

**Review Article**

**COVID-19 INFECTION AND VACCINATION IN PREGNANCY: A REVIEW**

**AJAY KUMAR SHUKLA<sup>1</sup>, SAURAV MISRA<sup>2\*</sup>**

<sup>1</sup>Department of Pharmacology, AIIMS Bhopal, India. <sup>2</sup>Department of Pharmacology, Kalpana Chawla Government Medical College, Karnal, India

\*Corresponding author: Saurav Misra; \*Email: saurav181087@gmail.com

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**ABSTRACT**

A higher frequency of severe COVID-19 has been associated to pregnancy. Pregnant women are now regarded potentially sensitive to severe SARS-CoV-2 infection based on clinical experience with pregnancies complicated by infection by other coronaviruses, such as severe acute respiratory syndrome (SARS) and Middle Eastern Respiratory Syndrome. The immune system, respiratory system, cardiovascular function, and coagulation are all affected by physiological changes during pregnancy. The consequences of SARS-CoV-2 on implantation, foetal growth and development, labour, and new-born health have yet to be fully determined, and a focussed, global effort is needed to find out. Asymptomatic infection adds to the difficulty of providing services, preventing infection, and managing it. Finding safe immunizations that induce protective immune responses in pregnant and developing foetus is crucial. Although pregnancy safety data is rapidly increasing and no warning signals have been identified, further information about birth outcomes, particularly among those who were vaccinated earlier in pregnancy, is required. The rate of COVID-19 infection, maternal antibody response, placenta antibody transmission, and adverse effects after COVID-19 vaccination in pregnancy are all summarised in this review.

**Keywords:** Pregnancy, Vaccination, COVID-19

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**INTRODUCTION**

The World Health Organization (WHO) has declared COVID-19 caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a pandemic in March 2020 [1]. More than 476,374,234 confirmed cases of COVID-19 had been reported to WHO by March 2022, with 6,108,976 deaths. Until present, a total of 10,925,055,390 vaccination doses have been given out [2]. So far, 43,016,372 confirmed COVID-19 cases have been reported in India, with 516,755 deaths, and 1,805,830,502 vaccine doses have been provided [3]. Viruses that cause pneumonia, such as the SARS coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), have long been known to be especially dangerous during pregnancy [4]. Reduced functional residual volumes, diaphragm elevation, and oedema of the respiratory tract mucosa, as well as alterations in cell immunity, can increase susceptibility to viral infections and worsen outcomes [5]. Due to the cytokine storm and immunological reactivity in pregnancy, studies have revealed that the virus has potential impacts on the neurological and pulmonary systems also. The infection of COVID-19 is more severe. This becomes even more complex in pregnant women with comorbidities like obesity, diabetes mellitus (DM), hypertension, chronic pulmonary disease, chronic heart disease, renal diseases, blood disorders, malignancies, women taking immunocompromised drugs and maternal age of more than 35 y. These pregnant women are more likely to have severe symptoms and be admitted to the intensive care unit (ICU) than non-pregnant women. Their presence is increasingly noticeable throughout the third trimester [6]. Venous thromboembolism, acute respiratory distress syndrome, ICU admission, pneumonia, sepsis, thrombocytopenia, viral myocarditis, cardiomyopathy, mortality, increased caesarean rate, miscarriage, preeclampsia, preterm labour, foetal growth restriction (FGR), stillbirth, neonatal morbidities and mortalities are all possible side effects of COVID-19 during pregnancy [4, 6, 7]. Vaccination against common infectious diseases, such as influenza and pertussis, is commonly recommended during pregnancy to reduce morbidity and mortality in both pregnant women and neonates [8, 9]. Many nations have established guidelines for COVID-19 vaccination during pregnancy to prevent severe COVID-19 and related consequences in this group

of population [7, 10]. Given the dearth of prelicensure evidence unique to this population, continuing safety monitoring is necessary to rule out the possibility of harmful maternal, foetal, or newborn outcomes. To date, emerging evidence from large epidemiological studies has found no significant increased risks of spontaneous abortion, preterm birth, or small-for-gestational-age birth following COVID-19 vaccination during pregnancy. However, there is limited evidence from large populations on other outcomes following COVID-19 vaccination during pregnancy [7, 11, 12].

