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Transitory Fetal Skin Edema as a Manifestation of SARS-CoV-2 Infection during Pregnancy: A Mini Review

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in late 2019 in Wuhan, China. Due to its hasty dissemination, the novel coronavirus has infected over 500 million people worldwide. Given that pregnancy is an immunocompromised state, pregnant patients have larger risk of contract SARS-CoV-2 compared with non-pregnant women.

Keywords: COVID-19; SARS-CoV-2; Infection; Pregnancy; Fetus

Introduction

Some maternal infections during pregnancy are associated with poor perinatal outcomes and fetal anomalies, such as classic TORCH infections constituted by toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, as well as *Treponema pallidum*, hepatitis viruses, human immunodeficiency virus, varicella, Parvovirus B19, or the recent Zika virus [1-6]. Infection with any of these agents (i.e., *Toxoplasma gondii*, rubella virus, cytomegalovirus, herpes simplex virus) may cause similar symptoms in affected new-born. The symptoms may include fever; difficulties in feeding; small areas of bleeding under the skin, causing the appearance of small reddish or purplish spots; enlargement of the liver and spleen (hepatosplenomegaly); yellowish discoloration of the skin, whites of the eyes, and mucous membranes (jaundice); hearing impairment; abnormalities of the eyes other symptoms and findings. Each infectious agent may results in additional abnormalities that may be variable, depending upon a number of factors (e.g., stage of fetal development). TORCH Syndrome refers to any of a group of infections in new-born due to one of the TORCH infectious agents having crossed the placenta during pregnancy.

Data regarding the effects of SARS-CoV-2 throughout pregnancy is still controversial. Particularly, evidence is still scarce regarding pregnancy outcomes in women with SARS-CoV-2 infection during the first and the second trimesters of gestation [7]. Additionally, the potential fetal consequences of the virus or its maternal immune response are not entirely known [8]. In this review, cases of transient fetal skin edema associated with maternal SARS-CoV-2 infection are analyzed.

Literature Review

Cases

Transient fetal skin edema has been reported in 3 cases as an ultrasound finding in pregnant patients with SARS-Cov-2 infection [9,10]. At our tertiary La Fe University and Polytechnic Hospital (Valencia, Spain), this fetal skin edema located in the head was described together with polyhydramnios in a 22-year-old gravida 2, para 1 woman who had a mild SARS-CoV-2 infection. With no relevant medical history, the patient proved positive for SARS-CoV-2 infection on RT-PCR of nasopharyngeal swabs at 28+3 weeks' gestation. The pregnancy was spontaneously conceived and developed uneventfully, with a low-risk first-trimester screening for trisomies 21, 18, and 13, and normal fetal anatomy visualized at the 20 weeks morphological ultrasound. Body mass index, temperature, blood pressure, respiratory rate, hemoglobin saturation by pulse oximetry, chest radiograph, fetal ultrasound, and blood tests revealed results within normal limits when SARS-CoV-2 infection was diagnosed, except for D-dimer (1680 ng/ml). Hence, the pregnant patient was discharged, and her well-being was assessed every 48-72 hours by phone calls. The symptoms of infection lasted for a total of 10 days, and the RT-PCR for SARS-CoV-2 became negative at 32+6 weeks. The subsequent follow-up with serial ultrasounds revealed transitory fetal skin edema in the axial plane of the head at 36+3 weeks, accompanied by polyhydramnios. Both ultrasound findings resolved spontaneously, and at 38+3 weeks' gestation they were not found by fetal ultrasound. Maternal serology and glucose level were within normal limits. Hence, other infections as well as gestational diabetes were ruled out. The patient underwent a spontaneous beginning of labour and a vaginal delivery at term. Both the newborn and the mother were discharged two days after birth [9].

The two other reported cases of transitory subcutaneous fetal edema were described by García-Manau et al. [10]. Both patients presented to the emergency department at Vall d'Hebron University Hospital (Barcelona, Spain) [10]. The first case was a 50-years-old primigravid woman at 22+6 weeks' gestation with a severe SARS-CoV-2 infection that required ICU admission, where she underwent intubation for mechanical ventilation on day 2. At 23+5 weeks, fetal skin edema predominantly in the scalp and trunk was observed in the absence of other signs of hydrops fetalis. A battery of tests was performed to rule out other causes of fetal skin edema. All the results were negative. Spontaneous resolution of fetal skin edema coincided with clinical improvement in the mother and a decrease in proinflammatory markers [10].

The second case described by García-Manau et al. (10 was a 30-year-old primigravid woman at 20+1 weeks' gestation diagnosed with mild SARS-CoV-2 infection [10]. At diagnosis, the patient was discharged to home isolation. On day 8 of infection (21+2 weeks' gestation), ultrasound revealed an isolated mild fetal skin edema. A battery of tests was performed to rule out other causes of edema without pathological results. At 23+2 weeks' gestation, fetal skin edema disappeared, just after the SARS-CoV-2 RT-PCR(Reverse Transcriptase-Polymerase Chain Reaction) test result was negative [10].

