Intrauterine Vertical Transmission of SARS-CoV-2 Infection Among Confirmed Cases of Pregnant Women: “A Double Burden for the Pregnant Women”—A Systematic Review

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Abstract

Introduction. The world health organization (WHO) has declared the outbreak of novel coronavirus (2019-nCoV), which is now known as Coronavirus Disease 2019 (COVID-19). Whereas, its quick global spread has resulted in a worldwide pandemic. The present review article was intended to evaluate intrauterine vertical transmission of SARS-CoV-2 infection among confirmed cases of pregnant women. Methods. Web of Science, EMBASE, PubMed, African Journals OnLine, Scopus, PsycINFO, HINARI, Cochrane Library, Wiley Online Library, and Google scholar were used for search. Result. A total of 43 articles were included in this systematic review. A total of 1,300 neonates born from pregnant women confirmed for COVI-19 were tested for SARS-CoV-2 infection by real-time reverse transcriptase–polymerase chain reaction (RT-PCR). From the 1,300 neonates tested for SARS-CoV-2 infection, 93 neonates were found positive for this infection by RT-PCR. From this systematic review finding, the vertical transmission rate of SARS-CoV-2 infection was 7.15%. This pandemic has stressed the entire public, particularly pregnant women and healthcare providers, while it challenged antenatal care and postnatal care by far. Thus, even being under lockdown in the middle of a global pandemic is stressful enough. Therefore, imagine the added burden of being pregnant, which could be a double burden for these women. Conclusion. There is no concrete evidence of vertical transmission of SARS-CoV-2. Therefore, due to the limited number of clinical evidences, obstetricians, pediatricians, and other healthcare providers should continuously update their knowledge and be conscious about the transmission of SARS-CoV-2 vertically during pregnancy.

Keywords
COVID-19, SARS-CoV-2, novel coronavirus, pregnancy, vertical transmission

Introductions

The COVID-19 pandemic was initially reported from Wuhan, China.1,4 The outbreak of infection with SARS-CoV-2 has developed in China and has spread across different countries since December 2019.5 Emergency action have been taken by Chinese government to control this outbreak.6 It has been brought to worldwide attention and stated as a pandemic by the WHO.7 Since this pandemic is an extremely contagious disease,8 it is spreading swiftly.9 It is spreading globally,10,11 and remains a worldwide challenge.12 This pandemic has a substantial mortality and morbidity rates,1,9,13 while it also causes an extensive economic crisis.14 This burden has required drastic measures across all continents.15 The COVID-19 has the potential to devastatingly influence young children’s development globally.16 Due to this, mental health is a key community problem.17 It has an enormous influence on the mental health of youth.18 Moreover, fears are growing regarding the impact of the virus on the sexual and reproductive health of women and girls. This is due to that the virus has an devastating effect on them.19 This pandemic has also put massive stress on healthcare workers, patients,
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and healthcare systems. The pregnancy care and fetal diagnosis should be continued. It has an extreme effect on pregnant mothers and women in the early postpartum period emotional wellbeing. There is the potential for pregnant women to be susceptible to mental problems during this pandemic.

The governments have applied lockdowns to limit the movements of people as methods to control the spread of the pandemic. Several countries have employed physical distancing, lockdowns, and stay-at-home actions to control it. Its spread has formed several of the problems for the society because of the absence of a vaccine and effective treatment. The extent of the COVID-19 crisis represents an extraordinary global challenge. This has resulted in problems such as isolation, mental health problems and economic instability. This pandemic has brought major deviations to social behavior.

There has been a hasty increase in the study in reply to the outbreak of this pandemic. Despite the researches are pertinent to control this pandemic, further quality study is required to offer reliable strategies to manage this health crisis in a short term and long term. Therefore, this systematic review was intended to evaluate the potential intrauterine vertical transmission of a novel SARS-CoV-2 among confirmed cases of pregnant women.

Methods

Research Question

1. “Is the Intrauterine Vertical Transmission of SARS-CoV-2 Infection being possible among confirmed cases of pregnant women?”
2. “Is there a controversy on the possibility of the Intrauterine Vertical Transmission of SARS-CoV-2 Infection among confirmed cases of pregnant women?”

