

## **Placental Swab in Supporting Diagnosis of Vertical Transmission in SARS-CoV-2 Positive Mothers**

I. Sweeney<sup>1</sup>, N. Al Assaf<sup>2</sup>, R. Khan<sup>2</sup>

1. School of Medicine, University of Limerick, Limerick, Ireland.
2. Department of Neonatology, University Maternity Hospital Limerick, Limerick, Ireland.

### **Abstract**

#### **Aims**

To review the evidence regarding the possibility of fetal vertical transmission in COVID-19 positive pregnant mothers by diagnosing through placental swabs.

#### **Methods**

The search terms 'pregnant COVID-19 positive mothers', 'fetal vertical transmission' and 'placental swabs' were used. 20 papers were selected.

#### **Results**

183 COVID-19 positive pregnant women were identified whose 184 placentas and 185 neonates were also analysed by RT-PCR or immunohistochemistry and/or in situ hybridization for the presence of SARS-CoV-2 (one case of monochorionic diamniotic twins and one case of dichorionic diamniotic twins). 183 liveborn neonates were successfully delivered primarily via caesarean section (99%). 2 mothers did not deliver liveborn infants due to severe preeclampsia resulting in a termination of pregnancy and a miscarriage, both occurring in the second trimester. 9 neonates tested positive for SARS-CoV-2 (5%). We report no neonatal mortality after live birth and no maternal mortality. 17 placentas tested positive for SARS-CoV-2 out of a total of 184 tested (9%). Of these 17, 7 cases of SARS-CoV-2 were identified in the maternal, neonatal and placental tissue.

#### **Conclusion**

There is no concrete evidence of vertical transmission occurring between mother and infant. We propose further research investigating the effects of COVID-19 on pregnant women by using RT-PCR to test the mother, placenta, vaginal fluid, breast milk and infant for SARS-CoV-2 at various stages of transmission.

## **Introduction**

On March 11 2020, the World Health Organisation declared that the pneumonia outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a pandemic.<sup>1</sup> Due to its highly transmissible nature, as of May 13 2021, there was a total of 159,949,065 confirmed cases of COVID-19, including 3,322,439 deaths across the five continents.<sup>2</sup> With COVID-19's sustained spread across the globe, pregnant women are unfortunately not indiscriminate from contracting the virus. This may be attributed to the changes to the cardiorespiratory and immune system during pregnancy thereby increasing a woman's susceptibility to severe infection and hypoxic compromise.<sup>3</sup>

Lopes de Sousa et al published a systematic review in June 2020 and concluded that there is no concrete evidence for vertical transmission of COVID-19 but acknowledged that significant knowledge gaps exist and they cannot rule out this possibility.<sup>4</sup> The presence of COVID-19 has been assessed in neonates born to COVID-19 positive mothers by examining the placenta<sup>5</sup>, and carrying out nucleic acid testing on breast milk<sup>6</sup> and vaginal mucus.<sup>7</sup>

Two epidemics in the past two decades, namely severe acute respiratory syndrome (SARS-CoV) in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2014 promote more serious complications than COVID-19 during pregnancy with approximately one third of infected pregnant women dying from the illness.<sup>3</sup> However, similarly to COVID-19, there have been no documented cases of vertical transmission seen in SARS or MERS to date.<sup>8</sup>

Today, the effects of COVID-19 on pregnancy and neonatal outcome are being studied in real-time by researchers across the globe. This paper aims to review the current literature regarding the possibility of fetal vertical transmission in COVID-19 positive pregnant mothers by diagnosing through placental swabs.

## **Methods**

Articles were searched using the following databases: Pubmed, ScienceDirect, Medline, Embase, Web of Science.

All studies in the review were selected using these databases, none were hand selected. Studies relating to pregnant COVID-19 positive mothers and fetal vertical transmission and placental swabs were selected.

We followed the guidelines according to PRISMA, MOOSE, Cochrane Handbook of Systematic Reviews of Interventions.

Search terms used were: Pregnant COVID-19 positive mothers + fetal vertical transmission + placental swabs.

