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Review Article

Trans-Placental Transfer and Vertical Transmission of SARS-CoV-2, HIV and HCV: A Comparative Review

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Abstract

Background: Although SARS-CoV-2 infection has spread fast throughout the world, information on the natural history of illness in pregnant women and the risk of mother-to-fetal transmission is limited. HIV and HCV also showed evidence of mother-to-fetal transmission.

Aim: Reviewing literature reports and published data regarding possibility of viral transmission to fetus, and to what extend it could occur for SARS-CoV-2, HIV, and HCV.

Discussion: According to certain research, there is no viremia detected in maternal or cord blood, and there is no indication of vertical SARS-CoV-2transmission. Infection can be transmitted transplacentally during the last pregnancy weeks. The absence of placental infection is supported by the finding that the SARS-CoV-2 receptor, the Angiotensin 2 Converting Enzyme (ACE2) required for cell integration, is only present at extremely low amounts in the placenta during the first third trimester. Studies indicated that HIV vertical transmission rates during pregnancy, birth, or breastfeeding range from 13% to 48%, but researches indicated that 90% of the babies protected against HIV during pregnancy. HCV-infected pregnant women have a 2% to 8% risk of viral transmission, but the presence of NK cells in the placentas of HCV-positive women contribute for protective effect.

Conclusion: The possibility of Trans-placental transmission of SARS-CoV-2, HIV, and HCV is possible with different incidence rates.

Keywords: SARS-CoV-2; Fetal; Trans-placental; ACE2; Viremia; Trimester; HIV; HCV

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SARS-CoV-1: Severe Acute Respiratory Syndrome Coronavirus 1; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; COVID-19: Coronavirus Disease 2019; ACE2: Angiotensin Converting Enzyme 2; HIV: Human Immunodeficiency Virus; CD4: Cluster of Differentiation 4; RNA: Ribonucleic Acid; HCV: Hepatitis C Virus; ER-alpha: Estrogen Receptor Alpha; CT: Cytotrophoblasts; HLA: Human Leukocyte Antigens; VCT: Villous Cytotrophoblasts; SCT: Syncytiotrophoblast; EVT: Extravillous Trophoblast; AIDS: Acquired Immuno Deficiency Syndrome; CNS: Central Nervous System; GI: Gastrointestinal; CDC: Centers for Disease Control and Prevention; RT-PCR: Reverse Transcription Polymerase Chain Reaction; mRNA: Messenger RNA; DC-SIGN: Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-integrin; CMV: Cytomegalo Virus; NK cells: Natural Killer Cells

Introduction

The pandemic caused by the developing Coronavirus SARS-CoV-2 began in late 2019 in China and swiftly spread around the world. This virus is the result of two earlier outbreaks of severe acute pneumonitis caused by the Coronaviruses SARS-CoV-1 and MERS-CoV [1].

SARS-CoV-2 infection produces the novel Coronavirus illness (COVID-19) and is mostly spread *via* droplets, however alternative modes of transmission have been proposed. Some examples of perinatal transmission have been reported, although it is unknown whether they were transmitted by the transplacental or transcervical routes, or through environmental exposure. To avoid neonatal infection, enhance pregnancy care, and eventually better understand SARS-CoV-2 biology, it is critical to determine if and how SARS-CoV-2 enters the fetus [2].

Severe COVID-19 infections are more common in adults than in children and in men than women, which may be related to differences in membrane ACE2 expression and/or age- related alterations in the renin-angiotensin system [3]. The limited frequency of vertical transmission observed thus far suggests that the placenta may play an important role in preventing intrauterine transmission of SARS-CoV-2 to the baby. SARS-CoV-2 has been found in the placenta in several recent individual case or cohort reports. However, vertical transmission is still debatable, and a cause-effect link between the pathophysiological response of the placenta and its association with newborn outcome has yet to be properly established [4,5].

Human Immunodeficiency Virus (HIV) is a worldwide illness for which there is presently no treatment or vaccine. Women living with HIV who become pregnant or catch the virus during pregnancy are at risk of maternal and perinatal morbidity and death, particularly if the infection is inadequately managed. Additionally, there is a danger of vertical transmission to the fetus throughout pregnancy, labour,

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and postpartum *via* lactation. Pregnancy does not appear to have any negative effects on the course of HIV infection, progression, or survival. The decrease in CD4 cell count in HIV-positive women during pregnancy usually resolves in the postpartum period and is caused by haemodilution. During pregnancy, HIV RNA levels appear to be constant, however some studies show an increase in viral load in the postpartum period [6].

