Review

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Vertical transmission and maternal passive immunity post-SARS-CoV-2

Hanie Karimi[1,4], Vahid Mansouri[2,4] & Nima Rezaei*[,3,4,5]

[1]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[2]Gene Therapy Research Center, Digestive Diseases Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

[3]Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, 14194, Iran

[4]Network of Immunity in Infection, Malignancy & Autoimmunity (NIIMA), Universal Scientific Education & Research Network (USERN), Tehran, Iran

[5]Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

*Author for correspondence: rezaei_nima@tums.ac.ir

Since 2020, the highly contagious nature and various transmission routes of SARS-CoV-2 have rendered the pandemic interminable. Vertical transmission (VT) through the placenta and breast milk, which is frequent for certain virus types, is thought to exist for SARS-CoV-2 and is hypothesized by many researchers. Conversely, antibodies are produced to counteract the effect of viruses. Since newborns' immunologic system cannot produce proper antibodies, maternal antibodies are usually transferred from mother to infant/fetus to meet the need. This theory leads to the hypothesis of transmission of antibodies through the placenta and breast milk following SARS-CoV-2 infection or vaccination. This paper further discusses these hypotheses, considering consequences of fetus/infant harm versus benefit.

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The novel COVID-19, which appeared in December 2019 in Wuhan, Hubei province, China, was first described by Huang *et al.* [1]. This disease is caused by SARS-CoV-2, a single-stranded RNA virus from the Coronaviridae family (*Betacoronavirus*), which is highly contagious and has spread worldwide. According to WHO reports, the COVID-19 global pandemic has affected more than 769 million people and killed more than 6.9 million people worldwide [2].

The SARS-CoV-2 virus is easily transmitted. Its main transmission route is via aerosol droplets, contributing to person-to-person transmission during direct contact. However, several other routes have also been proposed including airborne transmission, transmission from contaminated surfaces, animals and vertical transmission (VT) from mother to fetus [3].

Pregnant women are considered a population of great importance in the COVID-19 pandemic since pregnancy leads to an immune-compromised state, making pregnant women more susceptible to viral infections by SARS-COV-2 [4,5]. SARS-CoV-2 morbidity and mortality are considerably higher in pregnant women compared with non-pregnant women (0.9% vs 0.55% mortality, 4.31% vs 1.68% ICU admission) [6]. Moreover, there is an interdependent immune system between the pregnant woman and her fetus/neonate which could result in immune response alterations in this population [7]. Based on CDC reports, more than 23,434 pregnant women presented with symptomatic laboratory-confirmed COVID-19 in the first waves of COVID-19 [8]. Furthermore, of the 13% of 28,771 neonates born to SARS-CoV-2-infected women tested, 138 neonates tested positive for SARS-CoV-2 infection [9].

As mentioned, mother-fetus VT is a possible route of SARS-COV-2 transmission [10,11,12,13,14]. Maternal–fetal transmission of other viral infections including rubella, cytomegalovirus, herpes, Zika, and Ebola viruses have been proven [15]. Still, no evidence currently supports VT of other members of the Coronaviridae family, including SARS-COV and MERS-COV, although the 229E type of coronaviruses has been reported to be vertically

transmitted [16]. Maternal transmission through breast milk is also possible, but there is no current consensus as to whether this does occur [17,18]. The neonate's immature immune system might put them at risk of severe infection and subsequent complications, hence there is considerable interest in determining whether SARS-COV-2 can be transmitted by placenta or breast milk to the fetus/infant. The immature immune system of the fetus benefits from passive immunity through the transfer of IgG antibodies produced in response to infection by the infected mother through the placenta [19]. It is still unclear whether SARS-COV-2 antibodies follow this same pattern [20].

This paper aims to review the current evidence about the VT of SARS-COV-2 and its associated antibodies via the placenta. Additionally, it summarizes available knowledge regarding vertical passive immunity mediated by antibodies delivered in breast milk for newborns.

Current knowledge about vertical transmission & passive immunity of Coronaviridae

Except for SARS-CoV-2, Six types of coronaviruses have infected humans so far: NL63, HKU1, 229E, OC43, SARS-CoV and MERS-CoV; of which SARS-CoV and MERS-CoV are the most prominent ones, given their similarity to SARS-CoV-2 [21]. SARS-CoV-2 has 50 and 79% genetic similarity to SARS-CoV and MERS-CoV, respectively [13]. Among these coronaviruses, MERS-CoV has the highest mortality rate (up to 37%). SARS-CoV has a mortality rate of 10% in the general population and increased mortality of 25% in pregnant women, given its more severe infection and complications during pregnancy [22]. There is evidence that four other strains (229E, HKU1, OC43 and NL63) are only capable of causing common colds in humans [23].

Vertical transmission of human coronavirus 229E (HCoV-229E) has been demonstrated before; however, its mechanism is not well known. There has been an instance of HCoV-229E presence in a neonate's gastric sample suggesting a breast-feeding transmission of the virus, although further examinations were not implemented and its exact mechanism is still unknown [24]. To the best of our knowledge, no VTs of any other types of Coronaviridae, including SARS-CoV and MERS-CoV, have been reported yet [4,16,23,25,26,27].

There is a limited amount of information regarding passive immunity following infection with coronaviruses. In a study of a pregnant woman with suspected SARS-CoV symptoms and positive serum specimens for SARS-CoV antibodies 12 and 29 days after illness onset, no infection was reported in the infant. Viral RNA PCRs test of maternal nasopharyngeal and rectal swabs, amniotic fluid, placenta and breast milk were all negative, though it should be noted that the time of specimen collection was 130 days after illness onset. However, SARS-CoV antibodies were present in maternal serum, cord blood and breast milk, suggesting vertical passive immunity [28]. Another study assessing the presence of SARS-CoV antibodies at 12 and 30 days postpartum in the breast milk of a mother who experienced infection in her first trimester found no antibodies [29].

The evidence for VT and passive immunity in other Coronaviridae viruses is scarce. Moreover, based on the current literature, the incidence of VT or potential passive immunity following these infections are limited. However, SARS-CoV-2 has shown different characteristics with evidence for its VT and passive immunity during pregnancy accumulating, as discussed below.

Vertical transmission of SARS-CoV-2

Transplacental VT is one of the most serious consequences of viral infections in pregnancy [16]. As mentioned earlier, VT has been observed for several viral infections, however, controversy exists regarding the possibility of mother-fetus VT of SARS-CoV-2. This controversy roots in unreported VT for other Coronaviridae members and limited temporary occurrence of viremia (~1%) in SARS-CoV-2 patients, which in turn decrease the chance of transmission of the virus through the placenta [30]. However, there are some reported cases of VT of SARS-CoV-2.

