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Evaluation of vertical transmission of SARS-CoV-2 from mothers with Covid-19 to newborns and related maternal and fetal outcomes

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Abstract

Introduction: With the appearance of SARS-CoV-2 and its rapid and large-scale spread throughout the world, there is an increasing concern about its effects on pregnancy. The possible transmission of SARS-CoV-2 from mothers with coronavirus disease of 2019 (COVID-19) to the fetus and its outcomes stands as a very controversial concept for prenatal medicine since there is little evidence available in this regard.

Material and methods: The present study aimed at the possible, vertical transmission of coronavirus from 12 pregnant women with COVID-19 to their newborns in comparison to a group of healthy mothers.

Results: The results of real-time PCR tests of amniotic fluid and nasopharyngeal secretions of the newborns born from the mothers with COVID-19 were negative. The only difference between the two groups was a significant increase in the frequencies of preterm delivery, cesarean section, and intrauterine growth restriction of the newborns in the case group and there were no particular mother-newborn outcomes. Based on our results and similar investigations, vertical transmission of SARS-CoV-2 to newborns is not possible.

Discussion: According to the shortage of contradictory data about the effects of COVID-19 on newborns, a higher level of caution should be considered in the examination and monitoring of possible infections in neonates born from mothers infected with COVID-19.

Introduction

The spread of SARS-CoV-2 is the first pandemic of the present century. The appearance of SARS-CoV-2 as a new infection during late December 2019 and in the form of a new public health crisis, puts the healthcare systems and physicians into a unique challenge. One of the most important aspects of this challenge is the management of pregnant women infected with SARS-CoV-2 [1,2].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the family *Coronaviridae*, the members of which cause a wide spectrum of diseases from common colds to severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) [3,4]. The SARS-CoV-2 infection causes coronavirus disease (COVID-19), mainly transmitted via droplets; while other transmission routes are hypothetical. Up to now, it has been unclear whether SARS-CoV-2 is transmissible from the mother to the fetus (2). Currently very little is known about the different characteristics of the diseases, including maternal and fetal health. In recent years, the epidemics of viral infections have shown that pregnant women experience more favorable results than non-pregnant individuals [3]. Pregnant women have a greater risk of catching viral infections like SARS-CoV, MERS-CoV, Ebola, H1N1, and influenza A and these infections can bring about unwanted medical and pre-delivery outcomes such as mother's death, spontaneous abortion, stillbirth, and premature birth. Nevertheless, little is known about the COVID-19 in pregnancy [5].

Pregnant women are prone to a wide range of fetal and maternal complications, which may affect the consequences of any co-infection. During the first trimester, there is a major risk of abortion and growth abnormalities. Late in the second and third trimesters, there is a higher risk of maternal diseases such as gestational diabetes and hypertension, causing maternal complications and premature delivery [1]. Immunological and physiological changes occurring normally during the pregnancy can worsen respiratory infections because of systemic effects on the body. Tachycardia, higher oxygen intake, increased stroke volume, and decreased pulmonary capacity are the main physiological changes in cardiovascular and respiratory systems during pregnancy. Compared to non-pregnant populations, these changes aggravate COVID-19 complications in pregnant women [3,6]. On the other side, pregnancy suppresses the immune system. These factors pose pregnant women at a higher risk of getting infectious diseases. Furthermore, there is a risk of possible, vertical transmission of SARS-CoV-2 from mother to the fetus, causing serious infections in the fetus and newborn

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[3]. These concerns are based on the experiences gained from infections like Zika virus, Ebola virus, Marburg virus, and other infectious agents able to be transmitted vertically from mother to the fetus. These viruses can threaten the health and survival of the infected mother and her fetus [6].

Currently, the clinical characteristics and vertical transmissibility of COVID-19 in pregnant patients are uncertain. Although some cases of prenatal communication have been reported (7-9), it is not obvious whether these cases occur via placental and uterus routes or by being exposed to the surroundings. It is important to clarify whether SARS-CoV-2 reaches the fetus and how it takes place [2]. Therefore, to prevent fetal infection, optimized pregnancy management, and ultimately, a better understanding of SARS-CoV-2 biology is necessary. Here, we present a comprehensive case-control study, showing the presence of the SARS-CoV-2 virus in the amniotic fluid of mothers with COVID-19 with the aid of real-time PCR test. The present study also uncovers some maternal and fetal outcomes.

