COVID-19 in Pregnancy

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Evidence indicates that SARS-CoV-2 infection increases the likelihood of adverse pregnancy outcomes. Modifications in the circulatory, pulmonary, hormonal, and immunological pathways induced by pregnancy render pregnant women as a high-risk group. A growing body of research shows that SARS-CoV-2 infection during pregnancy is connected to a number of maternal complications, including pneumonia and intensive care unit (ICU) hospitalization. Miscarriages, stillbirth, preterm labor, as well as pre-eclampsia and intrauterine growth restriction are also among the most often documented fetal implications, particularly among expecting women who have significant COVID-19 symptoms, often affecting the timing and route of delivery.

Keywords: COVID-19 ; SARS-CoV-2 ; pregnancy ; maternal outcomes ; vaccination

1. Introduction

On 11 March 2020, the World Health Organization proclaimed the coronavirus disease 2019 (COVID-19) to be a pandemic. [1] It is induced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an RNA betacoronavirus that infects humans via angiotensin-converting enzyme 2 (ACE2), a receptor on the membrane of epithelial cells. This receptor is most commonly found in type II alveolar cells of the lungs and in the mucosa of the oral cavity, affecting both upper and lower respiratory systems [2][3]. It can also be present in organs such as the heart or the intestine, which can be additionally infected through systemic circulation [4]. Respiratory secretions are considered to be the main route of person-to-person transmission of SARS-CoV-2. Direct contact of an infected individual's virus carrying droplets, originating from speaking, sneezing, or coughing, with the mucous membranes of someone nearby can result in an infection. SARS-CoV-2 is expected to have up to a 14-day incubation period, with most cases occurring about 5 days after exposure [5].

2. COVID-19 in Pregnancy

Due to the cardiovascular, pulmonary, hormonal, and immunological changes that accompany pregnancy, pregnant women are believed to be at a heightened risk during the pandemic [2][3][4][6][7][8][9][10]. More specifically, the hormonal fluctuations and the prevalence of a Th2 cell-mediated immunological environment increase pregnant women's susceptibility to infections, while the elevated maternal oxygen needs, together with the diminished capacity of the lungs, due to the upraised level of the diaphragm, reduce women's tolerance to hypoxia and dyspnea. Thus, pregnant women's infection with SARS-CoV-2 has been correlated with more severe morbidity, affecting both the mother and the fetus [11][12][13][14][15].

SARS-CoV-2 infects respiratory epithelial cells, triggering an immunological response defined by the production of pro-inflammatory cytokines and a modest interferon response. A downstream signaling pathway due to membrane-bound immune receptors activates the Th1 cells' and CD14+ CD16+ monocytes' proinflammatory response. The subsequent infiltration of macrophages and neutrophils into lung tissue initiates a cytokine storm. This cytokine storm in COVID-19 is characterized by elevated levels of IL-6 and TNF- expression. A possible mechanism for this storm has been proposed by Hirano and Murakami, through the angiotensin 2 (Ang-II) pathway. Particularly, SARS-CoV-2 reduces the ACE2 expression and increases the expression of Ang-II. This stimulates the production of TNF-α and the soluble form of IL-6Ra via disintegrin and metalloprotease 17. IL-6 with its receptor forms a complex which activates the transcription 3 (STAT3). STAT3 and NF-B activation by SARS-COV-2 induce the production of proinflammatory cytokines and chemokines, particularly endothelial growth factor, monocyte chemoattractant protein 0 (MCP-1) and interleukin 8 (IL8). The levels of IL-1, IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1, TNF-, macrophage inflammatory protein 1 alpha, and granulocyte-CSF have

been shown to be elevated in individuals with a more severe condition, according to previous research. Among them, IL-6 presumably is the major cause of severe lung inflammation and pulmonary function. In addition, Liu et al. discovered a drop in lymphocyte counts, particularly CD8+T cells, and a rise in neutrophil counts in these patients. The severity of the disease is related to T-cell lymphopenia and the dynamic cytokine storm and especially the latter is considered as an important cause of death in these patients. A recent meta-analysis revealed that pregnant women had a crucially increased risk for severe COVID-19 characterized by this cytokine storm [16][17][18].

