

SARS-CoV-2: Pregnancy, Delivery and Postpartum. A Short Review

Sheila B. Pérez-Elizondo

CUCS, Universidad de Guadalajara. Guadalajara, Jalisco, México

Jessica G. Solis-Aguilar

CUCS, Universidad de Guadalajara. Guadalajara, Jalisco, México

Josue R. Solis-Pacheco

Department of pharmacobiology. CUCEI
Universidad de Guadalajara. Guadalajara, Jalisco, México

Jesús A. Amézcua-López

Department of pharmacobiology. CUCEI
Universidad de Guadalajara. Guadalajara, Jalisco, México

Celia M. Martínez-Gómez

CUCS, Universidad de Guadalajara. Guadalajara, Jalisco, México

Blanca R. Aguilar-Uscanga

Department of pharmacobiology. CUCEI
Universidad de Guadalajara. Guadalajara, Jalisco, México

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is the ninth documented coronavirus to infect humans and it is highly transmissible; has caused a global pandemic and dramatic loss of human life worldwide. Isolated in Wuhan, China in late 2019, it struck nations with significant economic and public health consequences. The International Committee on Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2 and the disease as COVID-19. However, few studies have been published on the effects that this virus can have during pregnancy, childbirth and postpartum, so the objective of this review is to alert about the possible problems that women can present during their pregnancy, and provide adequate and specialized. It has been described that SARSCoV-2 virus has a predilection for the angiotensin converting enzyme (ACE) II receptor present in pneumocytes, enterocytes and at the placental level. Placental involvement could lead to hypoperfusion and thrombosis, resulting in fetal intrauterine growth restriction and preterm delivery. Careful monitoring of pregnant patients who test positive for SARS-CoV-2 is recommended because of the potential complications that could occur in the mother and fetus. The recommendations include offering vaccines against SARS-CoV-2 to pregnant and breastfeeding women, the provision of comprehensive health care to the mother-child pair; for example, maternal support

networks and establishment of successful breastfeeding, which involves the development of the maternal-neonatal bond.

Keywords: Pregnancy, postpartum, lactation, SARS-CoV-2, vaccine.

INTRODUCTION

In late 2019, Wuhan, the capital of Hubei province in China, experienced an outbreak of a new coronavirus, which during the first 50 days of the epidemic killed more than 1,800 people and infected more than 70,000. This virus was reported to be a member of coronavirus group b and was named new coronavirus 2019 (2019-nCov). The International Committee on Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2 and the resulting disease as COVID-19 (Shereen *et al.*, 2020).

Initially, it was thought that infected patients may have had in common the fact that they had visited a seafood market where live animals were sold, or they may have used infected animals or birds as a food source. However, subsequent investigations showed that some people were infected even without visiting the seafood market. These observations indicated the spread of the virus among humans, and it was subsequently reported in more than 100 countries around the world. Person-to-person spread of the virus occurs due to close contact with an infected person through coughing, sneezing, small respiratory droplets or aerosols and subsequent inhalation of these through the nose or mouth.¹

On January 30, 2020, the World Health Organization declared the outbreak an international public health emergency. On February 11, 2020, the new coronavirus disease was officially named by the World Health Organization (WHO) as COVID-19 (WHO, 2020).

The progression of the pandemic in a country also depends on other relevant population factors, such as demographic characteristics. Therefore, in countries with disadvantaged social, political and economic characteristics, medical care and policies such as vaccination, access to diagnostic tests and screening of those likely to be infected play a key role (Angius *et al.*, 2021). Although the virus is prevalent in all age groups, immunocompromised individuals are disproportionately affected with respect to the severity of symptoms; and it has been previously described that pregnant women and their fetuses are particularly susceptible to infections due to physiological changes such as cell-mediated immunity, immaturity of the adaptive immune system, and cytokine dysregulation (Chen *et al.*, 2020).

SARS-COV-2 IN PREGNANT WOMEN

Current knowledge about the effect of SARS-CoV-2 infection during pregnancy has largely been obtained from case reports, case series, and population surveillance systems. These data have focused particularly on maternal outcomes of women with symptomatic disease and maternal death, stillbirth, and neonatal death; each has been reported to occur in about 1% of cases under this setting (Kachikis *et al.* 2021).

