The Association of COVID-19 Infection in Pregnancy and Vertical Transmission: Literature Review

Maria Carolina Beeter [1] • Ortiz Juan Fernando [1] • Feiyang Tao [1] • Jazmin Carolina Cozar [1] • Marcos A. Sanchez-Gonzalez [2]

[1] Division of Clinical & Translational Research, Larkin Health System, South Miami, FL, USA
[2] Universidad de las Américas (UDLA), Mexico City, Mexico
mari.beeter@gmail.com

Abstract. Coronavirus disease 2019 (COVID-19) is caused by a new beta coronavirus (severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2) and has resulted in a worldwide pandemic. Although previous research on other beta coronaviruses has found detrimental effects on pregnant women and neonates, it is uncertain whether vertical transmission of SARS-CoV-2 exists. We conducted a literature review to explore the association between confirmed COVID-19 infection during the pregnancy and potential vertical transmission of the virus. We searched PubMed using the following medical subject headings (MeSH): ("Coronavirus"[MeSH]) AND "Pregnancy"[MeSH]; ("Coronavirus"[MeSH]) AND "Infectious Disease Transmission, Vertical"[MeSH]. Inclusion criteria were full articles, female study objects, English language, papers published within one year, and human studies. Non-English papers, animal studies, meta-analysis, clinical trials, literature reviews, and systematic reviews were excluded from our data collection. Sixteen articles were eventually selected for this review. By July 2020, two cases have demonstrated high chances of vertical transmission, but definitive evidence is lacking; these women were nearly all infected in the second or third trimester, and most underwent cesarean delivery. The virus's effects earlier in pregnancy are mainly unknown; no neonates have been delivered from women infected in the first trimester of pregnancy. More research and data are needed to assess the presence and potential consequence of vertical transmission of SARS-CoV-2. The preferred approach to investigating a possible intrauterine viral infection is to detect the virus in the placenta, amniotic fluid, cord blood, or neonatal pharyngeal swab samples collected immediately after birth.

To cite this article
[Beeter, M. C., Fernando, O. J., Tao, F., Cozar, J. C. & Sanchez-Gonzalez, M. A. (2020). The Association of COVID-19 Infection in Pregnancy and Vertical Transmission: Literature Review. *The Journal of Middle East and North Africa Sciences*, 6(11), 5-11]. (P-ISSN 2412- 9763) - (e-ISSN 2412-8937). www.jomenas.org**. 2**

Keywords: Protecting Private Life; Access to Information; Direct Monitoring; Covid - 19.

1. Introduction:

The pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected more than 10 million people, including pregnant women, and this number keeps increasing every day (Shah et al., 2020; Pique-Regi et al., 2020). Over the history of coronavirus infections, the outcomes in pregnant women with the severe acute respiratory syndrome (SARS) during 2002–2003 have shown more than 50% of early abortion during the first trimester, 40% of intrauterine growth restriction, and 80% of preterm delivery if the virus was contracted during the second trimester. The outcomes with the Middle East respiratory syndrome (MERS) have reported the worst results with 25% of pregnant woman mortality, and 91% of adverse outcomes for neonates, including neonatal death (Mimouni et al., 2020)

It is uncertain whether COVID-19 can be transmitted vertically. The genome sequence of SARS-CoV-2 is 90% similar to that of a bat coronavirus, 80% similar compared with SARS coronavirus (SARS-CoV-1), and 50% with MERS-related coronavirus (MERS-CoV) (Van den Bosch, et al., 2003). Despite such similarity, there is little evidence for intrauterine or intrapartum transmission, the pregnant woman cases included have been tested positive for SARS-CoV-2 and also reverse transcriptase-polymerase chain reaction (RT-PCR) have been taken immediately after birth to verify the presence of the virus in the placenta, amniotic fluid, cord blood, neonatal throat swab samples after birth, and breastmilk samples. The immunological changes and physiological adaptation during pregnancy have been correlated to be more susceptible to COVID-19 infection than the general population [Shah, 2020; Luo & Yin, 2020; Lowe & Bopp, 2020).

