Effects of COVID-19 infection during pregnancy

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ABSTRACT

Women develop important changes in their cardiovascular and respiratory systems during pregnancy. They also have important changes in their immune system which are necessary to tolerate foreign fetal tissue. These expected alterations can increase the likelihood of poor outcomes with certain respiratory infections, especially viral infection. There is extensive literature describing COVID-19 in pregnant women, and there is evidence that this virus can infect the placenta, raising implications for maternal-fetal transmission. Women who contract COVID-19 during pregnancy are at increased risk of preterm labor and other perinatal complications when compared to non-pregnant women. Trials on the safety and efficacy of the COVID-19 vaccines during pregnancy are in progress; several reproductive societies have recommended that women who are planning to get pregnant or are pregnant should get vaccination since there are few reports of adverse events in pregnant women who have received vaccines. Healthcare providers will need to address concerns of infertility, the possibility of vertical transmission, and neonatal infection with women regarding timely vaccination against this disease and other necessary precautions.

Keywords: coronavirus, COVID-19, pregnancy, placental pathology, vertical transmission

INTRODUCTION

Pregnant women are particularly susceptible to infections from respiratory pathogens, in large part due to the physiological changes that occur in the immune and cardiopulmonary systems during pregnancy. The gravid uterus causes a reduction in functional residual volume with diaphragm elevation, and increased blood volume and fetal metabolic demand cause higher oxygen consumption, which can contribute to hypoxia. Pregnancy also involves a shift from cell-mediated immunity toward humoral immunity during the first trimester so that the female immune system can tolerate genetically foreign fetal antigens.[1–4] These changes may alter susceptibility to and severity of infectious diseases during pregnancy.

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Although community-acquired pneumonia is not uncommon in pregnancy (with *S. pneumoniae*, *H. influenzae*, and *M. pneumoniae* accounting for most bacterial infections), there is concern for maternal and fetal complications regarding Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2, also known as COVID-19) infections. This enveloped RNA virus is coated with spike glycoproteins, which are primarily responsible for host infection by binding to the angiotensin converting enzyme 2 (ACE2) receptor complexes and heparan sulfate residues on respiratory cells.[5] ACE2 is also widely distributed in reproductive organs, such as the vagina, uterus, and placenta; during pregnancy, estrogen and progesterone upregulate the concentration of ACE2, not only in these reproductive organs but especially in lung tissues to protect against preeclampsia, as the receptor complex contributes to vasodilatory effects and maintenance of fluid homeostasis.[6] The higher expression of ACE2 makes the alveoli more accessible for SARS-CoV-2 entry and is clinically evident with the rapid development of pneumonia, and bacterial and viral

co-infections are more prevalent among pregnant women than in non-pregnant patients.[7] Pregnant women with COVID-19 may experience worse *perinatal* outcomes than pregnant women without COVID-19. As the placenta represents the maternal-fetal interface during pregnancy, ACE2 receptor expression in placental cells may have an important role in facilitating the vertical transmission of SARS-CoV-2.

SARS-CoV-2 INFECTS THE PLACENTA IN PREGNANT WOMEN

Maternal hypoxemia in the setting of pneumonia can subsequently lead to placental hypoxia, causing the placenta to release antiangiogenic and pro-inflammatory factors that induce endothelial dysfunction. There is limited literature available about the mechanism by which SARS-CoV-2 is vertically transmitted, even with reports of neonates who tested positive for immunoglobulin G and immunoglobulin M antibodies, born to women with confirmed COVID-19 during the pregnancy.[8,9] Several systemic reviews have shown that although the majority of neonates may have negative RT-PCR results for SARS-CoV-2, these neonates are at risk for preterm delivery, pre-eclampsia, and low birth weight due to the hypoxia induced by severe pneumonia in mothers.[7,10–12] Because the placenta provides support for fetal growth, its histopathology may help explain the underlying cause of growth restriction and fetal prognosis. In maternal ischemic conditions, such as those seen with COVID-19 infection, spiral arteries and terminal vessels may not dilate normally and fail to extend into the decidua. Consequently, there is incomplete perfusion of the intervillous space leading to villous damage and possible fetal growth restriction.

