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COVID-19 in patients with gestational diabetes: review of literature

ABSTRACT

The risk of severe acute respiratory distress syndrome associated with coronavirus-2 (SARS-CoV-2) to maternal and newborn health has yet to be determined. Several studies showed that pregnancy with gestational diabetes increased the risk of maternal illness, but cases of gestational diabetes, preeclampsia and preterm birth have been reported rarely. Reports indicated placental infection and vertical transmission of COVID-19 were uncommon. Interestingly, despite the lack of SARS-CoV-2 placental infection, there were many records of major abnormalities in placental morphology. Continued research into offsprings of pregnant women with gestational diabetes infected with SARS-CoV-2 was vitally necessary. This study showed the impact of COVID infections on the fetus and the newborn in GDM pregnancy. There were very few data considering this subject and therefore, the findings have nowadays very debatable value. However, it's worthwhile to show the scientific community that nowadays we have no proof that COVID infection has a significant impact on pregnancy and the fetus. (Clin Diabetol 2020; 9; 6: 367–371)

Key words: COVID-19, patients, gestational diabetes

Introduction

Severe acute respiratory distress syndrome associated with coronavirus-2 (SARS-CoV-2), was an etiological agent of Coronavirus disease 2019 (COVID-19). It

was first identified in Wuhan, China, in December 2019 and is now a global pandemic. To date, more than 4 million cases and 300,000 deaths have been registered by the World Health Organisation. There has been a significant increase in awareness of the genetic, virological, epidemiological, and clinical aspects of COVID-19, but there are far fewer studies explaining the risks and unique impact of COVID-19 on pregnant females with gestational diabetes and their newly born infants. In this study, both peer-reviewed and non-peer-reviewed preprints were included in order to identify the most up-to-date information.

Pregnancy with gestational diabetes increases the risk of adverse obstetric and neonatal outcomes due to many respiratory viral infections. The maternal immune system is altered during pregnancy in order to prevent the rejection of the fetus and to contribute to the development of the fetus [1]. Some viral infections cause more serious or prolonged illness in pregnant women with gestational diabetes [2]. COVID-19 has resulted in elevated rates of abortion, infant mortality and preterm delivery [3]. Multiple influenza studies have shown an increased risk of maternal morbidity and mortality relative to non-pregnant women. On the other hand, the majority of results for pregnant women with gestational diabetes infected with SARS-CoV-2 [5–53] do not vary from the general population. Fever is the most common symptom of COVID-19 in these patients, but many also experience cough, shortness of breath, and diarrhea. Occasionally serious infections involved mechanical ventilation [2–46] but rarely resulted in death [4, 5].

COVID in pregnant women with gestational diabetes

Although the majority of COVID infections in pregnant women with gestational diabetes were mild, data indicated substantial placental pathology

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in SARS-CoV-2 pregnancy despite lack of detectable or very low levels of SARS-CoV-2 mRNA or protein [4–43]. There were, however, case studies suggesting COVID-19 virions in syncytio-trophoblasts in placental villous when examined by the electron microscopy [6–8] or (PCR) [5, 28, 36]. The significant questions that remains unanswered are, whether SARS-CoV-2 replicates in the placenta, whether it is the cause of the reported placenta abnormalities and, whether SARS-CoV-2 is an “innocent bystander.” It is also important to note that the identified placenta abnormalities occur mainly in women who are asymptomatic or have mild to moderate illness, indicating that these defects are not necessarily due to severe COVID disease.

Placenta abnormalities in diabetic women

The placenta abnormalities identified in an infected diabetic pregnant women with SARS-CoV-2 include diffuse perivill fibrin, fetal vascular malperfusion in fetal vessels, choriohemangioma, maternal vascular malperfusion, and multifocal infarctions [17, 26, 36]. In some cases, SARS-CoV-2 has been found in the placenta [5, 17, 28, 36]. Lack of controls and non-specific staining issues [16] complicate the interpretation of these findings in some of these studies. Importantly, the vast majority of placenta cases were negative for SARS-CoV-2 as calculated by PCR [12, 22, 26, 27, 36, 41, 43]. The anomalies observed in placenta pathology therefore indicated that the placenta was vulnerable to maternal COVID-19 disease, even in the absence of infection, because in many cases these disorders may be due to maternal co-morbidities such as hypertension, preeclampsia, and gestational diabetes. There is, therefore, a vital need for thorough systematic studies to determine the prevalence of infection and replication of SARS-CoV-2 in the placenta and its connection with placenta abnormalities.

Easy vertical transmission?

It still remains to be seen whether SARS-CoV-2 can be transferred from a diabetic pregnant woman to her fetus, a process called vertical transmission. Importantly, the transmission is predicted to have various effects over the three trimesters of pregnancy. Transplacental transmission of the virus typically increases with advanced gestational age, while there is a decrease in the incidence of fetal injuries from embryopathy and embryo/fetal death in the first trimester, from fetal infection and immune response during the second and third trimesters. Unlike many other viral diseases, viremia in SARS-CoV-2 is observed in just 1% of symptomatic patients and is usually mild and transient [19].

