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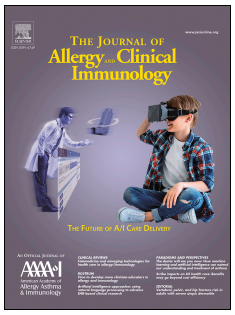

Maternal COVID-19 disease, vaccination safety in pregnancy, and evidence of protective immunity

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TITLE PAGE

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MANUSCRIPT

Over the past 18 months, the world has seen the largest pandemic, caused by the severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2). As of June 28th, 2021, the Center for Disease Control (CDC) reported 98,948 cases of COVID-19 infection in pregnancy and 109 related maternal deaths in the United States alone.(1) As the pandemic continues to evolve, the rapid and overwhelming increase in available evidence on the impact in pregnancy has resulted in studies of varying degrees of bias and quality. In this brief review, we seek to fill some of the knowledge gaps regarding maternal care considerations and answer some key questions about vaccination safety in pregnancy and evidence of protective immunity (Figure 1).

Effects of COVID-19 in pregnancy

Clinical findings: symptoms, labs, imaging

Maternal COVID-19 disease varies widely, but clinical course, laboratory findings, and radiological patterns found in pregnancy (Table 1) are similar to the non-pregnant population.(2) Although some patients may be asymptomatic, presence of any COVID-19 symptoms was found to be associated with increased maternal morbidity and mortality.(1)

(Table 1)

Maternal and neonatal outcomes

Maternal COVID-19 is associated with consistent and substantial increases in morbidity and mortality when infected pregnant versus non-pregnant individuals are compared.(1) A large study conducted by the Maternal-Fetal Medicine Unit (MFMU) Network including 1219

patients, reported that mothers with severe or critical COVID-19 disease and their neonates are at increased risk for a number of perinatal complications, including cesarean birth, hypertensive disorders of pregnancy, preterm birth, venous thromboembolism, neonatal intensive care unit (ICU) admission, and lower birth weight, compared to asymptomatic mothers.(3) Pregnancy is also independently associated with an increased risk for ICU admission, needing extracorporeal membrane oxygenation, and maternal death among patients with symptomatic COVID-19 infection. Moreover, comorbidities (body mass index higher than 35 kg/m^2, diabetes, and cardiovascular disorders) and advanced maternal age also appear to have an independent risk for adverse maternal outcomes.

Vertical transmission of SARS-COV-2, maternal immunity, and protection of the neonate

Vertical transmission is defined as evidence of transmission of the SARS-CoV-2 virus from the mother to the fetus or newborn. Studies have evaluated SARS-CoV-2 viral concentrations in umbilical cord blood and placenta. Real-time reverse transcription polymerase chain reaction (rRT-PCR) has been used to evaluate amniotic fluid, newborn blood, urine, nasopharyngeal, fecal, and rectal swabs. Positive samples have been rare and significant neonatal respiratory disease, even in the presence of SARS-CoV-2 positivity, is even more infrequent.(4) The CDC reported that transmission of SARS-CoV-2 virus to neonates occurred primarily through respiratory droplets during the postnatal period when neonates are exposed to mothers or other caregivers with COVID-19 disease. Overall, the risk of vertical transmission of the SARS-CoV-2 virus is approximately 3.2%.(5)

In utero fetal production of immunoglobulin (Ig) G and IgM antibodies start in the 20th week of gestation, therefore the majority of neonatal IgG is of maternal origin. IgG positivity cannot support or refute vertical transmission. IgM antibodies do not cross the placenta and therefore IgM presence in the fetus or neonate is thought to represent fetal or neonatal production in response to an infection. However, in case reports describing identification of COVID-19 IgM antibodies in the neonate, infants have been asymptomatic and tested negative for SARS-CoV-2 viral RNA at birth. While plausible that the presence of these IgM antibodies represents crossover from maternal to fetal circulation, the presence of IgM antibodies in these infants could provide evidence for intrauterine vertical transmission. There are some case reports demonstrating evidence of transplacental transmission, however these reports remain scare. Overall, there is limited evidence of the timing for the production of IgM and IgG during COVID-19 infection or the timeline for development of long-term immunity and more data are needed regarding the potential and appropriate testing to determine risk of vertical transmission.

