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Review

Possibility of Vertical Transmission of COVID-19 During Pregnancy, Labor and After Delivery: A Systematic Review Study

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Abstract

Background: In general, although the placenta is a good barrier to prevent infections, several cases of coronavirus disease 19 (COVID-19) transmission have been reported during pregnancy. Moreover, considering the potential for vertical maternal-fetal transmission, there is a concern that the fetus is at risk for congenital COVID-19. The aim of the present review and systematic study was to investigate the possibility of the vertical transmission of COVID-19 during pregnancy, labor, and postpartum using available data.

Methods: Studies conducted by February 12, 2021 were included in this systematic review study. Articles were searched in Medline, Magiran, SID, Civilica, Irandoc, ScienceDirect, PubMed, EMBASE, Web of Science, Scopus, and Google Scholar using English keywords such as "Coronavirus", "COVID-19, "SARS-CoV-2", "Vertical intrauterine transmission", "Vertical transmission", "Vertical fetal infection", "Maternal infection", and "Fetal infection". The inclusion criterion included all observational studies related to vertical maternal-fetal transmission. Overall, 31 articles were completely analyzed after reviewing and deleting non-eligible and duplicate articles.

Results: The results of reviewing 24 studies showed that collected samples were all negative but positive blood samples, *immunoglobulin M* (IgM) and IgG antibodies, and expression of placental factors were reported in seven studies.

Conclusion: Although contradictory results were found in this study, the results of the samples revealed the lowest probability of vertical transmission. There was also no evidence confirming the effectiveness of cesarean section in reducing the rate of transmission. In general, adherence to hygienic protocols can have a significant impact on reducing neonatal incidence.

Keywords: Vertical transmission, COVID-19, SARS-CoV-2, Maternal infection, Coronavirus, Neonate, Placenta, Pregnant mother

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Introduction

The new coronavirus causes acute respiratory syndrome (SARS-CoV-2), which belongs to the zoonotic beta-coronavirus and has been reported as a common disease in humans and animals (1, 2). On December 31, 2019, a new disease was first reported in China. The World Health Organization (WHO) officially named it coronavirus disease-2019 (COVID-19) on February 12 (3). As of March 12, 2020, the COVID -19 virus spread to 117 countries and killed more than 4000 people. Thus, the WHO officially declared a COVID-19 pandemic (4). The most common manifestations of COVID-19 include fever, cough, fatigue, or myalgia. The cause of COVID-19 (e.g., the previous two epidemics, namely, SARS-CoV-1 and MERS-CoV) is acute and severe viral pneumonia belonging to the Corona family of human viruses. It is mainly transmitted by respiratory droplets or contact and is highly dangerous to pregnant women (5). A total of 61911 cases of COVID-19 cases and 74 subsequent deaths were reported among pregnant American women between 22 January 2020 and 25 January 2021 (6). At the start of the COVID-19 epidemic, there was limited information about the consequences of the SARS-CoV-2 infection in pregnant women, and the risk of vertical or horizontal transmission to the infant was unknown. Due to the uncertainty of potential transmission from an infected mother to her infant, early guidelines recommended the mother-infant separation immediately

after delivery to minimize the risk of transmission (7).

Considering the current information, it does not seem that pregnant women are more prone to infection. They had no more severe respiratory complications than the vertical population in the suspected cases (7, 8). Studies show that except for the gastrointestinal symptoms, consistent with observations in non-pregnant populations, comorbidities such as lung disease and diabetes were associated with the increased risk of more severe SARS-CoV-2 infections during pregnancy. Pregnant women with pre-existing conditions require careful monitoring for the evolution of their symptoms during the SARS-CoV-2 infection (9).

Overall, although the placenta is a good barrier to prevent infections, several COVID-19 cases have been reported during pregnancy; and due to inconsistent data about the vertical transmission of the virus and high risks of vertical transmission, the present systematic review study investigated the possibility of vertical transmission during pregnancy, labor, and after delivery using the existing data (10, 11).

Materials and Methods

Search Strategy

This review study examined the possibility of the vertical transmission of COVID-19 until February 12, 2021. ScienceDirect, PubMed, Medline, EMBASE, Web of Science, Scopus, SID, Civilica, Irandoc, Magiran, and Google Scholar databases were used to access related articles. All articles having keywords such as "COVID-19", "SARS-CoV-2", "Maternal infection", "Neonate", "Placenta", "Pregnant Mother", "Coronavirus", "Vertical intrauterine transmission", "Vertical transmission", "Vertical fetal infection", Maternal infection", and Placental infection" in their titles were selected for this purpose. The applied Boolean operators included OR and AND. Additional keywords and related Boolean operators were employed to change the strategy. Non-relevant articles were excluded and possible related articles were identified after studying the abstract of each study. Based on inclusion and exclusion criteria, appropriate articles were included in the study.