Hepatitis C Virus (HCV) infection during pregnancy does not typically have a negative impact on mother health, but it is connected with negative consequences on the fetus due to prenatal complications and vertical transmission. In the United States of America, an estimated 1% to 2.5 % of pregnant women are infected with HCV, which has a 6% risk of viral transmission from mother to infant [7].

In terms of placental receptors, study results show that insulin receptors are present in all placental tissues. Furthermore, they are present in placenta's progenitor tissues and cells such as oocytes, spermatozoa, and pre implantation embryos in the majority of the species investigated. However, receptor densities differ between individual cells, cell types, and developmental stages. The bulk of insulin receptors are found on structures that are thought to stimulate placental development, such as syncytial sprouts and mesenchymal villi in first-trimester placentas and fetal endothelium at term [8]. The human placenta also contains the estrogen receptor alpha (ER-alpha) protein, which is found in villous Cytotrophoblasts (CT), vascular pericytes, and amniotic fibroblasts (Table 1) [9].

The comparison of HLA-A and HLA-B staining intensities inside the villous stroma suggests that fetal HLA-B proteins are expressed before HLA-A during the first trimester of pregnancy. Among the trophoblast populations, the syncytiotrophoblast lacks HLA class I staining, while extravillous cells express significant levels of HLA-G and HLA-C [14].

Based on scRNA-seq data from the early human placenta, it was discovered that ACE2 is highly expressed in four major cell types which are dS and dP cells in decidua, VCT and SCT cells in placenta. However, ACE2 expression was exceedingly low in EVT throughout the first trimester. Another research study of human placenta supported the findings, revealing increased expression of ACE2 in EVT at 24 weeks (Figure 1) (Tables 2 and 3) [15].

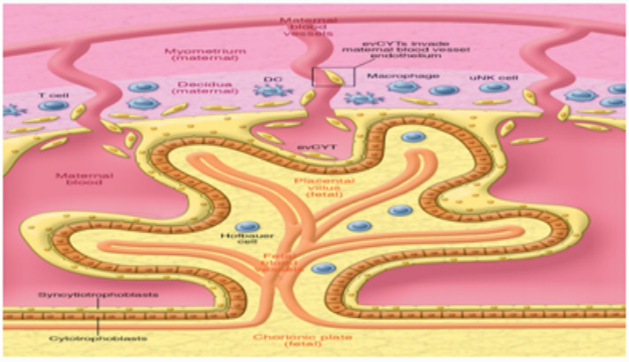


Figure 1: The structure of Placenta and different cells structures present [16]. The maternal decidua consists of pregnancy-specific differentiated stromal cells that house the maternal blood vessels and maternal immune cells including T cells, uterine NK (uNK) cells, macrophages, and DCs. Extravillous Cytotrophoblasts (evCYTs) invade the decidua and reach the maternal spiral arteries, establishing nutrient circulation between the embryo and the mother. The placental villus is in direct contact with the maternal blood and thus facilitates gas, nutrient, and communication exchange between the mother and developing fetus. It is formed by a double cell layer consisting of syncytiotrophoblasts and cytotrophoblasts. The villus contains the fetal blood vessels that are surrounded by fibroblasts and fetal macrophages (termed Hofbauer cells).

The goal of this study is to present and comment on available evidence addressing probable mother-to-child transmission of SARS-CoV-2, HIV, and HCV and its potential effects on perinatal and later outcomes.

Discussion

COVID-19 and placental facts

The available findings of placental pathology from COVID-19 patients came from the third trimester, and the most common Findings are Vascular Malperfusion (FVM), fetal vascular thrombosis and Maternal Vascular Malperfusion (MVM) (20% to 73%), massive infection with generalized inflammation (presence of M2 macrophages, cytotoxic and helper T cells, and activated B-lymphocytes) (13% to 20%), fibrin deposition and intervillous thrombosis [28].

These abnormalities result from direct infection of cells, systemic inflammation ("cytokine storm"), hypercoagulable state, and maternal hypoxia. Consequently, adverse perinatal outcomes: MVW associated

Table 1: Placental' receptors and their main role.

Receptor name	Role
Insulin receptors	Expressed on structures that are currently assumed to drive placental growth [8]
Estrogen receptor alpha	*Terminal differentiation of estrogen-dependent cells e.g. trophoblast [9]
	*Regulates important developmental events during primate pregnancy, including the production of progesterone, fetal adrenal maturation and the onset of parturition [9]
ACE2	Contributes to maintaining and adapting maternal hemodynamics during pregnancy [10]
Fc receptor (FcRn)	Transports IgG across the syncytiotrophoblast, and possibly the fetal blood vessel endothelium. [11]
Endothelin Receptor (ET)	Regulating the uteroplacental circulation [12]
CD147	Regulates several VEGF isoforms and Placental Growth Factor (PLGF) [13]

Table 2: Different Cell Structures Present in Placenta [17].