The first case of probable VT was demonstrated by Dong *et al.* [10]. A neonate was born to a SARS-CoV-2-positive mother with elevated anti-SARS-CoV-2 IgM and IgG levels along with abnormal cytokine levels two h after the birth, although the PCR test of the newborn's nasopharyngeal swab was negative (though no amniotic fluid or placenta PCR test was done for confirmation) [10]. Since IgM is a large molecule, it cannot cross the placenta from the mother to the fetus. It is therefore thought that the rise in IgM resulted from fetus infection either *in utero* or during delivery. However, IgM rise usually occurs 3–7 days after the infection, so the elevated IgM level two h after delivery can indicate a probable *in utero* VT of SARS-CoV-2. Furthermore, viral VT can allow entry of the virus into the bloodstream, eliminating the necessity for virus primary colonization in the nasopharyngeal region. It should be noted that serology tests have more false positive and/or negative results, making them less reliable than molecular tests [31].

Penfield *et al.* [32] carried out the first study that detected the SARS-CoV-2 RNA in placental or fetal membrane samples. The results of placental or fetal membrane swabs were positive for SARS-CoV-2 RNA in three of eleven pregnant women with severe to critical SARS-CoV-2 infection. Moreover, other studies by Hosier *et al.* and Baud *et al.* also found positive SARS-CoV-2 RNA in placental tissue and the fetal side of the placenta, respectively. Similar to the aforementioned studies, the swabs taken from the neonatal tissues were negative [33,34]. The first study to show positive SARS-COV-2 PCR results not only in the placenta but also in the neonates was conducted by Patane *et al.* In this study of 22 SARS-COV-2 confirmed pregnant women, two had positive PCR tests from the fetal side of the placenta and neonatal nasopharyngeal swabs [35]. Another study later showed positive rRT-PCR results from a newborn's pharyngeal swab 36 h after delivery from a SARS-COV-2-infected mother. However, the results of rRT-PCR tests for SARS-CoV-2 on cord blood, placenta and milk samples were negative and VT could not be definitely confirmed. Besides, the possible horizontal – not vertical – transmission of SARS-CoV-2 from the mother to the newborn could not be excluded [22].

It is difficult to draw a universal conclusion despite positive SARS-CoV-2 results of fetal tissues and membranes or newborn samples due to some inconsistencies between the tests. In a study by Yu Nan *et al.*, seven neonates from seven SARS-COV-2 confirmed pregnant women were evaluated: four did not have any problem and were discharged and three were tested for SARS-COV-2, one of whom had a positive rRT-PCR test 36 h after birth. But samples taken from the placenta and cord blood in this patient were negative for SARS-CoV-2, making intrauterine VT less probable [36]. In a similar case report, RT-PCR of the amniotic fluid sample and a subsequent nasopharyngeal sample of a neonate 24 h after delivery were both positive for SARS-COV-2, however, the sample obtained from the umbilical cord blood and vaginal secretions were negative for SARS-COV-2 [37]. A study by Hu X *et al.* demonstrated that VT is possible but not frequent. Of seven COVID-19 pregnant women, only one neonate had a positive rRT-PCR result for SARS-CoV-2 and none showed any symptoms related to SARS-COV-2. The transcervical pathway could not be completely ruled out in this case, despite the possibility that transplacental transmission is the most likely path [38]. Another study introduced maternal viral load as an influential factor for VT, however, precise viral load measurement is a mandate, which was missing in many studies to date [37].

On the other hand, several studies have reported negative results regarding the VT of SARS-COV-2. In a study by Huijun Chen *et al.* [39], nine pregnant women with positive maternal samples for SARS-COV-2 were evaluated in their third trimester. They had non-severe manifestations, and all underwent cesarean section (to reduce the risk of intrapartum transmission). Afterward, amniotic fluid, cord blood, breast milk and neonatal throat swab samples were gathered and tested, and there was no evidence of SARS-COV-2 infection or mother-fetus VT. Furthermore, in a study of 116 pregnant women with SARS-COV-2-associated pneumonia (65 laboratory-confirmed cases and 51 clinically diagnosed cases), 100 neonates were born and 86 were tested for SARS-COV-2 based on pharyngeal swab samples. All tests were negative. A further 86 amniotic fluid and ten cord blood samples were tested for SARS-COV-2, all of which were also negative. These results do not support VT of SARS-CoV-2 in the third trimester of pregnancy [40].

According to the findings of the above studies, there was a remarkable inconsistency regarding the study designs and the tests implemented, hindering conclusions about the VT of SARS-CoV-2. These inconsistencies were highlighted in a systematic review consisting of 33 studies (including most of the studies mentioned in this paper). Of 205 infants born to SARS-COV-2-positive mothers evaluated, only 6.3% had a positive SARS-COV-2 test at birth [41]. The incidence of vertical mother-to-fetus transmission was 22.2% case reports, 2.1% retrospective studies and 7.5% prospective studies [41]. Current studies provide different evidence as proof of VT and therefore lack uniformity. Some search for clinical signs, while others investigate serological or nucleic acid-based tests. Even studies which assessed expected pathological changes following the invasion of SARS-CoV-2 to the placenta found inconsistent results [42,43]. A clear definition for VT and uniform criteria is needed to deal with these differences. Accordingly, a set of criteria for definition of congenital SARS-COV-2 infection of neonates has been described. According to these, congenital infection should be confirmed by detecting the virus in amniotic fluid before membrane rupture or in blood early in life [44]. Vivanti *et al.* followed this classification and presented a proven case of transplacental SARS-COV-2 transmission in a neonate delivered from an infected mother in the third trimester of pregnancy. All the amniotic fluid, placenta, blood of mother and the neonate, nasopharyngeal swaps of mother and the neonate, and neonatal rectal sample were all positive for both E and S antigens of SARS-CoV-2 [14].

Another challenge regarding the VT of SARS-CoV-2 is that, although in some studies there are considerable evidence of infection of mother and the neonate especially in early h after delivery, they cannot prove whether

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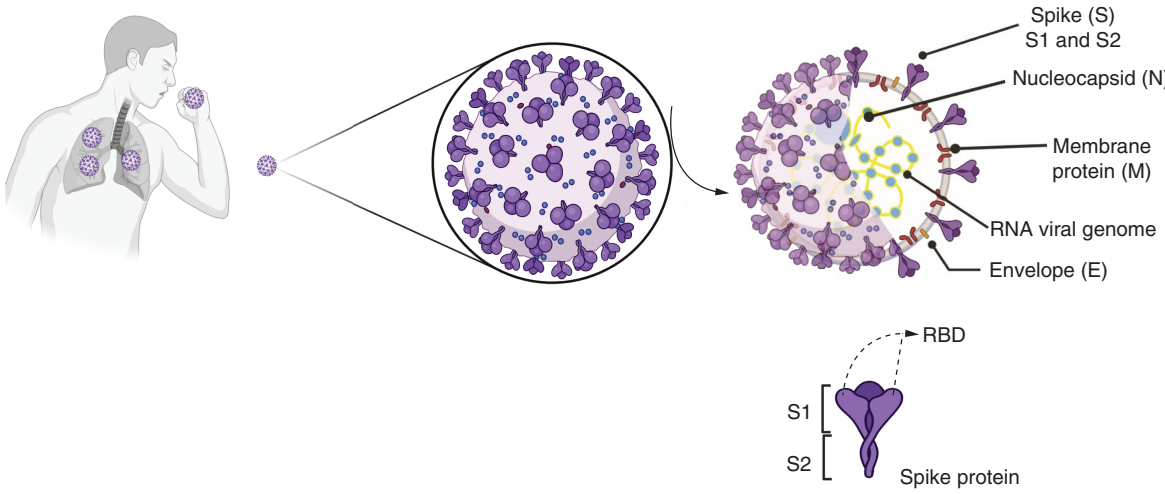

Figure 1. SARS-CoV-2 structure; an enveloped RNA virus containing four important structural proteins: spike, nucleocapsid, envelope and membrane proteins. Spike protein has S1 and S2 subunits, the receptor-binding domain in the S1 subunit attaches to the ACE-2 receptor of the target cell. Created with BioRender.com.
RBD: Receptor-binding domain.

the transmission has occurred through the transplacental route or has occurred peripartum and during the time of labor or contamination after birth.