Inclusion Criteria

Observational articles related to vertical transmission during pregnancy, labor, and postpartum.

Exclusion Criteria

Animal studies, review articles, case reports, brief reports, letters to the editor, and non-English articles.

Patient Characteristics

There were no restrictions on year, place of study, maternal age, and gestational age.

Data Extraction and Quality Evaluation

To assess the value of articles, they were reviewed based on the inclusion (observational articles related to vertical transmission during pregnancy, labor, and postpartum) and exclusion (animal studies, review articles, case reports, brief reports, letters to the editor, and non-English articles) criteria. To evaluate the quality of the remaining articles, the titles and abstracts of the articles were examined for their eligibility after removing irrelevant articles. Following reviewing the full texts of the articles, their methodological quality was investigated by three authors using a researcher-made checklist (including year, location, authors' name, article title, sample size, methods, samples, and results). For quality assessment, the 22-item STROBE checklist was used for observational studies (12). The scoring for each item is 0 and 1. The checklist items including article title and abstract (item 1), introduction (items 2 and 3), methods (items 4 to 12), results (items 13-17), discussion (items 18-21) sections, and other information (items 22) are eighteen common items to all and items 6, 12, 14, and 15 may vary depending on the design of the observational study (13). Scoring for each study was conducted by two authors and then confirmed after their agreement (Table 1).

Results

Overall, 855 articles were reviewed after searching in different databases, and 770 unrelated articles were excluded following reviewing the titles and abstracts and removing duplication. Further, a total of 85 articles were screened, and finally, 31 articles were included in the present study (Figure 1).

Studies published from the onset of the COVID-19 pandemic to February 12, 2021 were reviewed in the search strategy. Most studies focused on throat swab samples, amniotic fluid, and placental histopathological examinations by the polymerase chain reaction (PCR) and specific genetic tests in the third trimester (28-40 weeks of pregnancy).

A total of 24 studies on the swabs of the throat, urine, feces, breast milk, and amniotic fluid were all negative, and none of the infants showed any clinical, radiological, or hematologic evidence of COVID-19; therefore, there is no evidence of vertical transmission and pregnancy-related complications due to viral infection. Furthermore, in the mentioned studies, neonates were tested for SARS-CoV-2 nucleic acid after birth, as well as delivery history, and neonatal birth status including Apgar score, clinical features, amniotic fluid nucleic acid diagnosis, and blood sample collection. Neonatal cord blood and swabs were examined and tested by the q RT-PCR test. The results of all these tests were negative for COVID-19. Therefore, the SARS-CoV-2 infection in pregnant women causes no adverse outcomes in their infants (5, 14-36).