Cell name	Role
Cytotrophoblasts and syncytiotrophoblasts	*Cells forming the outer layer of a blastocyst, which provides nutrients to the embryo, and develops into a large part of the placenta.
	*Orchestrate the complex bio-molecular interactions between the fetus and mother.
	*Serve as an important endocrine organ that produces numerous growth factors and hormones that support and regulate placental and fetal development and growth
Villous core stroma cells	***Hofbauer cells** are the macrophages in the placenta villous stroma.
	***Hofbauer cells** are antigen-presenting cells in the placenta, which play a critical role in maintaining host defense. Also contribute to trophoblast differentiation and angiogenesis by producing various growth factors and cytokines.
Pericytes/endothelial cells	*Maintaining vessel stability and microvascular integrity.
	*Influence blood vessel functions including microvascular contractility, solute permeability, and smooth muscle stem cell function.

Table 3: Comparison of SARS-CoV-2, HIV, and HCV.

	SARS-CoV-2	HIV	HCV
Disease Course	Mild symptoms around 85% of cases, Critical cases around 3%-10%, and mortality is around 5%-7% [18]	Asymptomatic infection after the exposure. Onset of symptoms is 2 to 4 weeks, although, in some cases, it can be as long as 10 months [24]	The virus is detectable in plasma within days of exposure, often 1 to 4 weeks. Viremia peaks in the first 8 to 12 weeks of infection, and then plateaus or drops to undetectable levels, in the majority, 50% to 85% it persists [26]
Signs and Symptoms	**Most common symptoms:** Fever, headache, shortness of breath, cough, muscle aches, and tiredness	**Acute retroviral syndrome:** Fatigue, Muscle pain, Skin rash, Headache, Sore throat, Swollen lymph nodes, Joint pain, Night sweats, Diarrhea	Persistently infected individuals tend to be asymptomatic.
	Serious symptoms: Difficulty breathing, chest pain or pressure, and loss of speech or movement	**Chronic HIV infection without AIDS:** Thrush, Vaginal candidiasis, Oral hairy leukoplakia, Herpes zoster, Peripheral neuropathy, Bacillary angiomatosis, Cervical dysplasia, Cervical carcinoma in situ, Constitutional symptoms, Idiopathic thrombocytopenic purpura	Acute HCV infection may cause malaise, nausea, and right upper quadrant pain, followed by dark urine and jaundice
	Disorders in acute conditions: Hemoptysis, diarrhea, dyspnea, acute heart injuries, and ground-glass opacities[19]	**Chronic HIV infection with AIDS:** Multiple or recurrent bacterial infections, Recurrent pneumonia, Candidiasis, Cervical cancer, Coccidioidomycosis, extrapulmonary Cryptococcosis, chronic intestinal Cryptosporidiosis, Cytomegalovirus disease, Cytomegalovirus retinitis, HIV related encephalopathy, Herpes simplex[24]	**Signs of end-stage liver disease include:** 1) Temporal muscle wasting, cyanosis, icterus, enlarged parotid gland 2) Palmar erythema, asterixis, clubbing, Dupuytren contracture 3) Gynecomastia, small testes 4) Fetor hepaticus 5) Ankle edema, spider nevi, petechiae, scant body hair 6) Caput medusae, paraumbilical hernia, hepatosplenomegaly [26]
Treatment Options	**Antiviral agents** Ledipasvir / Sofosbuvir Sofosbuvir / Daclatasvir [20]	**Antiviral agents** Lopinavir/Ritonavir [22] Tenofovir disoproxil fumarate/ lamivudine [25]	**Nucleotide polymerase inhibitors** Sofosbuvir
	Antiviral agents Lopinavir/Ritonavir Remdesivir	**Antimalarials** [21] Chloroquine/ Hydroxychloroquine	**Non- nucleoside polymerase inhibitors** Dasabuvir
	Antimalarials [21] Chloroquine/ Hydroxychloroquine	**Antimalarials** [21] Chloroquine/ Hydroxychloroquine	**NS3/4A protease inhibitors** Simeprevir Grazoprevir
	Anticoagulants: Heparin		**NS5A inhibitors** Daclatasvir Ledipasvir Ombitasvir Velpatasvir [27]
	Steroids: Betamethasone		
	Antibiotics: Amoxicillin, Azithromycin, Ceftriaxone		
	Convalescent plasma Immunomodulatory agents: Tocilizumab		
	Interferons: Type I interferons (IFN-α/β) [22]		
Disease Complications	Interstitial and alveolar pneumonia.	Progression to (AIDS)	End-stage liver disease liver cancer [26]
	More severe disease in patients with cardiovascular comorbidities.	Tuberculosis (TB)	
	Acute kidney injury	Cytomegalovirus	
	Thrombocytopenia	Candidiasis	
	Thrombosis in pulmonary vessels in severe cases	Cryptococcal meningitis	
	Hypokalemia	Toxoplasmosis	
	AST elevation	Kaposi sarcoma	
	GI symptoms such as diarrhea, abdominal pain and vomiting	Neurological complications (AIDS dementia complex)	
	CNS symptoms as dizziness, headache, impaired consciousness, cerebrovascular disease, ataxia and epilepsy	Kidney disease [24]	
	Preterm birth, Intrauterine growth restriction, miscarriage, preeclampsia-like syndrome [23]		

