Review Article

A review of COVID-19's role in pregnancy and its association with the risk of miscarriage in pregnant women

UNDER PEER REVIEW

Abstract

Background and Aims: Since the new Coronavirus started spreading in December 2019, the virus has had enormous consequences on people's health and way of life in every nation on earth has been touched. A pregnant lady is more susceptible to infection than a healthy one because she is immunocompromised throughout pregnancy. The purpose of this present paper was to review relevant published literature and also aims to determine whether COVID-19 infection increases the risk of miscarriage in pregnant women.

Method: In this narrative review all publications published in the databases PubMed, Scopus, Embase, Science Direct, and Web of Science from December 2019 to August 2022 by conducting a complete search with the required keywords, including COVID-19, coronavirus illness 2019, SARS-CoV-2, and miscarriage, abortion, or pregnancy outcomes. There are few accessible data on the effects of COVD-19 on pregnancy. Every day, new information emerges on the management of pregnancy during the COVID-19 era.

Result: In this review, we assess the most recent research regarding the effects of SARS-CoV-2 infection during pregnancy. COVID-19 can cause fetal distress, miscarriage, respiratory distress, and preterm delivery in pregnant women, according to the reviewed literature.

Conclusion: Due to the absence of adequate data regarding the effects of COVID-19 on pregnancy, it is required to follow suspected pregnant women prior to and after delivery. For verified cases, both the mother and newborn should be thoroughly monitored.

Keywords: COVID-19, Pregnancy, miscarriages,

UNDER PEER REVIEW

1. Introduction:

In December 2019, an unidentified pneumonia outbreak was reported in Wuhan, Hubei Province, China [1]. Those who have COVID-19 typically experience viral pneumonia, with the most common symptoms being fever, cough, sore throat, myalgia, and weariness [2]. COVID-19 has afflicted over 170 million individuals globally, resulting in over 3.5 million deaths by the end of May 2021. Several COVID-19 vaccinations were introduced to prevent the spread of COVID-19 during the pandemic, and treatment regimens were quickly established with the introduction of new pharmaceuticals, including anti-SARS-CoV-2 monoclonal antibodies and antiviral treatments [3]. Coronaviruses are enclosed, non-segmented, single-stranded ribonucleic acid (RNA) viruses that cause illnesses ranging from simple colds to serious prenatal disorders. SARS-CoV, which causes severe acute respiratory syndrome (SARS), and MERS-CoV, which causes Middle East respiratory syndrome (MERS), are the two most well-known fetal viruses [4]. The World Health Organization declared a pandemic on March 12, 2020, due to the global spread of SARS-CoV-2 and thousands of deaths caused by coronavirus illness [1]. Due to physiological changes in the immunological and cardiopulmonary systems during pregnancy, pregnant women may be more likely to experience more severe symptoms after contracting respiratory viruses. MERS-CoV and SARS-CoV have also been linked to more serious

pregnancy problems and higher case fatality rates. On the effect of COVID-19 during pregnancy, there are, however, few reports. Because of this, it is uncertain how COVID-19 treatment may affect fetal and neonatal outcomes, and research are urgently needed to address this issue [5].

Pregnancy is thought to be a risk factor for severe sickness from COVID-19, which is caused by SARS-CoV-2 infection. Furthermore, pregnant women with COVID-19 may be at a greater risk of other negative outcomes, such as preterm delivery and abortion. An increasing body of evidence suggest linking of COVID-19 to abortion [6]. The immune system, respiratory system, cardiovascular system, and coagulation are all significantly impacted by physiological changes during pregnancy. These could accelerate or halt the progression of COVID-19 disease [7]. SARS-CoV-2 primarily spreads through the respiratory route, suspended on droplets or, less frequently, aerosols [8].

The chance of developing a serious COVID-19-related illness is increased in pregnant women. Compared to non-pregnant women, pregnant women are more likely to be referred to an intensive care unit (ICU) [9]. By conducting a systematic review that evaluated the prevalence of miscarriages in pregnant women with COVID-19, this paper is aimed to review potential causes of COVID-19 that may cause pregnancy losses based on the findings of human studies during the pregnancy, as well as the current evidence of the COVID-19-impact on pregnancy losses.

1.1 Impact of Covid-19 on pregnancy: The risk of COVID-19 to expectant mothers is minimal generally. However, those who are pregnant or have recently given birth run a higher chance of developing a serious illness from COVID-19. If the pregnant women have a serious sickness, they may need to be hospitalized and get critical care. Additionally, COVID-19-positive pregnant women are more likely to give birth before the 37th week of pregnancy (premature birth). Furthermore, COVID-19-positive pregnant women may be more likely to experience

UNDER PEER REVIEW

issues including stillbirth and miscarriage [10]. Some of the main issues include whether pregnant women are more susceptible to COVID-19, whether infected pregnant women have worse outcomes in terms of morbidity and/or death compared to non-pregnant women of the same ages, whether infected pregnant women have more severe disease, or whether they have worse maternal-fetal outcomes compared with uninfected pregnant women of comparable ages [11].

