

Possible Vertical Transmission of SARS-CoV-2 during the Third Trimester of Pregnancy, a Mini-Review

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Abstract The recent emergence of the COVID-19 pandemic was the reason why the effects and consequences of its transmission from pregnant women to their fetuses were not understood. However, recent studies have tried to decipher this virus by first confirming its vertical transmission and then identifying its pathogenesis and teratogenicity, if any. The objective of this mini-review is to conduct a review of recent studies for confirming the vertical transmission of SARS-CoV-2 during the third trimester of pregnancy. The literature search was performed using PubMed, Scopus, and Web of Science and Google Scholar databases. The research was conducted from September 1, 2021 to May 1, 2022 and the research was based on the following keywords: “(“Coronavirus” COVID-19”, “Vertical transmission”, “pregnancy” and “Third trimester”). Studies have shown that the occurrence of vertical transmission is possible, and this is confirmed by the presence of virus receptors in birth products such as the placenta, in addition to the appearance of IgM antibodies in neonates. Their mothers were positive for the SARS-CoV-2 PCR test, as well as the presence of viral RNA in the placenta, since the third trimester of pregnancy appears to be the most vulnerable period of viral infection, most cases of vertical transmission have been documented during this period. More studies are required to confirm vertical transmission during the first and second trimesters of pregnancy, in addition, study the effect of the virus on fetuses at the immunological, pathological and teratological levels during all periods of pregnancy and investigating the role of new variants of this virus in the incidence of vertical transmission and the consequences of infection with it.

Keywords: SARS-CoV-2, pregnant women, vertical transmission, third trimester

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1. Main Text

At the end of 2019, specifically the month of December, the world witnessed the emergence of a pandemic that caused a complete closure of various life activities for people in different countries of the world. The pivotal of this pandemic was a virus that originated in Hubei Province, Wuhan, China. On January 7th, 2020, the new coronavirus was identified in a throat swab sample of one patient, Chinese Center for Disease Control and Prevention [CCDC] then recognized it as a novel virus belong to the family of *Coronaviridae*, *beta-coronavirus* genus and named it as (2019-nCoV). Because of the high rate of spread of this virus, WHO announced this outbreak is a public health emergency of international concern [1]. On the 11th February 2020, the International Committee on Classification of Viruses officially renamed it with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease caused by SARS-CoV-2 has been declared by the WHO as coronavirus disease

2019 (COVID-19). Coronaviruses are a group of viruses that have a corona or crown (corona) shape when viewed under an electron microscope, the SARS-CoV-2 genome includes single-stranded RNA, containing 29,903 nt, this positive sense RNA acts directly as mRNA, which translates the two open reading frames (ORF1a and ORF1b) into proteins [2,3], Figure 1, [35].

Direct transmission of SARS-CoV-2 from human-to-human mainly occurs by the respiratory droplets with size (>10 µm) of virus exhaled [within one meter] from an infected person. The transmission of this virus also occurs by contact with contamination surfaces, such as skin to skin, and by touching the infected non-living objects and then transmitting it to the eyes and nose or mouth. Other studies show that the virus can remain in the air for a long time [4]. Clinical manifestations of COVID-19 are variable, and may include asymptomatic infection, acute respiratory illness, and pneumonia of varying severity [5]. In addition, some studies have indicated that the overall mortality rate as a result of infection with the Covid-19 virus among people show obvious symptoms and those asymptomatic has been around 5% [6].