Intrauterine Growth Restriction (IUGR), increased incidences of preterm births, higher rates of perinatal death, miscarriage, pre-eclampsia, cesarean section deliveries are observed [28].

Trans-placental transfer and vertical transmission of SARS-CoV-2

According to the Centers for Disease Control and Prevention (CDC), pregnant women with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection are more likely than non-pregnant women of reproductive age to require an intensive care unit stay or mechanical ventilation. According to this research, there is an elevated risk of fetal and maternal mortality in the presence of maternal SARS-CoV-2 infection [29-31].

While pregnancy-specific immunological and physiological changes may predispose women to increased morbidity in the presence of respiratory viruses, data on biological correlates of maternal disease severity in SARS-CoV-2 are lacking and have largely been extrapolated from non-pregnant populations or pregnant women infected with SARS-CoV-1 or Middle East respiratory syndrome. The majority of the information on the maternal immune response, vertical transmission, and placental infection has come from case reports, short case series, and systematic reviews. We provide significant biological findings from a large prospective cohort study of SARS-CoV-2 infection during pregnancy, including viral load, antibody response, trans-placental antibody transfer, and placental pathology [32-34].

A screening study yielded 67 trials, from which 1787 COVID-19 mothers' main data were discovered and their pregnancy outcomes were evaluated. Only 2.8% of children delivered to COVID-19-positive women tested positive, which matches the rates reported in previous Coronaviridae outbreaks [35].

A study was carried out to determine the viral load of SARS-CoV-2 in maternal and neonatal biofluids, the trans-placental transmission of anti-SARS-CoV-2 antibody, and the incidence of fetoplacental infection. According to the findings, 23 (36%) of women with SARS-CoV-2 infection were asymptomatic, 22 (34%) had mild disease, 7 (11%) had moderate disease, 10 (16%) had severe disease, and 2 (3%) had critical disease. There was no detectable viremia in maternal or cord blood and no indication of vertical transmission in viral load studies of 107 women. One of the 77 newborns tested for SARS-CoV-2 antibodies in cord blood exhibited detectable immunoglobulin-M to nucleocapsid.SARS-CoV-2 RNA was not found in any of the 88 placentas examined. Anti-SARS-CoV-2 antibody transmission from mother to neonate was substantially lower than transfer of anti-influenza hemagglutinin-A antibodies [36].

During the last weeks of pregnancy, trans-placental transmission of SARS-CoV-2 infection is feasible. Trans-placental transmission has been linked to placental inflammation and newborn viremia. Cerebral vasculitis-related neurological symptoms may also be present. This was the case of a 23-year-old woman, gravida 1, para 0, who was taken to the hospital at 35+2 weeks of gestation with a fever (38.6°C), severe cough, and copious expectoration for two days before to admission. SARS-CoV-2 was detected in blood, and in nasopharyngeal and vaginal swabs. Three days after admission a category III-fetal heart rate tracing was observed and therefore category II-cesarean section was performed, with intact amniotic membranes, in full isolation and under general anesthesia due to maternal respiratory symptoms. RT-PCR on the placenta was positive for both SARS-CoV-2 genes. The viral load was considerably greater in placental tissue than in amniotic fluid or maternal or neonatal blood in all RT-PCR data obtained in distinct maternal and neonatal tissues [37].

To our knowledge the published data indicate that perinatal transmission of SARS-CoV-2 is possible but uncommon. Transmission was suspected in 8 cases of 179 infants tested for SARS-CoV2 at birth from women with COVID-19, 5 with positive nasopharyngeal SARS-CoV-2 RT-PCR and 3 with SARS-CoV-2 IgM. These occurrences, however, are the result of maternal infection near to birthing, and there is no information on exposure during the first or second trimester of pregnancy [38].

