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Intrauterine Vertical Transmission of SARS-CoV-2. What do We Learn from Evolving Literature so Far?

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Abstract Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains at every one's toes all over the world with every aspect of life affected. Infection reports of SARS-CoV-2 in pregnancy seem to be on the raise in certain parts of the world. There is an apparent concern of possibility of intrauterine vertical transmission of this pathogen. This review aimed to analyze what is in the scientific literature so far in regard to the possibility of intrauterine vertical transmission of SARS-CoV-2 so as to offer suggestions that might contribute to future research and awareness of possible intrauterine transmission of SARS-CoV-2. It was noted that although seemingly sporadic, the published cases so far call for urgent need for a standard protocol for diagnosis of intrauterine vertical transmission of SARS-CoV-2, clear understanding of the mechanisms and risk factors for the transmission, as well as efforts towards ensuring accessibility of the necessary diagnostics for suspected intrauterine infections.

Keywords: *COVID-19, intrauterine vertical transmission, SARS-CoV-2*

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1. Introduction

SARS-CoV-2, the aetiologic agent for coronavirus disease 2019 (COVID-19) [1,2] is one of the world's greatest health burden with 580,045 registered deaths by July 15th, 2020 [3]. Several confirmed pregnancy infections with SARS-CoV-2 have been reported in various study reports across the globe [4]. Although not much harm has been reported so far, the numbers of infections in pregnancy seem to be on the rise in certain parts of the world. For example**,** Harishchandra et al. [5] in India recently reported an incidence of 14.43% of COVID-19 positive pregnant women only in a period from April 1st to May 15th, 2020. Many viruses such as cytomegalovirus, rubella, Herpes Simplex, Zika, parvovirus [6,7] are known to infect and/or cross the placenta and subsequently infect the unborn baby. Whereas previous study reports have revealed an unlikely risk of intrauterine transmission of SARS-CoV-2 [8,9], there is apparently an evolving body of evidence from case reports and other literature of placental and transplacental infections with this virus. A systematic review involving a total of 70 newborns born to mothers with proved SARS-CoV-2 infection from nine different studies by Fornari [10] could not exclude the possibility of transplacental transmission of the infection. Whereas 92.9% of cases from seven independent studies was negative for a transplacental infection (based on oropharyngeal or nasopharyngeal swab performed in the first hours or days of life), 5.7% of the cases had early infection detected on second day of life, and vertical transmission could therefore not be excluded. Interestingly in this study, one neonate had a negative throat swab but positive immunoglobulin (Ig)M and IgG count, and was therefore considered possibly infected in utero.

Most recently, Sisman et al. [11] presented a preterm infant born vaginally to a 37 year old gravid 4 para 3 confirmed case of COVID-19 at 34 weeks of gestation at their hospital. With all protocol for COVID-19 labour and delivery reportedly observed, the infant's nasopharyngeal swab was positive by Real Time Polymerase Chain Reaction (RT-PCR) for SARS-CoV-2 at 24 hours and 48 hours of life. This neonate's nasopharyngeal RT-PCR for SARS-CoV-2 was still positive on the fourteenth day of her life. Interestingly, placental studies such as immunohistochemistry for SARS-CoV-2 showed cytoplasmic staining in the syncytiotrophoblastic cells and ultrastructural examination by transmission electron microscopy revealed structures that were consistent with viral particles for SARS-CoV-2. This case clearly projects a brighter light on the possibility of intrauterine vertical transmission of SARS-CoV-2. It also attempts to reveal the relevance of placental studies in investigation of a possible intrauterine transmission. For example, in this particular case, even if neonatal workups were not positive, the placental immunohistochemistry alone was convincingly good enough to reveal a possible ongoing process, particularly of a placental infection. Vivanti et al. [12] also recently reported a 23 year old primigravida at 35 weeks and two days of gestation confirmed case of COVID-19. Placental histology and immunostaining was

as well consistent for SARS-CoV-2. Baby born preterm at 35 weeks and five days of gestation was found RT-PCR positive for broncho-alveolar lavage fluid, as well as for nasopharyngeal and rectal swabs following cleansing at one hour of life and including the repeated tests at three and eighteen days of life. Alzamora et al. [13] presented a newborn baby born preterm by cesarean section at 33 weeks of gestation to a 41 year old gravida 3 para 2 with confirmed severe COVI-19. Both baseline and follow-up neonatal serology obtained at birth and analyzed by solid-phase immunochromatographic assay yielded negative IgG and IgM titers. Nasopharyngeal swab of neonate for SARS-CoV-2 RT-PCR, obtained at 16 hours of life was reported positive. RT-PCR repeated 48 hours later for confirmation was also positive. Maternal serology on day one post-delivery showed negative IgG and IgM levels, followed by positive IgG and IgM on repeat testing on day four post-delivery, strict observations of preventive measures to prevent intrapartum transmission adhered to.

