 infection during the wild-type, Alpha, and Delta periods.[55] Compared with the wild-type period, infected women admitted during the Alpha period were more likely to require respiratory support (27.5% *vs.* 21.5%; adjusted odds ratio (a*OR*), 1.43; 95% *CI*, 1.15–1.77) and ICU admission (11.8% *vs.* 7.9%; a*OR*, 1.82; 95% *CI*, 1.38–2.39) and develop pneumonia (28.1% *vs.* 19.0%; a*OR*, 1.86; 95% *CI*, 1.53–2.26). Women admitted during the Delta period were associated with an increased risk of developing pneumonia (a*OR*, 2.52; 95% *CI*, 2.06–3.09) and ICU admission (a*OR*, 2.71; 95% *CI*, 2.06–3.56).[55] The newest and currently circulating variant, Omicron, is reported to be associated with less severe symptoms than the Delta variant[16,54]; this may be related to a higher vaccination coverage, the lower virulence of the Omicron variant, and infection-acquired immunity.[56] According to a population-based cohort study in Scotland, a lower maternal critical care admission risk was detected during the Omicron-dominated period than during the Delta-dominated period (0.3% *vs.* 1.8%; a*OR*, 0.25; 95% *CI*, 0.14–0.44).[19] Birol *et al.*[57] retrospectively analyzed data from two tertiary care facilities comprising 1286 unvaccinated pregnant women with SARS-CoV-2 infection and reported that maternal mortality, disease severity, and pregnancy complications were similar when compared between the Omicron wave and the pre-Delta period but conversely increased during the Delta wave. Similar evidence was reported by Adhikari *et al.*[58] Compared with the pre-Delta epoch, increased infections were observed in both periods of Delta and Omicron predominance (respective incidence rate ratio of 3.07, 95% *CI*, 2.46–3.82 for Delta and 10.09, 95% *CI*, 7.42–13.69 for Omicron), while severe or critical illness increased during the Delta period (*OR*, 2.93; 95% *CI*, 1.18–7.69), and illness severity decreased in the Omicron period (*OR*, 0.20; 95% *CI*, 0.05–0.83) after adjusting for vaccination.[58] Evidence from a retrospective cohort study showed that patients with SARS-CoV-2 infection had significantly higher rates of severe maternal morbidity events than

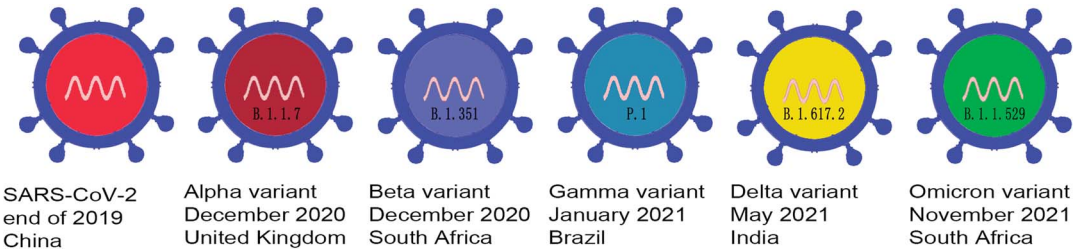

Figure 2. Timeline showing the detection of different predominant variants. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

