Minireview Article
The Impact of COVID-19 on Pregnancy : A Minireview

ABSTRACT

Background: Corona virus disease (COVID-19) has become a research priority since first reported case in Wuhan, China in December 2019. Pregnant women and fetuses represent a vulnerable group for which the disease may have effects not applicable to the general population. The aim of this study was to provide an overview of the association between COVID-19 and pregnancy in terms of the clinical manifestations, maternal and fetal outcomes, and the possibility of vertical transmission of the disease.
Methodology: Articles addressing the impact of COVID-19 during the perinatal period were obtained mainly from PubMed database. Most of the studies of a systematic review or meta-analysis used in the current study were published in the current year 2021.
Results: The present study discussed different issues. First, clinical manifestations were not different from the general population with fever and cough being the most common symptoms; while the course of the disease was milder in general compared to general population. Regarding vertical transmission, the current literature did not provide evidence supporting the transmission of SARS-Cov-2 to the fetus; although, there were few cases reported which do not exceed 4%.
Conclusion: In general, the clinical course and outcomes of COVID-19 do not greatly differ from the normal population. Cesarean section and premature birth were reported with no evidence of the presence of the novel coronavirus in the amniotic fluid nor the breast milk.

Keywords: Cesarian section, Clinical outcome, Fetus, , Prematurity, SARS-CoV-2, Vertical transmission.

1. INTRODUCTION

Coronavirus disease 2019 is the current pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which was first reported in December 2019, in Wuhan, China. The most common clinical manifestations of COVID-19 are fever, cough, fatigue, and shortness of breath (SOB), which are almost similar to what pregnant women with COVID-19 experience when infected [1]. Since other coronaviruses such as severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) have been associated with serious adverse pregnancy outcomes, which has a significant impact on maternal and neonatal morbidity and mortality, including preterm birth, miscarriage, and stillbirth, this raised the concern of whether COVID-19 infection is associated with any of these adverse pregnancy outcomes or not [1]. Another reason for this concern is that pregnant women due to immunological changes that occur during pregnancy, which include having increased inflammatory activity during the 1st and 3rd trimester as well as having reduced immunity in the 2nd trimester, are more vulnerable to COVID-19 infection [2]. According to Di Toro *et al.*, as concluded in their meta-analysis involving 1,100 pregnant women, that the clinical course of COVID-19 infection was not complicated in the majority of pregnant cases and that the pooled prevalence of maternal death and intensive care unit (ICU) admission rates were comparable to that of non-pregnant women [3]. Moreover, in the same meta-analysis, the pooled prevalence of preterm delivery was higher compared to healthy pregnant women, although it is still unclear whether COVID-19 is directly responsible for this complication or no [3]. Additionally, as stated in another systematic review done by Chi *et al.*, premature delivery is the most common adverse pregnancy outcome occurring in 24.74% of pregnant women [4]. Premature rupture of membrane (PROM) risk is higher among pregnant women with COVID-19, which can eventually lead to preterm delivery [5]. As per Salem *et al.*, pneumonia is considered one of the most common complications in pregnant women infected with COVID-19 and it is the major cause of hospital admission [6].

Vertical transmission is the transmission of the infection from the mother to the fetus while in utero [6]. The vertical transmission of SARS-CoV-2 in pregnant women is another topic that needs to be researched more; since theoretically, it can occur as angiotensin-converting enzyme 2 (ACE2) is expressed in abundance in the placenta and on which SARS-CoV-2 bind and trigger the infection [6]. The transmission can possibly occur through other various mechanisms as well, including breastfeeding as the SARS-CoV-2 virus RNA can be detected in the breast milk of infected mothers [3-4]. Although rare, and no clear evidence supports discontinuing breastfeeding [3-4]. However, more extensive research is required since data is lacking especially in terms of available samples [3].

The aim of this review article is to provide an overview of the association between COVID-19 and pregnancy in terms of the clinical manifestations, maternal and fetal outcomes, and the possibility of vertical transmission of the disease.

2. METHODS

Studies were obtained mainly from PubMed database. Various key words were used in the search; including pregnancy, COVID-19, SARS-CoV-2, vertical transmission, symptoms, maternal, neonatal, outcomes, and complications. The website tools were used to filter the results to include reviews of the current year (2021) and free access articles. The studies were appraised based on the study design, objectives, and clarity of results. The exclusion criteria were single center studies, and case reports.