Meanwhile Pulinx et al. [14] reported another case (June 2020) of a SARS-CoV-2-positive woman who gave preterm birth to two babies with SARS-CoV-2 positive amniotic fluid tests for a SARS-CoV-2. Although placental molecular studies were seemingly not performed, placental histology done revealed chronic intervillositis and extensive intervillous fibrin depositions with ischemic necrosis of the surrounding villi, lesions for which they could not find anything to attribute them to but a possible SARS-CoV-2 infection. Although no pathognomonic features for SARS-CoV-2 based on placenta histology have been identified so far [15], the authors noted that the findings supported a possibility of vertical transmission of SARS-CoV-2 infection and that miscarriage (which the mother encountered) due to the infection could not be ruled out. This probably adds a voice to other studies where adverse perinatal outcomes such as miscarriage, preterm birth and still birth have been reported [16,17].

Zeng et al. [18] reported a cohort of three infants; one born at 40 weeks of gestation, the second one at 40 weeks and four days of gestation and the third one at 31 weeks and two days of gestation all by cesarean section with possible intrauterine vertical transmission of SARS-CoV-2. Nasopharyngeal and anal swabs for RT-PCR on first and fourth day were positive for the first and third baby and positive on first day but negative on fourth day for the second baby respectively; amidst strict preventive measures for COVID-19 during delivery. The authors concluded that the source of SARS-CoV-2 infection in the neonate's upper respiratory tract or anuses were maternal in origin. Similarly, Zamaniyan et al. [19] reported a baby born preterm at 32 weeks to a 22 year old patient of COVID-19. Amniotic fluid samples obtained by intact membranes aspiration at cesarean delivery were found positive for SARS-CoV-2. Nasal and throat swabs of the newborn tested positive at 24 hours as well.

A remarkable number of preprints of case reports for intrauterine vertical transmission of SARS-CoV-2 have also been noted. For example, the one of Hosier et al. [20] which reports a 35 year old gravida 3 para 1011 woman that presented at 22 weeks of gestation with features of COVID-19 infection, analysis of which confirmed her with SAR-CoV-2. Molecular and immunohistochemical assays and electron microscopy revealed SARS-CoV-2 localized predominantly to syncytiotrophoblast cells at the maternal-fetal interface of the placenta [US CDC qRT-PCR assay for the placenta (3×10^7 virus copies/mg) and umbilical cord (2×10^3 virus copies/mg)]. Fetal heart and lung tissues were also tested and met the human RNA control (RNase P) standards and were reportedly negative for the virus RNA. This is a case of SARS-CoV-2 infection probably localized within the placenta (placental) but which had probably not crossed to involve the fetus. It is possible that certain factors like those involving a breach in the placental barrier enhance the risk of infection to the placenta and subsequently the fetus. In this particular case for example, the fact that the mother had concurrent preeclampsia (as is reported in the study report) could *per see* have attributed to the observed placental infection.

2. What do We Learn?

The definition criterion for intrauterine vertical transmission of SAR-CoV-2 seems to be an issue for purposes of standardization of cases and their reporting. According to Blumberg et al. [21], intrauterine vertical transmission of SARS-CoV-2 has likely occurred (even if the neonate is asymptomatic) if there is evidence of both early exposure and persistence, that is, at least one item in each of the following three categories: the mother is positive for SARS-CoV-2 between fourteen days prior to birth and two days after birth; OR, early exposure; in an instance where the virus is detected in any of either: a swab of the neonatal respiratory tract (nasopharynx, oropharynx, or saliva) in the first 24 hours of life, amniotic fluid, umbilical cord blood, or a neonatal blood sample in the first 24 hours of life; persistence: in an instance of either of a swab of the neonatal respiratory tract (nasopharynx, oropharynx, or saliva) is positive after 24 hours of postnatal life, or if the neonate has a positive SARS-CoV-2 IgM assay in the first seven days of postnatal life. This protocol however does not consider immunohistochemical detection of SARS-CoV-2 in the placenta or other possible placental related diagnostic studies for this virus. Amidst such challenges, case reports of possible intrauterine vertical transmission keep evolving and attention is worth paid for possibly more investigation and intervention.