A placental tropism of the virus, in which the virus infects placental cells and is therefore transferred to the fetal side, may be required for a maternal-fetal infection. Too far, no instance of SARS-CoV-2 placental infection has been described in a published research. SARS-CoV-2 was not detected in any of the seven placentas born from COVID-19 patients examined using RT-PCR in five publications. Furthermore, histological examination of three placentas revealed no major lesions. The lack of placental infection is supported by the fact that ACE2 required for cell integration, is only present at extremely low levels in placenta during the first third trimester, with no data on the expression of this receptor in second and third trimester of pregnancy. However, in a hypertensive rat model produced by a saline diet, the ACE2 receptor was expressed (mRNA) and showed substantial enzymatic activity in the uterus and placenta in late gestation (day 19-20). As a result, the likelihood of placental infection close birth, and therefore a possible transit to fetal infection, necessitated additional research (Figure 2) [39-42].

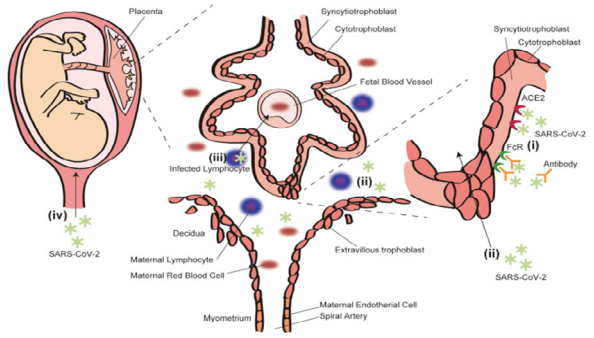


Figure 2: Possible mechanisms of SARS-CoV-2 vertical transmission [43]. (i) Direct infection of syncytiotrophoblasts and breach through the syncytial layers, (ii) passage through the maternal circulation to extravillous trophoblasts or other placental cells, (iii) passage through maternal immune cells, and (iv) Ascending infection via the maternal vaginal tract.

ISH revealed widespread SARS-CoV-2 positivity in perivillous trophoblastic cells in one instance, which was linked with enhanced apoptosis and severe villous infarction not seen in the other placentas. In the placental transcriptional response, there is overexpression of genes involved in innate antiviral defense and significant chemotactic and inflammatory responses, such as CXCL9, 10, and 11, CCL2 and 7, IL6, IL21R, CD8A, 68, and 163. This response is generated by a high viral load of SARS-CoV-2. The findings indicated that this transcriptional pattern is similar to that found in SARS-CoV-2 infected lungs, with some tissue-specific differences. Despite the fact of having a high SARS-CoV-2 viral load in the placenta, no viral transmission occurred to the baby. This finding suggests that the placenta may serve as a barrier against the virus, limiting intrauterine transmission to the fetus. However, like with other infections, viral infection of the placenta can produce fetal inflammatory responses, which can lead to organ damage and subsequent developmental abnormalities [44].

Perinatal outcomes of covid-19 infection may include increased risk of miscarriage, still birth, preterm labor, fetal growth, restriction, early onset of pre-eclampsia. Furthermore, the long term neonatal outcomes include neurosensorial development delay [45].

Trans-placental transfer and vertical transmission of HIV

According to studies, HIV vertical transmission rates from mother to child during pregnancy, delivery, or nursing range from 13% to 48% [46]. It was found that trophoblasts contain viral sequences in

HIV-1-infected women who did not receive antiretroviral treatment during pregnancy. However, throughout pregnancy, more than 90% of their babies are protected against HIV-1 [47].

The trophoblast cells and the terminal villi have CD4 receptors that may be infected by HIV-1. Furthermore, HIV-1 genomic materials have been detected in placental, cytotrophoblasts, macrophages (Hofbauer cells) and syncytiotrophoblast. Furthermore, HIV-1 replication and transmission may occur through CD4-positive endothelial tissues or CD4-positive Hofbauer cells in the placenta. Other research findings indicated that placental macrophages act as a barrier to initial HIV-1 infection [47,48].

Although this was seldom, it has been documented that HIV perinatal transmission occurred from mothers on antiretroviral combination treatment and had undetectable or extremely low levels of plasma HIV RNA. Also, HIV viral shedding in the genital tract has been shown in women with undetectable plasma HIV RNA. These examples suggest that maternal HIV plasma RNA levels may not be completely predictive of transmission risk (Figure 3) [49].