Nonimmunization; non-Caucasian ethnicity; a body mass index above 25 kg/m^2; a pre-pregnancy co-morbidity such as diabetes or hypertension; a maternal age of 35 years or older; increased socioeconomic deprivation; and employment in healthcare or other public-facing occupations are risk factors for both infection and hospitalization with COVID-19 [19][20]. In a study of nearly 400,000 women of reproductive age with symptomatic COVID-19, the Centers for Disease Control and Prevention (CDC) found that pregnant women had a vastly greater adjusted risk ratio (aRR) for mortality and morbidity than non-pregnant women of reproductive age (aRR 5 1.7, 95% CI 1.2–2.4) [21]. Comparable to this, Rozo et al. showed that the risk of mortality for pregnant women was considerably higher than that for non-pregnant women of reproductive age (aRR 5 1.82, 95% CI) [22].

Over two-thirds of confirmed pregnant women do not exhibit any symptoms, and pregnant women do not appear to be more or less susceptible to contracting SARS-CoV-2 than the general population [20] In symptomatic COVID-19 pregnant women, fever, coughing, shortness of breath, headaches, exhaustion, myalgia or arthralgia and taste loss appeared to be some of the most common symptoms. Fever, usually with a median temperature between 38.1 and 39 °C, is described as the most prevalent symptom and appears in the majority of the patients [13][14][15][23][24][25][26]. The aforementioned symptoms follow two different roads. Either they improve with early identification and conservative treatment or they lead to dyspnea and productive cough. Various cohorts have demonstrated that the median time of the appearance of dyspnea is 6 days after exposure. Secondary infection is always possible in about 12 days, while viral shedding is completed in about 20 days. Zhou et al. reported that the median time from the beginning of the illness until discharge was 22 days and the median time for death was 185 days. Fever stayed for at least 12 days and cough for 19 days in people who survived [26]. Concerning admission to the hospital, development of ARDS (acute respiratory distress syndrome) and admission to ICU with the need for mechanical ventilation is 8, 8.2, and 10 days, respectively.

2.1. COVID-19 and Maternal Complications

As indicated, COVID-19 is a very serious infectious disease, especially in pregnant women, who are considered a high-risk group, as there is always the possibility of developing all the aforementioned symptoms, along with complications. ARDS (acute respiratory distress syndrome) is the most common and severe complication, followed by sepsis and septic shock, kidney acute injury, and cardiac acute injury [26], Additionally, severe pneumonia was also present in a significant number of pregnant patients which, in the majority of the studies, leads to the observation that pregnancy can indeed amplify the risk of a SARS-CoV-2 infection to develop into pneumonia [27]. Furthermore, pregnant women have a stronger chance of being admitted to an intensive care unit, in contrast to pregnant women without the disease. Giampiero Capobianco et al. mentioned that 13% of pregnant women were admitted to the ICU [4]. Similarly, Ioannis Bellos et al. stated that 11% of infected pregnant women evolved into a dismal outcome and had to attend the ICU, while Kuma Diriba et al. inferred that 28% of the cases were transferred to an ICU. As a result, if the mother’s conditions worsen, even the danger of death lurks [5]. Cases of maternal deaths have been reported in the bibliography.

Pre-eclampsia (PE) and COVID-19 are both multisystematic disorders that have a variety of manifestations. They share overlapping pathogenic pathways and their symptoms reflect extensive endothelial dysfunction (ED), which frequently leads to vasoconstriction and end-organ ischemia. Pre-eclampsia and COVID-19 are symptoms of ED brought on by elevated levels of the anti-angiogenic hormone angiotensin II (Ang-II) and the circulating anti-angiogenic molecules sFlt1. Both of these disorders start in the placenta and lungs, respectively, and they both finish in the endothelium. During pregnancy, severe COVID-19 can cause PE-like symptoms. Furthermore, COVID-19 at pregnancy is independently related to PE, according to a new sub-analysis from the INTERCOVID research sample. According to evidence, PE is brought on by an imbalance of soluble plasmatic anti- and pro-angiogenic factors, which are essential for maintaining the vascular endothelium. Women with PE have lower levels of placental growth factor (PlGF), a potent angiogenic factor, and higher levels of soluble FMS-like tyrosine kinase 1 (sFlt-1), the primary anti-angiogenic factor, before clinical manifestation. Moreover, findings show that excessively high sFlt-1/PlGF ratios may aid in the detection of placental dysfunction even in SARS-CoV-2-positive pregnant women. Both COVID-19 and PE are connected to hypocalcemia, elevated lactate dehydrogenase and sFlt1, hypoalbuminemia, elevated levels of IL-6 and D-dimer, thrombocytopenia, and proteinuria [28][29].