Inclusion criteria: Studies performed on above terminologies along with overlapping of terminologies from September 2019 to 13 May 2021 were included and studies performed outside of this timeframe were excluded.

## Results

A review of studies focusing on pregnant COVID-19 positive mothers and placental swabs in the context of fetal vertical transmission has been performed. The 20 studies we reviewed are summarised in Table 1 [[view](#)].

### *Maternal Outcome*

This literature review comprises 183 COVID-19 positive pregnant women whose 184 placentas and 185 neonates were also analysed for the presence of SARS-CoV-2. We report no maternal mortality. A large number of women were asymptomatic although various mothers suffered from common COVID-19 symptoms such as myalgia, cough, sore throat, fever and fatigue. Comorbidities included obesity, hypertension, diabetes, preeclampsia, hypothyroidism and asthma.<sup>9-28</sup> One woman opted for termination of pregnancy due to symptomatic SARS-CoV-2 complicated by severe preeclampsia in the second trimester.<sup>20</sup> Another woman with symptomatic SARS-CoV-2 presented in the second trimester with a miscarriage.<sup>14</sup>

### *Neonatal Outcome*

183 liveborn neonates were successfully delivered primarily via caesarean section including one case of monochorionic diamniotic twins and one case of dichorionic diamniotic twins (99%). 9 neonates tested positive for SARS-CoV-2 (5%). We report no neonatal mortality after live birth.

Yu et al reported one positive neonate who had mild shortness of breath and x-ray findings of mild pulmonary infection.<sup>13</sup> Kirtsman et al described one positive neonate who had neutropenia, mild hypothermia, feeding difficulties and intermittent hypoglycaemic episodes.<sup>18</sup> Sisman et al reported one positive neonate who developed fever, respiratory distress and hypoxia.<sup>21</sup> Vivanti et al described a case of a positive neonate with neurological manifestations including poor feeding, axial hypertonia and ophistotonos.<sup>22</sup> Five positive neonates remained asymptomatic.<sup>16, 23, 24, 28</sup>

### *Laboratory Investigations*

RT-PCR or immunohistochemistry and/or in situ hybridization identified SARS-CoV-2 in 17 placentas out of a total of 184 tested (9%). Of these 17, 7 cases of SARS-CoV-2 were identified in the maternal, neonatal and placental tissue. These 7 mothers all displayed signs and symptoms of SARS-CoV-2 with 5 of the neonates delivered by caesarean section.<sup>16, 18, 21-24</sup> Interestingly, SARS-CoV-2 was also identified in the placentas of both mothers who did not deliver their neonate due to severe preeclampsia<sup>20</sup> and a miscarriage though both neonates tested negative.<sup>14</sup>

## Discussion

Baud et al and Hosier et al's studies describe two women suffering an adverse outcome during their pregnancy, notably miscarriage<sup>14</sup> and severe preeclampsia respectively.<sup>20</sup> The miscarriage occurred in a symptomatic 28 year old woman at 19 weeks gestation. Baud et al concluded that the miscarriage appeared to be related to placental infection with SARS-CoV-2 which demonstrated mixed inflammatory infiltrates composed of neutrophils and monocytes on histological examination. Contamination during delivery was deemed unlikely given that all swabs from the foetus including the axillae, meconium, mouth and fetal blood were negative.<sup>14</sup>

Wong et al reported a 57% miscarriage rate in a study of 12 pregnant women conducted during the 2002 SARS epidemic. They attributed this to acute or chronic placental insufficiency caused by severe maternal respiratory failure and hypoxemia thereby reducing uterine placental flow.<sup>29</sup>

Hosier et al's study showed a 35 year old COVID-19 positive woman who presented at 22 weeks gestation with severe preeclampsia. This patient chose to terminate her pregnancy due to her heightened risk of maternal morbidity and mortality. High levels of SARS-CoV-2 were identified in the placenta and the invasion of intervillous macrophages was also seen on histology. Hosier et al concluded that COVID-19 may have contributed to placental inflammation resulting in early-onset preeclampsia and worsening maternal disease. It is important to note, however, that this patient was previously diagnosed with gestational hypertension which is a risk factor for her later developing preeclampsia in this pregnancy. No definitive evidence for fetal infection was described.<sup>20</sup>