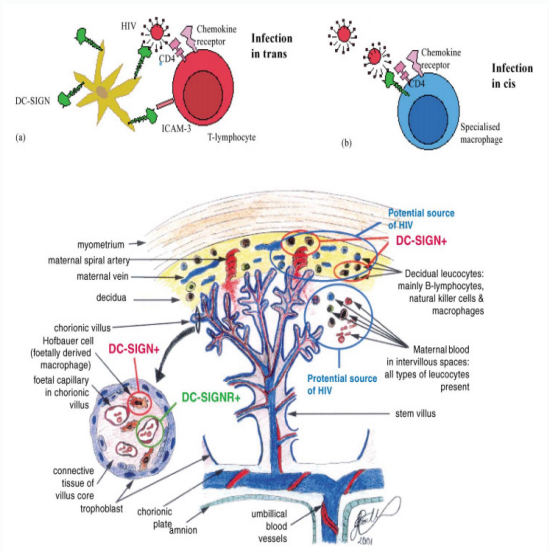


Figure 3: Schematic summary of placental structure that may lead to in HIV transplacental transmission [50].
(a) DC-SIGN-mediated enhancement of HIV infection in trans. DCs can absorb HIV and even after very thorough washing can mediate infection of T lymphocytes in trans during subsequent co-culture. HIV entry requires the expression of CD4 and a chemokine receptor, such as CCR5. DC-SIGN also interacts with ICAM-3 on T lymphocytes, thus being important for the activation of na¨ive T lymphocytes. (b) DC-SIGN-mediated enhancement of HIV infection in cis. Infection in cis occurs when DC-SIGN is co-expressed with CD4 and chemokine receptor (e.g. CCR5) on a permissive cell type, such as a macrophage.

Recently, the identification of the HIV binding lectins DC-SIGN and DC-SIGNR expression in the human placenta is considered a new breakthrough. The DC-SIGN is expressed on two cell populations which are maternal decidual macrophages and foetal Hofbauer cells in the connective tissue core of chorionic villi. HIV attaches to DC-SIGN, and the virus may remain viable and attached to DC-SIGN for extended periods of time. Being HIV is likely adsorbed to DC-SIGN cells, these cells may transport the virus to nearby lymph nodes, where there are many T lymphocytes that can become infected [51].

Opportunistic infections such as CMV and toxoplasmosis can cross the placenta and infect the fetus in HIV-positive untreated mothers, resulting in congenital defects. In prenatal or neonatal levels, HIV exposure can result in many children having mitochondrial abnormalities, which can contribute to the development of cardiac and nervous system problems later in life [52].

Trans-placental transfer and vertical transmission of HCV

Vertical transmission became the predominant source of paediatric HCV infection when hepatitis C blood product screening was adopted, and it is also the largest cause of paediatric chronic liver disease in developed countries [50]. Although vertical transmission that lead to chronic infection is documented in 4% to 8% of cases, transitory HCV perinatal infection occurs in 14% to 17% of cases [53,54]. Another study found that HCV-infected pregnant women have a 2% to 8% chance of transmitting the virus to their fetus. The process and timing of mother-to-child transmission, however, remain unknown [55].

Some researchers discovered high numbers of NK cells in the placentas of HCV-positive women. These cells were more cytotoxic in HCV-positive women. This might explain the relatively modest rates of vertical transmission, but the enhanced cytotoxicity of the NK cells could also contribute to an increased risk of premature birth [56].

Figure 4 represents the structural units of the placenta are the chorionic villi that float in maternal blood (inter-villous space). Villi are made up of a stromal core that contains blood vessels and is surrounded by cytotrophoblast progenitor cells. Extravillous cytotrophoblasts form a column at the tips of the anchoring villi and breach the uterine wall as part of their differentiation phase. Syncytiotrophoblasts, which cover floating villi, facilitate substance exchanges and passive IgG transfer from maternal blood to the fetus. HCV transmission to the fetus might occur by viral transcytosis across trophoblast cells, *via* HCV receptors expressed on the surface of placental cells, or *via* direct or indirect damage that compromises the integrity of the placental barrier.

Several circumstances, including prolonged membrane rupture, amniocentesis, and a higher HCV viral load in the mother, may enhance the likelihood of transplacental transmission. Further

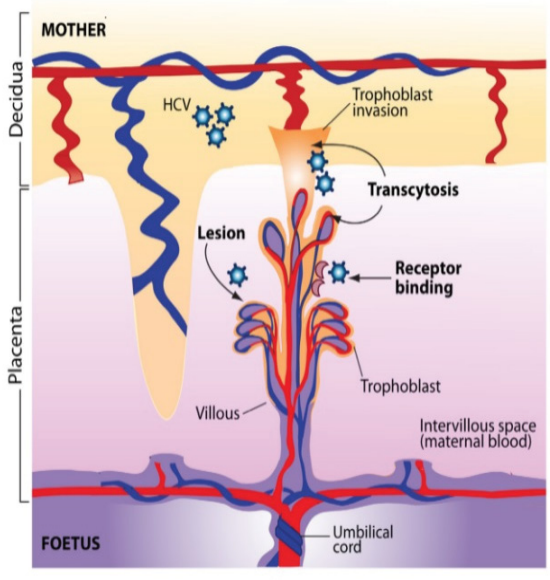


Figure 4: Possible pathways of Hepatitis C Virus (HCV) transmission [57].