Study Period, Setting, and Type

In this systematic review, studies published up to December 15, 2021 were comprised. During this, several studies from different countries were considered. Moreover, any reports in any setting in any country were considered for this study. Regarding to the included study types, different study types were included in to this systematic review. For instance; cross-sectionalas, letters to the editor, case report, short communications, case-control, case series, and cohort studies were included in to this study.

Study Subjects

The study subject for this systematic review was newborns delivered by COVID-19 infected women. Pregnant women infected by COVID-19 confirmed by RT-PCR laboratory were considered for this study.

Search Strategy

Web of Science, EMBASE, PubMed, African Journals OnLine, Scopus, PsyCINFO, HINARI, Cochrane Library, Wiley Online Library, and Google scholar were used for search. All electronic sources of information were searched for the articles. “COVID-19,” “SARS-CoV-2,” “pregnancy,” “neonates,” and “Newborn” were the search terms used to find the related articles. To integrate these search terms; “AND” and “OR” Boolean operators were used.

Study Selection Criteria

The inclusion criteria for this study were; (1) articles which reported findings from newborn/s born by pregnant women infected by COVID-19 (confirmed by RT-PCR laboratory) and for which the laboratory test was done and reported with in the article; and (2) articles published in English language. Whereas, the articles which didn’t reported the test results for newborn/s and pregnant women, articles with poor quality and articles which were not fully accessible were excluded from this study.

Outcome Interest

The primary outcome of this study was the potential vertical transmission of a novel SARS-CoV-2 infection in pregnant women. Thus, the outcome variable was the positive/negative vertical transmission of a novel SARS-CoV-2 infection in pregnant women as per the report of the included studies.

Data Extraction

Data were exported to Thomson Reuters EndNote version 8 after retrieval of the articles from the databases used. The articles were checked for the relevance of the title and abstracts to be included in to this study according to a pre-setted study selection criterion. A Microsoft Excel worksheet was used to extract the data from the selected articles. The prepared format has incorporated first author name, year of publication, sample size, study country, participants, study design, possible vertical transmission, and sample type and results.

Quality Assessment, Data Synthesis, and Reporting

The quality of each article was checked to include in to this study. The quality of articles which were case report
and case series were assessed by the “Methodological quality and synthesis of case series and case reports” prepared by Murad et al. The Newcastle-Ottawa Scale (NOS) quality assessment criteria was used for other studies. For this study, a modified NOS was used and ≥5 from 10 scores was used to classify the article as a high quality score and to include the articles in this study. This systematic review was conducted on the vertical transmission of a novel COVID-19 infection among pregnant women. For study screening, selection, and inclusion in this systematic review, a PRISMA flowchart diagram, and PRISMA checklist were used.

Ethics Approval and Consent to Participate
This study is a systematic review which was done by reviewing different articles published on different journals worldwide. There was no data collected from human. Therefore, Ethics approval and consent to participate were not applicable for this study.

Result
Search Results
A total of 7098 articles were identified through a search made by all the above listed databases. From these, 4090 articles were excluded because of the duplications found. From the remaining 3008 articles, 2862 were excluded by title and abstract due to irrelevance. From the total 146 articles screened for full text, 36 articles were omitted because of full text were not accessible. From the remaining 110 articles screened for eligibility, 25 articles excluded due to full text not in English, 23 articles excluded due to the outcome variable not well defined, and 19 articles excluded because of poor quality. Finally, 43 articles were included in this systematic review (Figure 1).

Study Characteristics
A total of 43 articles were included in this systematic review. This systematic review has included various articles from different countries such as China, Spain, United States, Central America, India, Iran, Italy, Timisoara, Rome, French Guiana, United states, and Brazil (Table 1).

Intrauterine Vertical Transmission of SARS-CoV-2 Infection
A total of 1300 neonates born from pregnant women confirmed for COVI-19 were tested for SARS-CoV-2 infection by RT-PCR. From the 1300 neonates tested for SARS-CoV-2 infection, 93 neonates were found positive for this infection by RT-PCR. From this systematic review findings, the vertical transmission rate of SARS-CoV-2 infection was 7.15% (Table 1).