Hypoxia induced by maternal SARS-CoV-2 infection may lead to vascular malperfusion (VM) findings in the placenta. Scientists have confirmed SARS-CoV-2 infection in the placental tissue by PCR and immunostaining and further showed that there may be sufficient hypoxemia in the setting of infection to change placental vasculature.[13–17] Relative to controls, COVID-19 third trimester placentas show increased prevalence of perivillous fibrin deposition, intervillositis, and decidual arteriopathy. These patterns of placental injury reflect abnormalities in oxygenation, which are often associated with adverse perinatal outcomes. Shanes et al. found some evidence of VM in 11/15 cases (72%), Smithgall et al. reported 38/51 placentas had evidence of VM, compared to 16/25 healthy controls, with the frequency of villous agglutination and subchorionic thrombi significantly increased in SARS-CoV-2 positive placentas, and Mulvey et al. reported all five of the placentas examined had vascular malformations, which were absent in controls.[13–16] In these three reports, there were no neonatal deaths and all infants were negative for SARS-CoV-2 by nasopharyngeal and throat swab RT-PCR testing. The current standard for diagnosis of COVID-19 in neonates is by RT-PCR analysis of specimens from nasopharyngeal swabs and to a lesser extent from swabs of the oropharynx. It is important to note that viral vertical transmission can occur through three different mechanisms (intrauterine hematogenous route and the ascending route, intrapartum, and postpartum skin-to-skin and breast milk routes) and that a positive RT-PCR swab does not necessarily mean that COVID-19 has been passed through the placenta from mother to infant. Clearly, this indicates that there are unanswered questions on the exact process of transmission from mother to fetus.

Considering the number of pregnant women who have been infected and the low number of neonates who have positive viral nucleic acid loads, vertical transmission of this virus seems to be rare. One possible explanation for low transplacental infection is that the lack of caveolin, a membrane structure that can cause endocytosis of certain viruses, in the syncytiotrophoblast results in a failure of SARS-CoV-2 in crossing into the placental villi.[18] While limited conclusions can be drawn about the effect of maternal SARS-CoV-2 placental infection on vertical transmission, as most lack control groups and most reports followed third trimester infection, there is no direct evidence that fetal demise has occurred directly from viral infection. The placental vasculature changes seen in mothers infected with COVID-19 are similar to mothers who have pneumonia secondary to other viral and bacterial pathogens, suggesting that the adverse perinatal outcomes, such as increased risks of miscarriage, preeclampsia, preterm birth, and stillbirth, are related to infection[11,19–21]

SARS-CoV-2 INFECTION IN PREGNANT WOMEN AND FETAL OUTCOMES

Increased severity of COVID-19 symptoms in pregnant patients is associated with higher risk of developing complications during and after pregnancy. Overall, pregnant patients present with similar clinical characteristics of COVID-19 when compared with the general population, but they may be more asymptomatic. The most common symptoms reported were fever (pregnant: 75.5%; non-pregnant: 74%) and cough (pregnant: 48.5%; non-pregnant: 53.5%), but only pregnant patients reported myalgias (26.5%) and chills (25%), while non-pregnant patients report dysgeusia (27%) and fatigue (26.5%).[21] Findings from the Gestational Research Assessments for COVID-19 study, which evaluated 1,200 pregnant women with COVID-19 who delivered at U.S. hospitals between March and July 2020, revealed that pregnant women who experienced severe symptoms of COVID-19 (versus asymptomatic pregnant women) show a higher prevalence of Cesarean delivery, hypertensive disorders of pregnancy, and preterm birth. Forty-seven percent of the women were asymptomatic, 27% had mild symptoms, 14% had moderate symptoms, 8% had severe symptoms, and 4% were critically ill.[22] Several systemic analyses have also assessed pregnancy outcomes, such as miscarriage, preterm birth, preeclampsia, preterm prelabor rupture of membranes, fetal growth restriction, and mode of delivery. Diriba et al. assessed maternal outcomes and found that in a study of 1316 women, rates of preeclampsia and miscarriage were 5.9% and 14.5% respectively. Moreover, 56.9% delivered by Cesarean section, 31.3% were admitted to ICU, and 2.7% of the mothers died.[12]