Vaccine safety in pregnancy

There are currently three approved vaccines for use in the United States (Table 2). Although not specifically included in the initial phase III vaccine trials, pregnant patients were not excluded as part of the Food and Drug Administration (FDA) issued Emergency Use Authorization (EUA). Given the increased risk of disease severity in pregnancy, professional organizations advocate for availability of vaccine for pregnant and lactating persons. Early data from developmental and reproductive toxicity (DART) studies for both the Pfizer and Moderna vaccine did not demonstrate direct or indirect harmful effects with respect to pregnancy, fetal development,

delivery or postnatal complications. Additionally, DART data on the Johnson & Johnson vaccine have not demonstrated adverse outcomes.

Since the EUA for the Pfizer and Moderna vaccines, over 128,306 pregnant patients have received the vaccine and registered with the CDC V-safe program. Recent data from the CDC V-safe program found side effects from the vaccine were similar between pregnant and nonpregnant women. Additionally, when evaluating 827 completed pregnancies, there was no increased risk in adverse pregnancy outcomes including miscarriage, preterm birth, small for gestational age, and neonatal death when compared to data prior to the COVID-19 pandemic.(6)

A recent study of 131 patients found the mRNA COVID-19 vaccines to be highly effective in producing vaccine-induced antibody titers in pregnant (median [interquartile range, IQR] 5.74 (5.06–6.22]) and lactating women (5.62 [4.77–5.98]), who had titers similar to those of nonpregnant women (median [IQR] 5.59 [4.68–5.89]).(7) All vaccine-generated titers were higher than those generated by SARS-CoV-2 infection during pregnancy. Furthermore, vaccine-generated antibodies were found in all umbilical cord and breast milk samples. This study provided reassuring data that pregnant individuals have a similar response to the vaccine as non-pregnant individuals. Another cohort study from Israel comparing vaccinated pregnant patients, PCR-confirmed SARS-CoV-2 infected pregnant patients, and unvaccinated non-infected pregnant controls looked at the effect of the mRNA vaccine (Pfizer-BioNTech) versus native infection on maternal humoral and transplacentally acquired fetal immune response. They found a robust maternal induced humoral response to the vaccine that effectively transfers to the fetus, also supporting the role of vaccination during pregnancy.(8)

Regarding timing of vaccine and antibody production, Prabhu, *et al* evaluated 122 pregnant patients who received an mRNA COVID-19 vaccine and found 44% of cord blood samples were positive for IgG antibodies following one dose of the vaccine, compared to 99% of the samples following both doses of the vaccine.(9) All patients and cord blood samples had detectable antibodies when delivered at least 4 weeks following the first dose of vaccine. They also found that the earliest antibody detection in maternal samples was 5 days following vaccine and 16 days following vaccine for cord blood samples.(9)

(Table 2)

COVID-19 related maternal morbidity and mortality is lower than that which occurred during prior coronavirus-related epidemics, however greater than observed in the non-pregnant population. Nevertheless, vertical transmission is rare. The novel FDA-approved mRNA and adenovirus vaccines have the ability to reduce the risk of severe maternal morbidity and mortality and induce an immunologic protection for neonates through antibody transfer in utero and during lactation. The benefits of these vaccines may outweigh the risks of COVID-19 disease in pregnancy and in the postpartum period. Ongoing research is needed on the effects of COVID-19 infection during pregnancy spanning all times in gestation as well as long term studies related to effect of COVID vaccine in pregnancy.