In summary, VT of SARS-CoV-2 is plausible, though prevalence is likely low. Supplementary Table 1 depicts the summary of the available studies. Nonetheless, further well-designed studies with clear definitions and valid tests are needed to draw a strong conclusion about the extent of VT and its possible mechanisms. Note that, for reaching an authentic definition and reliable tests for VT, it would be necessary to consider the possible mechanisms of VT. For example, if colonization of virus in nasopharyngeal region is not a part of the VT process, then considering the nucleic acid test of nasopharynx swap is not a reliable investigation and would lead to several inconsistencies.

Mechanism of SARS-CoV-2 vertical transmission

The SARS-CoV-2 virus has four structural proteins: spike (S), membrane (M), nucleocapsid (N), and envelope (E) proteins. The Spike protein, which is responsible for infectivity, consists of two subunits (S1 and S2); the S1 subunit has a receptor-binding domain (RBD), with which attaches to the ACE (angiotensin-converting enzyme)-2 receptor on its target cell (Figure 1); and the S2 subunit is responsible for entry and replication of the virus by connecting to TMPRSS2 (transmembrane protease serine 2), fusing the virus to the cell membrane and inserting its RNA into the host cell, which eventually causes lysis of host cell and propagation of the viral infection (Figure 2) [45,46].

There are several hypothetical mechanisms describing the VT of SARS-CoV-2. The first hypothesis asserts that ACE-2 receptors are expressed in placental cells [47] and are responsible for transplacental transmission of SARS-COV-2 by using host proteases (including TMPRSS2) [48,49,50,51]. In line with this hypothesis, it has been demonstrated that between the 6th and 14th gestational weeks, RNA expression of ACE-2 is very low in the trophoblast [52]; therefore, it has been shown that transmission of SARS-COV-2 through the placenta is almost impossible in the first trimester [13]. Furthermore, some data suggest that TMPRSS2 is not expressed earlier than the 24th gestational week, showing that the most likely time interval for transplacental transmission is after 24 weeks of pregnancy [21]. This is corroborated by most of the reported cases of possible VT in pregnant women, who were mainly in their third trimester of pregnancy.

On the other hand, another hypothesis states that the term placenta has a low expression of ACE-2, while early placenta has ACE-2 and TMPRSS2 co-expression in the decidua, villous cytotrophoblast and syncytiotrophoblast that enables the virus to pass through the placenta in early pregnancy. However, the reason for lower VT in early pregnancy goes back to the lower co-expression of ACE-2 and TMPRSS2 in fetal tissues. In other words, it has been shown that expression of viral receptors both on maternal and fetus tissues is necessary for successful VT. It is demonstrated that mostly after the second trimester, there is a considerable co-expression of ACE-2 and TMPRSS2

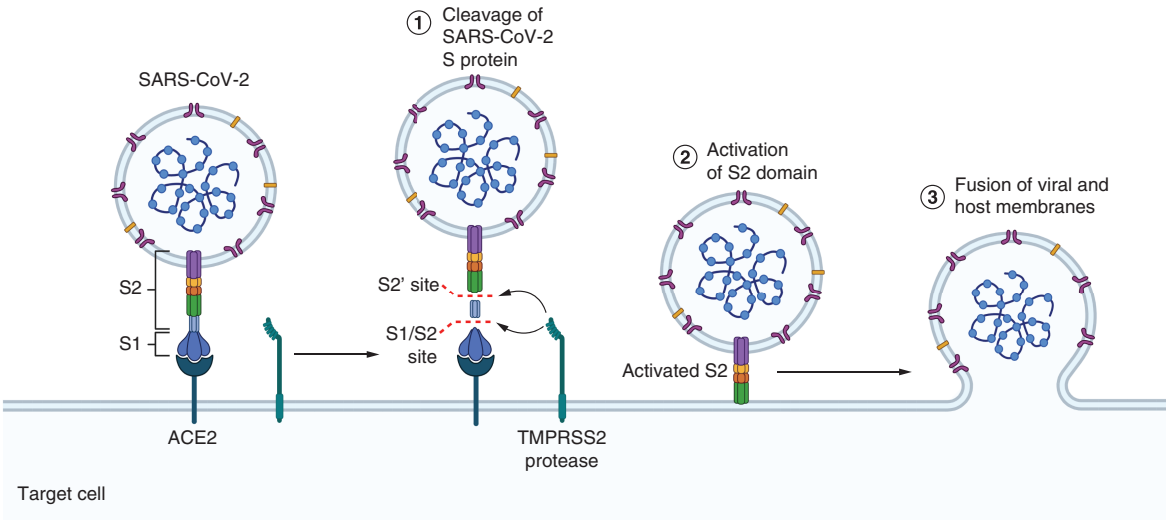

Figure 2. How SARS-CoV-2 infects the target cell. SARS-CoV-2 virus connects to its target cell by receptor-binding domain domain located at the S1 subunit of the spike protein, S2 subunit of spike protein connects to TMPRSS2 and imports the virus to the target cell; finally, the fusion of viral and host membranes and virus replication occurs. Created with BioRender.com.

in two fetal tissues (intestine and kidney). As the stomach and intestine are exposed to amniotic fluid, the likelihood of fetal infection increases with the presence of SARS-CoV-2 in the amniotic fluid after second trimester [53,54].

Another hypothetic scenario was based on the possible bacterial infection of the uterus (e.g., chorioamnionitis); maternal ACE-2 expressing monocytes and neutrophils migrate to the placental tissues and, as a vector, transport SARS-CoV-2 to the placental tissue, causing placental infection and thereupon VT [55]. Furthermore, it has been suggested that the hyper inflammation state caused by maternal SARS-CoV-2 infection during pregnancy can be a responsible for VT by affecting the placenta and increasing its permeability to the SARS-CoV-2 virus [56,57]. Some other mechanisms including canonical cell deficiency in the trophoblast and the lack of cavelion hindering SARS-CoV-2 from entering the placental villi in early pregnancy [58] and existence of alternative receptors, including DPP4 and CD147 and proteases like Furin, are thought to play a role in VT [59].