Pregnancy affected by SARS-CoV-2 infection was more likely to result in premature births and growth restriction. Neonatal outcomes, such as fetal distress, Apgar score <7 at 5 minutes, admission to a neonatal intensive care unit, perinatal death, were measured to determine the effects of maternal COVID-19 infection on fetal health. DiMasco et al. found that for all coronavirus infections, the pooled proportion of miscarriage was 64.7%. Premature prelabor rupture of membranes occurred in 20.7%, preeclampsia in 16.2%, and fetal growth restriction in 11.7%.[23] When focusing on COVID-19, the most common adverse pregnancy outcome was preterm birth (as birth occurring before 37 weeks of gestation), occurring in 41.1% of cases. Similarly, Khalil et al. conducted a systematic review of observational studies (2567 pregnancies) and found preterm birth to be common at 21.8%, with maternal intensive care unit admission being required in 7.0% and intubation in 3.4%.[24] Of the reported neonates who have had positive tests for COVID-19, some have been asymptomatic, while other neonates have had symptomatic illness. Zeng et al. reported that among 33 neonates whose mothers had COVID-19 infection in Wuhan, China, there were 3 delivered by Cesarean section who developed fever and pneumonia and tested positive for the virus on the second day of life.[8] Possible mechanisms explaining the pathophysiology of fetal intrauterine growth restriction and demise include exaggerated maternal inflammatory and cytokine storm, subsequently causing microvascular injury and coagulation disruption in the fetus; others believe it may be related to the fetal, not maternal, ACE2 polymorphisms.[25,26]

Pregnant women are treated on a symptomatic basis as there is an absence of an exclusive antiviral treatment against SARS-CoV-2. The National Institutes of Health (NIH), American College of Obstetricians and Gynecologists (ACOG), and Society for Maternal-Fetal Medicine recommend dexamethasone for pregnant women hospitalized with COVID-19 requiring mechanical ventilation and may be considered in pregnant women who require supplemental oxygen, but not mechanical ventilation.[29–31] There are currently no clinical indications that Cesarean section for women with COVID-19 reduces the risk of vertical transmission to the newborn.[31] Consequently, route of delivery should be determined as per usual guidelines, and respiratory deterioration due to COVID-19 may prompt urgent delivery on a case-by-case basis.

CURRENT RECOMMENDATIONS ON BREASTFEEDING AND VACCINATION

It is a well-known fact that immunoglobin G and A are the only antibody classes to cross the placenta and breast milk, respectively, providing passive immunity from the maternal to the fetal circulation

for up to 6 months. While these maternal antibodies do not confer long-lasting immunity for neonates, there are questions as to whether antibodies against COVID-19 from a natural infection in mothers protect against coronavirus in those 6 months. Several studies have documented negative RT-PCR of vaginal swabs, amniotic fluid, placenta, cord blood, neonatal blood, and breast milk testing for COVID-19.[9,30–32] Yet Rodrigues et al. reported that in 163 cases with amniotic fluid, placenta, and/or cord blood analyzed for the SARS-CoV-2 virus, 10 were positive. Four breast milk samples from 92 cases showed evidence of SARS-CoV-2.[33] Based on the limited data of neonates contracting infection from these secretions, most researchers and the ACOG encourage breastfeeding or bottle-feeding with expressed breast milk, even in women that have had COVID-19 infection, as it remains the gold standard of nutrition and is a beneficial source of antibodies for the neonate, even though they may not be long-lasting ones.[34]

There has been uncertainty regarding the risks and benefits of vaccinating pregnant women against COVID-19 because this population was excluded from the initial Pfizer/BioNTech and Moderna clinical trials. Only the RECOVERY trial included pregnant women (n=6). There is often hesitancy and delay in enrolling pregnant women in clinical trials due to the portrayal of them as a vulnerable population and need for companies to produce rapid trial results on safety and efficacy. Both the Society of Maternal-Fetal Medicine and ACOG have supported vaccination of women who are both pregnant and breastfeeding. The Society of Maternal-Fetal Medicine cites the fact that the vaccines for TDAP and Ebola have been administered during pregnancy and thus far show an acceptable safety profile. Current clinical trials are now including pregnant women to address the vaccine's safety and efficacy; Pfizer/BioNTech announced a global placebo-controlled, observer-blinded study in 4,000 women, in which they will compare the tolerability and immunogenicity of their 2 doses administered 21 days apart for 10 months.[35] The current plan includes assessing the safety of the vaccine in infants of vaccinated mothers and investigating whether antibodies from the mother are transferred to the infant 6 months after birth.