**SARS-CoV-2 infection in pregnancy**

Pregnancy increases the risk of admission to intensive care, invasive ventilation, and extracorporeal membrane oxygenation in those infected with SARS-CoV-2, according to a meta-analysis of 92 studies comparing outcomes for pregnant patients with COVID-19 with age and sex-matched non-pregnant [13]. A recent meta-analysis of 111 studies reported that infection increased the odds of premature delivery (OR 1.48), pre-eclampsia (OR 1.6), stillbirth (OR 2.36), neonatal mortality (OR 3.35), and maternal mortality (OR 3.08) [14]. Galang *et al.* in his systematic review which included articles on MERS-CoV, SARS-CoV, and SARS-CoV-2 infection in pregnant women. Similar to the overall population of patients, the clinical presentation and course of sickness ranged from asymptomatic to severe terminal disease. There have been reports of severe morbidity and mortality in pregnant women infected with MERS-CoV, SARS-CoV, or SARS-CoV-2, as well as negative pregnancy outcomes such as pregnancy loss, preterm delivery, and laboratory evidence of vertical transmission [15].

The clinical course and outcome of pregnancy in 79 pregnant women with COVID-19 and 85 non-pregnant women with COVID-19 were compared in one of the case-control studies by Hazari KS *et al.* Although pregnant women had fewer symptoms than non-pregnant women, such as fever, cough, sore throat, and shortness of breath, they had a significantly more severe course of disease. When pregnant women with COVID-19 were compared to nonpregnant women with COVID-19, they had significantly higher levels of laboratory parameters of severity, with values above reference ranges for C-reactive protein and D-dimer with  $p < 0.001$ . They had higher ICU admissions (12.6% vs 1.2%) with  $p = 0.0036$ ; and they had

greater COVID-19 infection complication (11.4% vs 1.2%) with  $p=0.0066$ , especially in late pregnancy [16].

Villar *et al.* conducted the INTERCOVID Multinational Cohort Study on 2130 pregnant women in 18 countries. COVID-19-positive women had a higher risk of a composite maternal morbidity and death index. When compared to newborns of women who did not have COVID-19, newborns with COVID-19 had significantly higher severe neonatal morbidity and severe prenatal morbidity and death indices. When pregnant women with COVID-19 were compared to pregnant women without COVID-19, women with COVID-19 had a higher risk of preeclampsia/eclampsia (RR=1.76), severe infections (RR=3.38), intensive care unit admission (RR=5.04), maternal mortality (RR=22.3). Fever and shortness of breath for any length of time were linked to a higher risk of severe maternal problems (RR= 2.56) and newborn complications (RR=2.56). (RR=4.97). Only maternal morbidity (RR=1.24) and preeclampsia were associated with asymptomatic women with COVID-19 (RR=1.63). It was also found that 54 (13%) of the neonates of women who tested positive (98.1%) by real-time polymerase chain reaction also tested positive. Cesarean delivery (RR=2.15) was linked to an elevated risk of newborn test positivity as compared to breastfeeding (RR=1.10) [17].

Another systematic review of published research on the relationship of SARS-CoV-2 infections with pregnancy, foetal, and newborn outcomes during COVID-19 was conducted by Akhtar H *et al.* Intrauterine/foetal discomfort (14%) and early rupture of membranes were the most prevalent maternal/foetal problems (8%). Shortness of breath (6%), gastrointestinal problems (4%), and fever (3%) were the most prevalent infant clinical signs of COVID-19. Infection with COVID-19 during pregnancy increases the risk of preterm birth, PROM, and, in rare circumstances, maternal mortality. There is no indication that SARS-CoV-2 infection can be transmitted vertically to an unborn child [18]. In one of the retrospective observational study by Sunder *et al.*, in pregnant women infected with COVID-19, fetal growth restriction (FGR) was discovered as the obstetric complications. When a trimester-by-trimester comparison was made between the gestational time at diagnosis and the pregnancy outcome, miscarriage were significantly higher ( $p$ -value<0.01). There were no significant relationships between gestational age (GA) at diagnosis and delivery, problems related to maternal age and BMI, or maternal morbidity or mortality [6]. SARS-CoV-2 infection has also been linked to an elevated risk of maternal morbidity and mortality [19], preterm birth (PTB), and neonatal death in many additional investigations in pregnancy [20, 21]. There was additional evidence that the Delta variant of the SARS-CoV-2 virus had worse maternal and newborn outcomes than the previous other variant [22, 23].

