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Coronavirus Infection During Pregnancy and Fetal Growth: How Should We Monitor These Pregnancies? A Literature Review

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1. Abstract

During pregnancy, coronavirus infection affects about 15% of women, more than half of whom remain asymptomatic. Pregnant women who show symptoms and have risk factors represent the portion of the population most at risk of adverse outcomes. The aim of this re-view is to analyze and summarize the current data regarding fetal ultrasound monitoring in pregnancies affected by coronavirus and to understand what the most appropriate care pathway is. The effects of coronavirus on the fetus and newborn have been extensively inves-tigated, along with the role of biometry, and the recommendations have long been uncertain. At the beginning of the pandemic, guidelines for pregnant women with suspected COVID-19 infection recommended bimonthly biometric and Doppler flowmetry monitoring. In the later years of the pandemic, the most recent literature data have scaled back the concept of per-forming serial ultrasound checks in pregnancies affected by COVID-19, especially after con-stant comparison with clinical practice. It is necessary to continue collecting data to improve clinical decisions for mothers and their newborns.

2. Introduction

Coronavirus disease was named Coronavirus Disease 19 (COVID-19) by the World Health Organization (WHO) in February 2020. After the first case was described in Wuhan (China) in December 2019, there have been thousands of fatalities, and to date, there are approximately 776 million cases worldwide [1]. The virus belongs to the Beta-Coronavirus family and shares some similarities with the viruses causing Middle East Respiratory Syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV), however, it is more contagious and aggressive [2,3]. The virus undergoes various mutations, evolving into variants classified based on changes observed in the Spike protein (S-protein) [1]. Coronavirus can spread from the mouth or nose of an infected person through small liquid particles. These particles range from larger respiratory droplets to smaller aerosols [4]. During the pandemic, it has been observed that most people infected with the virus experience mild to moderate respiratory symptoms and recover without special treatment. Howev-er, older people and those with preexisting medical conditions such as cardiovascular disease, diabetes, chronic respiratory disease, or cancer are more likely to develop complications from the infection and thus severe disease [4]. Complications associated with COVID-19 disease include severe interstitial pneumonia, hypoxemia, and respiratory distress syndrome, which often lead to intensive care unit admis-sions and

deaths [5]. During pregnancy, coronavirus infection affects about 15% of women, fortunately, more than half of the pregnant women infected with the virus remain asymptomatic [6]. In Ameri-ca, data on coronavirus infection in pregnancy report over 225,000 cases of infection during pregnancy, a total of 306 deaths, and over 34,000 hospitalizations up to 2022 [7]. Pregnant women with comorbidities such as preexisting diabetes, body mass index (BMI) >25 kg/m², and gestational diabetes treated with insulin are at higher risk of contracting COVID-19 infection [8]. Most patients who develop symptoms during pregnancy are in the third trimester [9,10] and constitute the portion of the population most at risk for adverse outcomes [9]. The risk factors that appear to be associated with hospitalization for severe COVID-19 symp-toms are non-vaccination, being from a Black, Asian, or other minority ethnic background, body mass index (BMI) ≥ 25 kg/m², pre-pregnancy comorbidities (preexisting diabetes or chronic hypertension), maternal age ≥ 35, and living in areas or households with high socio-economic deprivation [8]. One-quarter of pregnant women with coronavirus pneumonia re-quire mechanical ventilation and/or intensive care unit admission [11], and infection con-tracted during pregnancy appears to be associated with a range of adverse obstetric events [12-14]. Of 2,888 infants born from pregnancies complicated by infection, 11.6% were admitted to intensive care, while the stillbirth rate was 0.7% [15]. Vertical transmission of coronavirus infection during pregnancy or delivery is uncom-mon. If it occurs, it seems to be influenced by the type of delivery, delayed cord clamping, skin-to-skin contact, breastfeeding, or the mother and baby staying together (rooming-in). However, transplacental transmission of antibodies against COVID-19 following maternal in-fection appears to be effective [8]. Several studies have shown the presence of immunoglobu-lin G (IgG) in umbilical cord blood samples, suggesting that passive immunity could be trans-ferred to the newborn. The maximum maternal antibody response during pregnancy (over 70% IgG positivity) was recorded between 15 and 30 days after infection, while in sera col-lected at delivery, the maximum response was detected for both mother and newborn be-tween 31 and 60 days from the infection diagnosis (again with over 70% IgG positivity) [16]. Six months after birth, IgG antibodies against COVID-19 were detected in newborn blood samples following infection during pregnancy [8]. From the beginning of the pandemic to date, numerous studies have been conducted with the aim of evaluating the possible outcomes of COVID-19 infection in pregnant women. It is im-portant to clarify whether special obstetric surveillance protocols should be implemented for this particular population; in particular, it is crucial to understand whether these fetuses are indeed at higher risk of intrauterine growth restriction and whether more frequent ultrasound checks are necessary compared to the general population of pregnant women. In summary, the aim of this review is to analyze and summarize the current data regarding fetal ultrasound monitoring in pregnancies affected by coronavirus and to understand what the most appro-priate care pathway is, in terms of maternal-fetal safety, in order to prevent adverse obstetric outcomes.