One concern regarding the vaccine is whether the vaccines cause infertility in women. This arose when a former Pfizer researcher highlighted that the COVID-19 spike protein (targeted by the mRNA vaccines) is structurally similar to the syncytin-1 spike protein expressed in the placenta. The suggestion was that a cross-reaction from antibodies developed from the vaccine could, theoretically, cause the body to attack the placenta, causing infertility. There is no evidence that this is true as syncytin-1 is not contained in the SARS-CoV-2 spike protein; furthermore, the SARS-CoV-2 spike protein and syncytin-1 share only five amino acid residues, which is a small number of overlaps given that humans have other proteins in the body with greater amino acid similarity.[36,37]

Additionally, during the Pfizer/BioNTech vaccine clinical trials, 23 people became pregnant even after receiving the vaccine. The Centers for Disease Control (CDC) reported on January 27, 2021 that about 30,000 pregnant people had enrolled in the V-safe registry, which facilitates reporting of side effects following vaccination; a CDC update on March 1, 2021 stated that there have been 275 completed pregnancies, including 232 live births.[38,39] Moderna submitted data from a Developmental and Reproductive Toxicity (DART) study in rats to the Food and Drug Administration on December 4, 2020, that concluded there were no adverse effects of a standard mRNA vaccine dose on female reproduction, fetal development, or postnatal growth while Pfizer/BioNTech is currently conducting DART studies to determine if there are negative side effects of the COVID-19 vaccine in pregnancy.[40]

Conclusion

The gold standard of diagnostics of SARS-CoV-2 infection remains testing for viral nucleic acids for both adult and neonatal populations. There is no evidence that pregnant women are more susceptible than the general population in the severity of COVID-19 infection. Vertical transmission of coronavirus from the pregnant woman to the fetus has not been proven, but there is evidence of SARS-COV-2 viral load in the placenta. With histological evidence of damage to the placental vasculature and function, COVID-19 may indirectly cause premature rupture of membranes,

premature labor, and fetal distress. The most common perinatal outcomes in mothers positive for COVID-19 were preterm births and admission to the NICU for respiratory distress. Most cord blood and breast milk samples from infected patients were free from the virus, but there remains a small percentage with virus in breastmilk. Consequently, ACOG and other obstetric societies continue to encourage breastfeeding for neonatal acquisition of protective antibodies.

As current clinical trials are including more pregnant women to assess the efficacy of the vaccines, information will become available regarding COVID-19 and its effects on pregnancy. Pregnant patients with this infection should be cared for by a multidisciplinary team, and identifying the mechanism of neonatal COVID-19 infection will be useful in determining the need for Cesarean delivery, neonatal resuscitation in intensive care, safety of rooming-in, skin-to-skin contact, and breastfeeding.

ADDENDUM

Gray et al. recently published a report on March 25, 2021 of 131 women focusing on whether the COVID-19 vaccines could be beneficial in pregnancy. Participants were between the ages of 18- to 45-years and received either the Pfizer or Moderna injections at the Brigham and Women's Hospital, Massachusetts General Hospital, and the Ragon Institute; 84 were pregnant, 31 were lactating, and 16 were not pregnant. Blood samples collected after the first and second doses of the vaccine and again after six weeks showed that antibodies generated against the receptor binding domain of the virus were similar among the groups of women.[41] In addition, the study found antibody titers after vaccination were higher than antibody levels in women who acquired immunity through natural COVID-19 infection during pregnancy. This underscores the importance of vaccination as the finding suggests that people (not just women) who receive the vaccine may develop a more robust antibody response than the antibody response after actual infection. Umbilical cord blood (n=10) and breast milk (n=31) antibody titers revealed that with the second vaccine dose, there was an increased IgG for SARS-CoV-2, but not IgA, in these maternal samples, suggesting

that pregnant women who received the COVID-19 mRNA vaccine in the 3rd trimester had transplacental transfer of IgG to the infant. Another study of 27 pregnant women, with 64% receiving the Pfizer doses and 14% receiving the Moderna dose (some did not know which they received) in their third trimester showed higher levels of IgG against COVID-19 in the umbilical cord blood in 28 newborns (26 singletons, one set of twins).[42] In these pregnant women, a longer time between vaccination and delivery was associated with a more effective transfer of for SARS-CoV-2 specific antibodies to the newborns. Based on these results, the CDC, ACOG, and other obstetric societies continue to encourage women to obtain the vaccine (while still practicing social distancing and facial covering) to confer passive immunity during pregnancy and the postpartum period through transplacental and breast-milk transfer.

REFERENCES

1. Contreras G, Gutiérrez M, Beroíza T, et al. Ventilatory drive and respiratory muscle function in pregnancy. Am Rev Respir Dis 1991;144:837–41. https://doi.org/10.1164/ajrccm/144.4.837.
2. Kolarzyk E, Szot WM, Lyszczarz J. Lung function and breathing regulation parameters during pregnancy. Arch Gynecol Obstet 2005;272:53–8. https://doi.org/10.1007/s00404-004-0691-1.
3. Lederman MM. Cell-mediated immunity and pregnancy [J]. Chest 1984;86(3 Suppl):6S–9S.
4. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis 2006;12(11):1638–1643. doi:10.3201/eid1211.060152

5. Armin S, Wakil A, Tarbox J, Iwuji K. COVID-19 vaccination: An attempt to control the pandemic. The Southwest Respiratory Critical Care Chronicles 2021;9(37):1–8.