researches indicated that perinatal HCV transmission is almost exclusively limited to women who have detectable HCV RNA in their peripheral blood, and mother-to-child transmission is uncommon if the maternal viral load is less than 1×10^5 HCV RNA copies/mL plasma [58].

There has been very little research that looks at the effect of maternal hepatitis C infection on pregnancy outcomes. The available data show that HCV-infected pregnant women had a higher risk of gestational diabetes (described in patients with excessive weight gain), preterm membrane rupture, and a higher rate of caesarean birth than anti-HCV-negative pregnant women. Furthermore, HCV-infected mothers had a greater incidence of preterm delivery, placental abruption, low birth weight, prematurity, poor Apgar scores at 1 minute, increased neonatal jaundice, congenital abnormalities, and infant perinatal death. Membranoproliferative glomerulonephritis is one of the most common extra-hepatic manifestations of chronic HCV infection in children, although unlike adults, neither cryoglobulinemia nor lymphoma has been documented. The involvement of the central nervous system in HCV-infected children might explain some of the developmental delays, learning problems, and cognitive impairments that have been observed in some cases [59].

Maternal and neonatal SARS-CoV-2 immunoglobulin G antibody levels

After messenger RNA (mRNA) COVID-19 vaccination during the second trimester of pregnancy Antibody levels were measured for 129 women (mean age, 31.9 years) and 114 neonates, with 100% of the tests having positive results. The mean gestational age at administration of the second vaccine dose was 24.9 weeks. Neonatal IgG titers were 2.6 times higher than maternal titers (median [range], 3315.7 [350.1-17 643.5] AU/mL *vs.* 1185.2 [146.6-32 415.1] AU/mL) [60].

A positive correlation was demonstrated between maternal and neonatal antibodies (r=0.92). Multivariable analysis revealed that for each week that passed since receipt of the second vaccine dose, maternal and neonatal antibody levels changed by -10.9% (P=0.002) and -11.7% (P=0.005), respectively. For each 1-year increase in the mother's age, maternal and neonatal antibody levels changed by -3.1% (P=.007) and -2.7% (P=0.04), respectively [60].

Neonatal and maternal outcomes

One study demonstrated that infants of hepatitis C-positive mothers were more likely to be small for gestational age, require assisted ventilation, be admitted to the intensive care unit, or have low birth weight. Another study made similar inferences, suggesting that infants born to infected mothers are at risk for low birth weight, preterm birth, and congenital anomalies, although confounding factors, such as polysubstance abuse, were not controlled for. A more recent study demonstrated impaired intrauterine fetal growth of infants born to hepatitis C-infected mothers [61].

Participating 145 HCV-positive pregnant women were monitored during pregnancy and their infants were followed to assess them for HCV infection. Observed rates of intrauterine fetal death, preterm delivery, small for gestational age, and low birth weight infants were 3.4%, 17.9%, 11.3%, and 12.5%, respectively, without a significant association with maternal HCV RNA status. The rate of cholestasis was 5.6% in the HCV RNA-positive group and 2.8% in the HCV RNA-negative group (P=0.496) [62].

Results from the multivariate analysis revealed four predictors associated with Low Birth Weight (LBW). HIV positive (OR 1.93), rural residency (OR 2.44) and having Preterm Delivery (PTD) (OR<34 weeks 7.60, OR34-36 weeks 15.04) were positively and independently associated with LBW. Furthermore, HIV was associated with Preterm Delivery (PTD), and Low Apgar score [63].

Maternal HIV infection in women who have not received antiretroviral therapy has been associated with adverse pregnancy outcomes such as preterm birth, Low Birth Weight (LBW), Small for Gestational Age (SGA) and stillbirth, especially in Sub-Saharan Africa (SSA). The proportion of women with anaemia and severe anaemia at delivery was also higher in HIV- infected (49.4% and 4.1%) than in those HIV-uninfected (40.6% and 1.8%). Foetal anaemia was higher among infants born to HIV-infected (10.6%) than in those born to HIV-uninfected mothers (7.3%) [64].