Urgent questions that need to be addressed promptly include whether pregnant women with COVID-19 will transmit the infection vertically to the neonate and what are the outcomes for fetus during pregnancy and neonates after birth. Published data have indicated that pregnant women positive for COVID -19 are not likely to have an increased risk of severe disease until to date. However, actual data

available have been reported during the second and third trimester. In this study, we present the association between confirmed COVID-19 infection during pregnancy and potential vertical transmission of the virus to fetuses and neonates.

2. Pathophysiology of the Novel Coronavirus:

Coronaviruses are a group of viruses that can cross species barriers and become human pathogens. Although most human coronaviruses cause mild illness, SARS–CoV-1, MERS-CoV, and the novel enveloped RNA betacoronavirus responsible for SARS–CoV-2 have been associated with severe lower respiratory tract infections, acute respiratory distress syndrome, and death (Segars et al., 2020).

SARS-CoV-2 infects host respiratory epithelial cells through angiotensin-converting enzyme 2 (ACE2), a membrane-bound aminopeptidase that functions as its putative receptor (Dashraath et al., 2020).

Although the expression of ACE2 is predominantly within type II alveolar cells of the lung, the receptor is also present in several extrapulmonary sites across the aerodigestive tract, including the oral mucosa (Dashraath et al., 2020). Previous studies reported that co-transcription of ACE2 is negligible in the placenta, thus not a likely path of vertical transmission for SARS-CoV-2 (Pique-Regi et al., 2020).

Compared to SARS-CoV-1 and MERS-CoV, which show preferential activation of type 1 T helper (Th1) immunity, resulting in the marked elevation of proinflammatory cytokines, patients with COVID-19 demonstrated activation of both Th1 and type 2 T helper (Th2) immunity over similar periods in the disease course (Dashraath et al., 2020).

Adaptive immunity in pregnancy is based on Th2 system dominance, which protects the fetus, leaving the mother vulnerable to viral infections, which are more effectively contained by the Th1 system (Dashraath et al., 2020). The hormonal changes in pregnancy influence immunological responses to viral pathogens, favoring the expression of anti-inflammatory cytokines, which may serve as the predominant immune response to SARS-CoV-2, resulting in the lesser severity of COVID-19 compared to that in nonpregnant individuals.

The most convincing evidence of intrauterine transmission of COVID-19 would be to confirm the replication of SARS-CoV-2 in fetal pulmonary tissues, which is technically almost infeasible (Wang et al., 2020). Therefore, the approach to investigating a possible intrauterine viral infection is to confirm the presence of the virus in placenta, amniotic fluid, cord blood, or neonatal pharyngeal swab samples collected immediately after birth (Wang et al., 2020).

Among all the number of pregnancies reported so far, little or no evidence of transmission to the neonate has been suspected or observed; however, these women were nearly all infected in the second or third trimester and most underwent cesarean delivery. The effects of the virus earlier in pregnancy are completely unknown; there is no data available on neonates that have been delivered from women infected in the first trimester of pregnancy (Rasmussen & Jamieson, 2020), therefore, information about the effect of COVID-19 on the course and outcome of pregnancy in the first trimester is not available yet (Liang & Acharya, 2020).

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on neonates that have been delivered from women infected in the first trimester of pregnancy (Rasmussen & Jamieson, 2020). It is essential to point out that information about the effect of COVID-19 on the course and outcome of pregnancy in the first trimester is mainly unknown yet (Liang & Acharya, 2020).

COVID-19 Effects on Pregnancy and Neonate Outcomes:

Previous studies have shown that SARS during pregnancy is associated with a high incidence of adverse maternal and neonatal complications, such as spontaneous miscarriage, preterm delivery, intrauterine growth restriction, endotracheal intubation, admission to the intensive care unit, renal failure, and disseminated intravascular coagulopathy (Qiao, 2020). However, pregnant women with COVID-19 infection in the present study had fewer adverse maternal or neonatal complications and outcomes than would be expected for those with SARS-CoV-1 infection (Qiao, 2020).