It should be noted that in these latest two cases, the resolution of the edema was associated with maternal clinical improvement. Nevertheless, in the first case, the appearance of the edema was after the negative result of the PCR (Polymerse Chain Reaction) test.

Discussion

The mother-fetus binomial is unique in medicine. Thus, morbidity and mortality may affect both. There is still inconclusive evidence of trans-placentally acquired fetal infection. Although it has been demonstrated placental infection by SARS-CoV-2, it has not been associated with fetal abnormalities [11]. The severity of COVID-19 is divided into three categories: Mild, Moderate, and Severe, and each category consist of a few specific symptoms. Patients with moderate to severe symptoms of COVID-19 are hospitalized to prevent the progression of this disease. Pregnant women were more likely to experience mild to moderate COVID-19 symptoms with few cases progressing to severe COVID-19. However, the pregnant women with SARS-CoV-2 infection were more susceptible to several pregnancy complications such as preeclampsia during the delivery process. The World Health Organization (WHO) declared a global pandemic emergency, but many researchers saw a silver lining since it was found that the SARS-CoV-2 had a lower mortality rate as compared to SARS-CoV. Ultrasound is used during pregnancy to check the baby's development, the presence of a multiple pregnancy and to help pick up any abnormalities. This reduction was dependent on the time point of infection, indicating the most significant results occurred in the third trimester. The significant correlation between positive maternal PCR (Polymerase Chain Reaction) test and amniotic presence of SARS-CoV-2 near term might enhance exposure of the developing lung parenchyma to the virus. During pregnancy, IgG antibodies are the only class of antibodies that can transfer from the placenta to the fetus to their small molecular size whereas IgM antibodies are unable to cross the placenta due to their larger molecular weight. It is crucial to determine the virological and immunological characteristics of SARS-CoV-2 infection in pregnant women.

Pregnant patients are particularly vulnerable to infections due to immunosuppression and restricted cardiorespiratory capacity, and might develop adverse perinatal outcomes such as vertical transmission, fetal anomalies, preterm birth, or stillbirth [3-6]. It has been described that pregnant women with SARS-CoV-2 infection are prone to develop severe disease. A meta-analysis comparing outcomes of infected pregnant women with non-pregnant women has shown that pregnancy increases admissions to the intensive care unit as well as the need for extracorporeal membrane oxygenation, although the risk of all-cause mortality is not increased [12]. With regard to adverse maternal and perinatal outcomes associated with SARS-CoV-2 infection, preterm birth is the most common adverse pregnancy outcome among pregnant patients with severe disease [13-15]. Additionally, pregnant women with SARS-CoV-2 infection associate a higher risk of preterm delivery, stillbirth, as well as maternal and neonatal mortality, compared with pregnant patients without the infection [16]. The greatest risk of preterm delivery appears to have iatrogenic origin due to the requirement of delivery to improve a critical maternal situation. Nevertheless, the inflammatory changes affecting the placenta seem to explain the increased risk of stillbirth and pre-eclampsia [17]. Concerning transitory fetal skin edema, to the best of our knowledge, only three cases have been reported, and it has been hypothesized that it may constitute the expression of fetal infection or the consequence of a maternal infection in fetal physiology [11].

Authors have shown SARS-CoV-2 infection in neonates born to infected women, demonstrated mainly by a positive nasopharyngeal swab test. Nonetheless, infants who test positive may have been infected in utero or by horizontal transmission after birth. Although several studies have examined cord blood to identify those neonates infected by vertical transmission [18-20], no relevant results have been found [21].

The benefits of vaccination against some pathogens have been widely proven throughout history. As a result, influenza and pertussis vaccination are routinely recommended in pregnancy [22]. COVID-19 vaccination is recommended for pregnant women, breastfeeding, trying to get pregnant now, or might become pregnant in the future. Pregnant women have been vaccinated since December 2020 with mRNA-based COVID-19 vaccines, and it has been demonstrated that the vaccine does not elicit an immune response in the fetus by not detecting IgM in umbilical cord blood following vaccination [23,24]. These results indicate that the vaccine does not have a direct effect on fetal development.

Conclusion

Notwithstanding the overwhelming amount of data generated since the beginning of the pandemic, there is still limited information regarding the fetal impact of SARS-CoV-2 infection during pregnancy. The reported findings of transitory fetal skin edema in pregnant women with SARS-CoV-2 infection support the need for a close follow-up of patients with SARS-CoV-2 infection during gestation to understand the fetal consequences of the novel coronavirus.

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