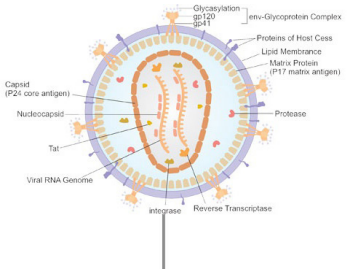
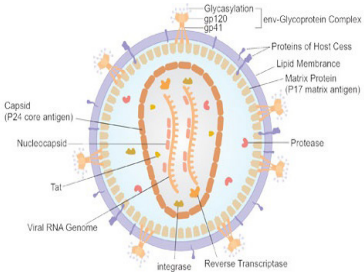
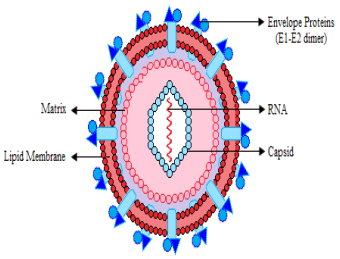
A study showed that during pregnancy, women with a COVID-19 diagnosis had higher rates of pregnancy-induced hypertension (RR, 1.46), preeclampsia/eclampsia (RR, 1.76), and infections requiring antibiotics (RR, 3.38), and there was an association with a greater risk of admission to ICU/high-dependency unit (RR, 5.04) and referral to a higher level of care [65].

A systematic review included nine eligible articles for inclusion (n=92) showed that, 67.4% (62/92) of COVID-19 infected women were symptomatic at presentation. Maternal mortality rate was 0% and only one patient required intensive care and ventilation. 63.8% had preterm births, 61.1% fetal distress and 80% a Caesarean section.76.92% of neonate's required NICU admission and 42.8% had a low birth weight (Table 4). There was one indeterminate case of potential vertical transmission [66,67].

Conclusion

From the presented review it can be concluded that, in the last stages of pregnancy, trans-placental transmission of SARS-CoV-2 is probable. The absence of ACE2 receptors in placental cells during the first third trimester of pregnancy might be a major cause for the absence of placental viral transmission. In general, the trans-placental transmission is uncommon during pregnancy. Although the incidence of HIV transmission is relatively high that may occur through CD4-positive endothelial tissues orCD4-positive Hofbauer cells, but studies indicated that 90% of the infants are protected against HIV during pregnancy. Compared to HIV, SARA-CoV-2, and HCV transplacental transmission considered modest. Pregnant mothers should perform an early screening for viral infections to overcome potential pre- and postnatal viral infection effects. This will aid in avoiding congenital abnormalities, fetal death, and undesired long term neonatal consequences.

Table 4: Comparison of Transplacental transfer and vertical transmission of SARS-CoV-2, HIV, and HCV.

	SARS-CoV-2	HIV	HCV
Structure [67-69]			
Prevalence in pregnancy	6.6%	5.3%	Nearly 3.6%
Probability of incidence	About 2.8%	Range from 14 to 48%.	Range from 2 to 8 %
Possible mode of transmission	During the last weeks of pregnancy Linked to placental inflammation and ACE2 receptors	Trophoblast cells and the terminal villi have CD4 receptors that may be infected by HIV-1 DC-SIGN cells may transport the virus to nearby lymph nodes, where there are many T lymphocytes that can become infected.	Mechanism and timing of transfer still unclear Prolonged rupture of membranes, amniocentesis, and elevated HCV viral load
/ Viral load	**The median viral load (expressed as PCR cycle thresholds) among SARS-CoV-2–positive placentas without severe injury was 32**	**In a study, for a 280 mothers with known transmission outcome and a delivery measurement the median maternal plasma RNA level at delivery was 20,700 copies/mL**	**Transmission is uncommon if the maternal viral load is less than 1 X 10^5 HCV RNA copies/mL plasma**
Placental Protective mechanism	The lack of placental infection is supported by the fact that the receptor for SARS-CoV-2,the angiotensin 2 converting enzyme (ACE2) required for cell integration, is only present at very low levels in the human placenta during the first third trimester of pregnancy. No data on the expression of this receptor in second and third trimester) placentas.	Placental macrophages act as a barrier to initial HIV-1 infection	High numbers of NK cells in the placentas of HCV-positive women
Effect on fetus and newborn	Fetal inflammatory responses, which can lead to organ damage and subsequent developmental abnormalities Long term neonatal outcomes include, neurosensorial development delay	Fetus congenital defects may occur Children may have mitochondrial abnormalities, which can contribute to the development of cardiac and nervous system problems later in life	Low birth weight, increased neonatal jaundice, congenital abnormalities, and infant perinatal death Children central nervous system effects like developmental delays, learning problems, and cognitive impairments One of the most common extra-hepatic manifestations in children (Membranoproliferative glomerulonephritis)

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