Methods

The present investigation is a case-control study of pregnant women hospitalized for delivery in Khalij Fars Hospital in Bandar Abbas, Iran. After serological tests and real-time PCR tests on nasopharyngeal secretions to check and confirm COVID-19 infection, the individuals examined participated in the study in two groups of 12 persons, including the patients with COVID-19 (case group) and the participants without COVID-19 (control group). To assess the extent of pulmonary involvement and its correlation with COVID-19 infection, a CT-scan examination was performed on the participants. The exclusion criteria included the history of background cardio-pulmonary diseases and the history of urinary tract infection and chorioamnionitis during pregnancy. 10 ml of the amniotic fluid was collected aseptically during cesarean section or vaginal delivery, before the neonate's emergence. The amniotic fluid samples were immediately sent to the molecular laboratory for the examination of SARS-CoV-2 virus presence and real-time PCR tests. The nasopharyngeal secretions of the newborns were also sampled and inspected molecularly.

The demographic data, including age, number of pregnancies, age of the pregnancy, C-reactive protein (CRP), saturation of oxygen, respiration rates, lymphopenia, fever, the type of delivery, hospitalization duration, required admission in intensive care unit (ICU) ward, and the results of real-time tests and pulmonary CT-scan examination were recorded in data collection forms. The neonates' data, including the results of molecular tests, Apgar score, hospitalization duration, and required admission in the Neonatal ICU (NICU) ward was also recorded. Data analysis was performed using SPSS Software Version 21.

Results

Descriptive analysis of the mothers with COVID-19 in the case group (positive RT-PCR result) showed that with an average age of 31.5±5.5 years, they were not significantly different from the control group with an average age of 27.5±5.3 years ($p = 0.083$). The results showed that although the CT-scan examination and RT-PCR test of all mothers in the case group were positive, molecular tests were not positive for any of the amniotic and nasopharyngeal samples of the newborns and all newborns of sick mothers were healthy. Comparative statistical tests indicated that the average age of pregnancy was significantly lower in infected mothers (245.28±2.4 days vs. 272.5±12.9 days for healthy mothers, $p = 0.008$). This recommends that COVID-19 infection can induce preterm delivery, such that 50% of the mothers with disease delivered before 37 weeks. The average CRP levels of the case group (34.7 mg/l) were also significantly higher than the normal so that 8 mothers having COVID-19 (66.6%) had CRP levels higher than 10 mg/L. The average RR score was 37.5 in mothers having COVID-19 and it was significantly above the normal level, and 8 sick mothers (66.6%) were abnormal in this regard ($p = 0.003$) (12-15 is normal and above 25 is abnormal). As well, the average body temperature of the case group (38.13) was significantly higher than the normal ($p = 0.002$), but there were not any differences in Saturation of the two groups studied. Half of the mothers with COVID-19 had lymphopenia with lymphocyte counts under 1100/ml.

Based on the type of delivery, COVID-19 infection in pregnant women has greatly and significantly increased the rate of cesarean section ($p = 0.010$) and most of them (83%) had a cesarean section, while most of the healthy women (66.6%) had natural childbirth. Results of statistical analysis indicated that COVID-19 infection causes mother's admission in the ICU wards ($p = 0.011$), but there were not any significant differences in the rates of neonates' rate of admission in the NICU ward between the two groups. The frequency of rupture of membranes (ROM) and the average Apgar number of newborns also had no significant differences. But the Apgar number of meconium excretion and intrauterine growth restriction (IUGR) was higher in neonates born from mothers with COVID-19 ($p < 0.05$) (Table 1).

Discussion and conclusion

Coronavirus disease of 2019 (COVID-19) caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2) has spread worldwide and is a global pandemic currently. One of the most important concerns is the maternal and fetal outcomes of COVID-19 in pregnant mothers, whether the SARS-CoV-2 could be vertically transmitted from mothers to their fetuses, and the possible congenital infection. Mother-fetus

Table 1. Comparison of the average of factors studied. *Significance level under 0.05.