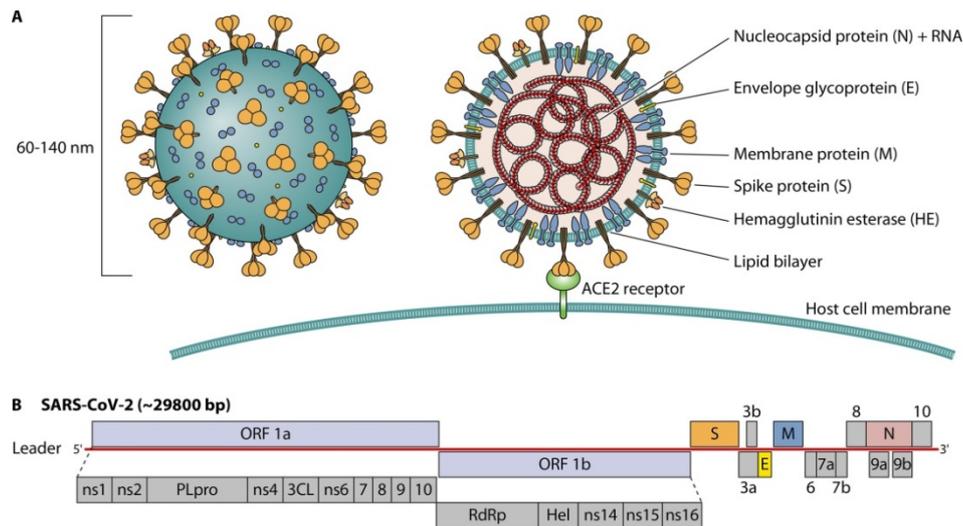


Figure 1. SARS-CoV-2 structure, Ref. [35]

The consequences of COVID-19 infection in pregnant women and their fetuses remain unexplored and unknown primarily due to the novel nature of the virus and its outbreak. Most cases of pregnant women infections are asymptomatic, but when symptoms appear, similar to non-pregnant patients, the most common symptoms are fever, cough and shortness of breath [7]. However, pregnant women and their newborns should therefore receive special attention because they are particularly vulnerable, and are in a unique state of immunosuppression [8]. Because of congenital malformations and fetal infection that occur as a result of infection with other viruses like cytomegalovirus, Zika, Parvovirus B19 and Rubella, in addition to epidemiological data collected from previous pandemics, such as Influenza and Ebola, suggest that pregnant women are more susceptible to severe complications and mortality from viral infection, and with the spread of the COVID-19 pandemic in the world. Infection among pregnant women with the SARS-CoV-2 and the possible risks of vertical transmission to the fetuses has become a major concern.

The characteristics of the anatomical structure of the respiratory system and the immune system and the accompanying physiological changes during pregnancy and the puerperium play a role in increasing this risk [9]. High levels of estrogen and progesterone lead to oedema of the upper respiratory tract, and also cause an increased risk of infection. The enlargement and expansion of the uterus causes the displacement of the diaphragm, which makes the expansion of the lung difficult and thus reduces the respiratory capacity and causes shortness of breath, for the pathogens mentioned above, the passage of these pathogens across the placenta tends to increase with increasing gestational age, while the adverse effects on the fetus increase with the early stages of pregnancy. Accordingly, Kotlyar and his colleagues [10] assume that the infection with COVID-19 during the early stages of pregnancy has adverse consequences and effects on the fetus. The bad history that linked infections with other members of the coronavirus family (such as SARS and MERS) to the morbidity and mortality of pregnant women, fetuses, newborns and to severe outcomes of pregnancy, such as miscarriages, premature births and stillbirth has

raised potentially significant new concerns about the exposure of pregnant women to the novel coronavirus-19 [11]. The first and third trimesters of pregnancy are periods when there is an increase in inflammatory activity, while immune activity decreases during the second trimester [12]. Despite the evidence of vertical transmission of many infectious pathogens between the mother and her fetus before birth and during childbirth, the possibility of transmission from the infected mother to the fetus or newborn was considered a recent point of discussion in most of the published literature reviews, at a time when a limited number of studies showed evidence to prove vertical transmission is not possible [13,14,15].

The fear of vertical transmission, which was denied by early studies, like a meta-review published clinical evidence that vertical transmission of SARS-CoV-2 did not occur from pregnant women to fetuses/newborns, and in the other hand, was confirmed by some other studies, came for strong reasons [16], including what was mentioned, let's know from the start that SARS-CoV-2 has always shown a viral tropism to the tissues that show receptors on their cell surfaces through which the virus binds and enters the cells, these are known as angiotensin-converting enzyme 2 [ACE2] receptor. The placenta, in particular, as well as the ovaries, vagina and uterus, are important sources of angiotensin-converting enzyme 2, as the placenta is the main source of expression for these receptors, as the activity of its expression increases during pregnancy [17,18] Figure 2, [34]. In addition, reports from other studies have been shown that the viral RNA and proteins of SARS-CoV-2 were detected in placenta and umbilical cord blood and vaginal mucosa, and the presence of anti-SARS-CoV-2-IgM antibodies in Chinese neonates were born to women with positive COVID-19 results, confirmed the transmission of the virus during pregnancy [19,20,21,22]. Besides transplacental transmission, vertical intrauterine transmission of viruses can occur during aspiration or swallowing of fetuses of cervical-vaginal secretions [23]. An interesting recent study indicated that ACE-2-receptor-expressing immune cells in the mother's circulation may play a major role in the transmission of SARS-CoV-2 to the placenta, which contributes to an increased risk of vertical transmission to the fetus [24].