6. Dhaundiyal A, Kumari P, Jawalekar SS, et al. Is highly expressed ACE 2 in pregnant women "a curse" in times of COVID-19 pandemic?. Life Sci 2021;264:118676. doi: 10.1016/j.lfs.2020.118676

7. Jafari M, Pormohammad A, Sheikh Neshin SA, et al. Clinical characteristics and outcomes of pregnant women with COVID-19 and comparison with control patients: A systematic review and meta-analysis [published online ahead of print, 2021 Jan 2]. Rev Med Virol 2021;e2208. doi:10.1002/rmv.2208

8. Zeng H, Xu C, Fan J. Antibodies in infants born to mothers with COVID-19 pneumonia. JAMA 2020.

9. Dong L, Tian J, He S. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA 2020.

10. Wang X, Zhou Z, Zhang J, et al. A case of 2019 novel coronavirus in a pregnant woman with preterm delivery. Clin. Infect. Dis 2020;71:844–846.

11. Wenling Y, Junchao Q, Xiao Z, et al. Pregnancy and COVID-19: management and challenges. Rev Inst Med Trop Sao Paulo 2020;62:e62. doi:10.1590/s1678-9946202062062

12. Diriba K, Awulachew E, Getu E. The effect of coronavirus infection (SARS-CoV-2, MERS-CoV, and SARS-CoV) during pregnancy and the possibility of vertical maternal-fetal transmission: a systematic review and meta-analysis. Eur J Med Res 2020;25(1):39. Published 2020 Sep 4. doi:10.1186/s40001-020-00439-w

13. Mulvey JJ, Magro CM, Ma LX, et al. Analysis of complement deposition and viral RNA in placentas of COVID-19 patients. Ann Diagn Pathol 2020; 46:151530. doi: 10.1016/j.anndiagpath.2020.151530

14. Shanes ED, Mithal LB, Otero S, et al. Goldstein J.A. Placental pathology in COVID-19. Am J Clin Pathol 2020;154:23–32. doi: 10.1093/ajcp/aqaa089

15. Smithgall MC, Liu Jarin X, Hamele Bena D, et al. Third trimester placentas of SARS CoV 2 positive women: histomorphology, including viral immunohistochemistry and in situ hybridization. Histopathology 2020 doi: 10.1111/his.14215. his.14215

16. Mongula JE, Frenken MWE, van Lijnschoten G, et al. COVID-19 during pregnancy: non-reassuring fetal heart rate, placental pathology and coagulopathy. Ultrasound Obstet Gynecol 2020;56(5):773–776. doi:10.1002/uog.22189 OR Ren, J., Xu, L. et al. Placental pathology of the third trimester pregnant women from COVID-19. Diagn Pathol 16, 8 (2021). https://doi.org/10.1186/s13000-021-01067-6

17. Shah PS, Diambomba Y, Acharya G, et al. Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates. Acta Obstet Gynecol Scand. 2020;99:565–8.

18. Celik O, Saglam A, Baysal B, et al. Factors preventing materno-fetal transmission of SARS-CoV-2. Placenta 2020; 97:1–5. doi: 10.1016/j.placenta.2020.05.012.

19. Chen YH, Keller J, Wang IT, et al. Pneumonia and pregnancy outcomes: a nationwide population-based study. Am J Obstet Gynecol 2012;207(4):288.e1–288.e2887. doi: 10.1016/j.ajog.2012.08.023

20. Stanek J. Placental hypoxic overlap lesions: a clinicoplacental correlation. J Obstet Gynaecol Res 2015;41(3):358–369. doi:10.1111/jog.12539

21. Jani S, Jacques SM, Qureshi F, et al. Clinical characteristics of mother-infant dyad and placental pathology in COVID-19 Cases in Predominantly African American Population. AJP Rep 2021;11(1): e15–e20. doi:10.1055/s-0040-1721673

22. Media Advisory: Severe COVID-19 in pregnancy associated with preterm birth, other complications. Eunice Kennedy Shriver National Institute of Child Health and Human Development. Available at https://www.nichd.nih.gov/newsroom/news/012821-GRAVID. Published January 28, 2021. Accessed March 22, 2021.

