



COVID 19 Vertical Transmission: A Growing Concern

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Abstract

Context: COVID 19 vertical transmission is a great concern in different aspects of mother, child, healthcare staff and community safety and protection. There is lack of definitive evidence confirming or declining mother to child COVID 19 transmission. This article is an update on this challenging issue.

Evidence Acquisition: This article is a comprehensive search in scientific major database from 1 January 2020 up to 25 April 2020 with the key words of "COVID 19" and "vertical transmission" or "neonatal". Two researchers reviewed all selected articles to extract data about neonatal COVID 19 and vertical transmission. Those reports that provided the results of PCR on fetus or neonate blood, amniotic fluid or pharyngeal secretion samples or elevated COVID 19 specific IgM were included. Those reports based on clinical COVID 19 characteristics or radiological findings were not included in data extraction. Thirty six articles have been reviewed and evidence supporting or against COVID 19 Vertical transmission have been extracted and discussed.

Results: Most previous studies on vertical COVID 19 transmission have been tested placenta, amniotic fluid, cord blood and newborn blood or pharyngeal swab sample using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) that may show false negative results due to suboptimal sampling or inefficient viral load. Increased COVID 19 specific IgG/IgM antibodies have been reported in newborns from COVID 19 mothers; however, data is limited and longitudinal follow up is needed. Evidence supporting COVID 19 vertical transmission: Recent reports indicated that pharyngeal PCR test turned positive in first few hours of life in several neonates. Also increased level of COVID 19 specific IgM and IgG antibodies in newborns to COVID 19 positive mothers were observed. Rate of perinatal complications were higher among newborns of COVID 19 mothers. Evidence against COVID 19 vertical transmission: All tissue or blood specimens and pharyngeal swab qRT-PCR tests among neonates born from COVID 19 mothers were negative. Rate of cross reactivity and false positive results are high in serologic studies.

Conclusions: COVID 19 vertical transmission is a growing health care concern that needs further investigation; however, it is suggested to be equipped with PPE on contacts with both COVID 19 pregnant woman and her newborn baby and apply early separation, isolation, testing and close follow up for both mother and child.

Keywords: Pregnancy, Newborn, Neonate, Fetus, Vertical Transmission, COVID 19

1. Context

The first case of new coronavirus 2019 disease was officially reported on 31 December 2019 in China, where a new epidemic initiated and rapidly spread all around the world. WHO declared a state of global health emergency on this new evolving outbreak on 30 January 2020 (1).

Almost 3000 thousand infected COVID 19 patients are diagnosed worldwide at the time of this article on the end of April 2020. About 220 thousand deaths are reported and health system faces a serious challenge worldwide (2).

COVID 19 is highly contagious with estimated mortality rate of 3.4% (3). Human to human transmission is documented for 2019-nCoV mainly through direct contact, respiratory droplets or touching the contaminated surface (4, 5). Feco-oral transmission, mother to child vertical transmission or transmission through breast milk and infected

blood products are yet to be assessed and confirmed (6-8).

Recommended approach for COVID 19 infection control is summarized in applying hand hygiene and face masks in community, early detection and isolation of new cases and standard personal protective equipment for healthcare workers.

qRT-PCR assay of nasopharyngeal swab specimen is suggested as the best method of screening and diagnosis confirmation for COVID 19 although the results may be affected by the sampling technique, viral load and other technical issues (9).

Mother to child vertical transmission was a hypothesis that raised a great concern as a route of COVID 19 transmission because of challenges in healthcare protection, mother-child relation, emotional and breast feeding issues and expected complications.

Several cases of COVID 19 pregnancy have been published; however, there is lack of definitive evidence confirming or declining this hypothesis.

This article is an update in form of a narrative review on COVID 19 vertical transmission that is a growing concern these dates.

2. Evidence Acquisition

This article is a comprehensive search in scientific major database including Medline, Scopus, EMBASE, SciELO, Cochrane Database and Google scholar from 1 January 2020 up to 25 April 2020 with the key words of "COVID 19" and "vertical transmission" or "COVID 19" and "neonatal". All published or unpublished (pre-print or even pre-proof accepted literature in English) were included and 43 articles were listed primarily. Those articles that reported or discussed about COVID 19 in perinatal period were eligible to include in this narrative review.

36 full texts were reviewed after title selection and excluding duplicate articles.