This review included several case reports and case series related to COVID-19 infection in the second or third trimesters of pregnancy and its relation to maternal outcomes, vertical transmission, and neonatal outcomes. An important fact to keep in mind is the lack of evidence of infection in the first trimester. Due to the novelty of this virus among humanity. We conducted a literature review by using the following MeSH terms: ("Coronavirus"[MeSH]) AND "Pregnancy"[MeSH]; ("Coronavirus"[MeSH]) AND "Infectious Disease Transmission, Vertical"[MeSH] for the data collection. We apply the following inclusion/exclusion criteria.

Inclusion Criteria include: Full papers, Sex: Female, English Language, Papers published within the last year. And Studies in humans.

Exclusion Criteria include: Non-English Papers, Animal studies, Meta-analysis, Clinical Trials, Literal Reviews, Systematic Reviews

Table 1 detailed the total number of articles after applying Inclusion/exclusion criteria in the following order, using Medical Subject Heading (MeSH) strategy of Mesh terms “Coronavirus [Mesh]) AND "Pregnancy"[Mesh].

Table 1: *The Total Number of Articles:*

("Coronavirus"[Mesh]) AND "Pregnancy"[Mesh]	
Total records	235
Inclusion/Exclusion	
Full text papers	183
Papers published within one year	103
English language	86
Sex: Female	85
Studies in humans	82

From Table 1 ten literature reviews were removed, leaving 72 papers. From the 24 papers on Table 2, 22 had duplicated results, leaving two papers to be added to the total from Table 1. From the 74 resulting articles, 36 articles were removed for one of the following reasons:

1. Data extraction not possible
2. Duplication of the Data
3. Tittle Relevance

The remaining 38 articles were carefully screened, and then we proceeded to remove 22 additional articles because those articles did not follow our outcome of interest. In the end, 16 articles were used for the discussion of this review.

Table 2 detailed the total number of articles after applying Inclusion/exclusion criteria in the following order, using MeSH strategy with MeSH terms “Coronavirus [Mesh]) AND " Infectious Disease Transmission, Vertical "[Mesh].

Table 2: *The Total Number of Articles:*

("Coronavirus"[Mesh]) AND "Infectious Disease Transmission, Vertical"[Mesh]	
Total records	41
Inclusion/Exclusion	
Full text papers	37
Papers published within one year	27
English language	24
Studies in humans	24
Sex: Female	24

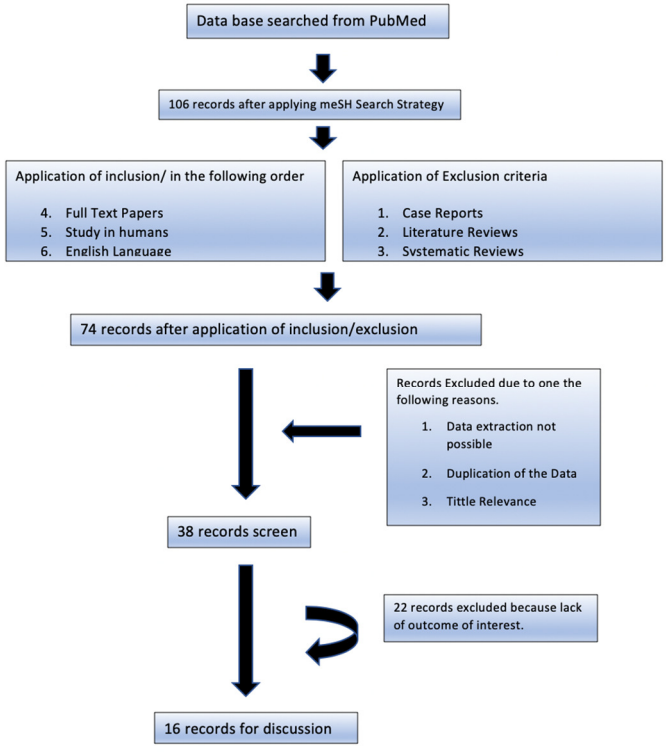

Figure 1. Flow chart of the methods used for this review.

