

Exploring the emergence of vertical transmission of SARS-CoV-2: A Rapid Review

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Summary. Novel Coronavirus, SARS-CoV-2 is responsible for the global pandemic of COVID-19. It has been shown to spread through respiratory droplets, direct contact and environmental fomites. The possibility of its spread by other modes viz. airborne, fecal-oral, vertical, etc. is being explored and can have implications in planning preventive strategies and disease management. A systematic analysis was carried out using the keywords; “COVID 19 vertical transmission”, “SARS-CoV-2 pregnancy”, and “SARS-CoV-2 vertical transmission”, and the cases suggestive of possible vertical transmission of SARS-CoV-2 were studied in detail. The available evidences point at a possibility of vertical transmission of SARS-CoV-2. (www.actabiomedica.it)

Key words: Amniotic fluid; vertical transmission; SARS-CoV-2; COVID-19 pandemic

Introduction and background

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) is responsible for the global pandemic of COVID-19 (Coronavirus Disease 2019). The current research and evidence suggest that the novel coronavirus predominantly spreads from person to person through direct contact or by inhalation of droplets generated through coughing, sneezing and speaking, originating from the infected person (1,2). It has also been established that the virus may spread by touching the environmental fomites and infected surfaces (3). According to recent communications, it has been cautioned that the airborne transmission is an important factor and contributes to the spread of the virus especially in the crowded places with poor ventilation (4,5). After eight months of continuous research, not much is known about the modes of transmission of this novel virus, however, the possibility of its spread by some other modes of transmission such as the fecal-oral, vertical, through flatus, ocular surface, blood borne, animal-to-human etc. is being explored and can

have implications in planning preventive strategies and disease management (6).

Vertical transmission of SARS-CoV-2 is plausible due to some of its unique features. For one, its receptor Angiotensin-converting enzyme -2 (ACE-2) is suitably expressed in the human placenta (7). Second, it has an alleged structural similarity to HIV-1 proteins (8) and shows therapeutic response to anti-retroviral drugs. Third, it is an RNA virus like Zika. Materno-fetal transfer is well-established in both Zika and HIV.

Clinically, COVID-19 can be suspected in adult patients with non-specific clinical presentations like fever, cough, sore throat, anosmia, body ache etc., the majority of cases remain asymptomatic and maternal diagnosis must therefore be established by laboratory testing. The clinical dilemma of diagnosing a neonate with COVID-19, especially asymptomatic presentations, also requires the same confirmatory test. While real time reverse transcriptase PCR on respiratory specimens for detection of SARS-CoV-2 RNA remains the gold standard for diagnosis of COVID-19

in all age groups (9). Various newer approaches like antigen testing, antibody detection and serum inflammatory markers have been tried worldwide with various degrees of diagnostic success (10).

Most of the existing reviews and meta-analysis on this topic have focussed on RT-PCR COVID-19 positive mothers and the possibility of vertical transmission in their outcomes. However, there is a paucity of reviews focussed solely on neonates with RT-PCR confirmed COVID-19 diagnosis soon after birth.

A review and analysis of studies regarding vertical transmission of SARS-CoV-2

With this background, a systematic analysis of the available literature was carried out using the keywords; “COVID 19 vertical transmission”, “SARS-CoV-2 pregnancy”, and “SARS-CoV-2 vertical transmission”. Among all reported COVID-19 pregnancies only those cases with RT-PCR confirmed new-borns were studied in detail for the plausibility of Vertical transmission of SARS-CoV-2. A total of 12 new-borns (11-17) with confirmed COVID-19 infections were identified in literature at the time of writing.

While a review of 55 pregnancies (7) did not show any evidence of vertical transmission, a total of 6 studies comprising 11 new-borns (11-15,18) has presented striking arguments in favour of vertical transmission of SARS CoV-2 (Table 1). Pregnancy with COVID-19 has been associated with pre-term birth in >20% cases and perinatal death in 7% which suggests that fetal risk associated with the infection is worth investigating (19).

Among the reported cases, demonstration of SARS-CoV-2 RNA in amniotic fluid by RT-PCR at the time of delivery (15) is a strong argument in favour of vertical transmission, at least in cases where maternal infection was severe in peripartum period. The fact that the nasopharyngeal RT-PCR was positive in three neonates born by LSCS, which obviated the possibility of acquisition of the virus from the birth canal (11,14,15), further strengthens the possibility of vertical transmission. The neonates reviewed in this study had all been delivered via caesarean section, however, it has been previously established that there

is no measurable safety of LSCS over vaginal birth in COVID-19 pregnancies (20).

Since all the maternal SARS-CoV-2 reports were confirmed before delivery, the claim of strict adherence to contact, droplet and airborne precautions during the peri and postpartum period in all these cases, is believable, rendering the possibility of nosocomial acquisition by the new-born very low. The detection of IgM in the new-born, also favours the possibility of in-utero contact with the virus, as being a large molecule, it does not cross the intact placenta and cannot be acquired from the mother.

The results of neonatal RT-PCR positivity alone may not be sufficient to prove vertical transmission. A recent review and meta-analysis may have prematurely asserted a vertical transmission rate of 3.2% based on a combination of positive neonatal nasopharyngeal, cord-blood, rectal swab and serology (21). We feel it would be prudent to gather more definitive evidence before a consensus opinion can be agreed upon.