2.2. COVID-19 and Fetal Complications

SARS-CoV-2 infection during pregnancy can also affect the fetus directly. Firstly, cases of miscarriages and perinatal deaths have been stated. An approximately twofold increase in the chance of stillbirth and a possible rise in the prevalence of small-for-gestational-age infants are both linked to maternal COVID-19 infection. Preterm births that are largely iatrogenic appear to be two to three times as common than background births in women with symptomatic COVID-19 [20]. Pradip Dashraath et al. outlined that approximately 2% of infected pregnancies have resulted in a miscarriage [2]. In Jie Yan's study, an unexpected miscarriage occurred in a 5-week pregnancy, accompanied by fever and fatigue [15]. Additionally, J. Juan et al. mentioned four cases of miscarriages [4]. In the same study, a neonatal death due to asphyxia was inferred. One case of neonatal death was also described by Zhu H et al. [30]. The newborn appeared with gastric bleeding, refractory shock, disseminated intravascular coagulation, and multiple organ failure, possibly caused by viremia, combined with an immature immune system. Moreover, Ioannis Bellos et al. showcased three incidents of stillbirth and two of neonatal deaths, both delivered by seriously infected women who were transmitted to the ICU [10]. Daniele Di Mascio et al. revealed in their study that in 7% of the infected pregnancies, perinatal death occurred. To be more exact, there was one case of stillbirth and one of neonatal death [28]. Some stillbirths were also mentioned by John Allotey et al. [6]. Both studies underlined the higher frequency of miscarriages and perinatal deaths among infected pregnant women with SARS-CoV-2 than among women without the disease. In India, the stillbirth incidence during the COVID-19 pandemic appeared notably higher than what was documented in 2019 (13.9 per 1000 births) [8]. The Netherlands Obstetric Surveillance System's most recent statistics show that 58 of the 9620 known SARS-CoV-2-infected pregnancies in The Netherlands ended in stillbirth from 1 March 2020 to 7 December 2021. Nevertheless, there was no information provided for the same time about the number of stillbirths in uninfected pregnancies [11]. Studies with a significant study population have shown that SARS-CoV-2-positive women have a higher incidence of stillbirth than women who did not contract the virus [31][32][33][34]. However, data are debatable, since some smaller studies found no appreciable increase in the stillbirth incidence among SARS-CoV-2-positive pregnant women. It is vital to acknowledge whether any rise in the stillbirth rate is brought on directly by the maternal SARS-CoV-2 infection or due to modifications in healthcare availability, in pregnant women's or medical professionals' behavior during the pandemic.

The most common fetal complication of COVID-19 appears to be preterm birth [9]. Giampiero Capobianco's review mentioned that preterm births appeared in almost all of the studies, with a mean percentage of 23% among the cases [7]. Several other studies confirmed the rate of preterm births among pregnant women infected with SARS-CoV-2 to be between the rank of 25–44% [26][28][29][30][35][36]. Moreover, Pedro Castro et al. reported that 19.41% of the infected pregnancies were delivered before 37 weeks and 15% before 34 weeks [36]. Additionally, Daniele Di Mascio et al. stated that preterm birth below 37 and 34 gestational weeks occurred in 41.1% and 15% of the pregnancies, respectively [3]. The same study underlined the higher tendency of preterm birth among pregnant women with COVID-19, in comparison to those without the disease. In agreement with the above statement were John Allotey et al., Rong Yang et al. and Chiu-Lin Wang et al. [6][11][24].

In general, COVID-19-diagnosed women had lower rates of spontaneous labor onset but greater rates of caesarean section, indicating the higher rates of obstetric morbidity in this group. The INTERCOVID Multinational Cohort Study revealed that the increased risk in this group (RR, 1.97; 95% CI, 1.56–2.51) is attributable to the fact that 83% of preterm deliveries (*n* = 130) among women with a COVID-19 diagnosis had medical evidence, with pre-eclampsia/eclampsia/HELLP (31 [24.7%]), small for gestational age or intrauterine growth restriction (24 [15.5%]) [37].