Considering all the hypothetical mechanisms, some factors should be considered as they may play an important role in VT. First is the necessity of SARS-CoV-2 presence in the blood (viremia) for VT. Since this usually happens in severely ill patients, the presence of mentioned receptors in the placenta would be necessary but not sufficient for VT [60]. Another point to be considered is the difference between various variants of SARS-CoV-2, as it has been shown that there is slight difference between variants regarding the use of viral receptors on the host cell. For example, omicron type is known to have a lower ability to use TMPRSS2 which might reduce its ability to invade cells; this can also reduce its possible VT [61,62]. Another crucial issue in severe COVID-19 cases is hypoxemia. It has been shown that infected pregnant women may suffer from hypoxemia especially in severe cases, causing placenta damage, which in turn facilitates intrauterine blood contact and subsequent VT [50]. Lastly, the route of delivery should be considered. Generally, it was thought that cesarean section has been a safer route for delivery in infected mothers, as it may limit mucosal contact and decrease the chance of viral transmission. However, in a recent study, all newborns with SARS-CoV-2-positive RT-PCR testing were delivered via cesarean section. Cesarean section may not always be more safe than vaginal delivery in transmitting the SARS-CoV-2 virus from the mother to the newborn [63]. Furthermore, the cervicovaginal route for VT, which occurs during the delivery for other viruses, is shown to be infrequent in SARS-CoV-2 [60,64].

Maternal passive immunity of SARS-COV-2

During pregnancy, maternal immunoglobulin G (IgG) is transferred from mother to fetus by neonatal Fc receptors (FcRn) through the syncytiotrophoblast layer of the placenta. This provides passive immunity for the newborn against diseases in early life. Maternal passive immunity has been observed in viruses including HIV (human immunodeficiency virus), CMV (cytomegalovirus) and Zika [33,65]. IgG transfer from mother to fetus begins at the end of the first trimester (12th week of gestation). Later, maternal IgG concentration in the fetus's body is gradually

increased and reaches 10% and 50% of maternal concentration at 17–22 and 28–32 weeks of gestation, respectively. The IgG concentration rises again until the delivery time, when it reaches its peak, which is 20–30% higher than the maternal concentration [66,67]. This higher concentration depends on the active transportation of immunoglobulins through the syncytiotrophoblast, which itself depends on multiple factors including concentration, quantity, type, and glycosylation of maternal IgG, gestational age, infection duration and birth weight [67,68]. Like VT, maternal passive immunity of SARS-COV-2 is still an open debate, and there is limited evidence on passive immunity in neonates born to SARS-COV-2-positive mothers.

Maternal passive immunity for SARS-CoV-2 occurs when the mother is positive for both IgG and IgM antibodies, and the fetus is positive for IgG but negative for IgM antibodies and SARS-COV-2 nasopharyngeal swab PCR test [69]. In a study of SARS-CoV-2 passive immunity, six pregnant women with mild symptoms of SARS-CoV-2 gave birth to six asymptomatic neonates with negative RT-PCR on blood and throat swabs. With the reference range of <10 A.U./ml for IgG and IgM, 3 neonates had positive IgG but negative IgM and two neonates had both positive IgG and IgM in serology tests. It is well known that IgG production in neonates is scarce in early life [70], and the measured IgG largely consisted of the antibody transferred through the placenta. Due to the large structure of IgM, the presence of IgM in two neonates could not have a maternal origin. Instead two possible causes were discussed; first, the transmission of the virus to the fetus and subsequent IgM production in the infant body; second, pathologic structure or function of the placenta due to SARS-COV-2 invasion which allows the IgM to pass through the placenta [43].

Considering the current reports of passive immunity against SARS-CoV-2, it is more likely that IgM would also be transferred to the fetus along with IgG due to placental damage or fetal infection earlier during pregnancy that provides the time for production of IgM antibodies. There are several reports of co-existence IgM and IgG in the newborn born to infected mothers [10].

A systematic review has evaluated IgG and IgM levels in pregnant women and their neonates. They found that 72.73% of infected mothers had positive IgG against SARS-CoV-2 and 67.16% of neonates born to SARS-COV-2-positive mothers had elevated IgG (anti-SARS-CoV-2) levels in their serology tests; however, the prevalence of IgM rise in the neonates was lower (20.6%). They found a significant relationship between infants and their mothers' IgG and IgM levels with a coefficiency of 0.85 (CI: 0.67–0.93) and 0.43 (CI: 0.06–0.70), respectively [71].

A prospective study described serology conversion in 26 laboratory-confirmed COVID-19 pregnant women and their 27 newborns. All neonates had both negative tests for SARS-CoV-2 RT-PCR and IgM in their serology tests. 21 of 26 mothers (80.8%) had positive IgG against SARS-COV-2, and 12 of 27 neonates (44%) had positive IgG against SARS-COV-2, indicating the development of passive immunity in approximately 50% of newborns of IgG-positive mothers [72]. According to this study, probability of IgG transfer depends on maternal antibody concentration and the interval between the onset of maternal infection and delivery. Rates of IgG transfer were 18.8 and 81.8% for the infection beginning less than two weeks and more than two weeks before delivery, respectively. With the increase in the duration of maternal infection, antibody (IgG) titer rises and the probability of anti-SARS-CoV-2 IgG transfer would increase.

Although the possibility of passive immunity is to a large degree accepted, the extent of transplacental antibody transfer depends on several factors. A study demonstrated that maternal infection, regardless of symptoms or severity, does not affect efficient transplacental antibody transfer [73]; However, another study suggested that symptomatic pregnant women have higher levels of antibodies [15]. Moreover, it has been shown that women with moderate to severe disease might have a high concentration of antibodies to transfer through the placenta to their fetus [74]. To the best of our knowledge, most of the available studies agree that a high concentration of IgG can lead to a more effective antibody transfer through the placenta to the fetus. For instance, a study has demonstrated that maternal SARS-COV-2 IgG levels as well as oxygen consumption in pregnant women (an indicator for disease severity) can predict the amount of IgG transferred to neonates through placenta [7]. Another important factor influencing the extent of antibody transfer is the timing of the infection in the mother during pregnancy. Theoretically, infected mothers need a reasonable interval for production of IgG in response to the infection. Only after that can they transfer the antibodies to their fetus. Moreover, infected mothers would remain seropositive for the SARS-CoV-2 antibodies after infection, so recovered mothers can also transfer their antibodies to their fetus. Therefore, passive immunity can be witnessed independent of active infection in the mother. However, mothers who become infected in late periods of pregnancy might be unable to transfer the associated antibodies to their fetus, despite the VT of SARS-CoV-2. Flannery *et al.* reported that 72 (87%) out of 83 females who were seropositive during pregnancy had positive IgG antibodies against SARS-CoV-2 in their cord blood samples, while there was no evidence of IgM

antibodies present. Of 11 newborns who were SARS-CoV-2 seronegative, 45% had mothers with positive serology tests only for SARS-COV-2 IgM, and 55% were born to mothers with a low concentration of SARS-COV-2 IgG. Additionally, no significant difference was found regarding antibody transfer in the preterm deliveries as 9 cases of antibody transfer in deliveries before 37 weeks of pregnancy (with the earliest at 31 weeks) were reported [73]. Another study, described seven pregnant women with a history of SARS-COV-2 infection in their pregnancy and current negative PCR test. All seven pregnant women had positive antibodies against SARS-COV-2; however, no symptoms of SARS-COV-2 at the time of the study were observed. Seven neonates born to them had positive IgG and negative IgM serology tests without clinical SARS-COV-2 infection. However, 22 women with positive SARS-COV-2 PCR test and active disease did not have an antibody against SARS-COV-2, probably due to the new onset of the disease, and none of their neonates were seropositive for SARS-COV-2 antibodies [57].