The type articles used for this review were: one observational study, one editorial, one review, one clinical study, seven case reports and five case series.

In one report series, Chen H, Guo J, Wang C, et al. reviewed nine confirmed cases of third-trimester pregnant women infected with the novel coronavirus. None of the patients developed severe pneumonia or died. All nine live births had high Apgar scores. Amniotic fluid, cord blood, neonatal throat swab, and breast milk samples from six patients were tested for SARS-CoV-2, and all came back negative (Chen et al., 2020). Some studies lack the most reliable form of detection of vertical transmission by not testing cord blood and amniotic fluid. A survey from Khan et al. (2020a), conducted a case series study on 17 pregnant women infected with SARS-CoV-2 admitted to Hubei general hospital (Renmin Hospital) from January 25 to February 15, 2020. From the 17 patients, 12 tested positive; five had a positive CT scan, five had complications, and three had a fever. Neonatal pneumonia occurred in five of the 17 neonates. In 15 neonates, SARS-CoV-2 was not detected in the throat swab. The swab samples were tested within 24 hours after the delivery was positive in only two neonates. However, intrauterine tissue samples such as placenta, cord blood, or amniotic fluid were not tested. That makes it impossible to differentiate vertical transmission from transmission due to respiratory exposure from the mother or staff members. Succeeding the same pattern from the previous study cited, Yu N, Li W, Kang Q, et al. included in their research seven patients, admitted to Tongji Hospital from January 1, to February 8, 2020 (Yu et al., 2020).

Clinical manifestations were fever, cough, and shortness of breath. The outcomes of pregnant women and neonates were free of complications. Three neonates were tested for SARS-CoV-2, and one neonate was infected 36 hours after birth. Even with no vertical transmission evidence, most clinicians recommended infected pregnant women to deliver their neonates by a cesarean section to prevent a possible exposure during vaginal birth. Some studies mentioned vaginal delivery due to patient preference, but they were the exception.

In another study by Liang H and Acharya G, 18 pregnant women were diagnosed with COVID-19 in their third trimester; all but two neonates were delivered vaginally, and none of them were infected by SARS-CoV-2 (Liang & Acharya, 2020). In a retrospective review of medical records and case reports by Chen et al., 2020, nine patients in their third trimester were accessioned. Evidence of intrauterine vertical transmission was assessed by testing for the presence of SARS-CoV-2 in amniotic fluid, cord blood, and neonatal throat swab samples. Breast milk samples were also collected and tested from patients after the first lactation. All underwent a cesarean section. The clinical characteristics of COVID-19 pneumonia in pregnant women were similar to those reported for non-pregnant adult patients who developed COVID-19 pneumonia; some symptoms presented were fever and cough in some of the patients, but none developed severe pneumonia, and none required ventilation. Eight patients showed typical findings of chest CT images—multiple patchy ground-glass shadows in the lungs. Nine live births were recorded, and no neonatal symptoms were observed. Amniotic fluid, cord blood, neonatal throat swab, and breast milk samples from six patients were tested for SARS-CoV-2, and all samples tested negative for the virus (Chen et al., 2020). Succeeding a similar outcome from previous reports, Li et al., 2020 reported one case of a woman with coronavirus disease in her 35th week of pregnancy, which delivered an infant by cesarean section in a negative-pressure operating room.