Controversy on intrauterine vertical transmission of SARS-CoV-2 infection. Below is a brief summary of studies conducted among COVID-19 positive pregnant mothers who gave birth. According to these studies, there are controversies upon the outcome of neonates born from confirmed cases of COVID-19 women. Discrepancies were seen between the currently existing literatures. Some of the studies are reported that there were no positive infants born from COVID-19 positive pregnant women. This because of that the findings from some studies showed that there were SARS-CoV-2 positive infants born to SARS-CoV-2 positive women (Table 1).

Discussion
A total of 43 articles were included in this study. This systematic review has included various articles from different countries such as China, Spain, United States, Central America, India, Iran, Italy, Timisoara, Rome, French Guiana, United states, and Brazil. A total of 1300 neonates born from confirmed COVI-19 pregnant women who were tested for SARS-CoV-2 infection by RT-PCR.

From the 1300 neonates tested for SARS-CoV-2 infection, 93 neonates were found positive for this infection by RT-PCR. From this systematic review finding, the vertical transmission rate of SARS-CoV-2 infection was 7.15%. According to the studies, there are controversies upon the outcome of neonates born from confirmed cases of COVID-19. Discrepancies were seen between the currently existing literatures. Some of the studies are reported that there were no positive infants born from COVID-19 positive pregnant women. This because of that the findings from some studies showed that there were SARS-CoV-2 positive infants born to SARS-CoV-2 positive women.

The vertical transmission of several microorganisms to the fetus from an infected mother can lead to shocking consequences. This can be happened during antenatal or per-partum, but perinatal or postnatal transmission can have severe results. The evidence revealed that COVID-19 causes some histopathological changes. Even though the vertical transmission of the virus is clear not yet, however, the available data indicated that there was an indirect effect of the virus on the fetus.

The earliest data have reported as there is no concrete evidence for vertical transmission of SARS-CoV-2 virus because of intrauterine infections. It will probably
be a rare that fetuses will be uninfected at the time of their birth, if intrauterine transmission of SARS-CoV-2 occur.83 There is no information found for vertical transmission of this virus from confirmed pregnant mothers to fetuses. However, the women could be at augmented risk for more severe respiratory complications.84 The available data revealed that the vertical transmission of this virus from infected mothers in a third trimester maybe doesn’t happen.85 The vertically transmission, short-term, and long-term harm of SARS-CoV-2 to offspring is still uncertain.52

Currently, there is no strong evidence of intrauterine transmission of SARS-CoV-2.86 The earliest data showed that COVID-19 may not lead to the augmented risk in the pregnant population. Besides, they were not confirmed the vertical transmission.87 The earliest study showed that the clinical features of infected pregnant women with this virus in late pregnancy were found to be similar to those of nonpregnant patients.88 However, since the impact of this virus on pregnant women is still limited, they should be given a consideration including their newborns, about COVID-19 management and

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**Figure 1.** PRISMA flowchart of a study selection for systematic review on the Vertical Transmission of a Novel COVID-19 Infection Among Pregnant Women. It was adapted from "Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Journal of Clinical Epidemiology. 2009;62:1006–12."34
Table 1. Characteristics of the Studies Included in the Systematic Review on the Vertical Transmission of a Novel SARS-CoV-2 Infection in Pregnant Women and Who Then Gave Birth.