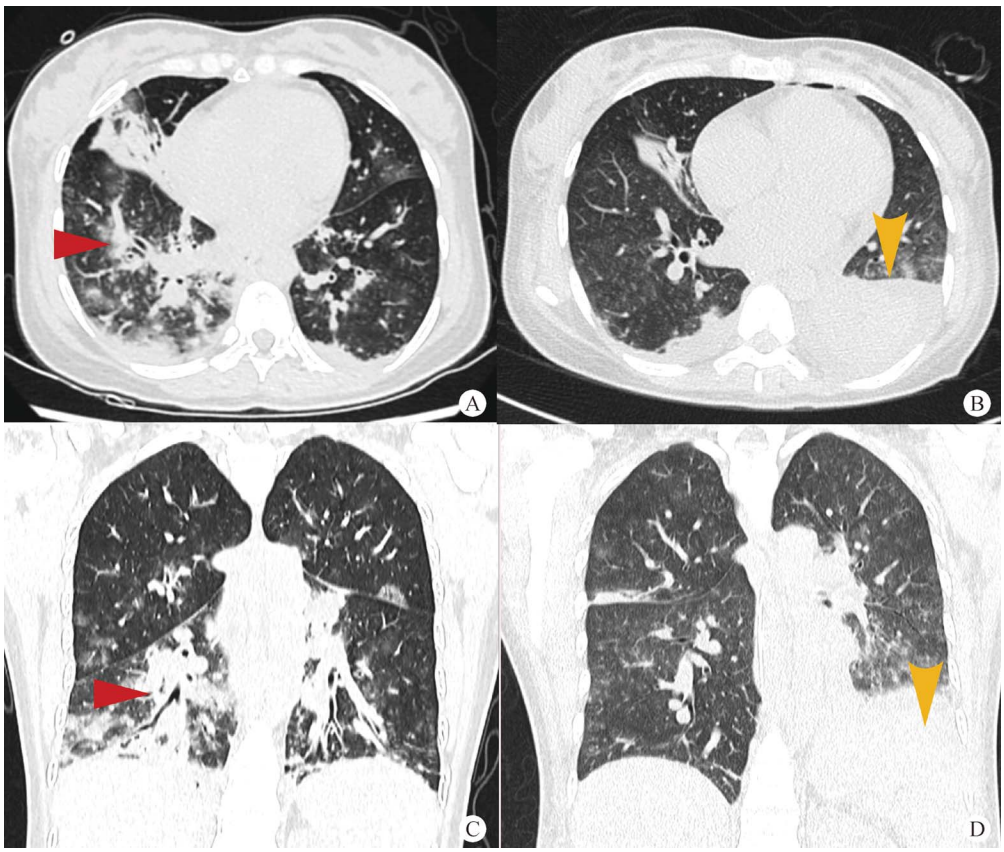

Figure 3. Chest CT image of a pregnant woman infected by COVID-19 before (A and C) and after (B and D) ECMO treatment. A (axial plane) and C (coronal plane) show bilateral ground glass opacities admixed with patchy areas of consolidation, especially in the right lower lobe (red arrow). B (axial plane) and D (coronal plane) show reduced ground glass opacities and consolidative changes in the right lower lobe after ECOM treatment but with extensive consolidation in the left lower lobe (yellow arrow). COVID-19: Coronavirus disease 2019; CT: Computed tomography; ECMO: Extracorporeal membrane oxygenation.

those without infection during all time periods except for Omicron (2.7-fold for the wild-type strain, 2.57-fold for the Alpha variant, and 7.69-fold for the Delta variant).[20] These associations were strengthened by the findings of placental pathology after SARS-CoV-2 infection, in which maternal vascular malperfusion, including decidual artery injury, varied during the eras associated with the Alpha, Gamma, Delta, and Omicron variants; the highest rate occurred during the Delta era.[59]

We reviewed 25 studies reporting specific information relating to SARS-CoV-2 variants, including 3667 pregnancies with the wild-type strain, 1740 pregnancies with the Alpha variant, 35,673 pregnancies with the Delta variant, and 11,968 pregnancies with the Omicron variant.[17–20,51,52,54,57,59–75] Table 1 shows the clinical characteristics and maternal outcomes of pregnancies with SARS-CoV-2 infection. Maternal deaths arising from COVID-19 infection were rare, irrespective of whether the cases involved the wild-type strain or variants. However, severe maternal morbidity was more frequent in the Delta variant (10.3%), followed by the Alpha (4.7%), wild-type (4.5%), and Omicron variants (2.9%).

Perinatal mortality and morbidity

Perinatal outcomes in COVID-19–positive pregnancies are of significant concern. This is because activation of the maternal immune system by SARS-CoV-2 has been shown to dysregulate the fetal immune system.[76,77] A body of evidence suggests that the risks of miscarriage, congenital anomalies, neonatal mortality, and length of hospital stay do not increase above baseline.[78–89] However, the risks of preterm birth and stillbirth were reported to be higher in some large cohort studies.[80,90–92] However, spontaneous or iatrogenic preterm birth was not distinguished in some studies, although the latter was mostly associated with adverse uterine environments resulting from critical maternal COVID-19 disease. In some low-income countries, a rise in stillbirths might be attributed to disruptions in maternal care and maternal supportive services during the pandemic.[46] Long-term outcome data in offspring exposed to maternal SARS-CoV-2 infection are limited, although some evidence suggests the possibility of neurodevelopmental sequelae.[93]