At the onset of the SARS-CoV-2 pandemic, WHO designated pregnant women as a vulnerable group based on preliminary reports of increased risk of fetal death, preterm delivery, and intrauterine growth restriction, in addition to experience previously gained with already known respiratory virus outbreaks; pregnant women were assumed to be at increased risk of

morbidity and mortality from SARS-CoV-2 infection, particularly when symptomatic; The clinical features of COVID-19 pneumonia in pregnant patients are similar to those reported in non-pregnant patients who developed COVID-19 pneumonia, with clinical findings ranging from asymptomatic presentation to severe disease and even death in some cases. The most common symptoms in the pregnant woman with COVID-19 are fever, cough, and muscle pain (Chen *et al.*, 2020).

It has been previously described that SARSCoV-2 virus has a predilection for the ACE II receptor present at the placental level. Placental involvement could cause hypoperfusion and thrombosis, leading to intrauterine growth restriction and/or preterm delivery (Oltean *et al.*, 2021). The first studies regarding the placental histopathological changes in women with late pregnancy and COVID-19, showed placental tissue analyzed showed fibrin deposits and infarcts, which could condition placental hypoperfusion due to the presence of ACE II receptors in the placenta Chen, *et al.* (2020).

The increased risk of pregnancy could be explained in part by impaired placental function. A trial conducted by Radan *et al.* (2020), evaluated placental weight, birth weight/placental weight ratio, and metabolic scale exponent β , an indicator of normal fetus-placental growth, as well as, SARS-CoV-2 during pregnancy, which is associated with a higher incidence of low-birth-weight placenta, increased birth weight/placental weight ratio, and abnormal β -scale exponent in the cohort of 153 patients. Emphasizing intensified fetal surveillance in these pregnancies (Radan *et al.*, 2020).

For this reason, it is important to advise pregnant women of the risks of SARS-CoV-2 infection; for example, the aforementioned risks of preterm delivery, intrauterine growth restriction and maternal admission to the intensive care unit (Anderson, 2020). With the ongoing concern about SARS-CoV-2 around the world, the focus is on treatment in general; pregnant and lactating women in this case (Bastug *et al.*, 2020; Halasa *et al.*, 2021).

After much effort, several vaccines were developed and approved for emergency use; thereafter, a massive mass vaccination campaign was initiated. SARS-CoV-2 vaccines prove to be quite effective in preventing COVID-19 and because SARS-CoV-2 is associated with adverse events in pregnancy recommendations should offer SARS-CoV-2 vaccines to pregnant and lactating women, despite their lack of inclusion in initial clinical trials (Angius *et al.*, 2021; Kachikis *et al.*, 2021; Lipkind *et al.*, 2021; Romero-Ramírez *et al.*, 2022).

One point to consider is the doubts and concerns among pregnant women regarding the safety of vaccines, which represent a persistent barrier to the acceptance of vaccines. Nevertheless, a prospective cohort study reported that COVID-19 vaccines, were well tolerated among persons who were pregnant, breastfeeding, or planning a pregnancy. Reactions on day 1 after the first dose with BNT162b2 and mRNA-1273 vaccines were similar between groups and comparable to findings among pregnant women. All groups reported an increase in reactions after the second dose of these vaccines (Kachikis *et al.*, 2021).

Nir *et al.* (2020) conducted a study in women who were immunized with the messenger RNA vaccine BNT162b2 during the pregnancy period, demonstrated an efficient transfer of SARS-CoV-2 immunoglobulin G across the placenta to their newborns, with an adequate correlation

between antibody concentrations found in maternal serum and cord blood; since the comparison between immunized patients and those otherwise recovered from COVID-19, revealed significantly higher levels of immunoglobulin G in maternal serum and cord blood among the former mentioned. Concluding that, in addition to achieving maternal protection against SARS-CoV-2, the vaccine could also prove useful in providing humoral immunity to the newborn (Nir et al., 2021).