Like the previously described passive immunity for other diseases, the transfer of immunity against SARS-CoV-2 is limited through time. IgG usually rises to a peak, three to seven weeks after the onset of symptoms, followed by a plateau phase, which attenuates after 8 weeks of symptom onset when antibody levels will decrease [72]. Likewise, with the antibody response following infection with SARS-CoV-2, passive immunity decreased to undetectable levels approximately six weeks after delivery [10,69]. Similar patterns in kinetics of passive immunity were described for other diseases. Generally, passive immunity is limited to the first two months of life. Antibody concentrations usually drop to one-tenth of their initial concentration at delivery by the end of the second month. Interestingly, in a study of passive immunity in newborns, the rate of IgG decline was slower in neonates with concurrent detectable IgM compared with newborns who just had positive serology tests for IgG [75].

Summary of the findings are further described in Supplementary Table 2. There is a greater prevalence and likelihood of SARS-CoV-2 maternal passive immunity compared with VT. Except in a few studies [11,70,76], most other investigations have demonstrated the common presence of IgG in neonatal sera, indicating passive immunity [7,43,71,72,73]. Furthermore, it has been established that maternal IgG concentration and timing of infection are essential elements in transplacental antibody transfer. Higher mother's IgG concentration results in higher neonate's IgG titers [7], which in turn provide longer-lasting and higher-quality immunity [77]. However, further investigations are required for assertion and better determining the protective level of IgG antibodies in the newborns.

SARS-CoV-2 & its associated antibodies transmission through the breast milk

Since the presence and transmission of some viruses encompassing HIV, human T lymphotropic virus 1 (HTLV-I), CMV, hepatitis C, Ebola and Zika virus in breast milk are demonstrated in previous studies [78,79,80], the concept of SARS-CoV-2 transmission through breast milk has been suggested.

The first cases of SARS-CoV-2 RNA detection in human breast milk were introduced by Groß R *et al.*, reporting two mothers and their infants, all with positive SARS-CoV-2 PCR tests. The breast milk samples of both mothers were collected in the same controlled condition, but one had positive and the other had negative results for SARS-CoV-2 rt-qPCR tests [81]. Furthermore, SARS-CoV-2 nucleic acid detected in breast milk following positive PCR test regarding infant's nasopharyngeal samples [82]. In a larger survey of 68 human milk samples of infected mothers, nine samples had detectable SARS-CoV-2 RNA. Four out of six infants exposed to those positive breast milk for SARS-CoV-2 had positive PCR test [18]. However, it is unclear that positive results of human milk PCR tests are due to the contamination or actual transmission of virus through breast milk [83].

After detecting the SARS-CoV-2 virus RNA in the breast milk, the critical question is whether this virus can infect the infant? The answer to this question is not straight forward, as obviously breast milk is not the only possible transmission route of SARS-COV-2 and it would be hard to assess whether infection occurred as a result of viral transmission through breast milk. In other words, the presence of the virus in the breast milk along with the neonatal positive nasopharyngeal PCR test, would not necessarily confirm the infection through breast milk since there is always a possibility of virus transmission by close contact [59]. There are a great range of variations in current studies; some studies have shown positive SARS-CoV-2 PCR test of breast milk in addition to the reported infection in infants [82,84,85]; some others with proven SARS-CoV-2 infection in infants have obtained negative breast milk PCR results [86,87,88,89]. Some studies have found SARS-CoV-2 RNA in breast milk, while the infants' nasopharyngeal RT-PCR tests were negative and no symptoms related to SARS-CoV-2 were detected [90,91,92]. Interestingly, a cohort study found that SARS-CoV-2 RNA detected in the breast milk is no longer infectious due to the absence of subgenomic RNA in the breast milk samples, which is a marker of infectivity [93]. Besides, it is also demonstrated that whey proteins and lactoferrin (LF), mucin1 (MUC1) and α-lactalbumin (α-LA) which

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are present in the breast milk can inhibit the infection due to their antiviral activities against the B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.1 (Kappa) variants and inhibit some steps involved in the infection process like viral attachment, entry and replication [94,95].

In summary, while SARS-CoV-2 RNA has been detected in the breast milk of infected mothers, there are several factors to consider before drawing definitive conclusions. One such factor is the adequacy of the milk collection method, which must ensure that samples are not contaminated. Additionally, the mere presence of the virus in breast milk does not necessarily indicate successful transmission to the infant, as antibodies or other factors in the milk may render the virus inactive. Along with the possibility of transmission of SARS-CoV-2, breast milk could naturally provide passive immunity against early diseases. This double-sided effect opened a debate about the beneficence of breast feeding in women with active infection or later after.

Antibodies in breast milk can protect infants from enteric and other infections. These antibodies are produced by plasma cells that are part of gut-associated lymphoid tissue (GALT) in the mother. These plasma cells migrate to the mammary gland and produce antibodies in reaction to antigens found in the mother's mucose-associated immune system. Human milk antibodies usually consist of approximately 90% IgA, 8% IgM, and 2% IgG (most of the IgA and IgM are in their secretory forms). They have a joining (j) chain that lets them actively transport through the secretory epithelium by binding to polymeric immunoglobulin receptor (pIgR). After binding to pIgR, they would cleave, and their receptor fragment (secretory component [SC]) would bind to the immunoglobulin [96,97]. SC protects the antibodies from destruction in the infant's mouth and gut [98]. Secreted antibodies prepare immunity in the newborn's intestine and other mucosal tissues [96].

Some evidence is available regarding the presence of anti-SARS-CoV-2 antibodies and other antiviral components in human breast milk and suggests that these factors, if present, can neutralize and inactivate the SARS-CoV-2 in breast milk and also provide passive immunity for the infant [99]. A study reported the presence of SARS-CoV-2 IgA in the milk of a SARS-COV-2-infected mother while no IgG was detected; given that SARS-COV-2 infection was not detected in the infant until the 45th day of life, they concluded that IgA could be a protective factor against SARS-CoV-2 infection [100]. Similarly, another report has found positive IgG and negative IgM against SARS-CoV-2 in the breast milk sample of an infected mother [89]. Additionally, in a case report of a SARS-COV-2-infected mother with a non-infected infant, breast milk samples were positive for IgG and IgA against SARS-CoV-2 with their levels reaching their highest amounts after five weeks. Although, the neonate had detectable levels of SARS-CoV-2 IgG for 1.5 months, it remained unknown whether the origin of IgG antibodies was from breast milk or the placenta [101].