REFERENCES:

1. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study. JAMA Pediatr. 2021.
2. Molteni E, Astley CM, Ma W, Sudre CH, Magee LA, Murray B, et al. SARS-CoV-2 (COVID-19) infection in pregnant women: characterization of symptoms and syndromes predictive of disease and severity through real-time, remote participatory epidemiology. medRxiv. 2020.
3. Metz TD, Clifton RG, Hughes BL, Sandoval G, Saade GR, Grobman WA, et al. Disease Severity and Perinatal Outcomes of Pregnant Patients With Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2021;137(4):571-80.
4. Amaral WND, Moraes CL, Rodrigues A, Noll M, Arruda JT, Mendonca CR. Maternal Coronavirus Infections and Neonates Born to Mothers with SARS-CoV-2: A Systematic Review. Healthcare (Basel). 2020;8(4).
5. Kotlyar AM, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. Am J Obstet Gynecol. 2021;224(1):35-53 e3.
6. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med. 2021.
7. Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, et al. COVID-19 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol. 2021.
8. Beharier O, Plitman Mayo R, Raz T, Nahum Sacks K, Schreiber L, Suissa-Cohen Y, et al. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. J Clin Invest. 2021.
9. Prabhu M, Murphy EA, Sukhu AC, Yee J, Singh S, Eng D, et al. Antibody Response to Coronavirus Disease 2019 (COVID-19) Messenger RNA Vaccination in Pregnant Women and Transplacental Passage Into Cord Blood. Obstet Gynecol. 2021.
10. Papapanou M, Papaioannou M, Petta A, Routsi E, Farmaki M, Vlahos N, et al. Maternal and Neonatal Characteristics and Outcomes of COVID-19 in Pregnancy: An Overview of Systematic Reviews. Int J Environ Res Public Health. 2021;18(2).

TABLES

Table 1. Clinical findings, laboratory parameters, and radiologic findings in order of frequency in pregnancies affected by COVID-19 disease

Sign and symptoms	Range of frequency in pregnancy
Clinical Findings	
Fever	32.8-78% (10)
Cough	34-70% (10)
Dyspnea	7.3-35.6% (10)
Asymptomatic	8-32.6% (10)
Myalgia	6-24.4% (10)
Sore throat	3.4-22.2% (10)
Fatigue	9.5-18.5% (10)
Diarrhea	4-10.4% (10)
Laboratory Parameters	
Elevated CRP	40.8-70.3% (10)
Lymphopenia	29-68.2% (10)
Leukocytosis	13-45.8% (10)
Leukopenia	<45.3% (10)
Abnormal liver function test	8-27.3% (10)
Thrombocytopenia	2.7-8.4% (10)
Radiologic Findings	
Ground glass opacities	41.5-81.6% (10)

Table 2. COVID-19 Vaccines

Vaccine	Pfizer-BioNTech BNT162b2	Moderna mRNA 1273	Janssen Biotech Ad26.COV2.S	AstraZeneca -SKBio AZD1222

Type	mRNA vaccines	mRNA vaccines	Adenoviral-vector vaccine	Adenoviral-vector vaccine
FDA issued EUA in the US	Yes	Yes	Yes	No
Age eligibility	≥12 years	≥12 years	≥18 years	≥18 years
Number of pregnancies in placebo vs. treatment arms	11 in the placebo arm vs 12 in the treatment arm	7 in the placebo arm vs 6 in the treatment arm	N/A	N/A
Number of doses and frequencies	2 doses, 21 days apart	2 doses, 28 days apart	1 dose	2 doses, 4 to 12 weeks apart
Efficacy	95.0% (95% CI, 90.3%–97.6%) after the second dose	94.1% (95% CI, 89.3%– 96.8%) after the second dose	72% moderate; 85% severe; 100% COVID related hospitalization and death	60%(per EMA) to 63.09% (per WHO) after the second dose
Contain live virus?	No	No	No	No
Mechanism of action	Contain mRNA, a genetic material that encodes the SARS-COV-2 spike S protein	Contain mRNA, a genetic material that encodes the SARS-COV-2 spike S protein	Uses an adenovirus to carry the gene for the coronavirus spike S protein, which is produced by the host cell and expressed on the cell membrane, where it is detected by	Uses an adenovirus to carry the gene for the coronavirus spike S protein, which is produced by the host cell and expressed on the cell membrane, where it is detected by the host