#### SARS-CoV-2 and the placenta

The cellular receptors for SARS-CoV-2 like angiotensin-converting enzyme 2 (ACE-2) and transmembrane serine protease 2 (TMPRSS-2), are expressed in the placenta. SARS-CoV-2 viraemia in pregnancy appears to be rare, and placental co-expression of ACE-2 and TMPRSS-2, which are essential for virus entry into cells via the canonical pathway, is rare. Furthermore, ACE-2 expression in the placenta decreases throughout pregnancy. These components may protect the placenta from infection with SARS-CoV-2 in addition to the placenta's typical defences against viral infection. Placental infection does appear to be uncommon. Even in the absence of placental infection, SARS-CoV-2-related coagulation and inflammation can occur, most typically presenting as intervillous thrombosis and fibrin deposition. The decidua of SARS-CoV-2-affected foetus showed local activation of maternal natural killer cells and T cells, as well as the expression of gene signatures linked to pre-eclampsia. SARS-CoV-2 placentitis is a more severe inflammatory condition that arises when the placenta becomes infected. Histiocytic intervillitis, perivillous fibrin deposition, and trophoblast necrosis are all symptoms of this condition, which is emerging as a risk factor for foetal distress or death [24-29].

To emphasize on the histological abnormalities attributed to SARS-CoV-2, Resta L *et al.*, undertook a case-control study. The prevalence of maternal vascular mal-perfusion did not change substantially between cases and controls (54.3% vs. 43.7%,  $p = 0.19$ ); however,

there were significant differences in foetal vascular mal-perfusion (21.1% vs. 4.2%). Decidual arteriopathy (40.9% vs. 1.4%), decidual inflammation (32.4% vs. 0.7%), perivillous fibrin deposition (36.6% vs. 3.5%), and foetal vessel thrombi (22.5% vs. 0.7%) were all more common in cases than controls. There were no significant differences between the two groups in terms of terminal villous hyperplasia and chorioamnionitis [30].

A complete clinical, morphological, and molecular examination of placental tissues from pregnant women with and without SARS-CoV-2 infection was presented by Cribiù FM *et al.* SARS-CoV-2 virus was detected in half of the placental tissues of SARS-CoV-2-positive women. The presence of the virus did not appear to be linked to any specific pathological, maternal, or neonatal outcomes. All but one patient had a low SARS-CoV-2 tissue load, which resulted in significant placental damage and neonatal neurological symptoms. The immunopathology profile of the placental transcriptional response caused by the high viral load of SARS-CoV-2 was similar to postmortem results of lung tissues from individuals with severe COVID-19. In placental tissues from SARS-CoV-2-positive women with low viral tissue load and SARS-CoV-2-negative women, however, there was no inflammatory response. There was no indication of SARS-CoV-2 vertical transmission in any neonates, implying that the placenta may serve as an effective maternal-neonatal barrier to the virus, even in the context of severe infection [31].

In a case-based retrospective clinico-pathological analysis of placental and autopsy pathological findings from 64 stillborns and 4 neonatal deaths with placentas testing positive for SARS-CoV-2 following delivery to mothers with COVID-19. David A *et al.* undertook this study to find if the placenta has a role in stillbirth and newborn death after maternal infection with COVID-19 and found placental positive for SARS-CoV-2. SARS-CoV-2 placentitis is defined by increased fibrin deposition and villous trophoblast necrosis in all 68 placentas, as well as chronic histiocytic intervillitis in 66 of them. There was extensive perivillous fibrin accumulation in 63 placentas. SARS-CoV-2 placentitis caused severe destructive placental illness with an average of 77.7% tissue involvement. Multiple intervillous thrombi (37%) and chronic villitis (32%) were also discovered. Except for intrauterine hypoxia and asphyxia, the majority of the autopsy indicated no serious foetal abnormalities. SARS-CoV-2 was found in a body specimen in 16 of the 28 cases analysed, with nasopharyngeal swabs being the most common source. SARS-CoV-2 was found in the internal organs of four stillborn babies who were autopsied. SARS-CoV-2 placentitis is caused by pathologic anomalies that induce widespread and severe placental damage, culminating in placental mal-perfusion and insufficiency. Intrauterine and perinatal death are most likely caused by placental insufficiency and foetal hypoxic-ischemic damage in these circumstances. There was no evidence that the fetus's exposure to SARS-CoV-2 played a role in the deaths [32].

