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Relationship between COVID-19 and orofacial clefts

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Abstract. The work presents the connection between the infection of COVID-19 during pregnancy and non-syndromic orofacial clefts (NSOFC). Aim of the study was to compare the incidence of COVID-19 disease during mother´s pregnancy between a group of the children with NSOFC and a control group of the children without NSOFC. COVID-19 was confirmed by polymerase chain reaction (PCR) test. The study showed significantly higher incidence of COVID-19 disease in the group of mothers who gave birth to a child with NSOFC in comparison to the group of mothers who gave birth to a child without NSOFC. Our results indicate the possible participation of the infection of COVID-19 in the formation of NSOFC.

Key words: Orofacial clefts — COVID-19 — Pregnancy

Introduction

Coronaviruses are pathogens belonging to the *Coronaviridae* family and the *Nidovirales* genus, which mainly attack the human respiratory system (Poon et al. 2019). The first case of the COVID-19 infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered in December 2019 in Wuhan, the capital of Hubei province, in central China. It was detected in humans for the first time. The virus spread from China to the whole world.

When COVID-19 and other coronaviruse pathogens infect pregnant women, it increases the risk of adverse effects not only on the mother and her pregnancy but also on newborns and causes severe respiratory disease and various problems. SARS-CoV-2 is more infectious than SARS-CoV and MERS-CoV, causing severe perinatal complications, premature birth, intrauterine growth restriction, respiratory dyspnea, nervous system dysplasia, immune system defects (Dang et al. 2020). From the beginning of February 2020, Zhu et al. (2020) for the first time describe the clinical symptoms of 10 newborns born to mothers with confirmed SARS-CoV-2 infection, i.e. with COVID-19. Infection may have adverse effects on newborns, causing problems such as fetal distress, premature labor, respiratory distress, thrombocytopenia accompanied by abnormal liver function, and even death.

Mullins et al. (2021) describe that pregnant women with COVID-19 have a higher number of premature caesarean sections. In addition, this infection can cause adverse effects during pregnancy as well as restricted fetal growth, premature birth and perinatal mortality (Juan et al. 2020; Li et al. 2020). COVID-19 and preeclampsia are also strongly associated and both have been described to have negative effects during pregnancy (Papageorghiou et al. 2021). Authors Huntley et al. (2020) reported that a low percentage of both maternal and neonatal mortality and vertical transmission of SARS-CoV-2 was detected dur-

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ing the early pandemic. From a literature review, Diriba et al. (2020) found that coronavirus infections (SARS-CoV-2, MERS-CoV and SARS-CoV) during pregnancy were mainly associated with a relatively higher number of caesarean sections, premature birth, preeclampsia, spontaneous abortion and perinatal mortality. They also state that none of the studies have yet demonstrated the transmission of coronaviruses from mother to fetus *in utero*. The possible transplacental transmission of the virus has not yet been clarified (Rosen et al. 2021), but vertical transmission has been described in several cases of infection with COVID-19, complicating pregnancy as well (Taglauer et al. 2020; Wang et al. 2020). Parazzini et al. (2020) describe an increase in IgG antibodies in three cases of newborns born to mothers with COVID-19, but the polymerase chain reaction (PCR) test was negative. It points to the transplacental passage of antibodies, as did Mesa et al. (2022), who found that a significant immune response passes to the fetus.

Some works also point to a possible connection between COVID-19 and birth defects. Children born to women with COVID-19 during pregnancy recorded e.g. congenital cardiovascular defects, heart rhythm abnormalities, metabolic disorders, and perinatal respiratory disorders at an increased rate compared to children born to women who did not have COVID-19 during pregnancy (Miller et al. 2023). The authors Abdelkader et al. (2022) describe the case of a 34-year-old pregnant woman who had a COVID-19 infection in the first month of pregnancy and had a premature birth at 34 weeks. A congenital heart defect and hydrops were present in the fetus. After giving birth, the girl was cyanotic, had bradycardia and was generally in a bad condition, she was admitted to the ICU and died 5 days later. Although congenital heart disease can occur for a variety of reasons, the authors hypothesize that COVID-19 may play a role in the development of congenital heart defects. Morhart (2022) found severe eye malformation (unilateral microphthalmia, optic nerve hypoplasia, and congenital retinopathy) associated with maternal SARS-CoV-2 infection. This embryopathy could not be explained by other infectious agents, genetic factors, drug use, or other maternal illness during pregnancy.

