

SARS-CoV-2 infection in pregnancy and risk of stillbirth

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ABSTRACT

The COVID-19 pandemic has changed the lives of millions of people across the globe. As of November 2021, WHO has reported more than 250 million confirmed cases of SARS-CoV-2 infection with more than 5 million deaths. Despite the continuous efforts being made by the medical community to address the fundamental questions posed by the SARS-CoV-2 infection in pregnant women and its impact over the mother and the offspring.

The aim of this paper is to assess the evidence accumulated since the emergence of the pandemic concerning the impact of SARS-CoV-2 infection on the mother and fetus, especially addressing the risks of intrauterine death in SARS-CoV-2 positive mothers.

We searched different databases up to November 2021 for variations of the sentence: "SARS-CoV-2 infection and COVID-19 and pregnancy and fetal death, stillbirth, intrauterine death".

The changing physiological and immune responses during pregnancy make a pregnant woman more prone to developing severe forms of COVID-19, causing sometimes serious pregnancy complications such as fetal loss. At times mild general symptoms related to COVID-19 can cause serious fetal complications, suggesting that placental changes are responsible for fetal outcome. Infection with non-Delta variant increases the risk of fetal loss in the third trimester two times compared to healthy population, while Delta variant increases this risk four times. The exact mechanism of vertical transmission is still to be established and these aspects need further research especially assessing COVID-19 variant particularities.

Keywords: vertical transmission; fetal death; stillbirth; intrauterine death, COVID-19, SARS-CoV-2 infection

INTRODUCTION

The COVID-19 pandemic has changed the lives of millions of people across the Globe. As of November 2021, WHO has reported more than 250 million confirmed cases of SARS-CoV-2 infection with more than 5 million deaths (1). As more and more patients are impacted by the SARS-CoV-2 infection, its challenging medical aspects continue to be the focus of attention of medical practitioners worldwide.

In this paper we highlight the evidence accumulated since the emergence of the pandemic concerning the impact of SARS-CoV-2 infection on the mother and fetus, especially addressing the risks of intrauterine death in SARS-CoV-2 positive mothers.

An online literature inquiry was performed to find publications on the topic of SARS-CoV-2 infections and its effect on the unborn children of infected mothers. Articles published up to November

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2021 were identified by searching the following databases: PubMed, Web of Science, The Cochrane Library, Science.gov, UpToDate and Elsevier. We searched for variations of the phrase “SARS-CoV-2 infection and COVID-19 and mother and child and pregnancy and fetal death and stillbirth”. In order to prevent omissions, cited articles in the relevant studies were carefully examined. We excluded articles that had one or more of the following criteria: letters to the editor, animal studies.

The World Health Organization (WHO) COVID-19 LENS (Living Evidence Synthesis) working group proposed a classification system in order to establish the timing of mother-to-child transmission based on 3 aspects: 1) documented maternal infection, using the WHO COVID-19 case definitions (2), anytime during pregnancy for in utero infection and near the time of birth for intrapartum; 2) tests to evaluate the likelihood of early in utero or intrapartum exposure; and 3) tests to evaluate the later exposure/persistence of the virus or virus-specific immune response in the fetus/neonate (3). Thus, the following categories were proposed in order to classify the timing of mother-to-child transmission: 1) confirmed; 2) possible (evidence is suggestive but not confirmatory for infection); 3) unlikely (little support for diagnosis but infection cannot be completely ruled out); and 4) indeterminate (when tests required to define classification have not been performed) (3).

In a systematic review published by Lei Goh et al. including 303 participants from 17 studies, the mean incidence of vertical transmission was 16 per 1,000 newborns (95%CI 3.40 to 73.11) and 9 out of 330 newborns presented a positive RT-PCR for SARS-CoV-2 (4).

In a systematic review which included 936 neonates from mothers infected with SARS-CoV-2, 27 neonates had a positive nasal swab for SARS-CoV-2 by RT-PCR, indicating a pooled proportion of 3.2% (95% confidence interval, 2.2-4.3) for vertical transmission. Viral SARS-CoV-2 RNA was detected in 2.9% of the neonatal cord blood samples (1/34), 7.7% of placenta samples (2/26), 0% of amniotic fluid (0/51), 0% of urine samples (0/17), and 9.7% of fecal or rectal swabs (3/31). The neonatal blood samples tested positive for IgM against SARS-CoV-2 in 3 out of 82 samples (3.7%) (5).

