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Possibility of Vertical Transmission of COVID-19–A Narrative Review

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ABSTRACT

COVID-19 (Coronavirus disease-2019) pandemic stopped the world altogether. Even though essential workers everywhere were busy combating the deadly virus, healthcare systems were overburdened and underprepared. The virus affected people with comorbidities, with lesser immunity and at the extremes of ages more. Neonates, being at that extreme of age are especially susceptible to diseases. Understanding the routes and rates of transmission of the COVID-19 virus will help us better prevent and treat it. This article aims to assess the vertical transmission of the said virus, based on currently published literature. Vertical transmission is the transfer of pathogens, immunoglobulin, molecules or drugs from the mother to the foetus or neonate. Although theoretically, vertical transmission can occur only through the amniotic fluid, umbilical cord and breast milk, proving it can be tricky since 100% aseptic conditions cannot be guaranteed. The most firm evidence of vertical transmission would be the confirmation of viral replication in the foetal lungs. Proving the occurrence of vertical transmission requires the evidence of either the pathogen itself, or a part of it, or the antibodies produced against it in the fluid from the amniotic cavity, umbilical cord blood and blood of the foetus/neonate. Most studies found negligible evidence of vertical transmission of COVID-19 virus. And those that did, could not prove beyond a reasonable doubt the existence of 100% aseptic conditions during testing, delivery and post-partum, meaning the virus could have been transmitted via other sources nosocomial or community acquired. Best precaution against vertical transmission of COVID-19 virus was ensuring maximum aseptic conditions during delivery and educating mothers and caregivers regarding prevention of spread of the virus.

Key words: COVID-19, Vertical transmission, Neonate, Respiratory distress

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INTRODUCTION

COVID-19

The WHO announced Coronavirus disease 2019 as a pandemic on 11th March 2020. Since then it has spread rapidly across the globe, with countries reporting deaths in hundreds of thousands. The developing world bore the brunt of it, due to poor infrastructures, lack of hospital beds, medications and funding. Even with vaccines available, they are still extremely slow to reach the majority of people who need it the most (countries in Asia and Africa, with rampant poverty, overpopulation and a debilitated healthcare system now overstretched due to the pandemic). Delay in vaccination, uneven distribution of vaccines among financially stable versus struggling countries, can lead to formation and spread of deadlier mutations. As countries the world over are coming to terms with the pandemic and vaccination programmers are underway everywhere, the virus is mutating into concerning variants. Although, most of them are susceptible to the vaccines, the dissemination occurs at rapid speeds, often infecting individuals before their vaccination schedule is complete or before the immunity kicks in. While the medical community is still trying to assess its impact, pathogenesis, treatment and complications; the general consensus is that the disease affects the elderly, immune compromised and people with comorbidities more as compared to children and healthy adults. Neonates are especially susceptible and generally have a higher risk of infection as compared to other groups of children. This is explained by their poorly developed immune system, as they are mostly dependent on maternal antibodies that have transferred in utero, or the immunity conferring substances present in breast milk [1]. In the developing world, where rural healthcare is limited, understanding the routes of transmission of

COVID-19 in neonates will better help prevent maternal and neonatal morbidity and mortality.

A lot has been researched and published with regard to transmission of COVID-19 to neonates, both vertically and horizontally. This article attempts to summarize said works and find the possibility and probability of vertical transmission of COVID-19 (from previously published literature).

LITERATURE REVIEW

Coronavirus disease 2019 also known as COVID-19 disease caused due to the SARS-CoV-2 and RNA virus from the single stranded RNA Coronaviridae family of viruses, which includes viruses like MERS-CoV-2 and SARS-CoV-1. SARS-CoV-2 is homologically similar to SARS-CoV-1 when it comes to receptor binding pattern, although it is genetically nearer to two bat derived SARS like Coronaviruses. This means its vertical transmission and replication can be expected to be similar to SARS-CoV-1 [2]. The spiked surface glycoprotein also known as S, the small Envelope forming protein (E), Matrix producing protein (M) and Nucleocapsid forming protein (N) are the four structure forming proteins of SARS-CoV-2 virus (N). The S gene in Coronaviruses produces the protein that binds to the receptor and that allows the Coronavirus to transfer inside cells. This spike protein is involved in receptor binding and cell membrane fusion which affects transmission abilities. The other three of the structural proteins, other than the spike protein, actually are required for virus' normal functioning. These proteins are required in protein assembly, budding, envelope formation and pathogenicity, as well as encasing the RNA [3].