3. CLINICAL MANIFESTATIONS

The clinical presentation of COVID-19 in pregnant women does not seem to be different from normal population. The vast majority of studies reported fever and cough as the most common symptoms among pregnant women [4, 6]. Furthermore, many cases of SARS-CoV-2 among pregnant women were asymptomatic, for which the diagnosis was made by a nasal swab [3]. However, serious symptoms were reported among those with pre-existed chronic diseases [6]. It is important to note that comparison of pregnant women with the general population cannot be taken into count as most of the pregnant women are in a younger age than most of the complicated cases which mostly found among the elder population who have other comorbidities [1]. Pregnant women generally have a mild course of COVID-19 disease. This can be explained by the fact that pregnant women tend to be more caring with regard to their health, nutrition, and disease prevention. This is said in comparison with the general population of both genders and different age groups, which would result in a biased comparison [2]. It is worth mentioning that pregnant women may experience less frequent symptoms other than fever and cough, these symptoms include; fatigue, anosmia, ageusia, sore throat, headache, and poor appetite [7]. Laboratory findings were not of great clinical importance. Chi *et al.* [4], in his systematic review reported that the usual laboratory findings among pregnant women include lymphopenia and leukocytosis [6]. On the other hand,

computed tomography (CT) findings in the lungs are present in almost all the investigated cases as reported by Salem *et al*. [6].

4. MATERNAL and NEONATAL OUTCOMES of Sars-Cov-2 INFECTION

The apparent maternal mild course of the disease does not mean that COVID-19 has no negative impact on the mother or the neonate. In fact, most of pregnancy complications may not appear before birth. Previous studies have reported the maternal and neonatal outcomes of SARS-CoV and MERS-CoV, the two viruses cause a SARS similar to SARS-CoV-2 [5]. While the true impact of COVID-19 on pregnancy has not been established yet, until now, COVID-19 is considered to cause less complications [8]. Higher case fatality rates were associated with SARS-CoV and MERS-CoV [9]. Moreover, SARS-CoV was associated with premature birth, intrauterine growth retardation, and abortion. This is indeed, favors the outcomes of SARS-CoV-2 in pregnancy [6]. Despite that COVID-19, and up to date, is associated with a better prognosis, complications such as pneumonia, PROM, increase the rates of Cesarean deliveries, and fetal distress were reported [6]. Pneumonia is the most common maternal complication of COVID-19 [8]. Interestingly, in single center study, the diagnosis of pneumonia confirmed in all the cases of COVID-19. Although, no acute respiratory distress nor the need of mechanical ventilation were reported [2]. This is also is similar to the fact that most pregnancy COVID-19 cases are asymptomatic and diagnosed accidentally by nasal swab. The fact that pneumonia is prevalent among pregnant women diagnosed with COVID-19 was based on CT findings with no suggestive symptoms [10]. As regard neonatal complications, in a systematic review of 324 pregnancies diagnosed with COVID-19, only eight neonates had a birth weight less than 2,500 grams, while one third of them required the admission to neonatal intensive care unit (NICU) [8]. In the same study, one case of asphyxia and one case of neonatal death were reported [8].