The serotypes and reactivity of breast milk antibodies were also noticed. A study by Fox *et al.* examining breast milk samples of eight recovered and seven suspected COVID-19 women found that SIgA is the most abundant form of antibodies in breast milk post-SARS-COV-2 infection. Since it was durable in the mucosa, this could play a crucial role in the mucosal immunity [98]. A study evaluated the presence of antibodies against S1 and S2 subunits and nucleocapsid protein of SARS-CoV-2 in 41 women - not necessarily infected - during the SARS-COV-2 pandemic. They have found that 97.6%, 68.3%, and 58.5% of mothers had S1 + S2 reactive SIgA (secretory IgA)/IgA, SIgM (secretory IgM)/IgM, and IgG in their breast milk, respectively. Detected antibodies are not only against the SARS-CoV-2 virus, as there is a likelihood of cross-reactivity against other viruses, e.g., other members of the coronavirus family and HCoV-OC43, providing expanded passive immunity for infants [46]. It is already known that SIgA is the most prevalent antibody in human breast milk, and SARS-CoV-2 associated antibodies are not an exception. In another study it has been shown that women with viral symptoms within a year of assessment had higher SARS-CoV-2 SIgA/IgA levels against S1-S2 subunits and SIgM/IgM against S2 subunit in their breast milk, while there was no difference in the IgG levels [102]. A large study including 2312 lactating mothers and a recent study of 87 unvaccinated women also found a high prevalence of IgA antibody presence in the breast milk samples, which was shown to remain in breast milk up to 10 months (23.1% and 87%, respectively) [103,104]. A recent systematic review showed that 82.6% of the breast milk samples contain SARS-CoV-2 antibodies. Out of the evaluated samples, 78.5% were positive for IgA antibody and about half of them showed neutralization ability *in vitro* [105].

In summary, the presence of SARS-CoV-2 RNA and its antibodies in human breast milk is reported in several studies. The expression of ACE-2 receptors in breast tissue [59,106] may be the hypothetical route of entrance of virus into breast milk. Among the breast milk samples with SARS-CoV-2 RNA, it is not definitely clear whether it has the potential to infect infants or not; however, some studies demonstrated the neutralizing effect of antibodies on the viruses. Moreover, antibodies against SARS-CoV-2 in breast milk samples could provide long-term passive

immunity for newborns. This evidence has led to some recommendations regarding the therapeutic potential of extracted SARS-COV-2 antibodies from breast milk [46,98]. However, more research is needed to assess the retrieved antibodies' neutralizing capacity both *in vivo* and *in vitro*. More research on the precise protective level of antibodies in breast milk is needed to provide the optimum protection for infants and to tradeoff between the risk of infection and passive immunity through breast feeding. The summary of the related studies is further demonstrated in Supplementary Table 3 & 4.

SARS-CoV-2 passive immunity post-vaccination

There is an increased risk of infectious diseases during the pregnancy and postpartum period for both Infants and mothers [107]; therefore, vaccinating pregnant women against vaccine-preventable pathogens might protect both the mother and infant. Vaccination against pathogens like influenza, acellular pertussis, diphtheria and tetanus toxoids during the pregnancy reduces maternal and infantile mortality and hence, is highly recommended [108,109]; however, the transfer of maternal-produced antibodies starts to decrease since the second month of life, and they lose their effect in the infant's bloodstream after 6 to 12 months [74]. Recently the similar potential effect of SARS-CoV-2 vaccines has been questioned. Still, the data is limited due to the exclusion of pregnant and lactating women in the first clinical trials of the SARS-COV-2 vaccine.

A study evaluating SARS-COV-2 antibody titer in cord blood after administration of SARS-COV-2 mRNA vaccine (BNT162b2) in 16 pregnant women found that all maternal and cord blood (infant) samples were positive for antibody against SARS-CoV-2 S protein. But the SARS-CoV-2 antibody against nucleocapsid - a result of prior infection with SARS-CoV-2- was not detected in either maternal or cord blood samples [110]. Additionally, it has been demonstrated that a rise in the cord blood anti-S antibody titer is evident as the interval (weeks) between the first dose of vaccination and delivery increases. Similarly, a positive correlation exists among the number of weeks from the first or second vaccination to delivery and the ratio of umbilical cord to the maternal SARS-CoV-2 anti-S antibody [111]. Corroborated with it, another study was conducted on 27 vaccinated women, mostly being vaccinated with Spikevax (Moderna) and BNT162b2 (Pfizer) and four with unknown SARS-CoV-2 vaccine, and their infants. 74% of mothers had their both doses before the delivery. Of the 28 infants (including one twin), all had positive IgG against SARS-CoV-2 except three whose mothers had received their first dose of vaccine less than three weeks ahead of delivery. Like previous studies [112], higher IgG concentration in newborns occurred in mothers who received both vaccine doses before the delivery, especially those with longer time between vaccination and delivery [113]. In another report encompassing 122 pregnant women, of whom 55 had received their first and 67 their second mRNA vaccines before the delivery, demonstrated that the production of maternal antibodies began 5 days after receiving first vaccine dose. And transplacental antibody transfer started after the 16th day post-vaccination. 99% of women who received both vaccine doses had detectable IgG in their cord blood samples; while, 44% of women who had received one vaccine dose had detectable cord blood SARS-CoV-2 IgG. Again, transplacental antibody transfer is positively correlated with the number of weeks between the second vaccination dose and delivery [110].

A recent study found that the most optimal time of SARS-CoV-2 vaccination is early in the second trimester, which provides protection for both mother and fetus during the pregnancy and after the delivery [114]. Besides, it is hypothesized that at least four weeks interval between vaccination and delivery is required to appropriately protect infants against SARS-CoV-2. Since adequate antibody production is achieved two weeks following the second vaccine dose (considering 21 or 28 days or more interval between the first and second doses in various vaccines) and the beginning of the transplacental antibody transfer usually occurs approximately at 17 weeks of gestation, vaccinating pregnant women at the onset of the second trimester might lead to the highest antibody transfer levels [74]. The comparison between the early and late third-trimester vaccination has shown that early vaccination increases antibody transfer through the placenta and increases the neonatal neutralizing antibodies [115]. On the other hand, in a recent study, increased immunogenicity of vaccines was observed in women vaccinated in the first and third trimesters compared with the second trimester which is undoubtedly due to some immunomodulatory changes in the second trimester that reduces the response to non-self-antigens and helps the mother to tolerate the developing semi-allogenic fetus. All in all, the highest transplacental antibody transfer occurred in the women vaccinated in the first trimester, followed by the second trimester. An increase in interval for higher antibody production or the better quality of antibody Fc or the combination of both might be responsible for the highest antibody transfer rate. Of note, the antibody titer declined more when vaccination occurred in the first trimester, highlighting the need for vaccine boosters in the third trimester [116,117].

Some studies evaluated the protective effect of vaccine-induced antibodies against SARS-COV-2. It has been demonstrated that vaccination can provide immunity for infants in the first four to six months of life [118,119]. Furthermore, It was shown that anti-RBD IgA and IgG in child were positively correlated with the child's age and the breastfeeding length [120]. Additionally, binding and neutralizing antibodies against various variants of SARS-CoV-2 has been found in the cord blood after vaccination, however, the neutralizing antibody titers were reduced in the B.1.1.7 and B.1.351 variants [109]. Antibodies against the both wild-type and delta variants of SARS-CoV-2 in pregnant women could be transferred to the fetus. Amount of antibodies against both kinds of SARS-CoV-2 in the cord blood peaks 4–8 weeks following complete maternal immunization [121]. Among others, the data on the omicron variant is limited. It is shown that two doses of vaccination are insufficient for this variant; since the antibody levels measured 1 month after the third dose of Pfizer and BioNTech vaccination against the omicron variant are comparable to those after two doses of vaccines against the wild type [122]. Therefore, it can be hypothesized that only after the third dose of SARS-CoV-2 vaccination, effective amount of antibodies against omicron variant can pass through the placenta and reach the fetus.