After discovering the expression patterns of angiotensin-

Table 1. Main Characteristics of the Overviewed Studies and Their Findings

Author, Year, Place, and Reference	Sample Size	Methods and Sample	Results	STROBE Score
Liu et al (2020), China (14)	19	Pregnant women who have been diagnosed with COVID-19 in late pregnancy (RT-PCR)	Negative	16
Chen et al * (2020), China (15)	9	Samples of amniotic fluid, umbilical cord blood, and neonatal swabs. In addition, breast milk samples were collected during the first breastfeeding postpartum (PCR)	Negative	16
Hijona Elósegui et al (2020), Spain (16)	4	Diagnosis of the virus in the vaginal and amniotic fluid secretions of four pregnant women with mild acute symptoms of COVID-19 in the second trimester of pregnancy (RT-PCR)	Negative	14
Gulersen et al (2020), America (17)	50	Histopathological characteristics of each placenta were evaluated, and the results were compared with the placenta of those diagnosed with acute respiratory syndrome and symptomatic and non-symptomatic individuals (RT-PCR)	Negative	18
Popofsky et al (2020), America (18)	160	This observational longitudinal cohort study examined mothers with COVID-19 and their infants during pre-pregnancy, postpartum, in-hospital, and after discharge and any possible COVID-19-related changes)PCR).	Negative	17
Fan et al (2020), China (19)	2	Collection of serum, umbilical cord blood, placenta, amniotic fluid, vaginal swab, breast milk, and nasopharyngeal swabs (PCR)	Negative	14
Zhou et al (2020), China (20)	17	Evaluation of the risk of metabolic complications in women with COVID-19 and its possibility of transmission to the fetus (PCR)	Negative	15
Yan et al (2020), China (21)	116	Collection of a sample of neonatal swab amniotic fluid (PCR)	Negative	16
Pereira et al (2020), Spain (22)	60	Laboratory test results (PCR) and imaging evidence	Negative	14
Fenizia et al (2020), Italy (10)	31	Vaginal, umbilical cord blood, milk, and placenta samples (PCR)	Positive	16
Ferrazzi et al (2020), Italy (23)	41	Tested anti-SARS-CoV-2 antibody and expression of genes involved in inflammatory responses in the placenta and maternal plasma and umbilical cord (Pair biomarker)	Negative	15
Kc et al (2020), Nepal (24)	22907	Reports on the method of delivery and its immediate outcomes on a baby born to a mother with SARS-CoV-2	Negative	16
Yu et al (2020), China (25)	7	Collection of statistical and birth-related information from patient's medical records and performance of health workers by direct observation (PCR)	Negative	15
Patanè et al (2020), Italy (37)	22	The required information was obtained from the swap samples of mothers and placentas about the vertical transmission (PCR)	Positive	14
He et al (2020), Italy (11)	22	Evaluation of immunological indexes including IgG and IgM in the neonates of mothers with COVID-19 (PCR)	Positive	17
Marín Gabriel et al (2020), Spain (26)	42	Review of the medical records of 42 pregnant women diagnosed with COVID-19 in the third trimester of pregnancy, (Clinical symptoms)	Negative	15
Yang et al (2020), China (27)	7	Determination of Apgar score, clinical symptoms, blood, tests, umbilical cord and amniotic fluid samples, and throat swabs (PCR)	Negative	14
Griffin et al (2020), USA (28)	28	Fourteen infants whose mothers' tests were positive and all samples(cases) of this study were tested by PCR.	Negative	17
Hecht et al (2020), Canada (29)	19	The histopathological characteristics of each placenta were evaluated (IgM and IgG tests)	Negative	19
Zhu et al (2020), China (5)	10	Clinical characteristics and outcomes of 10 infants from the affected mothers (PCR)	Negative	16
Pique-Regi et al (2020), USA (30)	33	Confirmed nCoV-2019 infection in five hospitals from January 20 to February 5, 2020 was retrospectively analyzed (PCR)	Negative	14
Bloise et al (2020), Canada (31)	87	Evaluation of the placental villi of placental cells and the presence and expression of ACE2 TMPRSS2 and viral RNA receptors (PCR)	Negative but the placenta is more likely to become infected in the first trimester of pregnancy	17
Facchetti et al (2020), Italy (32)	15	Polyestrase chain reaction and RNA sequencing and the PCR	Negative	18
Oncel et al (2021), Turkey (38)	125	Immunohistochemical analysis, electron and molecular microscopy of the placenta, and PCR	Positive	16
Halici-Ozturk et al (2021), Turkey (39)	210	Cohort evaluation of clinical characteristics of newborns born to affected mothers RT-PCR	Positive placental RT-PCR was reported in 24 out of 210 cases	15

Table 1. Continued.

Author, Year, Place, and Reference	Sample Size	Methods and Sample	Results	STROBE Score
Chen et al (2020), China (40)	286	Investigation of the presence of SARS-CoV-2 RNA in placental tissues with the RT-PCR	Positive The potential risks of the SARS-CoV-2 infection during embryonic development (IgM antibodies have been detected in blood samples in neonates)	16
Xu et al (2020), China (33)	64	Considering ACE2 and TMPRSS2 (Histopathological examination)	Negative	16
Qiancheng et al (2020), China (34)	82	Evaluation of symptoms in pregnant women with COVID-19 (PCR)	Negative	16
Zhang et al (2020), China (35)	18	Comparison of clinical courses and outcomes between pregnant and non-pregnant women (PCR)	Negative	16
Dashraath et al (2020), Singapore (41)	55	Clinical manifestations, tests, and chest CT were analyzed (PCR)	Positive	14
Choudry et al (2020), Pakistan (36)	90	Histopathological examination of the placenta of pregnant women with COVID-19 in the third trimester and their newborns	Negative	16

Note. COVID-19: Coronavirus disease-19; RT-PCR: Real-time polymerase chain reaction; SARS-CoV-2: Coronavirus causes acute respiratory syndrome; IgM: *Immunoglobulin M;* IgG: *Immunoglobulin G; ACE2, Angiotensin-converting enzyme 2.*