Two researchers reviewed all selected articles to extract data about neonatal COVID 19 and vertical transmission. Those reports that provided the results of PCR on fetus or neonate blood, amniotic fluid or pharyngeal secretion samples or elevated COVID 19 specific IgM were included.

Those reports based on clinical COVID 19 characteristics or radiological findings were not included in data extraction.

We designed this narrative review in two main parts including the evidence supporting or against COVID 19 vertical transmission and discuss about the final conclusion and recommendations.

3. Results

3.1. Evidence Supporting COVID 19 Vertical Transmission

Back to the history of well-known viral infections and previous outbreaks such as Zika virus, Ebola or Marburg virus, we would figure out that vertical transmission and adverse effects of viremia on fetus has been proven for these viruses. TORCH syndrome with maternal morbidity and adverse effects on fetus brings up serious concerns on the risk of COVID 19 in pregnancy (10).

Angiotensin-converting enzyme 2 (ACE2) expression has a key role in pathogenesis of COVID 19 as a surface receptor. ACE2 expression in placenta supports the potential for placental involvement in COVID 19 (11).

COVID 19 behave like SARS-Cov-1 in terms of affecting receptors. Previous studies revealed a low risk of vertical

transmission for SARS-Cov-1 and this is also anticipated for COVID 19 (12).

Primary observations suggested that children are less likely infected with COVID 19 (13). Along with evolving outbreak and widespread screenings, several asymptomatic infected children were identified in family clusters although children showed a mild and subtle disease that may be explained by their different innate immune response. Further investigations are needed to illuminate pathogenesis of COVID 19 in fetus, newborns and infants.

In early stage of COVID 19 pandemic, evidences were supporting the absence of vertical transmission as all tissue or blood specimens and pharyngeal swab qRT-PCR tests were negative for COVID 19. Different immune response and disease course in children may also alter the validity of COVID 19 diagnostic tools that are applied in children based on the experiences in adults. A negative pharyngeal swab test in a newborn with probable hematogenous infection supposed to be less reliable compared to adults with respiratory tract contamination via droplets containing the virus.

Blood and tissue sample PCR test may become positive for COVID 19 but it is not common even in a symptomatic patient confirmed with positive test on respiratory tract secretions. COVID 19 disease could not be ruled out neither by the negative pharyngeal swab test nor by negative blood and placenta PCR results (14, 15). Better understanding of COVID 19 pathogenesis in fetus and newborn may help us to identify other targeted organs and shows the optimal methods of diagnosis in early neonatal period. The result of qRT-PCR test depends on the viral load and false negative results may be expected during the early stage of disease (16, 17). so there is doubt about real validity of a negative pharyngeal swab RT PCR test in a newborn considering all these limitations (15).

Although several articles indicated negative COVID 19 PCR results on vaginal secretion samples but Scorzolini et al. reported positive RT-PCR test of vaginal fluid a week after COVID 19 symptoms in a 65 year-old woman that supported the risk of COVID 19 vertical transmission in vaginal delivery (18).

Most of reported cases of COVID 19 pregnant women were in the third trimester and mothers became symptomatic during the final weeks of gestation. Short interval between probable contamination and delivery may decrease the chance of detecting vertical transmission as the pandemic is a recent outbreak and emerging health issue (11). Rubella infection also is demonstrated to affect the fetus during the first trimester and commonly its fatal consequences reduced significantly in late pregnancy infections (19).

Recently we encountered some reports from China, India, Iran and UK in favor of neonatal COVID 19 and as the time passes, we may expect more cases of COVID 19 in neonatal period that could be justified by increased risk of vertical transmission in pregnancies that were affected by COVID 19 as early as first or second trimester. A same vertical transmission pattern had been observed for Cytomegalovirus (11).

Some neonates born to pregnant COVID 19 mothers revealed positive results in pharyngeal swab samples qRT-PCR testing few hours after birth (11). Although we have to consider the possibility of cross infection during first hours after birth but this is very unlikely as mothers were known cases of COVID 19 and early separation and full protection were applied. Wang et al. reported a case of COVID 19 positive pharyngeal swab test in a newborn just 36 hours after birth however the mother had been wearing N95 mask during emergent cesarean section and prompt separation and isolation of newborn was conducted after delivery and breast feeding was prevented (16).