Only limited information is available on the effects of COVID-19 on the development of congenital malformations during the first trimester of pregnancy (Hernández-Diaz et al. 2022). In the study, they reported that no specific pattern of malformations was observed. Although the results are not compatible with any major teratogenic effects associated with maternal SARS-CoV-2 infection, relative risk estimates were imprecise and larger studies are justified. Long-term neurodevelopmental sequelae are a potential concern in neonates after *in utero* exposure to SARS-CoV-2. Benny et al. (2023) described two newborns born to mothers positive for SARS-CoV-2. Both showed early-onset (day 1) seizures, acquired microcephaly, and significant developmental delay over time. Sequential magnetic resonance imaging (MRI) showed severe parenchymal atrophy and cystic encephalomalacia. Neither child was positive for SARS-CoV-2 (nasopharyngeal swab, reverse transcription polymerase chain reaction) at birth, but both had detectable antibodies to SARS-CoV-2 and elevated blood inflammatory markers. Placentas from both mothers showed SARS-CoV-2, fetal vascular malperfusion. One child died. The dead dieter's brain showed SARS-CoV-2. The constellation of clinical findings, placental pathology, and immunohistochemical changes strongly suggest that maternal SARS-CoV-2 infection with placentitis triggered an inflammatory response and fetal brain damage. Demonstration of SARS-CoV-2 in the brain of the deceased infant also raises the possibility that SARS-CoV-2 infection of the fetal brain directly contributed to the brain damage. In both infants, the neurological findings at birth mimicked the presentation of neonatal hypoxic-ischemic encephalopathy. This study offers the first direct evidence that the SARS-CoV-2 virus can penetrate the placenta (COVID-19 can cross placenta, harm infants: Case study; https://www.beckershospitalreview.com/patient-safety-outcomes/covid-19-can-cross-placenta-harm-infants-case-study.html; Carbajal 2023).

Another aspect to consider is the psychological stress caused by the COVID-19 pandemic in pregnant women. COVID can be associated with acute changes in behavior, including anxiety and depressive disorders. It can worsen an already existing mental illness or result in a traumatic stress disorder. In addition to being more susceptible to infections during the pandemic, pregnant women routinely lacked regular prenatal consultations. Social isolation, fear, insecurity and lack of prenatal care contribute to maternal mortality and can interfere with fetal development. An example of this is the increased risk of preeclampsia in women who experience depression or anxiety during pregnancy. Vasoactive substances, hormones and other neuroendocrine mediators have an altered secretion during depression, which contributes to an increase in blood pressure, which in turn increases the risk of preeclampsia. Several studies have investigated the association between stress and non-syndromic orofacial clefts (NSOFC). Sharif et al. (2023) conducted a systematic review to determine the association between maternal periconceptional stress and NSOFC in newborns. They state that, based on currently available evidence, maternal exposure to periconceptional stress could be considered a risk factor for NSOFC. Aim of the present study was to compare the incidence of COVID-19 disease during mother´s pregnancy between a group of the children with NSOFC and a control group of the children without NSOFC.

Material and Methods

At the Clinic for Plastic Surgery, Ruzinov Hospital in Bratislava (Slovak Republic), we recorded the arrival of mothers who had newborns with orofacial clefts from September 2021 to February 2023. The total number of these mothers was 38. From this number, we selected 13 mothers who overcame COVID-19 confirmed by a PCR test during the first trimester and without a genetic predisposition to orofacial clefts. The mothers signed an affidavit stating that they had a confirmation of overcoming COVID-19 by PCR test, also that they had overcome only a mild course of the COVID-19 infection without fever or with a temperature of 37.5 to 38°C at the most, they did not take any medications, had no chronic or other diseases, did not smoke, did not drink alcohol and also did not indicate any great stress or fear of COVID-19. As a control group, we had mothers who overcame COVID-19 in the first trimester in the same period and gave birth to healthy newborns at the Gynecology and Obstetrics Department at the Ruzinov Hospital in Bratislava. During the same period, there were 2,667 births, and of these, 11 mothers who gave birth to healthy newborns overcame COVD-19 in the first trimester.

Statistics

The data were analysed using GraphPad Prism 8.0.1 software using Chi-squared test with confidence interval of 95%, $p < 0.05$ was considered to be statistically significant.

Results

We compared the groups of children born in Ruzinov Hospital in Bratislava between September 2021 to February 2023 according to whether their mothers overcome or not COVID-19 infection in the first trimester of pregnancy. The statistical evaluation of the data revealed a significantly higher incidence of COVID-19 disease in the group of mothers who gave birth to a child with NSOFC in comparison to the group of mothers who gave birth to a child without NSOFC (Chi-square value = 361.111, $p < 0.01$). (Table 1 and 2).

Table 1. Evaluated groups of children and categories of mothers

Group/Category	Without COVID-19	With COVID-19	Total
Without NSFOC (C)	2667	11	2678
With NSOFC	38	13	51
Total	2705	24	2729

NSFOC, non-syndromic orofacial cleft; C, control.