The vertical transmission of COVID-19 has remained a topic of debate since the last 8 months but can it be proven at all? Theoretically, it will require SARS-CoV-2 RNA to be demonstrable in the respiratory secretions of the mother and newborn, as well as in the placenta, membranes or other products on conception in the same delivery outcome. Those seeking the answer will have to adopt a planned prospective approach and conduct molecular testing of all the specimens enumerated above, perhaps more than once, to rule out false negatives.

The development of more sensitive viral nucleic acid load detection methods remains the need of the hour. The non-detection of viral nucleic acid in umbilical cord blood, placenta, amniotic fluid and breast milk (11) in some studies could simply be due to low viral load, poor sensitivity of existing techniques, flawed timing of amniocentesis and effective pre-operative antiviral administration.

Conclusion

In light of the above findings, there seems to be a strong possibility of vertical transmission of SARS-CoV-2, if the same can be virologically proven. If

Table 1: A rapid review of cases suggesting possible vertical transmission of SARS-CoV-2

Parameter	Wang et al (11)	Dong et al (12)	Zeng et al (13)	Alzamora et al (14)	Zamaniyan et al (15)	Yu et al (18)
Number of new-borns	1	1	6	1	1	1
Gestational age	40 weeks (Emergency LSCS)	37 weeks, 6 days (Elective LSCS)	Full -term (Elective LSCS)	33 weeks; pre-term	32 weeks; pre-term (Emergency LSCS)	39 weeks + 6 days (Emergency LSCS)
Clinical symptoms	Asymptomatic	Asymptomatic	Asymptomatic	Mild respiratory difficulty on day 6	Fever at birth	Asymptomatic
Investigations undertaken on the new-borns:						
Nasopharyngeal aspirate RT-PCR	Positive after 36 hours of birth	Negative	Negative	Positive at 16 hours of birth	Positive after 1 week	Positive at 6hrs of birth
Cord blood RT-PCR	Negative	Not done	Not done	Not done	Negative	Not done
Serum RT-PCR	Not done	Not done	Negative	Not done	Not done	Not done
Anti- SARS-CoV-2 IgM	Not done	Elevated (at 2 hours of birth)	Elevated in 2 cases	Negative	Not done	Not done
Anti- SARS-CoV-2 IgG	Not done	Elevated (at 2 hours of birth)	Elevated in 5 cases	Negative	Not done	Not done
Inflammatory cytokine IL-6	Not done	Not done	Elevated in all 6 cases	Not done	Not done	Not done
Maternal investigations:						
Nasopharyngeal swab RT-PCR	Positive	Positive	Positive	Positive	Positive	Positive
Amniotic fluid RT-PCR	Negative	Not done	Not done	Not done	Positive	Not done
Anti- SARS-CoV-2 IgM	Not done	Positive	Elevated in 4 cases	Positive on post-partum day 4	Not done	Not done
Anti- SARS-CoV-2 IgG	Not done	Positive	Elevated in 5 cases	Positive on post-partum day 4	Not done	Not done
Placental tissue RT-PCR	Negative	Not done	Not done	Not done	Not done	Not done
Vaginal secretion RT-PCR	Not done	Negative	Not done	Not done	Negative	Not done
Breast milk RT-PCR	Negative	Negative	Not done	Not done	Not done	Not done
Associated maternal mortality	--	--	--	--	Yes (19 days post-LSCS)	-
Pre-op prophylaxis	Recombinant human interferon alfa 1b and Ganciclovir	Details not mentioned	Details not mentioned	Hydroxychloroquine and Oseltamivir	Hydroxychloroquine Lopinavir, ritonavir, and Oseltamivir	Oseltamivir, ganciclovir, interferon + antibiotics
Our inferences on possibility of vertical transmission	Neonatal Nasopharyngeal RT-PCR positive at 36 hours suggests possible vertical transmission	Elevated neonatal IgM at birth suggests possible vertical transmission	Elevated neonatal IgM at birth suggests possible vertical transmission	Positive neonatal Nasopharyngeal RT-PCR at 16 hours suggests possible vertical transmission	Positive amniotic fluid and neonatal Nasopharyngeal RT PCR suggests possible vertical transmission	Positive neonatal Nasopharyngeal RT-PCR at 6 hours suggests possible vertical transmission

proven, there would be an urgent need to device sensitive and economical screening tests in pregnancy, effective pre-operative anti-viral regimens, operative protocols, guidelines for new-born screening and safety of breastfeeding etc. The current evidence is limited by the non-availability of Maternal Serum viral RNA load which, akin to HIV, may be tried as a predictor of the risk of vertical transmission, paired with amniotic fluid testing in severe maternal illness. The same may be considered before elective COVID-19 caesareans in future studies. Any publications on fetal outcomes of mothers with severe infection, who could not receive timely hydroxy-chloroquine and pre-operative antivirals, will also fill the gaps in our current understanding of the topic. Global reporting of all COVID-19 pregnancies using COVI-Preg, a structured data collection (22) will assist in swift formulation of management guidelines for the same.

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