Menter T *et al.*, did a complete histopathologic description of morphological abnormalities as well as an examination of SARS-CoV-2 presence in foetal tissue. They found evidence of maternal and foetal malperfusion, as well as lymphohistiocytic villitis and intervillitis in the placenta. In 100% and 40% of instances, signs of maternal and/or foetal malperfusion were detected, respectively. The infants were not affected by the transplacental transfer. The presence of significant lymphohistiocytic villitis in acute COVID-19 could be due to SARS-CoV-2 infection of the placenta. There are also histological evidence of maternal and foetal malperfusion, which could be linked to the SARS-CoV-2-induced altered coagulative or microangiopathic condition [33].

#### SARS-CoV-2 and the fetus

SARS-CoV-2 infection in newborns born to infected mother has been observed in a number of studies. Most of the studies looked at infection through nasopharyngeal swab and found that between 0.9 and 2.8% of babies tested positive for SARS-CoV-2. Infants that test positive were not definitely infected in utero; they could have been infected after birth by horizontal transmission [4]. Several other studies have looked at umbilical cord blood to better identify newborns who have been infected by vertical transmission. Despite

the fact that the foetus produces both IgG and IgM between 12 and 20 w of pregnancy, maternal IgG can cross the placenta, therefore only the presence of IgM indicates foetal antigen exposure. Flannery *et al.* undertook cohort research to determine the relationship between maternal and newborn SARS-CoV-2-specific antibody concentrations. SARS-CoV-2 IgG and/or IgM antibodies were found in 83 of 1471 mother/newborn dyads (6%) at the time of delivery, while IgG was discovered in cord blood from 72 of 83 newborns (87%). Antibodies were not found in any infant born to a seronegative mother, and IgM was not found in any cord blood sample. Eleven infants born to seropositive mothers were seronegative: 5 of 11 (45%) were delivered to moms who only had IgM antibodies, and 6 of 11 (55%) were born to mothers who had much lower IgG levels than mothers of seropositive infants. IgG concentrations in cord blood were shown to be favourably linked with maternal IgG concentrations ( $r = 0.886$ ;  $P < 0.001$ ). Women with asymptomatic SARS-CoV-2 infections, as well as those with mild, moderate, and severe coronavirus illness, had placental transfer ratios greater than 1. The transfer ratios raised as the period between the beginning of maternal infection and delivery grew longer. These findings showed that the maternally produced SARS-CoV-2 specific antibodies protect newborns from coronavirus infection [34].

Even in the absence of placental infection, elevated levels of inflammatory cytokines were seen in the cord blood of neonates in another study. It is still unclear if these cytokines are formed locally by the foetus or are a reflection of maternal cytokines that have crossed the placenta. However, the findings that immune cells in cord blood create more cytokines if the pregnancy was disrupted by SARS-CoV-2 infection and that IL-8 concentrations in cord blood are often higher than in maternal blood suggest that the newborn may produce at least some of these cytokines [35-41].

SARS-CoV-2 nucleocapsid protein, viral RNA, and particles associated with coronavirus were detected in the placenta and foetal organs, along with RNA replication evidenced by double-stranded RNA (dsRNA) positive immunostain, according to Valdespino-Vázquez MY *et al.* They also found significant damage to the placenta and embryonic organs, as well as a hyperinflammatory process indicated by histology and immunohistochemistry. The findings revealed that congenital SARS-CoV-2 infection can occur during the first trimester of pregnancy, and that coronavirus can infect foetal organs such as the lung and kidney [42].

Carrasco *et al.* undertook a multicentric observational study to investigate clinical and epidemiological characteristics of a cohort of pregnant women infected with SARS-CoV-2 and their newborns exposed to SARS-CoV-2 during gestation. Overall, 30.8% of pregnant women had pneumonia, with 5 (4.8%) requiring invasive mechanical ventilation in the intensive care unit. Caesarean sections were performed at a rate of 36.2%, and they were linked to pneumonia during pregnancy (OR=4.203) and shorter gestational age at birth (OR=0.724). Prematurity was linked to pneumonia during pregnancy (OR= 6.970) and a positive SARS-CoV-2 at delivery (OR=6.520). The nasopharyngeal swabs in newborns was all negative at birth, but one was positive after 15 d. Although no vertical transmission has been documented in this cohort, SARS-CoV-2 infection during pregnancy may affect the prognosis of newborns because COVID-19 pneumonia increased the incidence of caesarean section deliveries and preterm births [43].

