



Effect on Covid-19 on Pregnancy

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Abstract

Introduction: The 2019 novel coronavirus disease (named COVID-19 and caused by the SARS-CoV-2 pathogen) has spread from Wuhan, China, to all over the world and became one of the most significant global health issues in recent times. The combination of a pro-inflammatory state and the exacerbated immune response in the face of a SARS-CoV-2 infection puts pregnant women in the spotlight regarding possible severe consequences of the COVID-19.

Methods: Both PubMed and Google Scholar databases were searched for articles published until January 2021 for this systematic review.

Results: About 18 articles concerning the impact of Covid-19 on pregnancy were included in this study.

Discussion: Premature birth is the most studied and significant event related to Covid-19. Other consequences such as small fetus for gestational age and Premature Rupture of Ovular Membranes were also discussed.

Conclusion: We need more time and data to understand better the pandemic's consequences on newborns of infected mothers. Information is crucial to counseling this specific population.

Keywords: Covid-19; SARS-CoV-2; Pregnancy; SARS; Protein

Introduction

By definition, a pandemic is the widespread of an infectious disease across the world [1]. The 2019 novel coronavirus disease (named COVID-19 and caused by the SARS-CoV-2 pathogen) has spread from Wuhan, China, to all over the world and became one of

the most significant global health issues in recent times, reaching more than 106,000,000 at this point [2]. After a median incubation period of 4 days, patients may present with fever, cough, or loss of smell and, some will develop pneumonia and acute respiratory distress syndrome [3,4].

Despite low fatality rates of 1%-2% [3,5], the infection among high-risk groups, such as pregnant women, raises concerns given that previous coronaviruses have been associated with adverse pregnancy outcomes [6,7].

Pregnancy is a particular condition due to multiple changes in the immune response. Overall, inflammatory activity increases during the first and third trimesters, while the second trimester is characterized by decreased immune activity [8]. Furthermore, the upper respiratory tract also adapts to pregnancy by swelling due to high estrogen and progesterone levels. Besides, restricted lung expansion makes the pregnant woman more susceptible to respiratory pathogens [8].

Recent evidence showed that in severe cases of COVID-19, there is a cytokine-storm, with increased plasma concentrations of interleukins 2 (IL-2), IL-7, IL-10, granulocyte-colony stimulating factor, interferon- γ -inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha, and tumor necrosis factor α (TNF- α) [8].

The combination of a pro-inflammatory state and the exacerbated immune response in the face of a SARS-CoV-2 infection puts pregnant women in the spotlight regarding possible severe consequences of the COVID-19.

This paper aims to study the most up-to-date evidence on the impact of COVID-19 on pregnancy.

Methods

Both PubMed and Google Scholar databases were searched for articles published until January 2021 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy was performed by using different combinations of the following entry terms: "Covid-19" [Mesh], "Coronavirus" [Mesh], SARS-CoV-2 [Mesh], "Pregnancy" [Mesh], "Miscarriage", "Early labor", "Premature Obstetric Labor" [Mesh], "Pregnancy Loss", and "Pregnancy Outcomes".

A manual search through references of the retrieved articles was performed as well. Studies evaluating the impact of Covid-19 infection on pregnancy were included if clinical outcomes such as abortion, premature labor and clinical complications of pregnancy were reported.

Only articles in English using human subjects were included. Meta-analysis and systematic reviews were not included in this analysis. The process of literature review and study selection is described in figure 1.

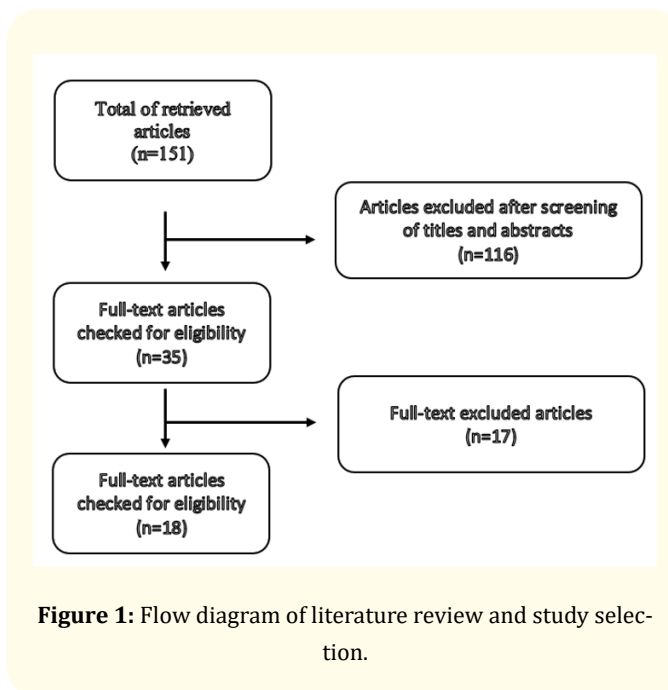


Figure 1: Flow diagram of literature review and study selection.

Results

Following the search strategy previously described, 151 studies involving pregnancy and Covid-19 infection were retrieved. After screening by title and summary, 35 studies remained, whose full texts were analysed. From these, 18 articles studying the direct relationship between Covid-19 infection and pregnancy, including a total number of 30,995 participants, were included in this study.

From the selected studies, four did not use any diagnostic test for Covid-19 [9-12] comparing groups of pregnant women during the pandemic to other periods. The other 14 studies performed RT-PCR on all participants.

Regarding the study design, eight studies were retrospective cohorts [13-20], four observational studies [9-11,21], two comparative retrospective studies [12,22], two prospective [23,24], one case control study [25] and one case report [26].