| S. N | Author          | Year | SS | Study design | Country | Mode of delivery | VT | Type of test and result                                                                 |
|------|-----------------|------|----|--------------|---------|------------------|-----|----------------------------------------------------------------------------------------|
| 1    | Dong et al      | 2020 | 1  | Case report  | China   | CS               | 0   | Sample used for RT-PCR tests: nasopharyngeal swabs.                                     |
| 2    | Zeng et al      | 2020 | 6  | Case series  | China   | CS               | 0   | Sample used for RT-PCR tests: neonatal throat swabs and blood.                          |
| 3    | Fan et al       | 2020 | 2  | Case series  | China   | CS               | 0   | qRT-PCR result: negative.                                                               |
| 4    | Liu et al       | 2020 | 19 | Case series  | China   | CS, VR           | 0   | Sample used for RT-PCR tests: throat swab, urine, and feces of neonate.                 |
| 5    | Lu et al        | 2020 | 1  | Case report  | China   | CS               | 0   | RT-PCR result: negative.                                                               |
| 6    | Pereira et al   | 2020 | 60 | Case series  | Spain   | CS, VR           | 0   | Sample used for qRT-PCR tests: nasopharyngeal swab and placenta.                       |
| 7    | Pierce-Williams et al   | 2020 | 64 | cohort study | United States | CS                   | 0   | Sample used for RT-PCR tests: nasopharyngeal swab.                                     |
| 8    | Schwartz        | 2020 | 38 | Case series  | China   | CS, VR           | 0   | Sample used for RT-PCR tests: all neonatal specimens tested.                           |
| 9    | Chen et al      | 2020 | 9  | Case series  | China   | CS               | 0   | Sample used for RT-PCR tests: throat swab, amniotic fluid, and cord blood.             |
| 10   | Khan et al      | 2020 | 3  | Case series  | China   | VR               | 0   | Sample used for qRT-PCR tests: cord blood and neonatal throat swab.                    |
| 11   | Li et al        | 2020 | 1  | Case report  | China   | CS               | 0   | Sample used for RT-PCR tests: oropharyngeal swab, blood, feces, and urine.             |
| 12   | Peng et al      | 2020 | 1  | Case report  | China   | CS               | 0   | Sample used for RT-PCR tests: urine, anal swab, throat swab, and serum.                |
| 13   | Xiong et al     | 2020 | 1  | Case report  | China   | VR               | 0   | Sample used for RT-PCR tests: rectal swab, amniotic fluid, and throat swab.            |
| 14   | Yan et al       | 2020 | 100| Case series  | China   | CS, VR           | 14  | Sample used for qRT-PCR tests: amniotic fluid, cord blood, and pharyngeal swab.        |
|      |                 |      |    |              |         |                  | 86  | qRT-PCR result: 86 of the 100 had negative results.                                     |
| S. N | Author                  | Year | SS | Study design     | Country            | Mode of delivery | VT | Type of test and result                                                                 |
|------|-------------------------|------|----|------------------|--------------------|------------------|----|----------------------------------------------------------------------------------------|
| 15   | Yang et al             | 2020 | 55 | Case control     | China              | CS, VR           | 0  | 55 • Sample used for RT-PCR tests: throat swab. • RT-PCR result: negative.             |
| 16   | Zambrano et al         | 2020 | 1  | Case report      | Central America    | VR               | 0  | 1 • Sample used for RT-PCR tests: nasopharyngeal swab and blood. • RT-PCR result: negative. |
| 17   | Zhu et al              | 2020 | 9  | Case series      | China              | CS, VR           | 0  | 9 • Sample used for RT-PCR tests: Pharyngeal swab. • RT-PCR result: negative.          |
| 18   | Chen et al             | 2020 | 4  | Case series      | China              | CS, VR           | 0  | 4 • Sample used for RT-PCR tests: Throat swab. • RT-PCR result: negative.             |
| 19   | Bandyopadhyay et al    | 2020 | 1  | Case report      | India              | VR               | 1  | 0 • Sample used for RT-PCR tests: Pharyngeal swab. • RT-PCR result: positive.         |
| 20   | Parsa et al            | 2020 | 25 | Case series      | Iran               | CS               | 9  | 16 • Sample used for RT-PCR tests: nasopharyngeal swab. • RT-PCR result: 9 out of 25 were tested positive. |
| 21   | Rabiei et al           | 2021 | 3  | Case series      | Iran               | CS               | 1  | 2 • Sample used for RT-PCR tests: nasopharyngeal swab. • RT-PCR result: 1 out of 3 were tested positive. |
| 22   | Hu et al               | 2020 | 7  | Case series      | China              | CS, VR           | 1  | 6 • Sample used for RT-PCR tests: amniotic fluid. • RT-PCR result: 1 out of 7 were tested positive. | Chest radiograph: normal |
| 23   | Nie et al              | 2020 | 26 | Case series      | China              | CS, VR           | 1  | 25 • Sample used for RT-PCR tests: throat swab. • RT-PCR result: 1 out of 26 were tested positive. |
| 24   | Wang et al             | 2020 | 1  | Case report      | China              | CS               | 0  | 1 • Sample used for RT-PCR tests: pharyngeal and anal swabs. • RT-PCR result: negative. |
| 25   | Yu et al               | 2020 | 3  | Cross sectional  | China              | CS               | 1  | 2 • Sample used for RT-PCR tests: Throat swabs. • RT-PCR result: 1 out of 3 were tested positive. | Chest CT: a few small pieces of patchy shadow in the upper lobe of the right lung |
| 26   | Zamanianiyan et al     | 2020 | 1  | Case report      | Iran               | CS               | 1  | 0 • Sample used for RT-PCR tests: nasal and throat swabs. • RT-PCR result: positive.    |
| 27   | Zeng et al             | 2020 | 33 | Cohort study     | China              | CS, VR           | 3  | 30 • Sample used for RT-PCR tests: throat and anal swab. • RT-PCR result: 3 out of 33 were positive. |
| 28   | Li et al               | 2020 | 34 | Case control     | China              | CS, VR           | 0  | 34 • Sample used for RT-PCR tests: throat and anal swab. • RT-PCR result: negative.   |
| 29   | Zhang et al            | 2020 | 10 | Case control     | China              | CS               | 0  | 10 • Sample used for RT-PCR tests: throat swab. • RT-PCR result: negative.             |
| 30   | Liao et al             | 2020 | 7  | Case control     | China              | VR               | 0  | 7 • Sample used for RT-PCR tests: throat swab. • RT-PCR result: negative.              |