Effect of COVID-19 on newly born infants

Most of the case reports documented that, the birth of a full term baby to COVID-19 positive mothers with mild to moderate illness is not carrying any significant risk to the baby itself [8–53]. Preterm births, on the other hand, are fairly common in women with severe illness, although there are sporadic reports of spontaneous preterm births [9–53]. Spontaneous abortion has also been reported twice in early pregnancy [5, 45] and fetal death has been reported 6 times [13, 18, 23, 24]. Case reports of newborns with symptoms requiring NICU admission for tachypnea, tachycardia, fever, gastrointestinal symptoms, and signs of CT pulmonary infection [2, 7, 12, 27, 41, 48, 52, 53] were reported; with 2 of 5 had NP swabs positive for SARS-CoV-2. Interestingly, some symptomatic infants tested negative for SARS-CoV-2. In one case, a positive SARS-CoV-2 infant born at 31 weeks of age needed resuscitation and was diagnosed with pneumonia, but the authors confirmed that they suspected sepsis with *Enterobacter* [52]. Thus, with the exception of these unusual cases, neonates were born healthy to infected mothers with SARS-CoV-2. However, it has yet to be known whether infection at an earlier stage would have a significant effect on neonatal health and whether it results in long term outcomes.

Actual mode of transmission

Newborns may be infected by viral infection from mother either directly by the virus through vertical transmission or passively, by the maternal reaction to the virus. Considerable evidence indicates the absence of vertical transmission of SARS-CoV-2. Multiple newborns were screened for SARS-CoV-2 at delivery and viral RNA was not found in cord blood, throat and nasopharyngeal swabs, urine, and feces [5, 51]. Amniotic fluid samples were also obtained from positive COVID pregnant mothers and were mainly screened negative for SARS-CoV-2 [5–49]. Neonatal testing, 24 hours or more after birth, have rarely been confirmed positive for the virus [27–52], but due to delays in testing, these infants may have already been infected after birth. There was one case report of COVID-19 neonates at birth, but the baby was symptom free with, perhaps, the exception of some minor initial nursing problems [28]. In addition, despite cautious isolation, the baby born at 33 weeks of age tested positive after 16 hours and again after 48 hours post-partum [2]. The authors indicated that this infant may have been infected either during the delivery of the cesarean or in the uterus. The baby needed admission to the NICU for low Apgar scores and ventilator support.

Antibodies were found in neonatal blood

Most babies in these studies were delivered by a cesarean section, and it is possible that newborns could potentially be contaminated during vaginal delivery. Vaginal swabs, however, were screened negative at 37 weeks of caesarean section delivery [12] and negative for SARS-CoV-2 in 6 women at hospital admission [45]. Intriguingly, despite the absence of virus present in neonate at birth, antibodies have been detected in neonatal tissue [51]. In particular, IgM has been documented to be elevated indicating fetal exposure to the uterine virus [51]. It is important to note that IgM antibody testing results in a high risk of false-positive [19] but these findings indicate that ongoing neonatal antibody testing can be useful.

Extracellular vesicles confer viral resistance to receptor cells

Overall, there is little evidence of vertical transmission in the majority of cases of positive COVID-19 birth. The fact that viremia is present in 1% of symptomatic patients and is usually mild and temporary may play a role [42]. However, other processes are likely to be just as important or more important in the defense of the fetus against vertical transmission. Maternal-fetal interface barriers protect the fetus from infection. For example, the syncytiotrophoblasts—organize the immune response to infection and also act as a physical barrier to the viral passage [29, 47]. Immune cells in the placenta also have anti-viral potential [47]. Finally, previous studies have shown that trophoblast-derived extracellular vesicles containing a special group of miRNAs, expressed as chromosome 19 miRNA clusters, confer viral resistance to receptor cells suggesting a paracrine role that allows contact between placental cells to control their immunity to viral infections [10].

The ability of the virus to replicate and infect the placenta is also dependent on the virus. In the case of SARS-CoV-2, the entry of cells requires the binding of the spike protein to ACE2 [15]. The virus is then produced by cellular proteases such as TMPRSS2 [15] and possibly cathepsin B/L7 [37] and furin [6]. Utilizing recently reported single-cell RNAseq results, researchers have observed robust ACE2 activity in the placenta [21, 37] though not in TMPRSS2 [37]. Two studies, using single nucleotide RNAseq or single-cell RNAseq, were recently performed during gestation and found expression of ACE2 but either no or very low levels of TMPRSS2 were detected in the placenta [3, 32]. There has been no systematic assessment of the presence and role of other proteases that lead to viral entry and replication in the placenta cell. ACE2 was observed by 133 IHC in

syncytio-trophoblast, cyto-trophoblast, endo-thelial and smooth muscles of the blood vessels [40].

Interestingly, ACE2 is involved in placentation, including the migration of trophoblasts, vascular remodeling, and maternal vasodilation [33, 39]. Complications such as abortion, ectopic pregnancy, and preeclampsia have also been implicated in ACE2 [40]. Therefore, if SARS-CoV-2 affects the expression of ACE2 in the placenta as shown by SARS-CoV-1 in the lung [20], there is a risk for placental defects and complications of pregnancy. The existence of ACE2 in the placenta could mean that there is a capacity to bind COVID-19 to cause viral infection, but there are mechanisms that underlie SARS-CoV-2's failure to infect and replicate in the placenta are unknown.

Conclusion

Vertical transmission of SARS-CoV-2 is considered unlikely at this time but there appears to be considerable potential for SARS-CoV-2 to affect the placental function and fetal development. Continued research is, therefore, needed focusing especially on the detection of SARS-CoV-2 at early gestational time points. Finally, careful longitudinal studies with adequate controls are needed before any conclusions about COVID-19's maternal or neonatal effects are drawn.

Conflict of interest

The author declare no conflict of interest.

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