5. VERTICAL TRANSMISSION

Vertical transmission of COVID-19 infection is a major concern and has been considered an interesting topic of controversy since the beginning of the pandemic mainly due to the decreased number of reported cases that included samples such as placenta, amniotic fluid and umbilical cord blood [11]. Vertical transmission can possibly occur through a variety of different mechanisms which are transplacental transmission after the placenta is infected since ACE2 is overexpressed, intrapartum transmission through ingestion of vaginal secretions during labor, or postpartum transmission through breastfeeding [4]. As per Chi *et al.*, in their systematic review involving 154 pregnant women with COVID-19 who gave birth and their 156 infants, the vertical transmission rate of COVID-19 infection in infants was 3.91% based on polymerase chain reaction (PCR) [4]. It is worthwhile to mention that the five affected neonates were delivered by cesarean section [4]. Moreover, 3/8 neonates who had negative throat swab tests, had high immunoglobulin M (IgM) and immunoglobulin G (IgG) against SARS-CoV-2 [4]. However, all of them had negative nucleic acid tests of amniotic fluid, breast milk, vaginal secretions, placental blood and placental tissues, thus not supporting vertical transmission [4]. This was further supported by a systematic review and meta-analysis conducted by Di Toro *et al.*, involving 1,100 pregnant women with COVID-19, as they concluded that there is still no clear evidence of vertical transmission of COVID-19, thus COVID-19 by itself should not be considered an indication of elective cesarean delivery [3]. According to a systematic review involving 3,985 pregnant women with COVID-19 conducted by Rodrigues *et al.*, among the available intrauterine samples that were analyzed, 11.9% of placentas (n=8/67), 1.8 % of amniotic fluid (n=1/54), and 2.4% of umbilical cord blood (n=1/42) were positive for SARS-CoV-2 [11]. Moreover, 61 (3%) newborns with at least one positive sample for SARS-CoV-2 confirmed by PCR were identified, and among 71 neonates with a neonatal serum sample, four were positive for IgM and seven were positive for IgG [11]. As for breastfeeding, according to a study conducted by Chen *et al.*, they stated in their retrospective study involving 9 pregnant women with confirmed COVID-19 pneumonia; the breast milk samples that were taken from the patients were negative for SARS-CoV-2 [12]. Furthermore, this notion was supported by a systematic review involving 3,985 pregnant women with COVID-19, in which they concluded that there is no sufficient evidence to firmly state that women with COVID-19 can transmit the infection via breast milk [11]. Lastly, Francesca Di Toro *et al.*, stated in their systematic review and meta-analysis that breastfeeding for pregnant women with COVID-19 should not be contraindicated which is consistent with the world health organization (WHO) guidelines, since viral RNA was rarely detected in maternal breast milk [3].

6. VACCINATION

Soon after approving the use of vaccine for the general population, rumors and social media started to worry the patients from the risk of the vaccine. The effect of the vaccine on the fertility and the pregnancy was unclear. However, this happens with the majority of the vaccines when released. In the case of COVID-19, the side effects of the vaccine with the short duration while developing the vaccine was an understandable concern, in addition to the fear of receiving an mRNA vaccine which is considered a new method [13]. The new method of utilizing mRNA in developing the vaccine has led to thoughts of developed antibodies toxicity to the placenta which may lead to miscarriage. The trials showed that vaccines do not prevent conception or cause harm to the pups of the rodents [14-15]. It is to be noticed that assessing the

outcomes and vaccine safety on pregnant women prospectively is extremely difficult. However, later reports showed that the outcomes of vaccinated pregnant women are similar to those who are unvaccinated [16]. Recent studies suggest that the outcomes of the vaccine should be thought on a long-term base and unfavored effects can result from the general situation due to the pandemic like changing health care systems and difficulty of providing usual health care needed for pregnant women [17-18]. In conclusion, while current evidences favors the safety of COVID-19 vaccine during pregnancy, data about COVID-19 vaccine safety for pregnant women are limited to animal trials and observational studies [19-20].

7. CONCLUSIONS

Pregnant women suffering from COVID-19 do not seem to have different clinical manifestations from the normal population; fever and cough were the most frequently reported symptoms. Unfortunately, pregnant women usually have a milder course of disease. Maternal and neonatal outcomes are not clearly addressed, with no COVID-19 unique complications reported up to date. Vertical transmission was rarely reported with a prevalence of less than 4%. The SARS-CoV-2 was not present in breast milk; therefore, breast feeding should not be discontinued according to the current literature. More studies addressing the impact of COVID-19 on pregnancy are recommended to prevent possible unreported complications.

List of abbreviations

- Corona virus disease (COVID-19)
- Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)
- Shortness of breath (SOB)
- Severe acute respiratory syndrome (SARS)
- Middle east respiratory syndrome (MERS)
- Intensive care unit (ICU)
- Premature rupture of membrane (PROM
- Angiotensin-converting enzyme 2 (ACE2)
- Computed tomography (CT)
- Neonatal intensive care unit (NICU)
- Polymerase Chain Reaction (PCR)
- Immunoglobulin M (IgM)
- Immunoglobulin G (IgG)
- World health organization (WHO)

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