(continued)
| S. N | Author          | Year | SS | Study design | Country     | Mode of delivery | (+ve) | (−ve) | VT        |
|------|-----------------|------|----|--------------|-------------|------------------|-------|-------|-----------|
| 31   | Yin et al<sup>56</sup> | 2020 | 17 | Cohort       | China       | CS, VR           | 0     | 17    |           |
| 32   | Yang et al<sup>57</sup>  | 2020 | 7  | Cross sectional | China   | CS               | 0     | 7     |           |
| 33   | Qiancheng et al<sup>58</sup> | 2020 | 23 | Cross sectional | China   | CS, VR           | 0     | 23    |           |
| 34   | Ferrazzi et al<sup>62</sup> | 2020 | 42 | Cross sectional | Italy  | CS, VR           | 2     | 40    |           |
| 35   | Citu et al<sup>59</sup>   | 2021 | 74 | Cohort       | Timisoara  | CS               | 0     | 74    |           |
| 36   | Conti et al<sup>72</sup>  | 2021 | 37 | Cross sectional | Rome    | CS               | 1     | 36    |           |
| 37   | Hcini et al<sup>73</sup>  | 2021 | 29 | Cohort       | French Guiana | CS, VR      | 4     | 25    |           |
| 38   | Jacob et al<sup>74</sup>   | 2021 | 342 | Cohort       | India      | CS, VR           | 49    | 293   |           |
| 39   | Kulkarni et al<sup>75</sup> | 2021 | 1  | Case report  | India       | VR               | 1     | 0     |           |
| 40   | Kumari et al<sup>60</sup>  | 2021 | 41 | Cross sectional | India  | CS, VR           | 0     | 41    |           |
| 41   | Lamba et al<sup>66</sup>   | 2021 | 70 | Cohort       | United states | CS, VR      | 2     | 68    |           |
| 42   | Maeda et al<sup>77</sup>   | 2021 | 54 | Cohort       | Brazil      | CS, VR           | 2     | 52    |           |
| 43   | Peter et al<sup>61</sup>    | 2021 | 27 | Cohort       | United states | CS, VR      | 0     | 27    |           |

Sample size is explained in number of newborns included in the articles.

Abbreviations: SS, sample size; CS, cesarean section; VR, vaginal route; SARS-CoV-2, severe acute respiratory syndrome coronavirus; RT-PCR, real-time reverse transcriptase–polymerase chain reaction; SARS, severe acute respiratory syndrome; CT, computed tomography; VT, Vertical transmission; qRT-PCR, quantitative real-time polymerase chain reaction;
COVID-19 in pregnancy were found to be related to maternal morbidity and preterm birth. The associated risk factors were age of women beyond 35 years, being overweight, and obesity. Besides, miscarriage, fetal distress, respiratory distress, and preterm delivery can be caused by COVID-19. Contrary, most of the experts have accepted approach the approach of isolating the infants from women suspected or confirmed with COVID-19 as a means of decreasing the risk of transmission to baby. Those infected pregnant women should obtain better consideration. This pandemic virus could asymptotically arise at gestation time. However, they get diagnosed after delivery.