As mentioned above, other fetal complications possibly correlated to SARS-CoV-2 infection were observed to be SGA or IUGR and pre-eclampsia. Pradip Dashraath et al. stated that fetal growth restriction occurred in approximately 10% of the pregnancies infected with SARS-CoV-2. This phenomenon was caused by the lack of oxygenation of the fetus, mainly due to the prolonged respiratory compromise and the hypoxia of the mother [2]. Similarly, Daniele Di Mascio et al. stated that 43% of the fetuses presented fetal distress, while Kuma Diriba et al. reported that SARS-CoV-2 increased the risk of fetal distress among pregnant women [38][39][40].

2.3. COVID-19 and Neonatal Complications

As far as the neonates are concerned, several complications have been reported. Giampiero Capobianco et al. stated a 39% complication rate among neonates born from infected women. In fact, fever, pneumonia and respiratory distress syndrome were the most frequent complications, indicating a possible outcome of the virus [39][40][41][42][43]. Other symptoms due to SARS-CoV-2 infection were also noticed. For example, tachycardia, thrombocytopenia, lymphocytopenia, leukocytosis, pneumothorax, vomiting, diarrhea, lethargy and septic shock [10][11][30][40]. Furthermore, there have been incidents of neonates, born from infected women, who attended the ICU. Daniele Di Mascio et al. and

Kuma Diriba et al. observed that 8.7% and 11% of the newborns were admitted to the NICU, respectively, after facing fetal distress [3][38]. Similarly, J. Juan et al. and John Allotey et al. mentioned that approximately 33% of the neonates were transferred to the INCU, proving that the risk is higher when the mothers are infected with SARS-CoV-2.

2.4. COVID-19 Vaccination in Pregnancy

The vaccination of pregnant women reduces the increase in maternal and fetal morbidity related with COVID-19; consequently, all pregnant women should be vaccinated parallel with the rest of the population, depending on their age group and comorbidities. The Centers for Disease Control and Prevention (CDC), the Royal College of Obstetricians and Gynecologists (RCOG), the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine, and the American College of Obstetricians and Gynecologists (ACOG) all recommend vaccination for all pregnant women [44][45].

Notably, three forms of COVID-19 vaccination are currently accessible globally: mRNA, viral vector, and inactivated. Vaccines employing mRNA particles (Pfizer or Moderna) are the most prevalent and have the greatest safety evidence. Antigen-presenting cells are responsible for mRNA uptake. These vaccines contain mRNA particles that induce muscle cells at the injection site to generate and activate a component of the SARS-CoV-2 spike protein [46].

In regions where mRNA vaccines are not easily accessible, viral vector and inactivated vaccines are also often administered to the general population; however, evidence on their safety in pregnant women is very limited. Notably, viral vector vaccines are not recommended for administration in pregnancy. Concerning timing of vaccination, the current research suggests that these immunizations are safe throughout pregnancy, even during the first trimester [47][48][49].

Despite the lack of randomized, pregnancy-specific evidence, there is absolutely no reason to expect that the efficacy of vaccinations would be compromised during pregnancy [50]. Immunogenicity studies reveal that mRNA vaccinations induce the same humoral immune response in pregnant and nonpregnant women [49][51]. Hence, mRNA vaccines are anticipated to provide the same degree of protection against SARS-CoV-2 infection and severe illness as those administered to nonpregnant patients.

Several longitudinal studies comparing the perinatal outcomes of vaccinated and unvaccinated pregnant women have showed good findings and no detrimental effects on pregnancy or the newborn. Vaccination with mRNA vaccines does not increase the risk of spontaneous abortion, premature delivery, low birthweight, maternal or neonatal intensive care unit admission, fetal mortality, congenital abnormalities, or pulmonary embolism [52].

Notably, the literature reports rare instances of mRNA vaccine-associated myocarditis, as well as vaccine-induced thrombosis and thrombocytopenia; however, evidence is still scarce [53][54].

Another concern is the necessity for pregnant women to receive booster doses, since the effectiveness of immunization diminishes with time [35]. Women who received inactivated or viral vector immunizations may benefit from a booster injection. Booster vaccinations are advised at least two months following a first immunization using viral vector vaccines; the booster dose should consist of an mRNA vaccine [45].

In conclusion, observational studies corroborate the findings of randomized trials that mRNA immunization is extremely effective in preventing severe SARS-CoV-2 infection in pregnant women, emphasizing that the potential maternal and fetal benefits of vaccination significantly outweigh the potential risks. To guarantee that pregnant women have unrestricted access to the COVID-19 vaccine should be a global priority.

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