Differences in perinatal mortality and morbidity have been detected among periods predominated by different SARS-CoV-2 variants. A national cohort in the UK suggested that neonates born during the Alpha period were more likely to require admission to the neonatal intensive care unit (NICU) than those born during the wild-type period.[55] During the subsequent emergence of the Delta wave, a significant increase in preterm delivery (26.4% *vs.* 4.4%, $P < 0.001$) as well as NICU admission (34% *vs.* 18.8%, $P < 0.001$) was observed in a prospective cohort study

Table 1

Clinical characteristics and maternal outcomes in pregnancy with SARS-CoV-2 infection.

Items	Data source	Wild-type strain, *n/N* (%)	Alpha variant, *n/N* (%)	Delta variant, *n/N* (%)	Omicron variant, *n/N* (%)
*N**		3667	1740	35,673	11,968
Obesity (BMI ≥ 30 kg/m^2)	17,54,57,59–63,73,74	158/978 (16.16)	137/834 (16.43)	410/6115 (6.70)	230/1782 (12.91)
Chronic respiratory disease	17,18,20,57,60,62–66,73–75	80/1104 (7.25)	54/769 (7.02)	526/6218 (8.46)	351/5589 (6.28)
Cardiovascular disease†	17,18,57,64–66,74,75	13/126 (10.32)	1/25 (4.00)	337/5426 (6.21)	75/4465 (1.68)
Diabetes	17,18,20,54,57,59,63,65,66,74,75	143/978 (14.62)	100/859 (11.64)	350/6228 (5.62)	178/5324 (3.34)
Hypertensive diseases of pregnancy‡	54,57,64,65,68,74	11/126 (8.73)	16/115 (13.91)	54/878 (6.15)	87/1275 (6.82)
Disease manifestation					
Symptomatic	17,19,54,59,61,65–70,75	898/2550 (35.22)	373/868 (42.97)	13,248/27,239 (48.64)	1264/4341(29.12)
Maternal mortality	17,18,51,52,57,60,65,66,68,74,75	1/2550 (0.04)	1/781 (0.13)	134/29,470 (0.45)	9/4965 (0.18)
Severe maternal morbidity§	20	44/978 (4.50)	35/744 (4.70)	70/681 (10.28)	21/726 (2.89)
ICU admission	17,19,51,54,60,63–68,70,71,74,75	48/2676 (1.79)	52/820 (6.34)	304/32,516 (0.93)	67/9978 (0.67)
Invasive ventilatory support	51,52,54,57,63,64,74	21/2676 (0.78)	21/756 (2.78)	40/2177 (1.84)	4/603 (0.66)
ECMO	51,54,57,60,68,74,75	3/2550 (0.12)	4/756 (0.53)	16/820 (1.95)	13/4513 (0.29) ‖
Cesarean section	19,54,59,61,65,66,68,74	757/2212 (34.22)	244/734 (33.24)	230/486 (47.33)	376/713 (52.73)
Vaginal delivery	19,54,59,61,65,66,68,74	1455/2212 (65.78)	490/734 (66.76)	249/486 (51.23)	333/713 (46.70)
Abnormal chest X-ray or CT	51,54,66,69,74,75	299/2550 (11.73)	126/762 (16.54)	35/422 (8.29)	76/4140 (1.84)

*Because the outcomes of interest were not shown in all included studies, the denominators varied from items and usually less than total case numbers.

†Cardiovascular disease includes rheumatic heart disease, congenital heart disease, and peripartum cardiomyopathy.

‡Hypertensive diseases of pregnancy include gestational hypertension; preeclampsia; hemolysis, elevated liver enzymes, and low platelet count syndrome; or eclampsia.

§Severe maternal morbidities includes acute myocardial infarction, aneurysm, acute kidney failure, adult respiratory distress syndrome, amniotic fluid embolism, cardiac arrest or ventricular fibrillation, conversion of cardiac rhythm, disseminated intravascular coagulation, eclampsia, heart failure or arrest during operation or procedure, puerperal cerebrovascular disorders, pulmonary edema or acute heart failure, severe anesthesia complications, sepsis, shock, sickle cell disease with crisis, air and thrombotic embolism, blood products transfusion, hysterectomy, temporary tracheostomy, and ventilation;

‖Included cases with invasive ventilation or ECMO.