Factors studied	Mothers with COVID-19 (the case group, n=12)	Mothers without COVID-19 (the control group, n=12)	p-value
Average age (years)	31.5 ± 5.5	27.5 ± 5.3	0.083
The Average age of the pregnancy (days)	245.28 ± 2.4	272.12 ± 5.9	0.008*
CRP (mg/**L**)	34.7 ± 4.3 8 cases (66.6%) above 10	< 10 normal	0.017*
Lymphopenia	1296.6 ± 552.7 6 cases (50%) under 1100	< 1100 Suspected of COVID-19	0.244
Saturation of oxygen	94.75 ± 4.8 3 cases (25%) under 95%	> 95% (normal)	0.860
Respiration rates	27.5 ± 6.8 8 cases (66.6%) above 25	12-20 normal, > 25 abnormal	0.003*
Average body temperature	38.13 ± 0.9	37	0.002*
Frequency of vaginal delivery	2 (16.2%)	8 (66.7%)	0.010*
Frequency of cesarean delivery	10 (83%)	4 (33.3%)	0.010*
Mother's need to ICU	5 (41.7%)	0	0.011*
Neonate's need to NICU	4 (33.3%)	2 (16.7%)	0.430
ROM	3 (25%)	4 (33.3%)	0.670
Apgar number at the first minute	7.16 ± 3.04	8.17 ± 0.7	0.289
Apgar number at the fifth minute	8.5 ± 3.06	6.1 ± 3.8	0.114
Meconium excretion	12 (100%)	5 (41.7%)	0.017*
IUGR	6 (50%)	0	0.007*

interconnecting cells play a key role in the fetus's growth regulation and mother's immune response regulation. The viral infections can interrupt the function of these cells, ending in placental dysfunction (10). The present investigation has examined this possibility in COVID-19-positive and healthy mothers and their newborns.

Our case group was selected based on the clinical symptoms and laboratory tests. The members of this group were significantly different from the control group in terms of fever, respiration rates, CRP levels, and lymphocyte counts. According to our observations, mothers with COVID-19 had fever, higher respiratory rates, increased CRP titers, and lymphopenia, which was consistent with the literature. In an examination of 245 pregnancies, including 48 cases of maternal SARS-CoV-2 infection, Chamseddine et al. [1] reported that in addition to clinical demonstrations like fever, fatigue, and shortness of breath, the most common laboratory abnormalities in pregnant women with SARS-CoV-2 infection are increased CRP levels, neutrophilia, and leukocytosis. As the laboratory findings of the studied pregnant women showed that 49% had higher CRP levels, 31.3% had lymphopenia, 28.6 had neutrophilia, and 12.2% had leukocytosis. In another meta-analysis including 20 papers (4062 patients), the most COVID-related symptoms were high body mass index, high respiratory rates, and a combination of underlying diseases, fever, and shortness of breath. The laboratory findings of this meta-analysis also confirm the correlation of increased white blood cell counts, hepatic enzymes, and CRP, and decreased lymphocyte counts and albumin levels with the disease [11]. Of course, COVID-19 infection does not always have constant symptoms and sometimes patients lack some of the symptoms or all of them. Examining 60 papers about the pregnant participants, including a total number of 1287 SARS-CoV-2-positive pregnancies, Pettirosso et al. [12] acknowledged that asymptomatic infection was observable in 43.5-92% of cases, and in symptomatic patients, fever was the most common symptom, observable in 10-100% of cases both at the time of admission and post-delivery.

Through supplementary pulmonary computerized tomography (CT) scan and real-time PCR tests on nasopharyngeal secretions, we also confirmed mothers' disease. It was expectable that because of disease complications, five patients needed admission in ICU wards. It is while none of the amniotic fluid and nasopharyngeal samples taken from the neonates born from mothers with COVID-19 were not positive in real-time PCR tests and consequently, in comparison to the neonates born from healthy mothers, they did not have higher rates of NICU admission.