			the host immune system to mimic components of the pathogen without causing disease	immune system to mimic components of the pathogen without causing disease
Enter cell nucleus/ integrated into the host DNA?	No/No	No/No	Yes/No	Yes/No
Other similar vaccines	None	None	Ebola, HIV, and RSV adenoviral vaccine	Ebola, HIV, and RSV adenoviral vaccine
Pregnancy test recommended prior to vaccination?	No	No	No	No
Vaccine contraindication	Acute illness	Acute illness	Acute illness	Acute illness
Risk of TTS in pregnancy	Not increased in pregnancy	Not increased in pregnancy	Not increased in pregnancy (Occurred in 8.9 in 1 million doses in nonpregnant women age 18-49)(6)	Not increased in pregnancy (Occurred in 6.5 in 1 million doses in nonpregnant women age <60, reported by EMA)
Safety data in pregnancy	Evidence from 827 completed pregnancies(6)	Evidence from 827 completed pregnancies(6)	N/A	N/A

169 COVID-19 - Coronavirus disease 19; EMA - European Medicines Agency; EUA - Emergency
170 Use Authorization; FDA - Food and Drug Administration; HIV - Human immunodeficiency
171 virus; N/A - Not applicable; RNA - Ribonucleic acid; RSV - Respiratory Syncytial Virus; SARS
172 - Severe Acute Respiratory Syndrome; TTS - Thrombosis with thrombocytopenia syndrome'
173 WHO - World Health Organization

Increased obstetric outcomes related to SARS-CoV-2 infection

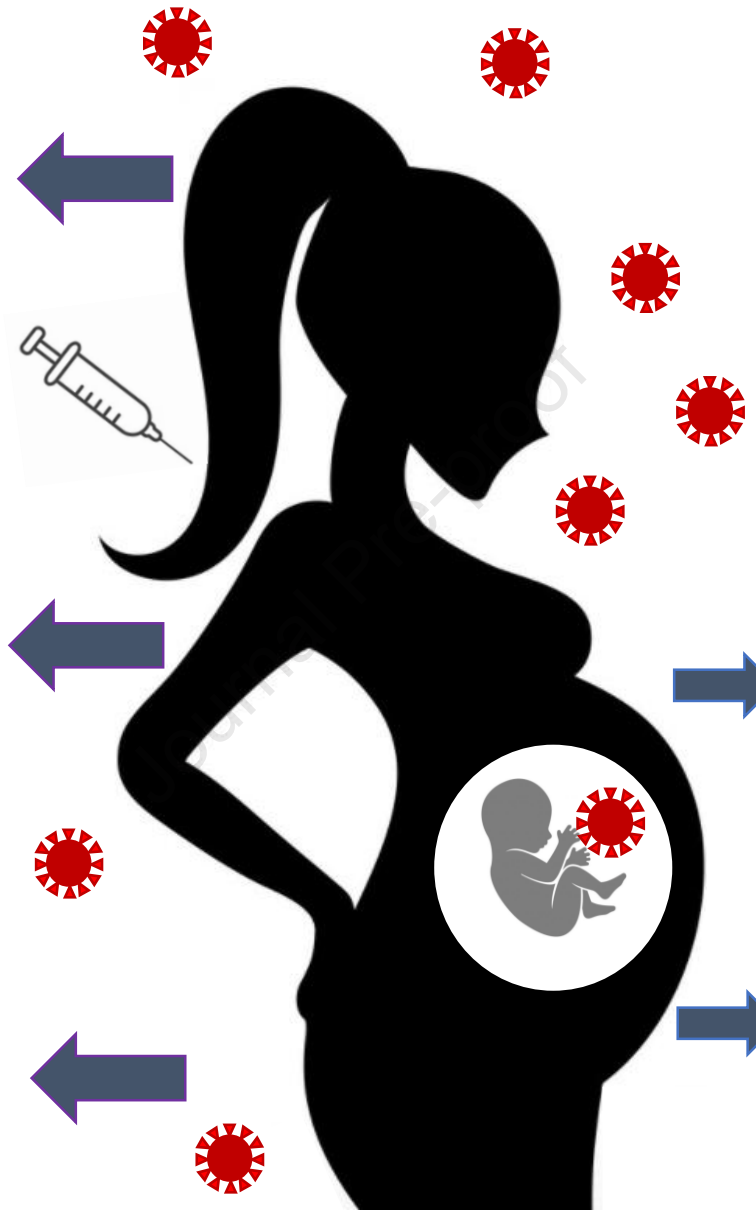
- Cesarean birth
- Hypertensive disorder of pregnancy
- Preterm birth
- VTE
- ICU admission
- ECMO
- Maternal mortality