Part of the studies included only pregnant women in their third trimester of pregnancy; six studies also included pregnant women

in their first and second trimesters [12,15-17,23,24] and five studies included only women in labor [9-11,18,21].

Two studies reported abortions, Yan [16] included a pregnant woman with a first-trimester abortion at five weeks and two days pregnant, and Mattar [23] reported two abortions, a first trimester and a second trimester.

The most described obstetric consequence in the studies was premature birth in 3,801 pregnant women with Covid-19 infection. It was described in eleven of the selected papers [9,10,14-19,21,24,25]. In four studies [9,10,18,21] their gestational ages were not described and in the other seven studies [14-17,19,24,25] deliveries occurred between 28 and 36 weeks of pregnancy. Li [25] referred that among the three pregnant women who had a premature birth, two had premature rupture of membranes, and one pregnant woman had placental abruption.

No case of maternal death has been described in the studies.

Discussion

Effects of Covid-19 infection on Pregnancy

The clinical presentation of pregnant women diagnosed with COVID-19 is quite variable. At first, it was believed that pregnant women would be more susceptible to respiratory diseases due to a possible state of immunosuppression. Pregnancy fits it due to increased cardiovascular demands and states of respiratory alkalosis compensated with metabolic acidosis. Thus, such a population would be one of the most affected. However, there is a similarity in clinical standards compared to groups of non-pregnant women [14]. When symptoms are present, the main complaints are cough, fever, fatigue, diarrhea, in addition to other respiratory complaints considered mild (sneezing, nasal congestion, and sore throat) [13,14,17]. Concerning laboratory changes, the main findings were in the third gestational trimester compared to other periods and lymphopenia was the most found [13-15,17]. Fortunately, the number of cases of pregnant women with pneumonia considered severe, secondary cardiomyopathies, progressing to intensive care and even death is very low, reaching a rate of less than 5% [16,23,25,26].

The studies that evaluated the abortion outcome [13,16,19,22-24] showed an absence or very low rate of this event compared to the general population.

Premature birth was the most studied event [9,10,13,14,17,19,21-25] since viral infections by several agents can increase the rate of this event, as well as Covid-19. In three articles, the prematurity rate was not significant, but the small number of participants limited the data's interpretation [13,22,23]. In the other studies [9,10,14,17,19,21,24,25], a higher rate than the average population for this event was observed, in accordance with other types of viral infections that affect pregnancy. Analyzing only the studies in which the diagnosis of Covid-19 was confirmed with RT-PCR, it is possible to notice a variation of 10.7 to 46.15% in the rate of premature births [14,16]. In studies in which the test was not performed (RT-PCR), bearing only a comparison of the outcome between the pandemic versus the pre-pandemic period, an increase in the number of premature newborns was found in the first group.

In deliveries with small fetuses for gestational age and low birth weight newborns 10 studies presented a variable rate from 3% to 22.22% [10,13-20,25], comparable to the rates of other lung diseases during pregnancy and different from the general average rate, which is around 13% [27].

Other obstetric outcomes, such as PROM (Premature Rupture of Ovular Membranes) [15,16,25] do not appear to be associated with SARS-CoV-2 infection. Intrauterine fetal deaths [18], stillbirths and neonates [9,14,16,17,24] have also been reported in some studies, but it is questioned if such outcomes are directly related to primary maternal infection or indirect factors, for example, the decrease in demand for prenatal consultations caused by the fear of patients leaving their homes and contracting the infection. Even with such data, the stillbirth rate was also not significantly higher compared to groups with negative PCR.

Acute fetal hypoxia requiring urgent Cesarean delivery [13,17,25] and other grave neonatal outcomes such as pneumothorax, liver dysfunction and thrombocytopenia, and neonatal ICU care [14,20] have been reported, but more related to the prematurity per se than to a primary neonatal SARS-CoV-2 infection.

The presence of obstetric comorbidities such as DHEG (hypertensive disease specific to pregnancy), DMG (gestational diabetes mellitus) and clinical (e.g. hypothyroidism) were suggested as possible factors of severity given the concomitant infection by COVID-19, however, the population number of the studies was low and such an association was evidently not sustained [25].

There was a higher rate of Cesarean deliveries both at term and premature in the groups of infected pregnant patients, most likely due to the medical apprehension of such cases evolving to more serious clinical presentations [11,13,17,22].

Study Limitations

Limitations of this systematic review should be acknowledged. First, we included all study designs, including observational and retrospective studies, with considerable heterogeneity across them. Second, four studies did not confirm the diagnosis of covid-19 by PCR or CT tests, which can lead us to unsettling conclusions. Third, there was little information regarding women infected in the early stages of pregnancy and observation of the whole pregnancy period. Some studies have shown just results at the time of admission to the hospital for labor. Fourth, the number of participants is limited in each study and may not represent the pregnant women populations' entirety. These results should be confirmed with better-delineated studies and for a more extended time.

Conclusion

In conclusion, preterm delivery seems to be more frequent in pregnant women with COVID-19 when compared with the general pregnant population. This systematic review also shows that clinical presentation and symptoms of the infected pregnant women seem to be similar to the general population, in contrast to previous viral diseases. However, Caesarean section was most often performed in patients infected, possibly not because of the consequences of the virus but related to babies' prematurity and the medical team's concern to evolve to a more serious presentation.

Although COVID-19 infection in pregnant women is not related to an increased risk of maternal death, medical services must be prepared to attend to these women with complications and protect the hospital staff from contamination. We will need more time and data to understand better the pandemic's consequences on newborns of infected mothers. Information is crucial to counseling this specific population.

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