Discussion

The risk and potential consequences of mother-to-child transmission of SARS-CoV-2 during pregnancy are still a matter of debate. There are still very few studies regarding the impact of COVID-19 on the development of birth defects, and therefore any work that deals with this issue is beneficial. Our study showed significantly higher incidence of COVID-19 disease in the group of mothers who gave birth to a child with NSOFC compared to the group of mothers who gave birth to a child without NSOFC.

The authors Komine-Aizawa et al. (2020) stated in their study that the vertical transmission of SARS-CoV-2 and the possible induction of pregnancy complications including abortion, fetal malformations, fetal growth restriction and/or stillbirth are a serious problem for pregnant women with COVID-19. According to clinical information, the incidence of vertical transmission of SARS-CoV-2 is still limited. Even if the newborn tests negative for SARS-CoV-2, frequent abnormal findings have been reported in mothers positive for COVID-19, including fetal and maternal vascular malperfusion. The primary receptor of SARS-CoV-2 is estimated to be angiotensin-converting enzyme 2 (ACE2). It is highly expressed in cells such as syncytiotrophoblasts, cytotrophoblasts, endothelial cells and vascular smooth muscle cells of primary and secondary villi. However, another route of transplacental infection cannot be ruled out. Pathological examinations have shown that syncytiotrophoblasts are often infected with SARS-CoV-2, however, fetuses were not always infected. The frequency and molecular mechanisms of intrauterine vertical transmission of SARS-CoV-2 have not yet been established.

In the study of Sabbagh et al. (2023) the factors related to COVID-19 that may be related to the risk of NSOFC in five Arab countries were assessed. These factors included infection with COVID-19, symptoms of COVID-19, stress, smoking and fear of COVID-19. They stated that NSOFC might also be related to the mother's exposure to stress from COVID-19 without a direct effect of the infection itself, however, our study did not confirm it.

SARS-CoV-2 infections in pregnancy can lead to placental lesions based on vascular events, which can be well visualized

Table 2. Chi-square points

Group/Category	Without COVID-19	With COVID-19
Without NSFOC (C)	0.059	6.689
With NSOFC	3.116	351.247

Chi-square = 361.111, $p < 0.01$. NSFOC, non-syndromic orofacial cleft; C, control.

on prenatal MRI of the fetus (Kienast et al. 2023). Although it is now known that SARS-CoV-2 infection during pregnancy can cause serious complications in mothers and fetuses, there are very few prenatal studies in the literature on possible intrauterine damage to fetal and extrafetal structures. A few histopathological studies deal with placental changes after infection, but due to postnatal examination, they can only provide limited information about pathological changes already present prenatally. Furthermore, the current body of studies on specific changes following SARS-CoV-2 during pregnancy is very modest. MRI has not been used for these purposes until now. In this study, prenatal MRI after SARS-CoV-2 infection in pregnancy reveals placental lesions based on vascular malperfusion. These changes provide an explanation for fetal morbidity associated with SARS-CoV-2, such as fetal growth restriction (Kienast et al. 2023).

Silasi et al. (2015) states that when coronaviruses infect pregnant women, it increases the risk of adverse effects on pregnancy and newborns, as well as severe respiratory disease. They describe that data from many impact studies, e.g. influenza and other respiratory infections such as respiratory syncytial virus and adenovirus, as well as others such as cytomegalovirus, herpes simplex virus and varicella zoster, have shown an increased risk of pregnant women and newborns compared to non-pregnant women and that they can cause congenital malformations during pregnancy, which is also in line with our previous studies (Molnárová et al. 2018, 2020). Such connections were found even when a pregnant woman was infected with either SARS-CoV or MERS-CoV (Schwartz and Graham 2020). There are still few published cases of coronavirus infections occurring during pregnancy and causing the possibility of transmission from mother to fetus, however, there is also concern that fetuses may be damaged by congenital infection with COVID-19 and other coronaviruses. Diriba et al. (2020) indicate that, so far, none of the studies have demonstrated the transmission of coronaviruses from mother to fetus in utero. Allotey (2022) found that the rate of SARS-CoV-2 positivity is low in children born to mothers with SARS-CoV-2 infection. However, evidence suggests confirmed vertical transmission of SARS-CoV-2, although this is likely to be rare. The severity of the mother's COVID-19 disease appears to be related to the SARS-CoV-2 positivity of the offspring. Thus, the risk of vertical transmission and the potential pathogenesis of fetuses infected with SARS-CoV-2 deserve further investigation.