Although the definitive proof of COVID-19 intrauterine transmission is the confirmation of SARS-CoV-2 proliferation in fetal pulmonary tissues, this is almost impractical technically looking. Practically, the method of checking for the presence of intrauterine viral infection is testing the placental, amniotic fluid, and pharyngeal swab samples of the newborn. This is important to emphasize that all of these samples must be collected aseptically immediately after delivery, as what we considered in the present study. In an investigation about the possible, vertical intrauterine transmission of COVID-19 in nine pregnant women with laboratory-confirmed, mild to moderate COVID-19 demonstrations during the third trimester, the amniotic fluid, umbilical cord blood, and neonatal pharyngeal samples were tested with the reverse transcriptase-polymerase chain reaction (qRT-PCR) for the SARS-CoV-2 infection. All of the samples were negative, showing that the fetal intrauterine infection had not occurred during the third trimester of the pregnancy [13]. Using a similar method, Lei et al. [14] found no evidence of the vertical transmission in four pregnant women with COVID-19 during the third trimester and the vaginal secretion samples were also SARS-CoV-2-negative. In a study by Chen and colleagues, the placental tissues of three pregnant women with confirmed COVID-19 during the third trimester and the neonatal pharyngeal swab samples were used to assess the potential risk of vertical intrauterine transmission and all samples were SARS-CoV-2-negative [15]. It is noteworthy that, as reported in a case report, it was proven that the SARS-CoV-2 test of pharyngeal swab sample was positive 36 hours after the birth of a neonate from a pregnant woman with COVID-19. But later, it was confirmed that the SASRS-CoV-2 qRT-PCR test was negative for placental and umbilical cord blood samples, suggesting that the vertical intrauterine transmission may have not happened [5]. As a result, regarding the available data, currently, there is no evidence of intrauterine infection caused by the vertical transmission in women with COVID-19 during the third trimester.

In the studies described above, most women had mild to moderate COVID-19 symptoms with symptoms of all cases emerging in the third trimester of pregnancy. Consequently, the time interval from the clinical demonstrations of SARS-CoV-2 to the delivery was short. Since pregnancy causes unique physiological changes, particularly in the immune and respiratory systems, pregnant women are prone to viral infections [16]. The placental barrier may transiently delay the transmission of viruses from mother to her baby, but it is unclear whether there is the risk of vertical transmission during infection transmission in the first or second trimester of pregnancy. Furthermore, it seems that there are mechanisms by which the SARS-CoV-2 can be vertically transmitted through the placenta, potentially causing the intrauterine infection. On the other hand, Zhao et al. [17] showed that angiotensin-converting enzyme 2 (ACE2), recently known as the cardiac surface receptor of SARS-CoV-2-sensitive cells, is expressed in the human placenta [18]. This makes it possible for the SARS-CoV-2 to be spread transplacentally through ACE2. As well, the placental damages caused by extensive maternal hypoxia in women with COVID-19 can potentially lead to the vertical transmission of SARS-CoV-2, bringing about the intrauterine infection.

Statistical analysis of our data showed that pregnant women with COVID-19 were exposed to a significantly higher risk of premature delivery. It seems that SARS-Cov-2 infection lowers the age of the pregnancy and greatly affects the type of delivery, leading it towards cesarean section; as our results indicate a four-fold reduction in mothers of the case group compared to the control group. Our results also showed that there was a significant increase in the intrauterine growth restriction rate of the infants born from mothers with COVID-19, whereas ROM and one- and five-minute Apgar scores of these infants were not influenced by mother's disease. The meconium excretion rate of infants born from mothers with COVID-19 was higher than other infants. Studies by Chen and coworkers established that pneumonia could increase the risk of low birth weight, premature delivery, restricted fetal growth, and five-minute Apgar scores greater than 7 [19]. Maternal pneumonia is accompanied by several adverse gynecological outcomes such as premature rupture of membranes (PROM), premature delivery, intrauterine growth restriction (IUGR), and infantile death [20]. Based on fetal and infantile outcomes, pregnancy pneumonia can increase the risk of premature delivery in comparison to the general population [19]. Our results are compatible with this observation. Fortunately, the preterm newborns were in good condition with Apgar scores comparable to those born from healthy mothers. The incidence of intrauterine growth restriction (IUGR) cause by its prevalence in the previous SARS infections during pregnancy

was a finding in this group. However, few reports are available about fetal IUGR in SARS-Cov-2-positive pregnancies. It is hypothesized that these pathological, morphological changes of placenta originate from the hypoxic conditions during the coronavirus infection lead to IUGR, meconium-contaminated amniotic fluid, or fetal distress. As the same way, the abortion and stillbirth can be caused by the coronavirus infection. Therefore, even after negative nucleic acid tests for SARS-CoV-2, pregnant women with COVID-19 should be closely monitored [21].