COVID-19 vaccination during pregnancy is associated with detectable maternal antibodies in maternal sera at delivery, breast milk, and infant sera indicating transfer of maternal antibodies during pregnancy (Hall *et al.*, 2022; Halasa *et al.*, 2021).

However, despite highly effective vaccines, some vaccines have recently shown a different efficacy against new variants of the virus. Genome variability is a common feature among viruses, but in a scenario such as the one we are currently in, it becomes relevant (Angius et al., 2021).

In addition to inequity in access to vaccines, bringing with it a large number of unvaccinated subjects who are particularly susceptible to infection. These conditions offer the virus more opportunities for mutation and prospective selection of variants, particularly those with greater transmissibility and immune escape potential; mutations affecting mainly the Spike (S) protein have recently been documented (Angius *et al.*, 2021).

For these reasons, health professionals have an obligation to recommend and clarify possible concerns about vaccination against SARS-CoV-2 to pregnant women and women planning to become pregnant, in addition to compliance with hygiene and social distancing measures (Stuebe, 2020a).

PROTOCOL FOR MEDICAL MANAGEMENT

All patients, whether pregnant or not, should be screened for symptoms of probable respiratory infection. Ideally, screening procedures should begin before delivery; for example, patients should be instructed at prenatal visits on what to do if they develop respiratory symptoms. In case of respiratory symptoms, they should be isolated from other patients and always wear a mask. Patients with suspected COVID-19 criteria should be isolated from other patients immediately (Chu *et al.*, 2004; Bai *et al.*, 2020). Healthcare workers should follow standard precautions depending on the type of exposure and that the equipment used is cleaned according to established regulations (Della Gatta *et al.*, 2020).

Childbirth is considered to be one of the most important events for individuals, their families and environment; despite this many hospitals have modified their usual practices at the time of delivery and during hospitalization in terms of visits and the number of birth attendants. There is no clear evidence on the optimal mode and timing of delivery; therefore, the mode and timing of delivery should be individualized according to obstetric indications and maternal-fetal status (Parazzini *et al.*, 2020).

COVID-19 ON POSTPARTUM AND LACTATION

The World Health Organization (2022), recommends that after delivery, the newborn and mother with diagnosed or confirmed suspected SARS-CoV-2 should remain together. Skin-to-

skin contact, kangaroo care, and rooming-in should be allowed during the day and night (Stuebe A., 2020a).

The benefit of separation of mother and newborn lies in minimizing the risk of transmission of SARS-CoV-2 from mother to newborn during the hospital stay. However, additional considerations must be taken into account; while it is true that separation prevents infection during the hospital stay, it does not contemplate for exposure once the newborn leaves the hospital (Stuebe, 2020b).

Disruption of skin-to-skin contact alters the physiology of the newborn, which is vitally important for the colonization of its microbiota. The interruption of skin-to-skin contact between the newborn and its mother increases stress levels and interferes with the supply of breast milk, resulting in the disruption of innate and specific immunity protection, as maternal antigen-specific antibodies begin to appear in the milk within 7 days, protecting the infant from acquiring various infections. In addition, breast milk contains multiple oligosaccharides and innate immunity factors that help mitigate the impact of viral infection (Stuebe, 2020b).

Newborns and infants may be more exposed than other children at pediatric ages; therefore, they deserve special attention because of the insidious and nonspecific symptoms that may present in them. The risk of the newborn child of an infected mother testing positive for SARS-CoV-2 is approximately 2.5% if the mother was admitted to the hospital with symptomatic disease (Mullins *et al.*, 2021; Salvatori *et al.*, 2020).

Despite this, few reports provide strong evidence of vertical transplacental transmission. Postpartum horizontal transmission from mother to newborn could occur through respiratory droplets and aerosols rather than through milk (Salvatori *et al.*, 2020; Mullins *et al.*, 2021).

The American Academy of Pediatrics (AAP) recommends that newborns not be tested for SARS-CoV-2 until 24 hours of age; some infants may test negative even at 24 hours (Stuebe, 2020b). By decreasing the likelihood of establishing successful breastfeeding with separation of the mother-newborn pair; those newborns who are not breastfed have a 3.6-fold increased risk of being hospitalized for pneumonia compared with newborns who are exclusively breastfed for at least 4 months; therefore, separating mother and newborn immediately after birth may make the latter more vulnerable to severe respiratory infections, including SARS-CoV-2, during the first year of life (Stuebe, 2020b; Salvatori *et al.*, 2020).