Symptoms most commonly include fever, breathlessness, fatigue, chest pain, sore throat and cold (in mild cases), cough, altered sense of smell and taste. Newer variants are presenting with symptoms like diarrhea, conjunctivitis, headache, rash over body. Reports of long COVID, *i.e.* symptoms persisting for more than 6 months or more are also common with the newer variants, with fatigue, joint aches, confusion and cloudiness being the major symptoms. Neonates can present with breathlessness, respiratory distress syndrome, fever and signs of sepsis, but a higher degree of suspicion is required in case of new born children, as these symptoms are highly non-specific and can have numerous other etiologies. Transmission of the virus is chiefly through dispersion of respiratory droplets which are exhaled during talking, coughing or sneezing. Aerosol transmission has also been implicated, though it is more important in hospital settings where procedures such as nebulisation and endotracheal intubation take place. Viral particles can also survive on surfaces for more than twenty four hours, so adequate sanitation measures must be taken. The COVID-19 virus can be transmitted to neonates horizontally *via* the mother, healthcare providers, caregivers, family members or through fomites or vertically in utero, during or post-partum. Therefore, sanitization of fomites, regular hand washing using soap or alcohol based sanitizers, proper ventilation and masks are key to stop the transmission. A single N_{95} mask (especially for healthcare workers), or a cloth and a surgical mask (also known as double masking) is now advised by the CDC and WHO.

Vertical transmission

Vertical transmission can be described as passing of pathogens from mother to child before, during or after birth. It can be passed *via* the placenta, breast milk or through direct contact.

IgG (Immunoglobulin g) and IgM (Immunoglobulin M) antibodies are formed in the mother and foetus in response to a pathogen. While the IgG antibody can cross the placental barrier, the IgM cannot. Hence the presence of IgM antibody or the virus/or its proteins in the cord blood, placenta, amniotic fluid, breast milk or the nasopharyngeal swab of the neonate can be construed as solid proof of vertical transmission from the mother to the foetus.

Diagnosis of COVID-19

Rapid and correct diagnosis of COVID-19 can be instrumental in containing the virus by prompt treatment, identifying the close contacts, their isolation and hence breaking the chain of transmission in a community. The most widely utilized approach for diagnosing COVID-19 disease using respiratory samples is RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction). The reverse transcription of SARS-CoV-2 RNA into complementary DNA (cDNA) strands is done. Then amplification of particular sections of the cDNA is done in the RT-PCR method [3]. Upper respiratory samples are generally advised. Nasopharyngeal swabs, nasopharyngeal washes, nasal aspirates and oropharyngeal swabs are examples of upper respiratory tract samples. A negative RT-PCR test result from upper respiratory samples does not exclude the chance of disease or infection due to the diversity of virus loads. Negative results could be due to poor sampling methodology, low viral load in the studied location, or viral genome alterations. Other methods to detect the virus include detecting the antigen for SARS-CoV-2 also known as the RAT (Rapid Antigen Test), CRISPR (Clustered Regularly Spaced), LFIA (Lateral Flow Immune Assay), biosensors, ELISA, cell culture, CRISPR etc. X-ray and CT scans are used to assess lung involvement.

For evidence of vertical transmission in neonates, presence of the virus, it's antigens or antibodies to it must be found in either the cord blood, nasopharyngeal swab of the neonate, amniotic fluid, placental tissue or the breast milk. It must be ensured that the samples are taken using strict aseptic measures in place.

Since contamination cannot be ruled out by a 100%, a proof of vertical transmission cannot be garnered by just the presence of the COVID-19 virus in the said samples.

METHODS

Studies were searched through PubMed and Google Scholar using keywords such as 'COVID-19', 'vertical transmission', 'neonate', 'SARS-CoV-2', 'respiratory distress', 'maternal morbidity', 'newborn', 'novel Coronavirus' etc.