3. Materials and Methods

For the bibliographic search, two biomedical databases, PubMed and Embase, were consulted. The search strategy did not include time limits; however, to draw clinically relevant conclusions, the focus was placed on studies from the last two years. The following keywords were used: COVID, pregnancy, fetal growth restriction, fetal ultrasound.

4. Results

3.1. ACE2 Receptor and Intrauterine Growth Restriction in COVID Pregnancies: is There Really this Connection?

Numerous studies conducted during the years of the pandemic have focused on the possible association between COVID-19 during pregnancy and the risk of intrauterine growth restriction (IUGR), affirming its potential existence [17-20]. Additionally, a sys-tematic review that included 42 studies reported an increased risk of low-birth-weight associ-ated with COVID-19 infection [21]. Among the causes attributed to the association between coronavirus infection and IUGR, the role of ACE2 receptors has been studied. Severe acute respiratory syndrome coro-navirus 2 (SARS-CoV-2), the virus responsible for COVID-19, as well as its analogue SARS-CoV, uses the ACE2 receptor as a functional receptor to infect human cells. This receptor is a car-boxypeptidase of the Renin-Angiotensin-Aldosterone System (RAAS), which degrades Angio-tensin II into Angiotensin 1-7, allowing optimal perfusion of many tissues and organs [22]. ACE2 is expressed in endocrine tissues, particularly in the ovaries, oocytes, uterus, and vagina [23]. The spike protein of SARS-CoV-2 uses ACE2 receptors as binding receptors on the host cell membrane [22], allowing the virus to enter cells following the proteolytic cleavage of the S protein by transmembrane serine protease 2 (TMPRSS2). This process results in the exposure of a fusogenic peptide that promotes the fusion of the viral envelope with the host cell mem-brane, followed by endocytosis and viral replication [24]. The main entry factors of SARS-CoV-2, including ACE2, TMPRSS2, and furin, are also expressed in placental trophoblasts [25]. Protective factors against the coronavirus entry mechanism are also present in placental tissue. Epap-1, for instance, affects the binding of the spike protein during early pregnancy, protecting against SARS-CoV-2 infection [23]. The entry of the virus into the human body through the ACE2 receptor leads to the de-pletion of this receptor in tissues where it is normally present in large quantities; this results in a state of hypoperfusion and chronic hypoxia, including at the placental level [26]. Numer-ous studies have definitively highlighted the role of the ACE2 receptor in the pathogenesis of placental hypoxemia and the consequent intrauterine growth restriction [27]. The state of placental hypoperfusion and chronic hypoxia not only increases

the risk of fetal growth altera-tion [24], [13] but also poses threats of miscarriage, oligohydramnios, neonatal death (28), and preterm birth [12]. However, recent studies indicate the absence of an association be-tween SARS-CoV-2 infection during pregnancy and fetal growth restriction [28-31].

3.2. The Placenta: its Role in COVID Infection

The placenta not only ensures the transport of blood to the fetus but also serves as a barrier against infections, including coronavirus [32]. Since human placental trophoblasts are directly immersed in maternal blood and a significant portion of the cardiac output reaches the human placenta, it is likely that hematogenous spread of bloodborne viruses to the placenta occurs [25]. Severe placental alterations have been reported in various case reports published since the beginning of the pandemic [33]. However, an Italian study that analysed 975 placentas from women who contracted coronavirus infection during pregnancy highlights that the analysed placentas did not show pathological findings attributable to COVID-19 infection and do not appear to be a preferential target for coronavirus infection. The study found a high incidence of inflammation signs, including chorioamnionitis, funisitis, villitis, and inter-villous fibrin deposition, which could be attributed to a possible immune response induced by the virus [34]. Some studies have also shown the virus's ability to infect the placenta [35-32] This can sometimes result in sudden and severe placental dysfunction, associated with a coagulopathy similar to disseminated intravascular coagulation, characterized by low platelets and low fibrinogen, a condition strongly linked to adverse perinatal outcomes [8].