With the evidence of SARS-CoV-2 antibody existence in breast milk after infection and the presence of protective influenza antibodies in human milk after influenza vaccination, the idea of examining breast milk for antibodies after SARS-COV-2 vaccination has come into the mind. A report conducted on fourteen lactating women with administration of two vaccine (BNT162b2 [Pfizer]) doses, showed a peak in SARS-CoV-3 IgA and IgG in the breast milk, 3 to 7 days following the second dose of vaccine. The amount of IgG was stable until 4–6 weeks, later which showed significant reductions. Notably, a minimal transfer of vaccine mRNA into several breast milk samples was observed. Breast fed infants experienced no adverse events throughout the 28 days follow-up [83]. Another report detected IgA and IgG antibodies in breast milk following 2 and 4 weeks after the first vaccination dose, respectively, whereas, they were not present before vaccination [123,124]. Although, there is a slight difference on reported timing needed for entrance of antibodies into breast milk, most studies suggested 3 to 14 days would be the necessary interval, preferably after second dose vaccination [123,125]. A recent systematic review concluded that after the first vaccine dose, 64 and 30% of breast milk samples were positive for IgA and IgG, respectively, which reached 70 and 91% after the second dose [126]. Of note, antibody response to vaccination has been shown to be durable for several months. The levels of post-vaccination IgA and IgG in breast milk samples in a study were measured at different time points. 100, 92.6 and 75% of the samples had IgG levels above the cut-off value at 1, 3- and 6-months post-vaccination, respectively. However, the IgA was detected in 50 and 25.9% of samples at one and 3 months post-vaccination [127].

Similar to what is seen following the influenza vaccination [128], the common point of most post-SARS-CoV-2-vaccination studies is IgG dominancy in breast milk samples [123,124,125]. In contrast, in post-infection mothers the IgA is the dominant antibody in the breast milk for almost ten months [98,129,130]. Although, both antibody types (i.e., IgG and IgM) were able to neutralize live SARS-CoV-2 virus, the difference in antibody types could be probably due to the intramuscular administration of vaccines which triggers systemic antibodies, not mucosal ones [125]. The origin of IgA antibodies in breast milk was also assessed by measuring its IgA1 (major subclass in serum) and IgA2 (major subclass in milk and other secretions) isotypes. No IgA2 antibodies against S and RBD were found in breast milk samples, indicating that the antibodies in breast milk after mRNA vaccination originated from serum rather than plasma cells of the mammary gland [131].

A comparison between different vaccine types was also conducted, which demonstrated that the levels of IgG and IgA were higher in the breast milk of women receiving an mRNA-based vaccine (no difference between the two manufacturers, i.e., moderna and pfizer) compared with an adenoviral-vectored vaccine. The mRNA vaccines were found to induce higher spike-specific antibody titers, functional antibodies and FcR binding compared with Ad26.CoV2.S vaccine. However, it is not proven whether the observed difference is due to the one-dose administration of the Ad-vectored vaccine versus the two-dose mRNA vaccine regimen [116]. The same outcome is reported in serum IgG levels, and the antibodies against SARS-CoV-2 variants like Delta (B.1.617.2) and Omicron variants after the mRNA vaccines [132,133,134].

The evidence is limited regarding the neutralizing ability of these antibodies. In a study including 34 milk samples post-SARS-CoV-2 infection that bear IgA and IgG antibodies, neutralizing capacity of these milk samples was compared with pre-pandemic samples. They found that 62% of the samples had an in-vitro neutralizing ability, while none of the pre-pandemic samples had this ability, suggesting that these antibodies have a role in infants' passive immunity [135]. Neutralization activity of breast milk samples at 1, 3 and 6 months post-vaccination was revealed to be 83.3, 70.4 and 25%, respectively, which was strongly correlated with IgG levels in milk samples [127].

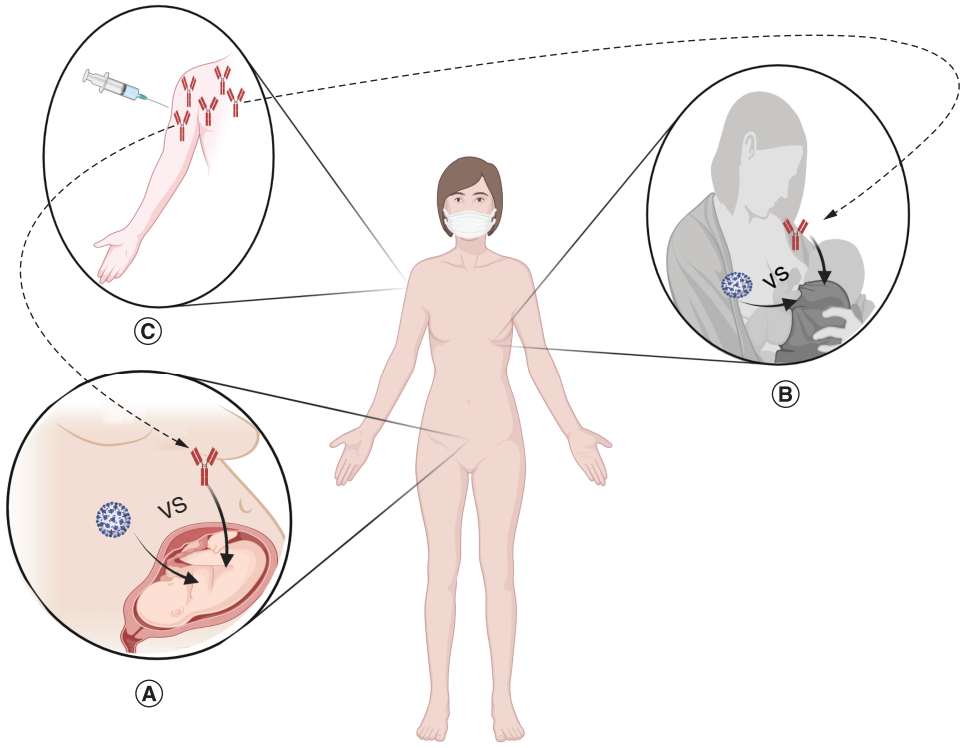

Figure 3. Transmission of SARS-COV-2 virus and its antibodies from mother to the fetus/infant through different ways. (A) Transplacental transmission of SARS-CoV-2 versus transfer of anti-SARS-CoV-2 antibodies from the infected mother to the fetus. **(B)** Transmission of SARS-CoV-2 versus transfer of anti-SARS-CoV-2 antibodies through the breast milk of infected mother to the fetus. **(C)** Transmission of SARS-CoV-2 produced antibodies in response to SARS-CoV-2 vaccination through the placenta and breast milk (dotted arrows). Created with BioRender.com.