One of the largest case series on COVID 19 pregnancy was published by Zeng et al. on 33 COVID 19 pregnant mothers. The results showed 3 infected neonates with positive nasopharyngeal test 2 days after birth, in the meanwhile they had symptoms and signs of pneumonia in chest radiography that was strongly suggested to be in uterus infection considering the COVID 19 incubation period (20).

Yu et al. followed 7 COVID 19 pregnant patients and reported one positive SARS-Cov-2 nucleic acid pharyngeal swab test in a newborn at 36 hours after birth (21).

Diaz et al. reported a newborn whose pharyngeal PCR test turned positive in first 36 hours of life; however, primary test was negative. Cluster involvement was also detected retrospectively in this family. Both vertical and horizontal transmission was possible in this case as early isolation was not applied (22).

One of the most comprehensive reviews on COVID 19 pregnancies by Gajbhiye et al. reported 12 positive RT-PCR tests for COVID 19 in first 48 hours of life over 108 deliveries from COVID 19 infected pregnant mothers (17). This study notably supports the possibility of vertical transmission with the estimated rate of 11%. Fourteen percent of neonates born to COVID 19 mothers developed pneumonia in early neonatal period that was higher than expected rate of neonatal pneumonia. This observation suggests that newborns of COVID 19 pregnancies may be affected by mothers' viral infection whether with direct vertical transmission or its indirect physiological side effects (17).

Two recent studies were assessed serum level of COVID 19 specific IgM and IgG antibodies in newborns born to COVID 19 positive mothers and observed high level of both

IgM and IgG (23, 24).

All 6 neonates who were born to COVID 19 mothers in Zeng et al. study revealed elevated inflammatory cytokines (IL6) and two of them showed elevated level of COVID 19 specific antibodies (23).

Another case report by Dong et al. reported elevated serum level of COVID 19 specific IgG and IgM and inflammatory cytokines two hours after birth in a girl from a COVID 19 mother. COVID 19 specific antibodies were remained elevated 2 weeks after birth (24).

Increased level of IgG could be explained by transplacental diffusion from infected mother while presence of IgM strongly indicates a self-immune response of newborns if we assume normal placentas in these cases (11). Although the interpretation of these immunological profiles in early neonatal period is difficult regarding our limited knowledge about fetus response to COVID 19 exposure (25).

An analytic study on the diagnostic value of COVID 19 antibody detection indicated increased level of IgM/IgG after the first week of COVID 19 infection while PCR test on COVID 19 RNA detection in pharyngeal swab specimens may be negative in early stage of disease.

Li et al. reported respiratory problems in a neonate born to a COVID 19 mother after two days from natural vaginal delivery and mentioned the probable risk of contamination in vaginal route (26).

Viral shedding is reported in body secretions of some COVID 19 patients such as faeces or peritoneal fluid which was also observed in previous SARS outbreak. This finding offers the risk of transmission during both vaginal and cesarean delivery (27). Regarding the experience on SARS CoV1, WHO discourage delayed umbilical cord clamping in COVID 19 deliveries because of the potential risk of vertical transmission (28).

3.2. Evidence Against COVID 19 Vertical Transmission

COVID 19 specific RT PCR test on respiratory secretions is accepted as the method of choice to screen and demonstrate COVID 19 infection. Several studies have been conducted on COVID 19 pregnant women to evaluate the effects of new coronavirus on fetus; however, PCR test on all specimens from amniotic fluid, cord blood, vaginal secretions and breast milk samples in infected mothers were negative (29). There is lack of evidence supporting transvaginal contamination and even some authors are doubtful about the superiority of cesarean section over vaginal delivery in COVID 19 patients (30).

Although there are reports of positive COVID 19 PCR tests obtained from nasopharynx of neonates during the first day after delivery, but absolute perinatal isolation and

optimal sampling method are not easy to apply during delivery and early neonatal period that may cause horizontal transmission or cross infection (22).

Two recent articles reporting increased COVID 19 specific IgM raised new concerns about vertical transmission of COVID 19 (23, 24). However, this evidence was not strong enough to draw a final conclusion. High level of IgM may be detected in radioimmunoassay in the absence of a targeted infection as it is reported in congenital rubella, syphilis, toxoplasmosis and Zika virus. This phenomena may happen due to interactions with rheumatoid factor, incomplete IgG removal, non-specific or cross reactivity with other viruses (31). On the other hand, a sudden decline in COVID 19 specific antibodies have been reported during 2 hours after birth that is in favor of maternal origin of antibodies (11).