3.3 Role of Fetal Biometry Control and Dopplerfluximetry in COVID Pregnancies

The assessment of fetal growth (FG) is one of the main objectives of prenatal care. FG depends on various factors, including proper uteroplacental function and the absence of re-lated maternal pathologies. Impaired FG is associated with an increased risk of perinatal mor-tality and morbidity, as well as long-term adverse outcomes for the newborn. Prenatal recognition of FG restriction is a crucial factor identified in strategies aimed at preventing intrauterine death [37]. Pregnant women who contract coronavirus infection represent a high-risk population, mainly due to physiological changes in the immune system and the potential ability of the virus to affect the mechanisms of a normally progressive pregnancy, including FG. The effects of the virus on the fetus and newborn have been extensively investigated, along with the role of biometry, and the recommendations have long been uncertain. At the beginning of the pan-demic, guidelines for pregnant women with suspected SARS-CoV-2 infection recommended bimonthly biometric and Doppler flowmetry monitoring due to the potential risk of intrauterine growth restriction [38]. Doppler flowmetry of the uterine arteries and serial biometric assessments were to be considered a fundamental part of managing these pregnancies to predict potential growth defects and the risk of maternal preeclampsia [39]. Some obstetric outcomes, such as preeclampsia, late FG restriction, and intrauterine fetal death, are indeed preceded by increased resistance values in the uterine arteries, reflecting placental dysfunction [40]. Some authors have suggested personalizing fetal surveillance in general and, in pregnancies affected by SARS-CoV-2, particularly in the third trimester, to consider closer an-tenatal and neonatal surveillance [41]. For pregnant patients with risk factors, the recommendation was for closer follow-up, specifically an ultrasound to assess FG within a month of infection, considering the association between SARS-CoV-2 infection and placental disorders, mainly FG restriction [42]. These recommendations were based on preliminary studies, some of which evaluated the presence of fetal vascular malperfusion and multiple placental thromboses in women with COVID-19, whose pathogenesis was attributed to the fact that Coronavirus is a pro-inflammatory disease [43]. Additionally, the similarity in levels of pro-inflammatory cyto-kines (IL-6, INF gamma, TNF alpha, etc.) in the mesenchymal stromal cells of the placentas of pregnancies complicated by COVID-19 led to the hypothesis that maternal cardiovascular and immunological changes could affect fetal circulation in the presence of infection [44]. In the later years of the pandemic, the most recent literature data have scaled back the concept of performing serial ultrasound checks in pregnancies affected by COVID-19, especial-ly after constant comparison with clinical practice, with numerous COVID-19-affected preg-nancies, and after following up on newborns born to coronavirus-positive mothers over time. These latter do not, in fact, require different ultrasound monitoring compared to newborns of pregnant women not infected with the virus, as there is no association between perinatal COVID-19 infection and intrauterine growth restriction [30]. Il tasso di basso peso alla nascita (<10th e <5th percentile) studiato su una coorte di 513 pazienti risulta simile in pazienti in gravidanza con e senza infezione da Covid-19. The rate of low birth weight (<10th and <5th percentile) studied in a cohort of 513 patients is similar in pregnant patients with and without COVID-19 infection. Additionally, there is no association between the trimester of COVID-19 diagnosis and the severity of the disease in low-risk patients [45]. The higher rates of low birth weight found among women with COVID-19 infection do not affect newborns defined as small for gestational age, probably due to the high rate of prematurity [46]. Ultrasound surveillance to assess intrauterine growth restriction in low-risk pregnan-cies with a COVID-19 diagnosis is not justified [45] nor is additional FG ultrasound assessment supported solely due to the infection [28].

4. Discussion and Implications for Practice

Since the early years of the pandemic and continuing to this day, scientific literature and obstetricians worldwide have questioned

the role of fetal biometry in pregnant women affected by COVID-19 and, more generally, whether these pregnancies should be managed differently from others. Numerous doubts and concerns have plagued obstetric staff regarding the possible negative effects of coronavirus infection on the mother-baby dyad. Fortunately, scientific literature and clinical practice have provided some, albeit limited, answers to the initial ques-tions. Regarding the role of fetal biometry and obstetric ultrasound in patients diagnosed with COVID-19 during pregnancy, the current guidelines recommend performing an ultrasound as-sessment of fetal growth, scheduled in the third trimester (30-32 weeks of gestation) or at least 14 days after symptom resolution or more than 21 days after the last fetal biometric ul-trasound, depending on the timing of maternal infection. For those who contracted the infec-tion in the first or early second trimester, the standard fetal anatomy scan is performed between 18 and 23 weeks of gestation [47]. Specific, although limited, data on the association between COVID-19 and fetal growth are reassuring [48, 31], as extensively described in the previous chapter. The Royal College of Obstetricians and Gynaecologists (RCOG) guidelines also recommend an ultrasound to assess fetal biometry within the first 14 days of recovery and to consider additional ultrasound monitoring on an individual basis for women who were severely or critically ill due to COVID-19 [49]. At the time of delivery, it is useful to perform a histological examination of the placenta in pregnant women infected with coronavirus to determine long-term effects, conduct fol-low-up on these children, and continue research to better define the clinical implications of placental morphology in SARS-CoV-2 infections [34]. A long-term follow-up of mothers infected with COVID-19 could also be useful to exam-ine the impact of the pandemic on long-term neurodevelopmental issues in children [32].

5. Conclusions

The COVID-19 pandemic has raised urgent questions among obstetricians regarding the optimal management of pregnancies complicated by Sars-CoV-2 infection. In this article, we focused on ultrasound monitoring and summarized the currently available data, concluding that pregnancies affected by COVID-19 do not require different treatment compared to those not complicated by the infection. Since the COVID-19 pandemic is not yet over, it is necessary to continue collecting additional data to improve clinical decisions for mothers and their newborns.

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