Another aspect to consider is that separate isolation of mother and baby requires twice the resources: two hospital wards, twice the number of trained staff to provide care, and two sets of personal protective equipment, one for each team member; and given the context of hospital overcrowding and resource shortages faced by healthcare institutions, this is particularly problematic (Stuebe, 2020b).

Promoting and supporting the initiation, duration and exclusivity of breastfeeding is a public health issue; it is therefore of utmost importance to recommend breastfeeding to the mother, thanks to the known importance for the lifelong health of mother and child. During the establishment of breastfeeding it is important to inform the mother that the available evidence indicates that transmission of the virus through breast milk is unlikely, although transmission

through respiratory secretions during breastfeeding is possible if appropriate isolation measures are not used: hand washing, use of a mask that adequately covers the nose and mouth in case of any respiratory symptoms, coughing and disinfection of surfaces that have been routinely touched (Stuebe, 2020b).

CONCLUSION

Careful follow-up of pregnant patients who test positive for SARS-CoV-2 is recommended because of the potential for maternal and fetal complications. This increased risk of adverse pregnancy outcomes could be explained in part by impaired placental function; including low-birth-weight placenta, fibrin deposits and infarcts, which could condition placental hypoperfusion due to the presence of ACE II receptors in the placenta.

Therefore, SARS-CoV-2 vaccines should be offered to pregnant and lactating women, and their inclusion in clinical trials of vaccine efficacy or potential treatments should be considered; they deserve to have information based on the best available scientific evidence for the prevention and treatment of medical conditions during gestation and postpartum.

As with all interventions, whether preventive, diagnostic, or therapeutic during pregnancy, the potential benefits and risks to the mother and newborn, e.g., alteration of innate and newborn-specific immunity, should be carefully considered. Routine preventive separation of a healthy mother and newborn should not be taken lightly because of the possible detrimental effects on feeding, maternal-neonatal bonding and the doubling of resources needed for medical care in the already overburdened health care system; it is therefore recommended, in the absence of contraindications, that mother and newborn remain together, in order to promote skin-to-skin contact, kangaroo care and decrease stress on both the newborn and the mother. Health professionals have to protect, promote and support breastfeeding, since lack of information can lead to the mistake of advising mothers to abandon breastfeeding. It is necessary to focus on the integral wellbeing of the mother-child binomial and always seek the maximum benefit for both.

ACKNOWLEDGMENT

We are grateful for the support of the University of Guadalajara and the Hospital Civil of Guadalajara “Fray Antonio Alcalde”, México.

References

- Anderson P. O. (2020). Breastfeeding and Respiratory Antivirals: Coronavirus and Influenza. *Breastfeed Med.* 15(3):128. doi: 10.1089/bfm.2020.29149.poa.
- Angius F., Pala G., Manzin A. (2021). SARS-CoV-2 and Its Variants: The Pandemic of Unvaccinated. *Frontiers in microbiology.* (12):1-5. doi: 10.3389/fmicb.2021.749634
- Bai L., Yang D., Wang X., *et al* (2020). Chinese experts' consensus on the Internet of Things-aided diagnosis and treatment of coronavirus disease 2019 (COVID-19). *Clinical e-Health.* (3):7-15. doi: 10.1016/j.ceh.2020.03.001
- Bastug A., Hanifehnezhad A., Tayman C., Ozkul A., Ozbay O., Kazancioglu S., Bodur H. (2020). Virolactia in an Asymptomatic Mother with COVID-19. *Breastfeed Med.* 15(8):488-491. doi: 10.1089/bfm.2020.0161.
- Chen H., Guo J., Wang C., Luo F., Yu X., Zhang W., Li J., Zhao D., Xu D., Gong Q., Liao J., Yang H., Hou W., Zhang Y. (2020). Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet.* 7(395):809-815. doi: 10.1016/S0140-6736(20)30360-3