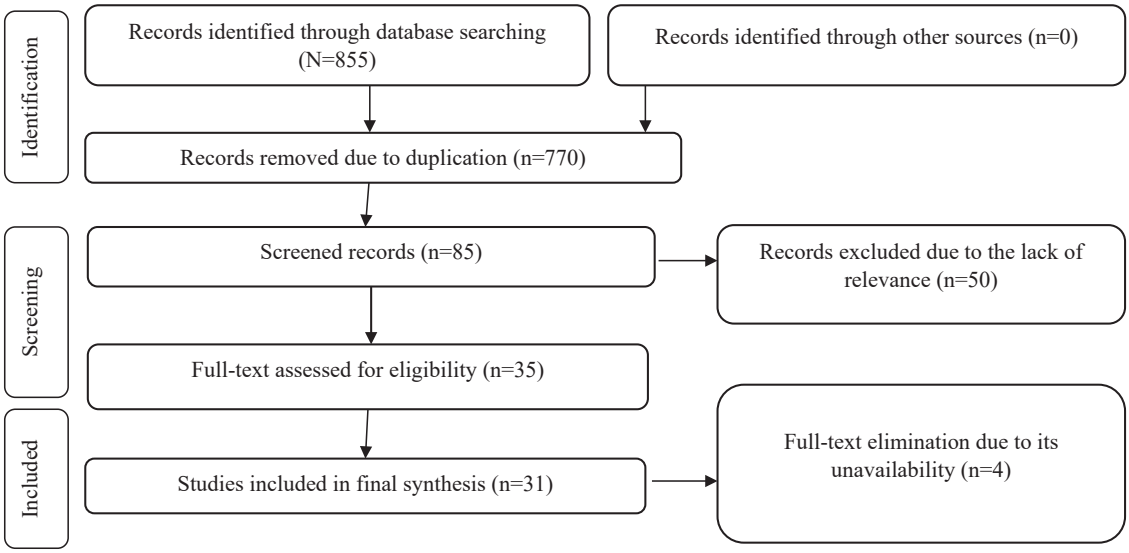

Figure 1. PRISMA Flowchart of Preliminary Studies

converting enzyme 2 (ACE2) and TMPRSS2 in embryos, mothers, and fetuses and using single-cell transcript data previously published in 7 studies, it was found that there may be different susceptibility to the SARS-CoV-2 infection in infants of both genders. However, the analysis of new single-cell nucleus RNA sequence data demonstrated negligible co-transcription of ACE2 and TMPRSS2 in the placenta, therefore, these receptors are unlikely to be involved in the vertical transmission pathway for SARS-CoV-2 (10, 11, 37-41).

Respiratory distress, thrombocytopenia, or death was reported among articles that addressed the relationship between COVID-19 and the complications of infants and fetuses. It is generally speculated that the likelihood of the vertical transmission of COVID-19 in pregnancy, similar to other pathogens, is higher due to the lack of complete immunological communication between the mother and the fetus in the first trimester (11, 18, 20, 37-39). The main findings from reviewing the related studies are summarized in Table 1.

Discussion

A systematic review of the preliminary data showed that the risk of the vertical transmission of COVID-19 was extremely low. The results of testing the swabs of the throat, urine and feces, breast milk, and amniotic fluid were all negative in most studies. In studies with negative responses, none of the infants represented any clinical, radiological, or hematologic evidence of COVID-19. Accordingly, there is no evidence of vertical transmission and pregnancy-related complications due to the viral infection in the third trimester of pregnancy (15, 16, 18, 19, 21-23, 26).

In the studies of Gulersen et al and Xu et al, the

histopathological characteristics of each placenta were evaluated, and then the results were compared with the placenta of those diagnosed with acute respiratory syndrome and non-symptomatic individuals. Based on the results, no placental histopathological findings were found in pregnant women diagnosed with SARS-COV2, and no differences were observed between the symptomatic and asymptomatic groups (17, 33).

Examining the placental expression of ACE2 and TMPRSS2 during pregnancy and chorioamniotic membranes in the third trimester and analyzing new data from the single-cell nucleus RNA sequence demonstrated that the placental co-transcription of ACE2 and TMPRSS2 is negligible. Thus, it is unlikely that these receptors are involved in the vertical transmission for SARS-CoV-2 (31, 41). Moreover, neonates were tested for SARS-CoV-2 nucleic acid after birth, as well as delivery history, neonatal birth status including Apgar score, clinical features, amniotic fluid nucleic acid diagnosis, and blood sample collection in the studies. Neonatal cord blood and swabs were examined and tested using the qRT-PCR test. The results of all these tests were negative for COVID-19 (5, 15, 23, 25, 27, 42).