Similarly, 60% and 85% of human breast milk samples depicted neutralizing capacity against the wild-type SARS-CoV-2 virus following the first and second vaccine doses, respectively. On the other hand, post-infection samples had 80 and 100% neutralizing capacity after 28 and 90 days following the COVID-19 infection [130]. A recent study found a 97% neutralizing capacity of post-infection antibodies in breast milk, however, no correlation between the neutralizing capacity and antibody level was found [136].

Interestingly, the existence of SARS-CoV-2 antibodies in cord blood or breast milk is shown to be more common and feasible after SARS-CoV-2 vaccination compared with actual COVID-19 infection [137,138,139]. A case report study suggested that post-vaccination immunity is greater than post-infection immunity, leading to greater immunity in infants whose mothers had received their vaccination during pregnancy [140].

Still, important questions remain addressing whether these cord blood antibodies have the effective neutralizing ability in-vivo in infants' bodies and what antibody level is efficient for an infant's passive immunity. Furthermore, post-vaccine studies involving multiple vaccine types are required to be implemented to obtain a definitive result in terms of SARS-CoV-2 vaccination, its impact on imparting protection for fetus/infant and the period of the antibodies persistence at which they provide immunity for the fetus/infant.

Conclusion

In conclusion, the current study reviews the following two probably opposing issues: SARS-CoV-2 VT from the mother to the fetus/infant during pregnancy or lactation versus transmission of antibodies (passive immunity) against SARS-CoV-2 from mother to fetus/infant through the placenta or breast milk during the pregnancy or after the vaccination. The first one can infect the fetus/infant and make them susceptible to many complications, whereas the second issue can protect them and assist them in fighting the virus; since their immature immune system is unable to protect them against SARS-COV-2 independently (Figure 3).

Although the current review highlights the importance of transplacental transmission of SARS-CoV-2, its exact role remains controversial; Since there is no single test for proving SARS-CoV-2 VT occurrence and various

methods are utilized in the several studies, it is hard to draw a clear conclusion. Yet, ignoring the possibility of contamination, VT of the SARS-CoV-2 is more prevalent compared with other members of the Coronaviridae family. Nonetheless, coming up with a single test for verification, minimizing the risk of contamination from other routes, and identifying additional transmission routes are key recommendations for future studies.

Furthermore, the presence of SARS-CoV-2 in breast milk has yielded mixed outcomes. In general, it could be demonstrated that SARS-CoV-2 RNA can be found in the breast milk of infected women. However, there are a few factors to take into account when analyzing these breast milk samples: first, whether the milk collection method was correct, ensuring that samples were not contaminated, and second, the presence of virus in breast milk does not guarantee the successful transmission of SARS-CoV-2 to the infant, given that the antibodies or other factors in the breast milk might render the virus inactive. Future studies with larger sample sizes should take these constraints into account as much as possible.

Maternal passive immunity, which is the transfer of SARS-CoV-2 antibodies through the placenta (mostly IgG) or breast milk (mostly IgA) to the fetus or infant; has been evaluated either after SARS-CoV-2 infection or vaccination, with the majority of them finding IgG transfer through these pathways. It can be inferred that the transfer of SARS-CoV-2 antibodies through the aforementioned routes to the fetus/infant is prevalent and occurs in many cases. However, it is not well known whether these antibodies serve as an effective maternal passive immunity and protect the fetus/infant from SARS-CoV-2 infection. Furthermore, the optimal level of the antibody that provides effective protection has not yet been adequately discussed; additionally, certain ambiguous aspects need to be clarified in future studies with appropriate design, such as the best trimester of pregnancy for antibody transfer or whether antibodies in breast milk would be digested in the GI tract, preventing its effects.

Antibody transmission through the placenta and breast milk after the SARS-CoV-2 mRNA vaccination has been proven to be substantially greater than actual COVID-19 infection, which was also increased after the second vaccination dose; yet, more studies are recommended on other vaccine types and larger sample sizes to determine the best trimester for vaccination to increase the effectiveness of this post-vaccination passive immunity in the infants.

Future perspective

As the SARS-CoV-2 pandemic continues, it is imperative to assess the possibility of vertical transmission (VT) and its mechanisms. However, this is not limited to COVID-19 alone, as emerging viruses from the Coronaviridae family or other fatal virus types may pose a threat in the future. By understanding the VT mechanism and probability of occurrence for various virus types, we can be better prepared for future unknown pathogens. This can be achieved by linking their characteristics with other viruses of the same family and developing strategies to prevent transmission to newborns and pregnant women. Additionally, understanding the existence of maternal passive immunity can aid in better management of infections in newborns. Furthermore, understanding the efficacy and proper timing of vaccination for neonates may lead to a revolution in disease prevention even before birth. Future research in this area is crucial for saving the lives of many newborns and pregnant women, especially in times of a global health crisis.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fvl-2023-0089

Author contributions

H Karimi was primarily involved in the writing of the manuscript. V Mansouri and H Karimi were responsible for editing and preparing the final version of the manuscript. N Rezaei was involved in final revisions and project administration. All authors reviewed and approved the final version of the manuscript.

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Executive summary

Current knowledge about vertical transmission & passive immunity of Coronaviridae

- Vertical transmission (VT) of other viruses of the Coronaviridae family is not reported yet, except for HCoV-229E.
- Antibody transfer from mother to fetus might have occurred for the SARS-CoV.

Vertical transmission of SARS-CoV-2

- VT of SARS-CoV-2 is plausible and more common than other Coronaviridae viruses, but the overall prevalence is low (less than 5%).

Mechanism of SARS-CoV-2 vertical transmission

- Different hypotheses are proposed for the mechanism of SARS-CoV-2 VT. The most prominent one is the expression of ACE-2 receptors in placental cells facilitating the transmission by using host proteases (including TMPRSS2).

Maternal passive immunity of SARS-COV-2

- Greater prevalence and likelihood of SARS-COV-2 maternal passive immunity was reported compared with its VT.
- Maternal IgG concentration is an essential element in transplacental antibody transfer with a positive correlation between the mother's IgG concentration and the neonate's immunity.

SARS-CoV-2 & its associated antibodies transmission through the breast milk

- The presence of SARS-CoV-2 RNA and its antibodies in human breast milk is possible, as the expression of ACE-2 receptors is also evident in breast tissue.
- Among the breast milk samples with SARS-CoV-2 RNA, it is not definitely clear whether it has the potential to infect infants or not.
- Among the breast milk samples with antibodies against SARS-CoV-2, these antibodies' neutralizing capacity or passive immunity in addition to their therapeutic potential need to be more investigated.

SARS-COV-2 passive immunity post-vaccination

- The presence of SARS-CoV-2 antibodies in cord blood or breast milk is shown to be more common and feasible after SARS-CoV-2 vaccination compared with actual COVID-19 infection.
- While, some prominent questions remain addressing whether these cord blood antibodies have the effective neutralizing ability in-vivo in infants' bodies and what antibody level is efficient for an infant's passive immunity.

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