Antepartum mother-to-child transmission of the SARS-CoV-2 infection typically occurs via hematogenous route but sometimes via ascending route. The cell-membrane associated angiotensin-converting enzyme 2 (ACE-2) receptor and transmembrane protease serine 2 (TMPRSS2) required for SARS-CoV-2 cellular entry have been identified in placental cells (6). However their paucity may be an explanation for the insensitivity to transplacental

infection. The placentas of pregnant women with SARS-CoV-2 infection were analyzed revealing sparse viral particles, vascular malperfusion and inflammation in the placenta (6). If the placenta is damaged due to malperfusion and ischemia, the virus could be transmitted directly without infection of the placental cells. There is clear evidence that the ACE-2 receptor is expressed by specific cell types of human fetal heart, liver and lung (7).

Sharps et al. performed a systematic review of 20 studies reporting histological findings in the placentas of 150 pregnant women, revealing evidence of both fetal vascular malperfusion (35.3% of cases; 95% Confidence Interval (CI) 27.7–43.0%) and maternal vascular malperfusion (46% of cases; 95% CI 38.0–54.0%) and signs of inflammation in the placentas (villitis 8.7% cases, intervillitis 5.3% of cases, chorioamnionitis 6% of cases) (8). Di Girolamo et al. describe in the latest review that mothers with SARS-CoV-2 infection express histopathologic placental anomalies involving increased perivillous fibrin deposits and intervillous thrombosis (9).

Vivanti et al. reported a case of a neonate with neurological symptoms of COVID-19 born to a mother infected with SARS-CoV-2 in the third trimester in which transplacental transmission was involved, emphasized by maternal SARS-CoV-2 viremia, placental infection and inflammation demonstrated by immunohistochemistry and very high viral load and neonatal viremia following placental infection (10). Other cases of probable transplacental transmission were reported (11), as well neonatal infections with viral RNA in cord blood that supports in utero transmission of SARS-CoV-2 (13) and symptomatic neonates with elevated IgM antibodies at birth suggesting intrauterine infection (4).

Centre of Disease Control and Prevention (CDC) published last week a report showing that women with COVID-19 are at increased risk for stillbirth compared with women without COVID-19, the overall adjusted relative risk is 1.90 analyzed from March 2020 to September 2021 (13). During the Delta variant period 1,171 stillbirths were registered, involving 2.70% of deliveries with COVID-19 compared with 0.63% of deliveries without COVID-19, resulting an adjusted relative risk of 4.04 (12). Comorbidities like chronic hypertension, multiple pregnancy, placental abruption, sepsis, shock, acute respiratory distress syndrome, mechanical ventilation was associated with a greater rate of fetal loss (13).

TRANSMISSION MECHANISM

During gestation placenta acts as an effective barrier that prevents maternal infection spreading to the unborn child. It is well known that some vi-

ruses can overcome this barrier (cytomegalovirus, varicella zoster virus or Zika virus), causing sometimes unfortunate outcome on the developing fetus. The variable rates of transmission and severity can depend, in part, on the stage of pregnancy when infection occurs. These infections may have only minor effects on the mother, and there is poor correlation between maternal symptomology and severity of fetal effects. In cases of SARS-CoV-2 positive mothers it can be hypothesized that placental vasculopathic pathology can trigger unfortunate fetal outcome, including stillbirth, regardless the severity of COVID-19. Infection with non-Delta variant increases the risk of fetal loss in the third trimester two times compared to healthy population, while Delta variant increases this risk four times. The ex-

act mechanism of vertical transmission is still to be established and these aspects need further research especially assessing COVID-19 variant particularities.

CONCLUSIONS

The changing physiological and immune responses during pregnancy make a pregnant woman more prone to developing severe forms of COVID-19, causing sometimes serious pregnancy complications such as fetal loss. At times mild general symptoms related to COVID can cause serious fetal complications, suggesting that placental changes are responsible for fetal outcome.

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