The literature review indicated a low risk of vertical transmission among mothers who were positive for COVID -19 using the qRT-PCR, even if the placenta contains COVID-19 virus particles (32, 43). Conversely, Bloise et al evaluated the placental villi of placental cells, as well as the presence and expression of ACE2 TMPRSS2 and viral RNA receptors and reported that the expression of some placental factors is obvious in COVID-19 transfer in the first trimester (31). In some studies focusing on the evaluation of the clinical and placental characteristics, 27 out of 335 samples were positive (38, 39). Therefore, there is a potential risk of the SARS-CoV-2 infection during embryonic development and pregnancy (40, 44) after discovering the expression patterns of ACE2, TMPRSS2, symptoms in embryos, mothers, and fetuses and using single-cell transcript data previously published in 7 studies (10, 11, 37-41), it was found that there may be different susceptibility to the SARS-CoV-2 infection in infants of both genders. In one study, the SARS-CoV-2 genome was identified in one cord blood sample, two placentas, one vaginal mucus sample, and one milk sample. IgG and IgM-specific antibodies against SARS-CoV2 were also detected in one cord blood sample and one milk sample. Additionally, the vertical transmission of SARS-CoV2 was associated with a strong inflammatory response in three cases. Overall, this study, although with little information, supports the hypothesis of the vertical intrauterine transmission of SARS-CoV2 (10). The data show that in the third trimester, the COVID-19 infection is associated with an increased risk of ketonuria and increased fibrinolysis, which may cause severe complications (5). COVID-19 also increases the inflammatory response of the placenta, fetus, and infant, probably leading to coagulation and regulatory problems in the organs. There was a potential risk of vertical transmission in women with high SRS-CoV2 titers because neonates were born with a fever and a positive COVID-19 test in a number of studies. SARS-CoV2 infection during pregnancy is not associated with an increased risk of miscarriage and preterm delivery (15). Pregnant and non-pregnant patients differ in symptoms such as fever and fatigue. Moreover, neutrophils, fibrinogen, D-dimer and erythrocyte sedimentation rate, and the disease severity are lower in affected pregnant women compared to affected non-pregnant women according to laboratory tests. Newborns had negative RT-PCR test results. Pregnant patients with H1N1 had a more serious condition in comparison with COVID-19 patients. Collection and analysis of recorded information on pregnancy and its outcomes on the infant showed that vaginal delivery is associated with a lower risk of the transmission of the COVID-19 infection (23).

Hospital deliveries have been reduced by half during quarantine, stillbirth and neonatal mortality and mortality rates have increased, and the quality of health care has represented a decline. Behaviors such as hand hygiene and maternal-infant skin contact during breastfeeding have demonstrated an improvement (24).

In some studies, there was no COVID-19 infection among all vaginal births, thus the vertical transmission of COVID-19 does not occur due to vaginal delivery or maternal infection in the late stages of pregnancy (9, 34).

With regard to COVID-19, mother-infant separation reduces the rate of breastfeeding both upon admission and after discharge as compared to mothers who have not been separated from their infants. Delayed infant-mother separation during breastfeeding can lead to the vertical transmission of the COVID-19 infection (18).

Nonetheless, more PT-PCR tests on the throat, umbilical cord blood, and amniotic fluid swab samples were negative and no clinical evidence was found in neonates. Therefore, the SARS-CoV-2 infection does not produce adverse fetal results in pregnant women with late pregnancy. However, it is necessary to separate the infants from the mothers to avoid possible health risks. It seems that the vertical transmission of COVID-19 is impossible if necessary and sufficient measures are taken after delivery (28, 44).

Some of the limitations of the present study include an inadequate number of large studies and high heterogeneity among data articles. It is hoped to achieve more reliable results by conducting extensive clinical studies. It is recommended that extensive studies address COVID-19 during pregnancy and its complications for pregnant women and infants due to the sensitivity of this period. Therefore, it is suggested that researchers perform extensive review studies to establish health protocols and programs.

Conclusion

Overall, although the literature review revealed contradictory results, the results of the samples showed the lowest probability of vertical transmission. There was also no evidence confirming that a cesarean section is preferred in reducing the transmission rate. Accordingly, adherence to health protocols and isolation of symptomatic mothers from newborns can have a significant effect on reducing the incidence of infection among newborns.

Authors' Contributions

NR and AR considered data gathering and wrote the first draft of the manuscript. AS, ZK, MA, and MN extracted the required data. FD edited the final manuscript. All authors contributed to the revision and confirmation of the final version of the manuscript.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Ethical Statement

This study raises no ethical issues as it reviewed the findings of previous research.

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