The study done among asymptomatic and symptomatic pregnant women in New York showed that the severity of this disease in pregnant women was mild, severe, and critical; appears similar to that in nonpregnant in 86%, 9.3%, and 4.7% of them respectively. According to the research conducted on 9 pregnant women with confirmed cases; 7 out of 9 were died, 1 out of 9 was remains critically ill, and 1 out of 9 was recovered after long hospitalization at the time of reporting. In pregnancy, the management of this pandemic comprises such as; infection control procedures, oxygen therapy, early isolation, avoidance of fluid overload, consideration of empiric antibiotics, laboratory testing, fetal monitoring, uterine contraction monitoring, separated delivery planning, early mechanical ventilation, and multidisciplinary consultation.

**Recommendations**

If the pregnant mothers are confirmed for infection of COVID-19, the choice of delivery judgment would be better if individualized depending on factors like maternal, fetal, gestational age, and delivery circumstances. Vaginal delivery via induction of labor, with eventual instrumental delivery to prevent maternal fatigue, should be selected to prevent needless surgical consequences. Besides, a study suggested that COVID-19 management for positive pregnant mothers must be adopted and performed by a multi-disciplinary team method.

A multidisciplinary team which includes obstetricians, intensivists, maternal–fetal medicine subspecialists, virologists, obstetric anesthetists, neonatologists, internal medicine, midwives, and infectious disease specialists are better to be undertaken during managing these patients. Furthermore, recognizing the extent to which COVID-19 affects women and men differently will be the essential to understand the bigger influence of this disease both during the crisis and during individual and societal recovery.

Overall, Since the SARS-CoV-2 vertical transmission has no evidence till now, it is important to keep all the specimens of SARS-CoV-2 infected and suspected pregnant women and their newborns for in-depth study and continuous follow-up observation of future generations. The study described that if the exposure arose at a delivery time, the virus may need a longer incubation period prior to test swabs show positive outcomes. As a result, nasopharyngeal testing instantly after delivery may not be the ideal method to assess vertical transmission. Particularly, the existence of viral RNA in placental and membranes samples by RT-PCR during the delivery shows the requirement for more research for likelihood of vertical transmission.

**Conclusions**

The quick global spread of COVID-19 has resulted in a worldwide pandemic. This pandemic remains a global challenge. Currently, it is a major and critical global health emergency. From this systematic review findings, out of 1300 neonates tested for SARS-CoV-2 infection, 93 neonates were found positive for this infection by RT-PCR. The rate of vertical transmission of SARS-CoV-2 infection was 7.15%. The present review found that the possibility of a vertical transmission of COVID-19 is recently a highly controversial issues across the worldwide. This is because there is a discrepancy of literatures were found. Some studies stated as the were no vertical transmission of SARS-CoV-2 in neonates born of COVID-19 confirmed women, whereas the other studies reported that as there was a vertical transmission of this virus.

To counteract and control this aggressive pandemic virus, the global healthcare system should update and modify their tools and practices accordingly with time manner. There is an increasing requirement for information concerning to the mother and neonate outcomes during COVID-19 pandemic. This study has addressed the significant issues for healthcare providers giving care for COVID-19 confirmed cases of pregnant, for stakeholders, for health policy makers and implementers, and for the pregnant populations as the whole.

The available data regarding to the pregnant mothers with COVID-19 provides a favorable outcome. However, the risks for maternal, and fetal should not be underrated. The available information is limited to the mothers who developed the COVID-19 in late gestation and mothers...
who delivered shortly after the diagnosis of COVID-19. But, the baby outcome from a long-standing of COVID-19 disease diagnosed mother, which occurred in early gestation are unknown. Because of the inadequate figure of clinical evidences, pediatricians, obstetricians, and other healthcare providers should continually update their knowledge and be conscious regarding the transmissions of SARS-CoV-2 vertically during pregnancy. Furthermore, it is expected that the future researches would offer more evidence on maternal and baby circumstances for obstetrical interventions. Lastly, the present review recommends that a further high-quality study is needed to conclude this critical issue of confusion concerning to the vertical transmission surely.

**Author’s Contributions**

The author made a substantial contribution to this study on the entire aspects.

**Declaration of Conflicting Interests**

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