BMI: Body mass index; CT: Computed tomography; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

performed in Turkey when compared with the pre-Delta period.[94] Similar findings were demonstrated by another large retrospective cohort study, with a higher rate of early preterm birth at less than 34 weeks of gestation in the Delta group than in the pre-Delta group (15.4% *vs.* 4.9%, $P < 0.001$).[57] In addition, SARS-CoV-2 placentitis was rarely reported during the first wave of outbreaks caused by the original strain but was increasingly common in the subsequent variant-predominated waves, especially the Delta period.[59,61,70,95] This suggests the possibility of placental damage, thus leading to fetal hypoxic–ischemic injury.[96] A study of 59 women delivering 61 infants with SARS-CoV-2 placentitis during the Alpha and Delta waves found that SARS-CoV-2 placentitis was probably associated with stillbirth or late miscarriage; however, approximately one quarter of infected mothers were asymptomatic.[70] Acute SARS-CoV-2 infection might induce significant placental lesions, and subsequent fetal distress was also proven by Dumont *et al.*[97] for the Alpha variant and by Shook *et al.*[61] for the Delta variant. In a national cohort study of Scotland, comprising more than 9000 infected pregnancies between May 2021 and January 2022, Stock *et al.*[19] reported lower rates of preterm birth within 28 days of infection (1.8% *vs.* 4.2%; a*OR*, 0.57; 95% *CI*, 0.38–0.87) and stillbirths (0.43% *vs.* 2.03%; a*OR*, 0.21; 95% *CI*, 0.05–0.95) during the Omicron-dominant period than during the Delta-dominant period, as well as a reduced trend in the prevalence of low Apgar scores (1.2% *vs.* 2.1%), neonatal infection within 28 days of maternal SARS-CoV-2 infection (1.76% *vs.* 0.21%), and neonatal deaths (0 *vs.* 0.63%). A lower incidence of stillbirths and neonatal deaths in the Omicron period than in the Beta and Delta periods (0% *vs.* 13%, $P = 0.067$) was also reported by Mndala *et al.*[18] based on data from a national maternal surveillance platform in Malawi. A recent meta-analysis of 18 studies revealed that pregnant women infected with the Delta variant were more likely to suffer preterm birth at less than 37 weeks of gestation than the pre-Delta group (*OR*, 3.45; 95% *CI*, 1.17–10.15), whereas those with Omicron infection had a lower risk (*OR*, 0.21; 95% *CI*, 0.11–0.40). Differences in other perinatal outcomes, such as stillbirth, were not significant when compared between the pre-Delta, Delta, and Omicron groups.[98] Even in full-term newborns during the Omicron period, neonates born to infected mothers had an increased risk of lower birth weight, lower Apgar scores, and an increased risk for respiratory support until 12 hours after birth when compared with those born to mothers without infection.[99] Boly *et al.*[100] described three premature newborns from women with confirmed Delta infection with very low birth weight (<1500 g) and reported that all three infants presented with hyperglycemia and bone marrow dysfunction. Delta variants also seem to affect children to a greater extent than other variants.[101]

Our results show findings consistent with those in previous literature. Table 2 presents the perinatal outcomes from pregnancies with SARS-CoV-2 infection based on the included studies. The rates of stillbirth were 0.8%, 4.1%, 3.1%, and 2.3%, respectively, in pregnancies infected with the wild-type strain, Alpha, Delta, and Omicron variants. Preterm birth and NICU admission were more likely to occur with the Delta infection (19.0% and 18.62%, respectively), while the risks were similar for wild-type (14.7%

Table 2

Perinatal outcomes in pregnancy with SARS-CoV-2 infection.