- Chen S., Huang B., Luo D. J., Li X., Yang F., Zhao Y., Nie X., Huang B. X. (2020). Pregnancy with new coronavirus infection: a clinical characteristics and placental pathological analysis of three cases. *Chinese Medical Journal*. 49(5): 418-423. doi: 10.3760/cma.j.cn112151-20200225-00138.
- Chu C. M., Cheng V. C., Hung I. F., Wong M. M., Chan K. H., Chan K. S., Kao R. Y., Poon L. L., Wong C. L., Guan Y., Peiris J. S., Yuen K. Y. (2004). Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 59(3):252-6. doi: 10.1136/thorax.2003.012658.
- Della Gatta A. N., Rizzo R., Pilu G., Simonazzi G. (2020). Coronavirus disease 2019 during pregnancy: a systematic review of reported cases. *Am J Obstet Gynecol*. 223(1):36-41. doi: 10.1016/j.ajog.2020.04.013.
- Garcia-Flores V., Romero R., Xu Y., Theis K., Arenas-Hernandez M., Miller D., Peyvandipour A., Galaz J., Levenson D., Bhatti G., Gershater M., Pusod E., Kracht D., Florova V., Leng Y., Tao L., Faucett M., Para R., Hsu C. D., Zhang G., Tarca A. L., Pique-Regi R., Gomez-Lopez N. (2021). Maternal-Fetal Immune Responses in Pregnant Women Infected with SARS-CoV-2. *Research Square*. 31:rs.3.rs-362886. doi: 10.21203/rs.3.rs-362886/v1.
- Halasa N. B., Olson S. M., Staat M. A., Newhams M. M., Price A. M., Boom J. A., Sahni L. C., Cameron M. A., Pannaraj P. S., Blin E. K., Bhumbra S. S., Bradford T. T., Chiotos K., Coates B. M., Cullimore M. L., Cvijanovich N. Z., Flori H. R., Gertz S. J., Heidemann S. M., Hobbs C. V., Hume J. R., Irby K., Kamidani S., Kong M., Levy E. R., Mack E. H., Maddux A. B., Michelson K. N., Nofziger R. A., Schuster J. E., Schwartz S. P., Smallcomb L., Tarquinio K. M., Walker T. C., Zinter M. S., Gilboa S. M., Polen K. N., Campbell A. P., Randolph A. G., Patel M. M. (2022) Overcoming COVID-19 Investigators; Overcoming COVID-19 Network. Effectiveness of Maternal Vaccination with mRNA COVID-19 Vaccine During Pregnancy Against COVID-19-Associated Hospitalization in Infants Aged <6 Months - 17 States, July 2021-January 2022. *MMWR Morb Mortal Wkly Rep*. 18;71(7):264-270. doi: 10.15585/mmwr.mm7107e3.
- Hall V. Foulkes S., Insalata F., Kirwan P., Saei A. Atti A., Wellington E., Khawam J., Munro J. K., Cole M., Tranquillini C., Taylor-Kerr A., Hettiarachchi N., Calbraith D., Sajedi N., I. Milligan, Y. Themistocleous D., Corrigan L., Cromey L., Price S., Stewart E., de Lacy C., Norman E., Linley A. D., Otter A., Semper J., Hewson S., D'Arcangelo M., Chand C. S., Brown T., Brooks J., Islam A., Charlett, and S. Hopkins (2022). Protection against SARS-CoV-2 after Covid-19 Vaccination and Previous Infection. *The New England Journal of Medicine*. doi: 10.1056/NEJMoa2118691
- Kachikis A., Englund J. A., Singleton M., Covelli I., Drake A. L., Eckert L. O. (2021). Short-term Reactions Among Pregnant and Lactating Individuals in the First Wave of the COVID-19 Vaccine Rollout. *JAMA Netw Open*. 4(8): e2121310. doi: 10.1001/jamanetworkopen.2021.21310.
- Lipkind H. S., Vazquez-Benitez G., DeSilva M., Vesco K. K., Ackerman-Banks C., Zhu J., Boyce T. G., Daley M. F., Fuller C. C., Getahun D., Irving S. A., Jackson L. A., Williams J. T. B., Zerbo O., McNeil M. M., Olson C. K., Weintraub E., Kharbanda E. O. (2022). Receipt of COVID-19 Vaccine During Pregnancy and Preterm or Small-for-Gestational-Age at Birth - Eight Integrated Health Care Organizations, United States, December 15, 2020-July 22, 2021. *MMWR Morb Mortal Wkly Rep*. 7;71(1):26-30. doi: 10.15585/mmwr.mm7101e1.
- Mullins E., Hudak M. L., Banerjee J., Getzlaff T., Townson J., Barnette K., Playle R., Perry A., Bourne T., Lees C. (2021). Pregnancy and neonatal outcomes of COVID-19: coreporting of common outcomes from PAN-COVID and AAP-SONPM registries. *Ultrasound Obstet Gynecol*. 57(4):573-581. doi: 10.1002/uog.23619.
- Nir O., Schwartz A., Toussia-Cohen S., Leibovitch L., Strauss T., Asraf K., Doolman R., Sharabi S., Cohen C., Lustig Y., Regev-Yochay G., Yinon Y. (2021). Maternal-neonatal transfer of SARS-CoV-2 immunoglobulin G antibodies among parturient women treated with BNT162b2 messenger RNA vaccine during pregnancy. *Am J Obstet Gynecol*. 4(1):100492. doi: 10.1016/j.ajogmf.2021.100492.
- Oltean I., Tran J., Lawrence S., Ruschkowski B. A., Zeng N., Bardwell C., Nasr Y., de Nanassy J., El Demellawy D. (2021). Impact of SARS-CoV-2 on the clinical outcomes and placental pathology of pregnant women and their infants: A systematic review. *Heliyon*. 7(3): e06393. doi: 10.1016/j.heliyon.2021.e06393.
- Parazzini F., Bortolus R., Mauri P. A., Favilli A., Gerli S., Ferrazzi E. (2020). Delivery in pregnant women infected with SARS-CoV-2: A fast review. *Int J Gynaecol Obstet*. 150(1):41-46. doi: 10.1002/ijgo.13166
- Radan A. P., Baud D., Favre G., Papadia A., Surbek D., Baumann M., Raio L. (2022). Low placental weight and altered metabolic scaling after severe acute respiratory syndrome coronavirus type 2 infection during pregnancy: a prospective multicentric study. *Clin Microbiol Infect*. 10:S1198-743X(22)00076-3. doi: 10.1016/j.cmi.2022.02.003.