Only articles from December 2019 to July 2021 were considered. Articles written in English only were selected.

A total of 256 articles were found, out of which 15 were selected based on the inclusion criteria, which included severity of infection, study sample size (no. of women analyzed), neonates tested positive, use of RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction) for diagnosis, time between onset of symptoms and delivery, presence of symptoms within 48 hours of delivery.

DISCUSSION

The most firm evidence of COVID-19 transmission during pregnancy would be confirmation of COVID-19 virus replication in foetal pulmonary tissues, but doing so is essentially impossible. In practice, testing for the presence of the Coronavirus in placenta, umbilical vessels blood, amniotic fluid and nasopharyngeal and oropharyngeal swab samples of the neonate are used to determine whether there has been intrauterine transmission of the virus. It is extremely important that all of these samples must be obtained 100% aseptically soon after delivery in order to ensure that they are not adulterated and accurately reflect circumstances inside the uterus. The human placenta expresses angiotensin converting enzyme 2 receptor, also known as ACE-2 receptor. Zhao, et al. had earlier discovered the said receptor as key in COVID-19 virus entry and further replication in host cells. This increases the chances of spread of the virus *via* the placenta to the foetus. Furthermore, maternal hypoxia and comorbidities aggravated by COVID-19 may also decrease immunity and help transfer the virus vertically to the foetus.

Moreno, et al. tested 21 neonates of COVID-19 positive mothers, using quantitative RT-PCR. All of which were negative for SARS-CoV-2 [5]. All the other studies, chest x-rays were mostly nonspecific, but some were suggestive of pneumonia [6-11].

Two studies looked into the chances of vertical transmission of COVID-19 virus in a total of seven infected women, using recently developed automated chemiluminescence immunoassays to look for SARS-CoV-2 specific antibodies Immunoglobulin G (IgG) and Immunoglobulin M (IgM) in baby's serum samples. Both concluded that SARS-CoV-2 might be transmitted inside the uterus after finding anti SARS-CoV-2 IgM antibodies in blood samples taken after the delivery of three neonates. However, upper respiratory tract swab samples from all three neonates were negative for SARS-CoV-2 RNA and samples from the umbilical arterial or venous blood and placenta were not tested, therefore there wasn't any direct proof of infection. It's worth noting that the sensitivity and specificity of the immunologic tests employed in the two trials were not thoroughly tested. Furthermore, IgM assays are known for generating false positive results [12].

Three of thirty three (9%) neonates were identified with newborn early onset infection with Coronavirus virus in a cohort study done by Zeng, et al. based on positive quantitative RT-PCR results in two consecutive naso and oropharyngeal samples taken 48 hours and 96 hours after birth. Despite the fact that thorough aseptic and circumvention measures were performed during the birth, postpartum neonatal sources infection cannot be totally ruled out due to the delay in testing. On day six of life, all three newborns were either inconclusive or negative for SARS-CoV-2 RNA.

The majority of studies did not report any unfavorable perinatal outcomes. Zhu, et al. on the other side, report one infant fatality and six admissions in the NICU neonatal critical Care Unit (ICU). The newborns' first sign was shortness of breath, which was detected in six of them. Fever, thrombocytopenia with impaired liver enzymes, increased heart rate, vomiting and pneumothorax was among the other symptoms. Six of the ten neonates in the Zhu, et al. cohort were born prematurely and 8 of the 10 were born by caesarean section, both of which may have contributed to the morbidity [13]. There were two instances of newborn SARS-CoV-2 infection reported early in the pandemic The first was a 17 day old baby who had had intimate contact with two proven cases of COVID-19 infection (mom and caregiver) and the 2nd was a newborn who was positive around 36 hours after birth. Because testing for the virus was delayed, it couldn't be ruled out that the infection was acquired *via* an infected contact or a carrier, in both cases. Schwartz, et al. mentions no occurrences of severe pneumonia or maternal fatalities in reports of the 38 pregnant women who tested SARS-CoV-2 positive, of whom 37 had RT-PCR confirmed SARS-CoV-2 viral infections. Although several of the women had comorbid illnesses, few of those were obstetric in origin, they did not lead to life endangering maternal COVID-19 SARS-CoV-2 infection. Preeclampsia, Pregnancy Induced Hypertension (PIH), eclampsia, Gestational Diabetes (GD) and uterine atony were among the concomitant maternal illnesses that did not look as risk factors estimated for vertical transmission of COVID-19 virus to the foetus.