23. Di Mascio D, Khalil A, Saccone G, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2020;2(2):100107. doi: 10.1016/j.ajogmf.2020.100107

24. Khalil A, Kalafat E, Benlioglu C, et al. SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes. E Clinical Medicine 2020; 25:100446. doi: 10.1016/j.eclinm.2020.100446

25. Stonoga ES, de Almeida Lanzoni L, Rebutini P, et al. Intrauterine Transmission of SARS-CoV-2. Emerging Infectious Diseases. 2021;27(2):638–641. doi:10.3201/eid2702.203824:

26. He J, Lu YP, Li J, et al. Fetal but not maternal angiotensin converting enzyme (ACE)-2 gene Rs2074192 polymorphism is associated with increased risk of being a small for gestational age (SGA) newborn. Kidney Blood Press Res 2018;43(5):1596–1606. doi:10.1159/000494449

27. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/whats-new/. Published March 05, 2021. Accessed March 22, 2021.

28. D'Souza R, Ashraf R, Rowe H, et al. Pregnancy and COVID-19: pharmacologic considerations. Ultrasound Obstet Gynecol 2021;57(2):195–203. doi:10.1002/uog.23116

29. Vogel JP, Tendal B, Giles M, et al. Clinical care of pregnant and postpartum women with COVID-19: Living recommendations from the National COVID-19 Clinical Evidence

Taskforce. Aust N Z J Obstet Gynaecol 2020;60(6):840–851. doi:10.1111/ajo.13270

30. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020;395:809–15.

31. Qiu L, Liu X, Xiao M, et al. 2 April 2020, posting date. SARS-CoV-2 is not detectable in the vaginal fluid of women with severe COVID-19 infection. Clin Infect Dis. doi:10.1093/cid/ciaa375.

32. Lamouroux A, Attie-Bitach T, Martinovic J, et al. 2020. Evidence for and against vertical transmission for SARS-CoV-2 (COVID-19). Am J Obstet Gynecol 223:91. e1–91. e4. doi: 10.1016/j.ajog.2020.04.039.

33. Rodrigues C, Baía I, Domingues R, et al. Pregnancy and breastfeeding during COVID-19 pandemic: a systematic review of published pregnancy cases. Front Public Health 2020;8:558144. Published 2020 Nov 23. doi:10.3389/fpubh.2020.558144

34. Vaccinating Pregnant and Lactating Patients Against COVID-19. American College of Obstetricians and Gynecologists. Available at https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-pregnant-and-lactating-patients-against-covid-19. Published December 2020. Accessed March 23, 2021.

35. Pfizer and BioNTech Commence Global Clinical Trial to Evaluate COVID-19 Vaccine in Pregnant Women. Pfizer. Available at https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-commence-global-clinical-trial-evaluate. Published February 18, 2021. Accessed March 23, 2021.

36. Gong R, Peng X, Kang S, et al. Structural characterization of the fusion core in syncytin, envelope protein of human endogenous retrovirus family W. Biochem Biophys Res Commun 2005;331(4):1193–1200. doi: 10.1016/j.bbrc.2005.04.032

37. Huang Y, Yang C, Xu Xf, et al. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin 41, 1141–1149 (2020). https://doi.org/10.1038/s41401-020-0485-4

38. Shimabukuro T. COVID-19 vaccine safety update Advisory Committee on Immunization Practices (ACIP). Available at https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/28-03-01/05-covid-Shimabukuro.pdf. Published March 21, 2021.

39. Medical experts continue to assert that COVID vaccines do not impact fertility. American College of Obstetricians and Gynecologists. Available at https://www.acog.org/news/news-releases/2021/02/medical-experts-assert-covid-vaccines-do-not-impact-fertility. Published February 4, 2021. Accessed March 23, 2021.

40. Zaks T. Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Presentation - Emergency Use Authorization (EUA) Application for mRNA-1273. December 2020. https://www.fda.gov/media/144583/download. Published December 17, 2020. Accessed March 23, 2021.

41. Gray KJ, Bordt EA, Atyeo C. COVID-19 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol. https://www.ajog.org/article/S0002-9378(21)00187-3/fulltext. Published March 25, 2021. Accessed April 1, 2021.

42. Mithal LB, Otero S, Shanes ED. Cord blood antibodies following Maternal COVID-19 vaccination during pregnancy. Am J Obstet Gynecol https://www.ajog.org/article/S0002-9378(21)00215-5/fulltext. Published March 31, 2021. Accessed April 2, 2021.