- Romero-Ramírez D. S., Suárez-Hernández M. I., Fernández-Vilar A. M., Rivero-Falero M., Reyes-Millán B., González-Carretero P, Pérez M. M. L., Carretero-Pérez M., Martín-Pulido S., Pera-Villacampa L., García-Bello M. Á., Mesa-Medina O. M., Roper S. (2022) Evaluation of Adverse Effects in Nursing Mothers and Their Infants After COVID-19 mRNA Vaccination. *Breastfeed Med*. doi: 10.1089/bfm.2021.0256.
- Salvatori G., De Rose D. U., Concato C., Alario D., Olivini N., Dotta A., Campana A. (2020). Managing COVID-19-Positive Maternal-Infant Dyads: An Italian Experience. *Breastfeed Med*. 15(5):347-348 doi: 10.1089/bfm.2020.0095.
- Shereen M. A., Khan S., Kazmi A., Bashir N., Siddique R. (2020). COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *J Adv Res*. 16 (24):91-98. doi: 10.1016/j.jare.2020.03.005
- Stuebe A. Protect Pregnant and Lactating Women with COVID-19 Through Research, Not from Research. (2020a). *Breastfeed Med*. 2020a;15(6):423-424. doi: 10.1089/bfm.2020.29155.ams423
- Stuebe A. Should Infants Be Separated from Mothers with COVID-19? First, Do No Harm. (2020b) *Breastfeed Med*. 15(5):351-352. doi: 10.1001/jamanetworkopen.2021.21310.
- World Health Organization. (2022, April 7). Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance, 19 March 2020. <https://apps.who.int/iris/handle/10665/331501>