The infant was negative for SARS-CoV-2 (Li et al., 2020). The Positive outcome, free of disease complications, was reported from the patient and her infant. Khan and colleagues reported three infected women on their third trimester, all three delivered vaginally, all three neonates tested negative and had positive outcomes (free of disease complications) (Khan et al., 2020b). Another case series of 19 pregnant women done by Liu et al., 2020, clinically diagnosed or laboratory-confirmed with COVID-19 during late pregnancy was reported. The delivery occurred in isolation rooms, and neonates were immediately separated from the mothers and isolated for at least 14 days. No vertical transmission of SARS-CoV-2 and no perinatal complications in the third trimester were found.

In this clinical pathologic study (Shanes et al., 2020), 16 placentas from patients with SARS-CoV-2 were examined. They found a placental injury pattern that reflects abnormalities in oxygenation. This is explained because it is associated with adverse perinatal outcomes in the intervillous space. Fourteen patients delivered at term (37-40 weeks), one born at 34 weeks, and one represented a 16-week intrauterine fetal demise. The placenta from a patient with intrauterine fetal demise showed villous edema and retroplacental hematoma. All infants were negative for SARS-CoV-2 by nasopharyngeal and throat swab. The fetal demise was attributed to placental complications due to severe COVID-19 infection, not due to placental-neonatal transmission (neonate tested negative).

Steroids were used to prevent respiratory failure in neonates if needed for preterm delivery, Following some maternal infection cases. In a case report by Peng et al., 2020, a patient in her third trimester (35 weeks) presented with cough and fever. The chest CT scan showed multiple patchy nodular opacities bilaterally with ground-glass opacities in the sub-pleural spaces. Her throat swab was positive for SARS-CoV-2. The mother was isolated in the hospital. Following hospitalization, she received interferon nebulization, oral lopinavir, intravenous antibiotics, oxygen supplement, and dexamethasone. She received the cesarean section on day seven of symptom onset. After

delivery, the nucleic acid test from the mother's amniotic fluid, vaginal secretions, placenta, cord blood, serum, and breast milk were all negative (Peng et al., 2020)

Another case report from Iqbal et al., (2020) reported a 34-year-old woman, 39 weeks of gestation, who tested positive for SARS-CoV-2 by PCR. The patient presented with lymphopenia and fever before delivery. Also, her chest CT showed reticular interstitial opacities. Delivery was vaginally and spontaneous, with Apgar scores of eight and nine. Delayed cord clamping was not performed, and skin-to-skin contact between the mother and infant was not permitted. There was no evidence of neonatal or intraamniotic infection. The neonate was nourished with formula and expressed breast milk. The mother was discharged home with the neonate on hospital day six with no signs of neonatal infection (Iqbal et al., 2020).

It is crucial to notice how, in most cases, the neonates were approached right after birth. All measurements of exposure precautions were taken, including all medical staff wearing the N95 mask, goggles, gown, and gloves, and mothers were wearing a N95 mask and did not have skin contact with the infants . All those measurements are essential to prevent exposure from the mother to the baby and possibly to the medical staff. Most cases reported a negative test from the neonate went against the probability of vertical transmission and transmission during neonatal care (Iqbal et al., 2020).

The option of delivering surgically instead of vaginally for women infected in their third trimester should be consider but is not a pre-stablished requirement; this case is a 27-yr-old woman at 36 weeks of gestation presented with 5 days of fever, low oxygen saturation and signs of fetal distress; she was submitted to an emergent cesarian section with spinal anesthesia. Her SARS-CoV-2 testing was positive in the sample of oropharyngeal swabs by rRT–PCR assay during her admission. The newborn was immediately transferred to a neonatal isolation ward for specialist neonatal treatment to minimize infection's potential risk. SARS-CoV-2 was negative in the mother and the newborn's oropharyngeal swabs on the third and fifth days after surgery (Xia et al., 2020).