Despite the presence of prenatal problems in some of the newborns, there were no incidences of reverse transcriptase test confirmed SARS-CoV-2 virus caused COVID-19 infection among the 29 neonates born to the women who were tested. One interesting finding was that when placentas were screened for COVID-19 virus, the findings came back negative. This nil evidence of maternal fetal vertical transmission of COVID-19 virus is at par with previous reports of other Coronavirus infections in pregnant women, such as SARS and MERS. An investigation into possible sources of contamination and/or transmission revealed that 11 of the 19 neonates who tested positive for SARS-CoV-19 had at least one

person related, who tested positive for COVID-19. This comprised eight infants whose mothers were the only parents diagnosed with COVID-19 [15]. Five of the 19 infants (26%) had a caregiver or mothers who tested negative for the virus SARS-CoV-2. And also there were four infected newborns (27%) with no clear household source of infection among the 15 positive neonates who had at bare minimum contact or family member tested.

Quantitative analysis found that 27 neonates out of 936 from mothers with Coronavirus illness received a RT-PCR confirmed positive result for the Coronavirus 2 viral RNA test using a nasopharyngeal swab, indicating a total proportion of 3.2 percent for vertical transmission. Only 10 (3%) of the 326 COVID-19 positive mothers' neonates were found to have received the Coronavirus *via* vertical transmission, which could not be proved (Table 1).

Table 1: Depicting no. of neonates tested positive in comparison to COVID-19 positive mothers.

Studies	No. of COVID-19 virus positive mothers	No. of COVID-19 virus positive neonates
Zeng, et al.	33	3
Chen, et al.	9	0
Schwartz, et al.	38	0
Zeng, et al.	6	0
Kotlyar, et al.	936	27
Sheth, et al.	326	10
Zhu, et al.	9	0

CONCLUSION

Vertical transmission was thought of in most studies if a newborn tested positive for COVID-19 viral particles in RT-PCR within the first 2 days of life while strict infection averting measures were in place at delivery. The best proof for vertical transmission would be evidence of SARS-CoV-2 viral replication or its parts in the foetal/ neonatal lungs. But since this is next to impossible, presence of viral antigens or the virus itself in nasopharyngeal swabs, oropharyngeal swabs, placental tissue, umbilical vessel blood or the breast milk of mothers, is the next best method. There seems to be very little/no vertical transmission of COVID-19 causing based on the current literature. Most of the neonates tested positive are suspected to be due to horizontal transmission. It is worth noting that male babies were more affected than female ones.

Although there are no concrete studies showing vertical transmission of the virus causing COVID-19, we have very little information regarding the short term, long term and permanent consequences of infection in neonates. Hence, strict antiseptic measures must be enforced during and after delivery of the baby. Even at home, mothers/care givers must be educated to maintain use of masks, isolation of newborn, social distancing, frequent hand sanitization, frequent surface sanitization and exclusive breastfeeding. COVID-19 positive suspected or confirmed mothers can continue breastfeeding taking all antiseptic precautions using N95/double masking, taking proper care to sanitize all fomites and surfaces touched, regular hand washing or using alcohol based sanitizers, coughing into a tissue and immediately discarding it. Vaccination is the best prevention against COVID-19. All women who are trying to conceive are pregnant or are breastfeeding are advised by the WHO to get vaccinated to prevent the rapid and deadly spread of infection causing significant morbidities and mortalities, both in the neonates and mothers. Till equitable and ethical distribution of vaccines is achieved the world over, newer and much more dangerous variants will keep arising and spreading. Social distancing, masking, awareness about symptoms, prompt diagnosis, isolation, close contact tracing, better treatment modalities will prevent and better manage this disease.

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