Basing on these case reports and series, it can be noted that for most of them, the routes of possible transmission of the infection to the intrauterine environment remains obscure. From a general point of view, pathogens are known to gain access to the placenta and the decidua as either an ascending infection from the lower genital tract especially in the case of ruptured fetal membranes, or iatrogenic spread such as in the case of invasive procedures like amniocentesis (as may be indicated for either diagnostic or therapeutic reasons), or via haematogenous spread in which the virus circulating in maternal blood stream enters the placental villus containing the fetal blood vessels, and is as such transmitted to the fetus. Blumberg et al. [21] highlights the potential maternal COVID-19 routes of transmission of SARS-CoV-2 to the fetus as haematogenous (through the placenta), or exposure to viral particles in amniotic fluid;

which may involve either inhalation or ingestion of the particles by the fetus. For most of the published literature about the cases of probable intrauterine vertical transmission so far, the source of the infection remains uncertain. Whereas it is more probable for one to think that most of these were possibly haematogenous infections arising from maternal viremia [which itself has been challenged in some literature due to the rare maternal viremia (1% of cases) and lack of the viral receptor Angiotensin Converting Enzyme 2 on the placental cells [22], we cannot underestimate the fact that recent reports have shown that fecal matter and vaginal secretions of a patient with COVID-19 are a possible route of spread of SARS-CoV-2 [23,24,25]. And in this regard, it is not uncommon that in some women, particularly those with non-intact membranes such as those with premature rupture of membranes (PROM) get lower gastrointestinal tract organisms (or probably, fecal lower genital tract contamination) gaining access to the genital tract with subsequent spread to the open intrauterine environment, usually in situations of pregnant women with poor hygiene. Whereas this is usually seen in bacterial infections, it is worth thinking about as well in the context of this ongoing situation of COVID-19. For instance, the case reported by Sisman et al. [11] was complicated with premature rupture of membranes and the authors partly attributed the transmission to have occurred due to ascending infection with the non-intact membranes and primary involvement of the maternal gastrointestinal tract. The relevance of all these modalities, in a situation of growing evidence of intrauterine vertical transmission of SARS-CoV-2 remains to be explored.

Also from the literature above, it may be clearly noted (among other 'variables') that most of the cases reported are preterm (below 37 weeks of gestation). This raises questions to do with fetal and/or maternal susceptibility to SARS-CoV-2 intrauterine vertical transmission and the depth of the mechanisms underlying this. As is noted, there is a possibility of placental infection without fetus infected. It is therefore worth suggesting that probably certain factors enhance the risk for this to happen. Future studies are desired to ascertain any associated risk factors for intrauterine vertical transmission of SARS-CoV-2.

The issue of accessibility of the necessary diagnostic tests (for most of the suggested protocols; take an instance of the one suggested by Blumberg and colleagues above) to confirm intrauterine vertical transmission of SARS-CoV-2 in certain settings is very crucial and is better thought about closely. For example, Sisman et al. [11] could not do amniotic fluid and breast milk PCR and cord blood antibody testing as they wished, for they were reportedly not available at their hospital. Zamaniyan et al. [19] was not able to measure neonatal specific IgM as it was not possible at their facility. This could be worse in low resource settings and could perhaps be partly responsible for the low number of the reported cases of possible intrauterine vertical transmission of SARS-CoV-2 among the many obstetric units in the world. Last but not least, the issue of quality control for laboratory assessment of intrauterine SARS-CoV-2 transmission for all suspected cases deserves serious consideration by future researchers.

3. Conclusion

The concern of possible intrauterine vertical transmission seems to be growing. Though seemingly sporadic, the published cases so far may justify the need for a standard protocol for diagnosis of intrauterine vertical transmission of SARS-CoV-2, clear understanding of the mechanisms and risk factors for the transmission, as well as efforts towards ensuring accessibility of the necessary diagnostics for suspected SARS-CoV-2 intrauterine infections.

Abbreviations

CDC: Centers for disease control and prevention, COVID-19: Coronavirus disease 2019, Ig: Immunoglobulin, PROM: Premature rupture of membranes, RT-PCR: Real time polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Conflict of Interest

None to declare.

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