Even with no pre-established guideline on whether the mother and neonate need to be separated after birth in confirmed maternal infection, most maternities preferred the separation to limit respiratory exposure. Lowe and Bopp reported a case from an Australian tertiary hospital describing an uncomplicated vaginal birth in a COVID-19 positive mother. This issue was one of the first cases related to a mother with COVID-19 not separated from her infant. Neonatal COVID-19 testing was performed at 24 hours post-delivery, which was negative. Management provided supports that it is possible to consider rooming-in post-delivery for COVID-19 positive parents. Encouragement of breastfeeding appears likely and safe when viral precautions are taken (Lowe & Bopp, 2020).

Most of the case reports and case series presented so far suggest against the nature of vertical transmission of COVID-19 infection from mothers infected on their second and third trimester of gestation to their fetus and neonates postpartum. Hence, two recent reports from the US - Texas (Sisman et al., 2020) and France (Vivanti et al., 2020) were concerning the possible risks of vertical transmission, not seen in previous reports.

The Pediatric Infectious Disease Journal: July 10, 2020. Sisman et al., 2020 reported a case of a preterm infant who developed a fever and mild respiratory disease on the second day of life. SARS-CoV-2 nasopharyngeal testing was positive at 24 and 48 hours of life. The mother was on her 34th-week gestation and the pregnancy was complicated by diabetes mellitus and obesity. The neonate, which was large for gestational age, was delivered via vaginal delivery. The Histopathologic examination of the placenta revealed SARS-CoV-2 infection by electron microscopy and immunohistochemistry (Sisman et al., 2020).

Immediately after birth, delayed cord clamping and skin-to-skin contact were not performed. The infant was separated from the mother and transferred to the NICU within 30 minutes for the management of prematurity, glucose monitoring, and SARS-CoV-2 exposure. The infant's nasopharyngeal swab was positive by RT-PCR for SARS-CoV-2 at 24 and 48 hours of life. The infant developed a fever and respiratory distress on the second day of life and required the nasal cannula with oxygen supplementation. Respiratory signs resolved three days after their onset and the infant was weaned to room air by day 5 of life. Nasopharyngeal RT-PCR for SARS-CoV-2 was still positive on day 14 of life. The infant was discharged home with her mother in a good clinical condition on day 21 of life. It is unlikely that this infant's respiratory distress was due to prematurity since it did not start until the second day of life. Although the infant had an elevated neutrophil count, the lymphocyte count was decreased as described in adults with COVID-19.

The second concerning case, also from July 2020, was reported by Vivanti et al., 2020, transplacental transmission of SARS-CoV-2 in a neonate born to a mother infected in the last trimester and presenting with a neurological compromise. The patient was a 23-year-old, 35 weeks, with fever and severe cough for two days before admission. During admittance, both the E and S genes of SARS-CoV-2 were detected in blood and nasopharyngeal and vaginal swabs.

Fetal distress was noted three days after admission; the cesarean section was performed, with intact amniotic membranes, in full isolation, and under general anesthesia due to maternal respiratory symptoms (Vivanti et al., 2020).

Tissue analysis after the birth by RT-PCR on the placenta was positive for both SARS-CoV-2 genes, and viral load was much higher in placental tissue, than in

amniotic fluid and maternal or neonatal blood. Placental histological examination revealed diffuse peri-villous fibrin deposition with infarction and acute and chronic intervillositis. Immunostaining with antibodies against SARS-CoV-2 N-protein was performed and it showed an intensive cytoplasmic positivity of peri-villous trophoblastic cells for the antibodies.

Neonatal resuscitation was provided immediately after birth due to low Apgar score and signs of respiratory distress. Intubation and invasive ventilation were provided. The neonate was transferred in full isolation to the neonatal intensive care unit (NICU) and was only extubated after 6h. Before the extubation, blood and bronchoalveolar lavage fluid were collected for RT-PCR, and both were positive for the E and S genes of SARS-CoV-2. Nasopharyngeal and rectal swabs were first collected after cleansing the baby at 1 hour of life, then repeated at 3 and 18 days of postnatal age: they were tested with RT-PCR and were all positive for the two SARS-CoV-2 genes. Routine blood tests (liver and kidney function) resulted in normal. Feeding was provided exclusively using formula milk. On the third day of life, the neonate suddenly presented with irritability, poor feeding, axial hypertonia, and opisthotonos. Cerebrospinal fluid (CSF) was negative for SARS-CoV-2. At 11 days of life, magnetic resonance imaging showed bilateral gliosis of the deep white periventricular and subcortical matter, with slightly left predominance. The neonate gradually recovered and was discharged from the hospital after 18 days. Succeed-up at two months of life showed a further improved neurological examination and magnetic resonance imaging; growth and clinical exam results were average. The woman remained hospitalized to monitor her clinical conditions and was discharged in the right conditions six days after delivery.