Over years, several studies have focused on maternal and infantile outcomes of the recent pandemics such as influenza A (H1N1), SARS-CoV, MERS, and respiratory syncytial virus (RSV). The case-control study by Riberio et al. [22] on Brazilian women infected with 1N1, compared to the women who had recovered, reported a higher rate of stillbirth and premature delivery among women ultimately dying of the infection. They observed that the initial antiviral therapy during 48-72 hours of symptoms onset was a protective factor [22]. A systematic review in 2017 about maternal influenza reported the rates of premature delivery (before the 37th week of pregnancy) to be 11.4%, 7.7%, 7.1%, and 6.3% in the United States, Canada, England, and Norway, respectively [23]. The rate of premature delivery has been reported to be 29% in the pregnancies of RSV-infected mothers, which is comparable to the 13% rate of premature delivery in non-infected women. Also, 57% of the infants born from mothers with RSV were RSV-infected [24]. However, the outcomes of SARS-CoV-2 vertical transmission are still unclear. A systematic review published in 2020, including maternal and infantile outcomes in patients infected with MERS, SARS-CoV, and SARS-CoV2 indicated that the SARS-CoV-2 had the highest rates of premature delivery, fetal distress, prenatal death, and cesarean section. In addition, none of the cases in SARS-CoV and MESR had abnormal Apgar scores of below 7 and only 2.4% of the SARS-CoV-2 cases had abnormal Apgar scores. There was no evidence of vertical transmission for each of the three infections [25].

The meta-analysis by Pettirosso et al. [12] suggested that in 22 works out of 66, focusing on pregnant women with COVID-19, the pregnant women delivered before the 37th week and premature delivery was reported in 10-100% of cases. Taking all studies into account, cesarean section was performed in over 40% of deliveries for the COVID-19 patients. Li et al. [26] compared the rate of premature delivery among pregnant women with positive and negative SARS-CoV-2 RT-PCR results. They reported an increased rate of premature delivery in the SARS-CoV-2-positive group (23.5% vs. 5% in the control group, $p < 0.05$). Of 201 delivery cases reported, 182 (89%) had cesarean section, which is significantly higher than the expected 15% of pregnancies in the general population and even higher than the complicated pregnancies affected by the influenza virus [27]. Similarly, in most studies, the rate of cesarean section is 40-100%, which is higher than the average rate in China and the Untitled States of 37% and 32%, respectively [26,28,29]. Cesarean sections are performed due to the delivery symptoms or because of uncertainties about the transmission of active infections from mother to her baby. In the special hospitals, the type of delivery is selected based on the delivery factors; while in others, because of SARS-CoV-2 infection, cellular section operation was performed preventively. According to some special advice, cesarean section may minimize the risk of cross-contamination and lowers maternal activity during delivery [29] However, noting the heterogeneous distribution of cesarean sections vs. vaginal deliveries, the differences of neonatal and maternal outcomes with vaginal delivery or cesarean section in SARS-CoV-2 pregnancies cannot be assessed. It is important to note that there is no contradiction to the vaginal delivery, as uncomplicated vaginal delivery indicates at least in five patients [13]. In this regard, both the Royal College of Obstetricians and Gynecologists (RCOG) and the International Federation of Gynecology and Obstetrics (FIGO) stated that the type of delivery should not be affected by COVID-19 (unless emergency delivery was required due to the severe respiratory difficulties) [12,30]. These recommendations have been presented after several cases being reported in this review. Our results also showed that even in mothers with COVID-19, who had vaginal delivery, the SARS-CoV-2 test was not positive for any neonates and the mother's SARS-CoV-2 infection itself may not dictate the cesarean section.

In conclusion, our results suggest that SARS-CoV-2 infection in pregnant women can cause premature delivery and fetal growth restrictions. Compared to the general population, the rate of cesarean section is also higher in these mothers, which according to the oxygen levels in patients' blood, it appears that this change is to prevent infection transmission; while there were not any cases of neonatal birth with COVID-19 and intrauterine vertical transmission. Examinations and collection of more data about this evolving, rapidly spreading pandemic are necessary to shed more light on the maternal and fetal outcomes.

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