An update on COVID vertical transmission that was published by Fornari on April 2020 reviewed several series of COVID 19 affected pregnancies that reported negative qRT-PCR tests on all collected samples from amniotic fluid, cord blood, neonatal throat swab, breastmilk and newborn blood (16, 19, 27, 32, 33).

Review of COVID 19 pregnancies didn't show significant increase in the rate of peri-partum problems. Schwartz et al. did not identify any serious maternal or fetal complication in a multi centric review of 38 pregnant women with COVID 19 (10). A joint mission by WHO also did not report considerable rate of complications over 147 pregnant women with COVID 19 infection in China (10, 34).

Khan et al. followed 3 COVID 19 patients during pregnancy and delivery and reported a high rate of preterm labor in their observation and literature review while all samples were negative in newborns. They concluded that the higher rate of perinatal complications may not associate with direct COVID 19 infection and vertical transmission however the pregnancy and labor may be affected by psychological consequences of COVID 19 infection indirectly (35).

Lack of maternal-fetal transmission had been reported in previous experiences with other members of coronavirus family including SARS and MERS (10).

4. Discussion

What we know about the behavior of this new Coronavirus is limited and uncertain. More updates are coming on every single issue related to COVID 19 every now and then.

COVID 19 vertical transmission is one of these controversial issues that has remained unclear up to date. Primary observations indicated no risk for mother to fetus

transmission that was mainly based on previous experiences on SARS an MERS and primary COVID 19 reports. Several cases of neonatal COVID 19 involvement are reported recently. These new evidences may change the old concepts and this article tries to provide all these evidences for a better conclusion. As the risk of vertical transmission is very important for neonatologists and neonatal health care providers in term of safety and disease control, COVID 19 vertical transmission is a great challenge for both patients and caregivers. Confirmed replication of COVID 19 in lung tissue specimen of a stillbirth from an infected pregnant case of COVID 19 could be the strongest evidence of disease vertical transmission (11). In the absence of such evidence, the diagnosis of COVID 19 in fetus or newborn remains a topic for discussion.

Most previous studies evaluating vertical COVID 19 transmission were focused on demonstrating presence of COVID 19 in placenta, amniotic fluid, cord blood and newborn blood or pharyngeal swab sample using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) (11).

qRT-PCR may show false negative results due to suboptimal sampling and inefficient viral load, therefore a negative RT PCR will not rule out COVID 19 infection (9).

Some authors reported increased COVID 19 specific IgG/IgM in newborns to COVID 19 mothers; however, data is limited and longitudinal follow up is needed to monitor the antibody profile of mother and child for better interpretation. Besides some other confounding factors should be evaluated such as abnormalities of placenta or the probable effects of COVID 19 on placental physiology.

Scorzolini et al. reported negative PCR results of vaginal swab in early stage of COVID 19 that turned positive on day 7 and 20 after COVID 19 symptoms, so they suggest cesarean section to preclude possible vertical transmission (18). This approach is rational while possibility of cross infection during vaginal labor is unclear.

Review of literature on COVID 19 mother to child transmission during pregnancy and labor revealed that COVID 19 vertical transmission is a growing concern that needs further investigations. Regarding limited data and evidence on COVID 19 vertical transmission, current expert consensus supports early separation of newborn from COVID 19 mother and elimination of breast feeding until two consequent negative tests (36). Both mother and newborn must be followed for at least two weeks (12).

Limitations of our study were lack of data on longitudinal follow up of COVID 19 IgM positive neonates and lack of reliable data on newborn isolation state among COVID 19 cases during neonatal period.

Considering the potential of COVID 19 vertical trans-

mission it is recommended to keep maximum personal protection during management of neonates born to COVID 19 mothers (33).

5. Conclusion

COVID 19 vertical transmission is a growing health care concern that needs further investigation; however it is suggested to be equipped with PPE on contacts with both COVID 19 pregnant woman and her newborn baby and apply early separation, isolation, testing and close follow up for both mother and child.

Footnotes

Authors' Contribution: Ahmed Athab Alzubaidi did the systematic search and provide the full text, Ameer Isam AlAasam and Sultan Muhsin Ghanim reviewed the articles and extracted the data, Reza Shojaeian wrote and design the manuscript and Sultan Muhsin Ghanim supervised and edited the draft.

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