3. Conclusion:

The novel coronavirus termed SARS-CoV-2 (COVID-19) is a major public health challenge. So far, it is unclear whether and how SARS-CoV-2 can be transmitted from the mother to the fetus. Further understanding of the risk factors that lead to in utero transmission of SARS-CoV-2 infection is needed. Pregnant women and their fetuses represent a high-risk population during infectious disease outbreaks. By May 2020, the outcomes of 55 pregnant women infected with COVID-19 and 46 neonates have been reported in the literature, with no definite evidence of vertical transmission. By July 2020, two cases described in this article demonstrated high chances of vertical transmission, with a particular difference that, on those cases, the patients did not only present with the classic respiratory symptoms of COVID-19: both cases presented patients with extra comorbidities (as diabetes and obesity), high virus load and neurological compromising, which open the doors for further research associated with the level of systemic infection of the mothers and their comorbidities or/and disease complications to the possibility (and probability) of vertical transmission.

It's important to reinforce the fact that there is no data of outcomes in infection on the first trimester of gestation, since the major worldwide spread took place early 2020, most of cases reported in the literature took place from January 2020. Further data need to be collected and more research need to be done to access outcomes and pattern of transmission during the first trimester, which vertical transmission could have higher rates, and which embryogenesis takes place and the effects of some infections could be devastating.

Corresponding Author:
Maria Carolina Beeter, MD.
Division of Clinical & Translational Research, Larkin Health System, South Miami, FL, USA.
E-mail: mari.beeter@gmail.com

References:

1. Dashraath, P., Jeslyn, W. J. L., Karen, L. M. X., Min, L. L., Sarah, L., Biswas, A., ... & Lin, S. L. (2020). Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. American journal of obstetrics and gynecology.
2. Chen, H., Guo, J., Wang, C., Luo, F., Yu, X., Zhang, W., ... & Liao, J. (2020). Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. The Lancet, 395(10226), 809-815.
3. Iqbal, S. N., Overcash, R., Mokhtari, N., Saeed, H., Gold, S., Auguste, T., ... & Wortmann, G. (2020). An uncomplicated delivery in a patient with COVID-19 in the United States. New England Journal of Medicine, 382(16), e34.
4. Khan S, Jun L, Nawsherwan, et al. (2020a) Association of COVID-19 with pregnancy outcomes in health-care workers and general women. Clin Microbiol Infect. 26(6):788-790.
5. Khan, S., Peng, L., Siddique, R., Nabi, G., Xue, M., Liu, J., & Han, G. (2020b). Impact of COVID-19 infection on pregnancy outcomes and the risk of maternal-to-neonatal intrapartum transmission of COVID-19 during natural birth. Infection Control & Hospital Epidemiology, 41(6), 748-750.
6. Li, Y., Zhao, R., Zheng, S., Chen, X., Wang, J., Sheng, X., ... & Fan, J. (2020). Lack of vertical transmission of severe acute respiratory syndrome coronavirus 2, China.
7. Liang, H., & Acharya, G. (2020). Novel corona virus disease (COVID‐19) in pregnancy: What clinical recommendations to follow. Acta obstetricia et gynecologica Scandinavica, 99(4), 439-442.
8. LIU, W., WANG, J., LI, W., ZHOU, Z., LIU, S., & RONG, Z. (2020). original: Clinical characteristics of