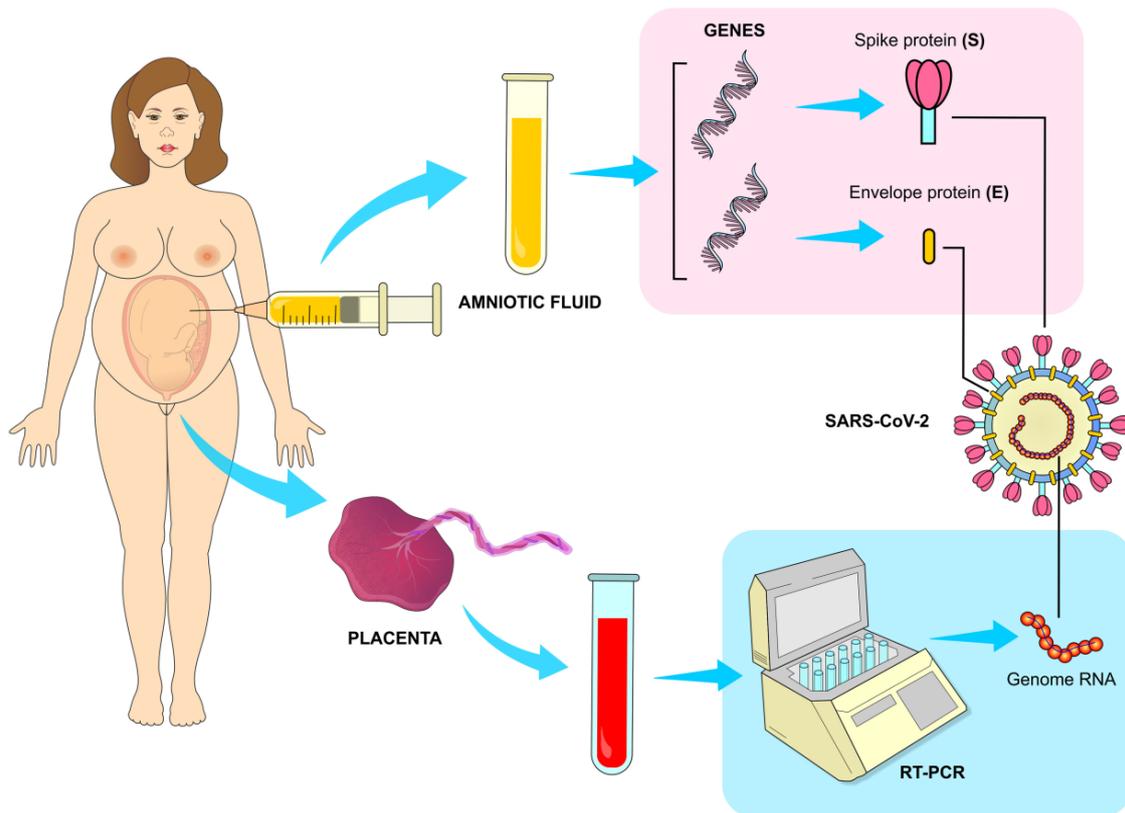


Figure 2. Vertical transmission of SARS-CoV-2, Ref. [34]