Sophia Stoecklein *et al.* found that foetal lung volumes were considerably reduced in gestational SARS-CoV-2-positive mothers when compared to age-adjusted 50<sup>th</sup> percentile reference values. The foetus had no infarctions or structural abnormalities. Furthermore, during the third trimester of pregnancy, lung volumes were dramatically lowered (69% versus 91% of the 50<sup>th</sup> percentile reference values in the second or first trimester). The duration of infection and pregnancy at the time of MRI scanning, as well as sex, had no impact on foetal pulmonary development [44].

#### Vaccine safety in pregnancy

Vaccination during pregnancy has a long and successful history of preventing maternal illness and mortality, as well as conferring passive immunity to the newborn. There have been numerous

incidents throughout history like smallpox vaccine, pertussis, influenza and tetanus vaccines, that have demonstrated the effectiveness of vaccines in pregnancy. In many countries, influenza and pertussis vaccinations are routinely given to expectant mothers [4]. IgM is not identified in umbilical cord blood after immunisation during pregnancy, which is a crucial discovery in terms of vaccine safety. This means the vaccine do not induce an immunological response in the foetus, implying that it does not cross the placental barrier. To add to this, one study that looked for SARS-CoV-2 spike mRNA or protein in the placenta and cord blood after vaccination failed to find it. In addition, COVID-19 vaccination during pregnancy is not linked to pathological alterations in the placenta. These findings suggest that immunisation has no direct influence on embryonic development. Local and systemic immunological reactions to COVID-19 immunisation do, however, occur in pregnant women to the same degree as they do in the general population [45-55]. The Centers for Disease Control and Prevention (CDC), [56] American College of Obstetricians and Gynecologists (ACOG), [8] Society for Maternal-Fetal Medicine (SMFM) [57], WHO [58] and Royal college of Obstetricians and Gynecologists (RCOG) [1] have all issued recommendations that all pregnant and lactating women, as well as those who are trying to become pregnant, should get the COVID-19 vaccine as it is safe for both mother and fetus.

In a cross-sectional study, Charles Egloff *et al.*, evaluated pregnant women's attitudes and acceptance of COVID-19 immunisation. In this study before a prenatal appointment, all pregnant women in seven French obstetrics departments were asked to complete an anonymous survey. About 29.5% of the 664 pregnant women who completed the survey said they would accept to get vaccinated against COVID-19. The main reason for not agreeing was that the SARS-CoV-2 vaccine's possible negative effects on the foetus were more concerning than COVID-19 [59].

Fell *et al.* studied peripartum outcomes following COVID-19 vaccination during pregnancy in a population-based cohort research in Canada. Among the 97,590 women who got at least one dose of COVID-19 (99% mRNA-based vaccine) vaccination during their pregnancy (63.6% received first dose in the third trimester). These findings revealed that COVID-19 vaccination during pregnancy was not related with an increased risk of unfavourable peripartum outcomes when compared to vaccination after pregnancy or no vaccination [7].

Zucche *et al.* used data from the CDC's v-safe COVID-19 vaccination pregnancy registry to calculate the risk of spontaneous abortion from 6 to less than 20 w of pregnancy. Participants with a singleton pregnancy who had received at least one dose of an mRNA Covid-19 vaccination before conception or before 20 w of pregnancy and who had not experienced a pregnancy loss before 6 w of pregnancy were included in this study. This study used direct maternal age-standardization to the reference population, the combined risk of spontaneous abortion from 6 to less than 20 w of pregnancy was 14.1% and 12.8%. The probability of spontaneous abortion increased as the mother's age increased. In the sensitivity analysis, the cumulative risk of spontaneous abortion from 6 to less than 20 w of gestation was 18.8% after age normalization, it was 18.5% [60].