Scientific evidence indicates that the causative agent of COVID-19, SARS-CoV-2, apparently crosses the placental barrier (Dong et al. 2020; Khan et al. 2020) and the blood-brain barrier (virus detected in cerebrospinal fluid) (Moriguchi et al. 2020). Since the virus can penetrate the placenta and the nervous system, the virus itself may have some adverse effects on functional brain development if pregnant mothers suffer from COVID-19. It also appears that the SARS-CoV-2 coronavirus can be transmitted from the mother to the fetus, as the virus uses an entry receptor, ACE2, and S protein proteases expressed in the developing human embryo. In particular, ACE2 and S protein proteases are expressed in early gametes, zygotes and 4-cell embryos (Colaco et al. 2020). Thus, direct transmission of SARS-CoV-2 blast cell infection may be possible, but remains to be confirmed. During embryonic development, the health of these epiblast cells is critical as these cells undergo organogenesis. Any functional changes in early embryonic cells by viral infection can lead to adverse birth defects. Because much is still unknown about COVID-19 and neurodevelopmental complications, there is an increased risk of birth defects if SARS-CoV-2 infection occurs during early pregnancy. Therefore, there is an urgent need to continue collecting data on clinical cases of COVID-19 infection in pregnancy, especially during the first trimester. We are also inclined to this opinion with our study.

SARS-CoV-2 infection poses increased risks of poor outcomes during pregnancy, including preterm birth and stillbirth. There is also developing concern over the effects of SARS-CoV-2 infection on the placenta, and these effects seem to vary between different viral variants. Despite these risks, many pregnant individuals have been reluctant to be vaccinated against the virus owing to safety concerns. We now have extensive data confirming the safety and effectiveness of COVID-19 vaccination during pregnancy (Male 2022). Meta-analyses of epidemiologic studies of vaccination against COVID-19 during pregnancy did not find an increased risk of any adverse outcomes. There is no evidence of direct or indirect harmful effects of SARS-CoV-2 on fertility, embryo/fetal development, pregnancy outcomes, delivery or short-term postnatal development of the offspring (Edlow et al. 2020). Evidence for associations between COVID-19 vaccination or SARS-CoV-2 infection and the risk of congenital anomalies is limited (Calvert et al. 2023). Their primary analyzes found no association between SARS-CoV-2 infection and any anomaly. Primary analyzes also found no association between any vaccination and any anomaly. These data provide reassurance about the safety of vaccination. The study adds to the growing number of epidemiological evidences that SARS-CoV-2 infection during pregnancy and maternal vaccination is not associated with the risk of congenital anomalies (Adhikari et al. 2020; Flaherman et al. 2021). Although the cases are rare, the authors claim that the findings underline the importance of vaccination in prevention "as the first line of defense".

The palate develops from two primordia: primary palate and the secondary palate. The steps in palate formation in humans take place between the 7th and 12th week and consist of outgrowth of palatal shelves from the paired maxillary prominences, reorientation of the shelves from vertical to horizontal, apposition of the medial surfaces, formation

of a bilayered seam, degradation of the seam and bridging of mesenchyme (Danescu et al. 2015). Major signaling pathways, such as Shh, Fgf, Tgf-β and Wn tare involved in regulating growth of the palatal shelves through epithelial-mesenchymal interaction. Recent studies on patients with nonsyndromic orofacial clefts have revealed that differential DNA methylation, epigenetic regulator mutations and low-frequency genetic variations in noncoding regions may contribute to cleft palate (Shaffer et al. 2019). Relevant signaling pathways, transcriptional factors as well as epigenetic variations may be targets to SARS-CoV-2 virus what in turn can result in congenital anomalis including cleft palate. Further studies involving also experimental animal models are needed to shed light on underlying mechanism(s).

Our results point to the possibility of the influence of COVID-19 on the development of NSOFCs, given that we do not assume other possible teratogens such as, for example, hyperthermia (the mothers only reported a temperature of up to 37.5 a maximum of 38°C), the use of drugs (they only had a mild course of infection), chronic and other diseases, they did not smoke, they did not drink alcohol, they ruled out any long-term stress or fear of COVID-19, they also did not indicate a genetic predisposition to orofacial clefts. The mothers ruled out these and other possible teratogens and signed an affidavit, in which there is also a statement about the confirmation of an overcome COVID-19 infection by a PCR test in the first trimester, we think that this is the probability of the influence of the COVID-19 infection. The mothers had a mild course of the disease with mild symptoms. However, their PCR test was positive. We can hypothesize the effect of the viral disease on the placenta and/or embryo might have been high enough to contribute to the cleft development.

Conclusion

The risk and potential consequences of COVID-19 infection during pregnancy are still not clearly investigated. In the present study, the incidence of COVID-19 infection during mother´s was evaluated pregnancy between a group of the children with NSOFC and a control group of the children without NSOFC. The data were from the Clinic for Plastic Surgery, Ruzinov Hospital in Bratislava from September 2021 to February 2023. The study showed significantly higher incidence of COVID-19 disease in the group of mothers who gave birth to a child with NSOFC in comparison to the group of mothers who gave birth to a child without NSOFC.

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