Items	Data source	Wild-type strain, *n*/*N* (%)	Alpha variant, *n*/*N* (%)	Delta variant, *n*/*N* (%)	Omicron variant, *n*/*N* (%)
*N**		3359	1547	1286	1492
Perinatal death	18,51,54,57,61,64–66,68–70,74	28/2381 (1.18)	39/737 (5.29)	22/611 (3.60)	17/667(2.55)
Stillbirth	18,51,54,57,64–66,68,70,74	20/2376 (0.84)	30/731 (4.10)	19/608 (3.13)	15/667(2.25)
Neonatal death	18,51,64,74	8/2378 (0.34)	3/658 (0.46)	1/292 (0.34)	2/352 (0.57)
NICU admission	51,64,68,72,74	266/2378 (11.19)	98/748 (13.10)	54/290 (18.62)	59/429 (13.75)
Preterm birth < 37 wk	20,54,57,61,62,64–66,68,72,74	162/1104 (14.67)	124/835 (14.85)	236/1256 (18.79)	147/1115 (13.18)

*Because the outcomes of interest were not shown in all included studies, the denominators varied from items and usually less than total case numbers.

NICU: Neonatal intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; wk: Weeks.

and 11.2%, respectively), Alpha (14.9% and 13.1%, respectively), and Omicron variants (13.2% and 13.8%, respectively).

Vertical transmission

Although the overall risk of vertical transmission of SARS-CoV-2 from mother to fetus/newborn is reported to be less than 2% of all maternal infections,[15] this mechanism still raises concern among obstetricians and pediatricians. Vertical transmission may occur in utero, intrapartum, or in the early postnatal period. The in utero transmission of infection mainly occurs via a hematogenous route through the placenta, especially in the third trimester.[16] The angiotensin-converting enzyme 2 receptor and serine protease TMPRSS2, as important components for SARS-CoV-2 cell entry, are minimally expressed in placental tissue,[102,103] which may account for the low risk of vertical transmission. However, even without placental infection, the virus can still reach the fetus in cases that involve placental ischemic injury.[104] Although several cases with positive vaginal swabs have been reported,[105–107] intrapartum transmission from contact with vaginal secretions is rare, and there is no evidence of any benefit from cesarean delivery. Postnatal transmission can occur via respiratory or other infectious secretions from infected mothers or caregivers; thus, appropriate protective measures should be used to reduce exposure of a newborn to the virus.

Although SARS-CoV-2 infection in the placenta has rarely been reported, the virus has been identified in a few cases; most of these cases occurred during Delta predominance.[59,61,70,95] In a previous study, Li *et al.*[108] reported that 158 newborns, whose mothers were infected with the Omicron variant during the third trimester of pregnancy, had favorable short-term outcomes without intrauterine infection caused by vertical transmission; this may have been the result of inefficient replication of the virus in placental tissue.[109,110] However, there was no difference in early neonatal infection within four weeks of maternal diagnosis when compared between the pre-Delta, Delta, and Omicron epochs, as reported by Adhikari *et al.*[58] Similar findings were also demonstrated by a recent meta-analysis featuring 99,567 cases of SARS-CoV-2 wild-type or prevariant infections and 33,494 cases of SARS-CoV-2 variant infections, thus suggesting a comparable prevalence of neonatal SARS-CoV-2 positivity between the pre-Delta, Delta, and Omicron groups.[98] Because the risk of vertical transmission for SARS-CoV-2 is rare, comparative information based on different variants is limited; thus, further research is needed to fully understand the mechanisms by which maternal COVID-19 infection affects fetuses and newborns with the emergence of more new variants.

Vaccination in pregnancy

Although COVID-19 vaccination has been proven to be effective in preventing SARS-CoV-2 infection and reducing the severity of illness in the general population,[111] the safety and efficacy of these vaccines in pregnancy remain a significant concern due to the special physiological changes that occur during pregnancy and in vulnerable fetuses/newborns, thus leading to a low vaccine acceptance in pregnant women of only 50%.[112–114] However, pregnant women have an increased risk of severe COVID-19 disease, and more severe maternal and perinatal outcomes have been observed in nonvaccinated pregnancies when compared with those who were vaccinated.[57,66,115,116] A population-based prospective cohort study in Scotland reported that pregnant women who were nonvaccinated were associated with 77.4% of SARS-CoV-2 infections, 90.9% of SARS-CoV-2 associated with hospital admission, 98% of SARS-CoV-2 associated with critical care admission, as well as all neonatal SARS-CoV-2 infections and perinatal deaths.[19] The significant efficacy of COVID-19 vaccination in pregnant women against SARS-CoV-2 infection, COVID-19–related hospitalization, the occurrence of stillbirths, and NICU admission has been proven by meta-analyses and multicenter cohort studies.[117–119] Evidence has also shown that effective neutralizing antibodies can be detected within maternal and cord blood as well as breastmilk after vaccination or natural infection with SARS-CoV-2,[120,121] thus indicating that newborns and young infants may acquire maternal antibodies through the placenta or breastmilk; this is useful as COVID-19 vaccines are not currently available for these populations. Among infants born to women who received COVID-19 vaccines, the risks of neonatal SARS-CoV-2 positivity and hospitalization for COVID-19 during the first six months of life were also reduced when compared with those born to women who were nonvaccinated.[122,123] The safety of vaccination has also been explored by a number of epidemiological studies; currently, there is no evidence to support the direct or indirect harmful effects of COVID-19 vaccines on fertility, embryo/fetal development, pregnancy outcome, parturition, breastfeeding, or the short-term postnatal development of offspring.[117–119,124–137] Of note, most of the vaccine data arising from pregnant women to date are based on mRNA vaccines (e.g., Pfizer/BioNTech, Moderna). Data from other types of COVID-19 vaccines, such as recombinant protein subunit-adjuvanted vaccines (e.g., Novavax)