Shanes et al examined 16 placentas in COVID-19 positive women. The placentas showed features of maternal vascular malperfusion, most prominently decidual arteriopathy and increased incidence of chorangiomas. Although, placental swabs were not performed which makes it unclear whether it was a local phenomenon or a systemic phenomenon.<sup>5</sup> Similarly, Hosier et al showed similar risk factors for maternal vascular malperfusion, i.e. gestational hypertension and preeclampsia.<sup>20</sup> This may tentatively imply a link between COVID-19 and severe preeclampsia.

Mulvey et al analysed five COVID-19 positive mothers' placentas and concluded a thrombotic fetal vascular malformation phenomenon along with probable placental thrombosis lead to placental insufficiency. All five newborns were successfully delivered which may be attributed to the mothers developing COVID-19 closer to full term. They hypothesize that infection earlier in the gestational course may have more serious consequences such as placental insufficiency with associated miscarriages or low birth weight infants.<sup>30</sup> This may be why the two adverse outcomes in our study described by Hosier et al and Baud et al occurred during the second trimester.

Linehan et al in Cork, Ireland described a case of third trimester maternal COVID-19 infection with demonstrable SARS-CoV-2 placentitis. They concluded that SARS-CoV-2 placentitis is an uncommon but noteworthy complication of maternal COVID-19 infection which can lead to placental damage, potentially resulting in fetal compromise. This may be due to placental pathologies such as fetal vascular malperfusion and maternal vascular malperfusion.<sup>31</sup>

Of the 20 studies we analysed for our literature review, 6 studies confirmed a high possibility of vertical transmission in utero. Notably, these 6 studies were the same ones which identified 7 cases of SARS-CoV-2 in the maternal, neonatal and placental tissue.<sup>16, 18, 21-24</sup> Vivanti et al reported a case of proven congenitally transmitted infection on the basis of confirmed SARS-CoV-2 virus in the amniotic fluid prior to the rupture of membranes.<sup>22</sup>

Dong et al showed elevated IgM antibody levels 2 hours after birth in a neonate born to a mother with COVID-19 suggesting that vertical transmission is possible, even if it is uncommon. This neonate also had elevated cytokines and a leucocytosis. IgM antibodies do not cross the placenta and normally appear 3 to 7 days after infection suggesting the infection occurred in utero. Confusingly, this infant repeatedly tested negative for SARS-CoV-2 on the nasopharyngeal swabs.<sup>32</sup> It is important to consider the accuracy of nasopharyngeal and oral swab RT-PCR assays for SARS-CoV-2 which is deemed to have a sensitivity of between 56% and 83%.<sup>33</sup>

The major limitation of our study is the small sample size of only 183 COVID-19 positive pregnant women and thus we cannot conclusively rule out the possibility of vertical transmission, though we deem it unlikely. However, we can consider that COVID-19 may affect the placental tissue due to the detection of the virus in certain cases.

After reviewing multiple studies and investigating the nature of placental physiology in SARS-CoV-2 positive mothers we conclude that there is no concrete evidence of vertical transmission occurring between mother and infant.

However, due to the novelty of the pandemic this small number of studies represent low levels of evidence due to the inconsistencies across the different studies reported. As the cases continue to rise worldwide, we expect the evidence to become more concrete on this topic with the development of more robust case control studies and long-term follow-up with the mothers and children.

Our literature review highlights the urgent need for a large scale study to be designed investigating the effects of COVID-19 on pregnant women by using RT-PCR to test the mother, placenta, vaginal fluid, breast milk and infant for SARS-CoV-2 at various stages of transmission.

**Declaration of Conflicts of Interest:**

There are no conflicts of interest to declare.

**Corresponding Author:**

Isabelle Sweeney

School of Medicine,

University of Limerick

E-Mail: [sweeneyi@tcd.ie](mailto:sweeneyi@tcd.ie)

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