Since the outbreak of the COVID-19 pandemic, several scientific studies conducted on infected pregnant women and the fetal or neonatal outcomes of COVID-19 infection have confirmed vertical transmission and most of these cases are in the third trimester of pregnancy. Salem, [25] indicated that the third trimester of pregnancy appears to be the most vulnerable period for viral infections. This is a possibility for several reasons, including high shortness of breath (dyspnea), as a result of increased oxygen consumption by the fetus, which leads to an increase in the oxygen requirements of the pregnant mother, in addition to the occurrence of gestational anemia in most pregnant women, which causes aggravation of breathing difficulties [26]. Altogether, Fenizia *et al.*, [19], in current data indicate that vertical transmission of utero SARS-CoV-2, in spite of the fact that at a low rate, but is possible. A systematic review conduct by Kotlyar *et al.*, [27] shows that vertical transmission of SARS-CoV-2 infection in the third trimester of pregnancy can occurrence with a low rate and is approximately 3.2%. In a recent study, He and his colleagues [28], discovered for the first time that infection with SARS-CoV-2 during the third trimester of pregnancy actually occurred and had serious complications on the renal development of the fetus, as the study showed elevated levels of cystatin C and β 2-microglobulin in newborns, which is further evidence of Vertical transmission from the pregnant mother to the fetus. Confirming that the susceptibility to infection with SARS-CoV-2 is greater during the third trimester of pregnancy, a retrospective analytical study [29] was conducted to investigate the role of care strategies that reduce and prevent nosocomial infections with COVID-19 and its complications. Those strategies that were implemented, it was enough to prevent this infection

and its transmission to pregnant women who are in their third trimester, and because the expression of ACE2 receptors in maternal-fetal interface cells changes significantly in the three different trimesters of pregnancy, according to the study [19]. Most case studies and literature review studies have shown that most cases of vertical transmission of SARS-CoV-2 from pregnant women to their fetuses were during the third trimester of pregnancy [30]. In a case study conducted by Vivanti *et al* [31] of a pregnant woman in the third trimester, the study showed potential occurrence of maternal viremia of SARS-CoV-2, which was followed by the virus reaching the placenta, the viral load was much higher in placental tissue compared to maternal blood or amniotic fluid. The study showed vertical transmission of SARS-CoV-2 to her neonate resulting in neonatal viremia after infection of the placenta.

The emergence of evidence of vertical transmission from pregnant mothers to fetuses in the uterus and during childbirth, especially during the last third of pregnancy shown by most recently published studies. One of the reasons for it, as indicated by a previous study, maybe the increased expression of ACE2 receptors in various organs such as the placenta and gravid uterus are twice as high compared to non-pregnant women, and thus it is one of the risk factors that are responsible for increasing the severity of SARS-CoV-2 infection [32,33], in addition to other factors such as those women in this period are free to move and go out compared to the first and second trimesters, and therefore are more susceptible to infection, and therefore the possibility of vertical transmission is greater. This encouraged researchers to conduct more studies on pregnant women during this period, a study conducted by Al-Taie, [35], to estimate the seroprevalence

rate of antibodies in Iraq that the prevalence of these antibodies was much higher among pregnant women in the third trimester compared to the first and second trimesters of pregnancy. However, it is necessary to conduct further studies to investigate the teratogenic consequences that may occur as a result of vertical transmission of the virus during the third trimester of pregnancy, as well as in the first and second trimesters of pregnancy, and to identify the most important factors that increase the severity of infection. More studies are required to confirm vertical transmission during the first and second trimesters of pregnancy, in addition to studying the effect of the virus on fetuses at the immunological, pathological and teratological levels during all periods of pregnancy.

2. Conclusion

Considering all the points discussed in this current mini-review, we conclude that vertical transmission is very possible, and because the third trimester of pregnancy is the period most susceptible to viral infection, the possibility of infection of SARS-CoV-2 and the occurrence of vertical transmission were high during this period of pregnancy compared to the first and second trimesters, which the researchers did not adequately address. However, there are many questions that still require scientific answers about the role of the last period of pregnancy in infecting fetuses with the virus at the immunological, pathological and teratogenic level, in addition to investigating the role of new variants of this virus in the incidence of vertical transmission and the consequences of infection with it.

Abbreviation

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2;

CCDC: Chinese Centre for Disease Control;

WHO: World Health Organization;

COVID-19: Coronavirus Disease 2019;

ACE2: Angiotensin-Converting Enzyme 2.

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Authors' Contribution

All authors equally contributed to the study and confirmed its submission.

Competing Interest

The authors declare that they have no competing interest.

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