Stock *et al.* used whole-population data from a national prospective cohort to describe COVID-19 vaccine uptake and SARS-CoV-2 infection in pregnant women in Scotland. Pregnant women (32.3%) had significantly lower vaccination coverage than the total female population (18-44 y) (77.4%). For women who gave birth within 28 d of a COVID-19 diagnosis, the prolonged perinatal mortality rate was 22.6 per 1,000 births; pandemic background rate 5.6 per 1,000 births; 452 out of 80,456. Overall, 77.4% of SARS-CoV-2 infections, 90.9% of SARS-CoV-2 associated with hospital admission, and 98% of SARS-CoV-2 associated with critical care admission, as well as all baby deaths, occurred in pregnant women who were [22].

Vaccine safety study in United Kingdom where community testing data was connected to vaccination data from the National Immunisation Management System (NIMS), cohort studies such as the COVID-19 Infection Survey, and GP electronic health record data. Pregnant women were given three vaccines: the Pfizer, AstraZeneca and Moderna vaccine. Although the findings were preliminary, no

safety concerns about COVID-19 vaccination of pregnant women have been discovered. In both pregnant and non-pregnant groups, the rates of vaccination side effects appears to be similar [61].

Pratama *et al.* included 13 observational studies with a total of 48,039 pregnant women who got mRNA vaccinations in their metaanalysis. Based on the existing evidence, mRNA-based vaccines (Pfizer–BioNTech and Moderna) were effective in preventing SARS-CoV-2 infections. These vaccines did not cause any obvious harm during pregnancy. Pain at the injection site, weariness, and headache were the most prevalent side effects. Antibody responses were quick following the first dose of the vaccination. Antibody responses were stronger after the booster, and this was linked to enhanced transplacental antibody transfer. Longer intervals between vaccination and delivery were also linked to increased foetal IgG antibody levels and a superior antibody transfer ratio [62].

Blakeway *et al.* carried out a cohort research in the United Kingdom to look into the uptake and safety of COVID-19 vaccination among pregnant women. 127 (90.7%) of individuals who were immunised received a messenger RNA vaccine, whereas 13 (9.3%) received a viral vector vaccine. Younger women with high levels of deprivation (ie, fifth quintile of the index of multidimensional deprivation), and women of Afro-Caribbean or Asian ethnicity had lower vaccination uptake than women of White ethnicity. Stillbirth (0.0% vs 0.2%), foetal abnormalities (2.2% vs 2.5%), postpartum haemorrhage (9.8% vs 9.0%), caesarean delivery (30.8% vs 34.1%), and small for gestational age (12.0% vs 12.8%) were all comparable in a propensity score-matched cohort of 133 women who received at least one dose of the COVID-19 vaccine during pregnancy (5.3% vs 5.0%). Intrapartum pyrexia was considerably higher (3.7% vs. 1.0%), however, the statistical significance was lost after removing women with prenatal COVID-19 infection. Mixed-effects Vaccination was not linked with birth at 40 w' gestation (hazard ratio=0.93), according to Cox regression (hazard ratio=0.93). These findings indicate that the COVID-19 vaccination is safe to use during pregnancy [63].

## CONCLUSION

SARS CoV-2 is a potentially fatal virus; however, there is little information about infected pregnant women. COVID-19 vaccination is recommended for pregnant women by several health care authorities because it reduces maternal and foetal mortality. Intrauterine transmission of SARS-CoV-2 appears to be uncommon, which could be due to low SARS-CoV-2 viremia and lower co-expression of ACE-2 and TMPRSS-2, which are required for SARS-CoV-2 entry into placental cells. Women infected with SARS-CoV-2 during pregnancy are more likely to have adverse pregnancy and neonatal outcomes, especially those with severe disease. Furthermore, the existing evidence suggests that SARS-CoV-2 antibodies are transmitted to the foetus after vaccination during pregnancy. High levels of SARS-CoV-2 antibodies in breast milk have been linked to the vaccination of breastfeeding women. The extent of protection supplied to the newborn by transplacental antibodies and those contained in breast milk, on the other hand, is uncertain. Pregnant women, despite their elevated risk of severe disease and the danger of bad pregnancy and neonatal outcomes if infected, are less likely to obtain a COVID-19 vaccine, according to vaccine coverage data. We need a strong public health information system, but we also need to make sure that midwives and obstetricians are well-equipped to advise their patients on the benefits of COVID-19 vaccination.

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## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICT OF INTERESTS

Declared none

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