and vector-based vaccines (e.g., Janssen/Johnson & Johnson), also remain limited, thus requiring further research. Because vaccination against COVID-19 is associated with reduced disease severity and improved outcomes in pregnant women, the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the Centers for Disease Control and Prevention, all recommend COVID-19 vaccination for all eligible individuals of reproductive-age, including those who are pregnant, lactating, trying to get pregnant, or may become pregnant in the future.[138,139]

Moreover, antibodies produced after vaccination decrease over time, thus indicating that full vaccination and boosters are necessary to maintain antibody levels. According to the findings from Shen *et al.*,[140] the superiority of neutralizing antibody levels in both maternal serum and cord blood was significant in women with full vaccination when compared with those with single-dose vaccination (97.46% *vs*. 4.01% for maternal blood; 97.37% *vs*. 1.44% for cord blood). Although COVID-19 disease was less severe during the Omicron-dominant period, which is considered to be the result of a higher coverage of vaccination, vaccination during pregnancy seemed to achieve better efficacy during Delta predominance than during Omicron predominance.[122,123,141] Sievers *et al.*[142] also found that boosters increases the magnitude of the neutralizing antibody response to different SARS-CoV-2 variants, while the Omicron variant was the most resistant to neutralization, with an increase in neutralizing titres after two vaccine doses against wild type, Delta, Beta, and Omicron of 128-, 91-, 40-, and 10.2-fold over baseline, respectively. These findings indicated the reduced protection of vaccines over time and highlight the need for the development of effective vaccine strategies with the emergence of new SARS-CoV-2 variants.

Conclusions

As COVID-19 remains a global pandemic, and new SARS-CoV-2 variants continue to emerge, the impact of different variants on maternal and infant health is of significant concern. Omicron infection is associated with less severe maternal and perinatal adverse outcomes, and the Delta variant is associated with worse pregnancy outcomes. The vertical transmission of SARS-CoV-2 is rare but possible, especially during Delta predominance. Vaccination during pregnancy is safe and effective to prevent adverse outcomes, although the protection afforded by the vaccine weakens over time, particularly against the Omicron variant. COVID-19 is not a benign disease in pregnancy, and continued research on the impact of new variants is essential.

Funding

This research was supported by the National Natural Science Foundation of China (82101774), the Science and Technology Planning Project of Shenzhen Municipality (JCYJ20220530160206014), and the Scientific Research Foundation of Peking University Shenzhen Hospital (KYQD2022111).

Author Contributions

Shangrong Fan did the concept and design. Qianwen Cui did the data acquisition. Zhangsong Xiao and Zengyou Liu did the literature search. Qiaoli Feng and Zhangsong Xiao did the manuscript preparation. Qiaoli Feng and Shangrong Fan did the manuscript editing and review. The manuscript has been read and approved by all the authors.

Conflicts of Interest

None.

Editor Note

Shangrong Fan is an Editorial Board member of *Maternal-Fetal Medicine*. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and the associated research groups.

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Edited By Dandan Shi

How to cite this article: Feng Q, Cui Q, Xiao Z, Liu Z, Fan S. Maternal and Perinatal Outcomes of SARS-CoV-2 and Variants in Pregnancy. Maternal Fetal Med 2023;5(2):104–114. doi: 10.1097/FM9.0000000000000189.