19 neonates born to mothers with COVID-19. Zhonghua Bing Li Xue Za Zhi.
9. Lowe, B., & Bopp, B. (2020). COVID‐19 vaginal delivery–a case report. Australian and New Zealand Journal of Obstetrics and Gynaecology.
10. Luo, Y., & Yin, K. (2020). Management of pregnant women infected with COVID-19. The Lancet Infectious Diseases, 20(5), 513-514.
11. Mimouni, F., Lakshminrusimha, S., Pearlman, S. A., Raju, T., Gallagher, P. G., & Mendlovic, J. (2020). Perinatal aspects on the covid-19 pandemic: a practical resource for perinatal–neonatal specialists. Journal of Perinatology, 1-7.
12. Peng, Z., Wang, J., Mo, Y., Duan, W., Xiang, G., Yi, M., ... & Sh, Y. (2020). Unlikely SARS-CoV-2 vertical transmission from mother to child: A case report. Journal of Infection and Public Health.
13. Pique-Regi, R., Romero, R., Tarca, A. L., Luca, F., Xu, Y., Alazizi, A., ... & Gomez-Lopez, N. (2020). Does the human placenta express the canonical cell entry mediators for SARS-CoV-2?. Elife, 9, e58716.
14. Qiao, J. (2020). What are the risks of COVID-19 infection in pregnant women?. The Lancet, 395(10226), 760-762.
15. Rasmussen, S. A., & Jamieson, D. J. (2020). Coronavirus disease 2019 (COVID-19) and pregnancy: responding to a rapidly evolving situation. Obstetrics and Gynecology.
16. Segars, J., Katler, Q., McQueen, D. B., Kotlyar, A., Glenn, T., Knight, Z., ... & Kawwass, J. F. (2020). for the ASRM Coronavirus/COVID-19 Task Force. Fertil Steril.
17. Shanes, E. D., Mithal, L. B., Otero, S., Azad, H. A., Miller, E. S., & Goldstein, J. A. (2020). Placental pathology in COVID-19. American Journal of Clinical Pathology, 154(1), 23-32.
18. Shah, P. S., Diambomba, Y., Acharya, G., Morris, S. K., & Bitnun, A. (2020). Classification system and case definition for SARS‐CoV‐2 infection in pregnant women, fetuses, and neonates. Acta Obstetricia et Gynecologica Scandinavica, 99(5), 565-568.
19. Sisman, J., Jaleel, M. A., Moreno, W., Rajaram, V., Collins, R. R., Savani, R. C., ... & Evans, A. S. (2020). Intrauterine transmission of SARS-COV-2 infection in a preterm infant. The Pediatric infectious disease journal, 39(9), e265-e267.
20. Van den Bosch, T., Van Schoubroeck, D., Timmerman, D., & Deprest, J. (2003). Uterine intramural bone after mid‐trimester termination of pregnancy may not affect fertility: a case report. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology, 22(4), 407-408.
21. Vivanti, A., Vauloup-Fellous, C., Prevot, S., Zupan, V., Suffee, C., Do Cao, J., ... & De Luca, D. (2020). Transplacental transmission of SARS-CoV-2 infection Wang, C., Zhou, Y. H., Yang, H. X., & Poon, L. C. (2020). Intrauterine vertical transmission of SARS‐CoV‐2: what we know so far. Ultrasound in obstetrics & gynecology.
22. Xia, H., Zhao, S., Wu, Z., Luo, H., Zhou, C., & Chen, X. (2020). Emergency Caesarean delivery in a patient with confirmed COVID-19 under spinal anaesthesia. British Journal of Anaesthesia, 124(5), e216-e218.
23. Yu, N., Li, W., Kang, Q., Xiong, Z., Wang, S., Lin, X., ... & Chen, S. (2020). Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. The Lancet Infectious Diseases.

Received September 23, 2020; reviewed September 30, 2020; accepted October 17, 2020; published online November 01, 2020