Vaccines in pregnancy

- Higher generated immune response than natural infection
- Protective immunity through the placenta and breastmilk

Treatment and interventions in pregnancy

- Multidisciplinary team-based approach
- Corticosteroids
- Remdesivir
- Monoclonal antibodies
- Delivery timing by obstetric indications



Legend:

SARS-CoV-2 viral particles

Maternal considerations

Fetal/neonatal care considerations

ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; NICU: Neonatal ICU; VTE: venous thromboembolism

Neonatal outcomes

- Prematurity
- NICU admission
- Low birth weight

Possible mechanisms of transmission to neonates

- Vertical transmission (approximately 3.2%)
- Respiratory droplets during the postnatal period

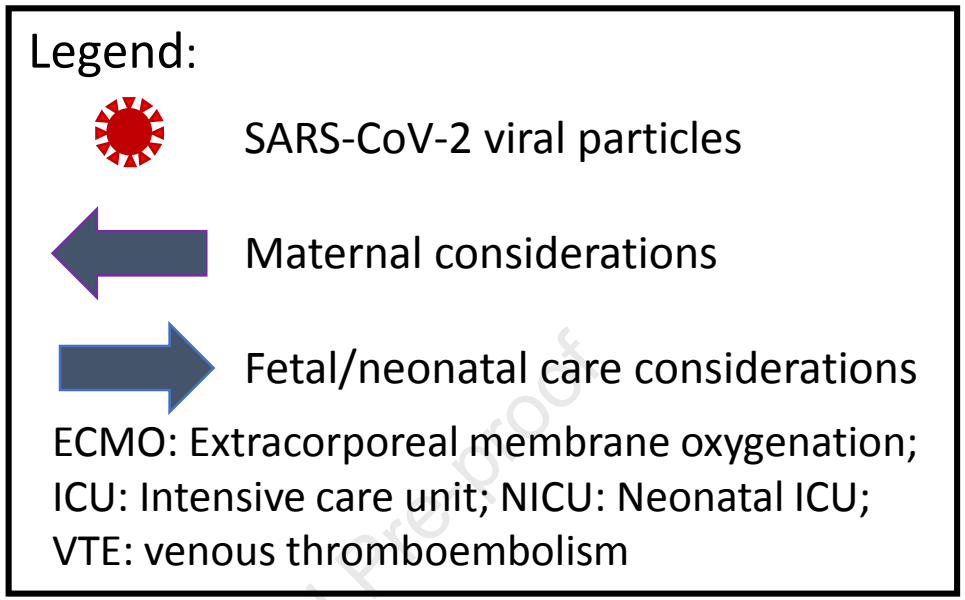


Figure 1: Pregnancy and Neonatal Considerations of SARS-CoV-2 Infection and Vaccination

Pregnant individuals with SARS-CoV-2 infection during pregnancy are at increased risk of cesarean delivery, hypertensive disorders of pregnancy, preterm birth, venous thromboembolism (VTE), intensive care unit (ICU) admission, Extracorporeal membrane oxygenation (ECMO), and maternal mortality. Treatment of pregnant infected individuals is similar to nonpregnant individuals and includes multidisciplinary team-based approach, corticosteroids, remdesivir, monoclonal antibodies and delivery timing based on obstetric interventions. Neonates exposed to SARS-CoV-2 have increased rates of prematurity, neonatal ICU admission, and low birth weight. Possible mechanisms of transmission include vertical transmission (approximately 3.2% of neonates exposed to SARS-CoV-2 in utero) or through exposure to infected respiratory droplets during the postnatal period. Vaccines against SARS-CoV-2 in pregnancy generate a higher immune response than natural infection and provide passive protective immunity through the placenta and breastmilk.