Compared to their contemporaries who are not pregnant, pregnant women with COVID-19 may be at higher risk for more serious sickness, according to the data that is currently available. These findings specifically show an increased likelihood of mechanical breathing and ICU hospitalizations. However, Table -1 shows some maternal symptoms which was caused in pregnant women during their gestational weeks. There hasn't been any evidence of a rise in mortality rates. Pregnant women with comorbidities like obesity and gestational diabetes may be at an even higher risk for serious illnesses than the general population with comparable comorbidities. It's significant that analyses performed thus far have been constrained by a significant quantity of missing data and the fact that many publications lack an adequate comparative control group that isn't pregnant [12].

1.2 COVID-19 infection and miscarriages: A miscarriage occurs when a pregnancy ends on its own before the 20th week. The majority of miscarriages happen prior to the 12th week of pregnancy [23]. Research has revealed that the COVID-19 virus adheres to a number of bodily organs. In early placental tissue, SARS-Cov-ACE2 protein is expressed, which makes the early pregnancy vulnerable to the effects of COVID-infection [24].

UNDER PEER REVIEW

During the periconceptional period, miscarriage and unsuccessful embryo implantation are more likely in women with COVID-19. Unbalanced immune hormones causes "cytokine storm" results a hypercoagulable state that is harmful to normal fetal development [25]. In fact, anomalies in the mother's immune system during the peri-implantation and early stages of pregnancy have been associated to repeated implantation loss and miscarriage [26].

2. Method

2.1 Study Design: This review intended to comprehensively analyze the risk of miscarriage in pregnant women who had COVID-19 during their pregnancy. This review period began in June 2022, with additional updates in July and August. The popular databases like databases PubMed, Scopus, Embase, Science Direct, and Web of Science during December 2019 to August 2022 were investigated using the following search terms: COVID-19, coronavirus illness 2019, SARS-CoV-2, and miscarriage, abortion, or pregnancy outcomes. The search was limited to English-language academic publications. EndNote X9 (Clarivate Analytics US LLC, Philadelphia, USA) was also utilized as reference management software. Additionally, a manual search of the references included in the chosen papers and reviews was done.

2.2 Data extraction and quality assessment: From the publications that were ultimately chosen, information about the place of origin, the number of pregnant patients with confirmed COVID-19, clinical symptoms, laboratory results, outcomes, and key findings were retrieved.

3. Discussion:

Pregnancy is a distinct immunological state in which complex physiological processes occur at the maternal-fetal contact. When this delicate equilibrium is troubled by infections, the system might collapse. Few data exist about the immunological response to SARS-CoV-2 infection

UNDER PEER REVIEW

during pregnancy, highlighting the significance of this review. Regarding the specific immunological features of COVID-19 in pregnant women, there is still no solid publication based on currently available scientific information. Regardless of study design, this review chose all studies pertaining to COVID-19, and pregnancy. All included papers are narrative reviews devoid of methodological and technical information regarding the selection of data.

Case reports and case studies from the pandemic have shown that moms who tested positive for SARS-CoV-2 have a higher risk of abortion. The majority of these research discussed how the virus affects the pregnant women and causes serious impact which slows down fetal growth and may cause abortion. A case report done by Fang, Nz in 2020 in USA resulted one miscarriages of a pregnant women with Covid 19 [27]. In Malaysia another case report was done by Wong, T.C. and miscarriages occurred in two of the cases during the first trimester of pregnancy where both pregnant women were infected by SARS-Cov 2 [28]. A study was done in 727 women made their first prenatal visit between June 29 and September 30, 2019, and 67 of them (9.2%) experienced a miscarriage. 542 women had their first prenatal appointment during the same time period in 2020, and 64 (11.8%) of them miscarried before 12 weeks' gestation. Prior to admission, SARS-CoV-2 was tested on all women who miscarried in 2020, and 4.7 percent (3/64) of the tests were positive [29].

According to the results of the current study, further investigation into the potential for vertical transmission of COVID-19 from mother to fetus is considered essential. Results from studies indicate that infected or suspected mothers should be closely monitored before and after giving birth. The recommendation is for women who believe they may have been exposed to COVID-19 to hold off on nursing until they have received formal clearance [30]. A study done by Chen et al., 2020 found that COVID-19 can induce fetal discomfort in pregnant women but does not

UNDER PEER REVIEW

infect infants [31]. A similar study was done by in China. They have found that there is no evidence of intrauterine COVID-19 infection caused by vertical transfer to the fetus [32]. According to a study in Iran, women who are suspected or know for sure that they have COVID-19 should not breastfeed their babies for at least two weeks after they are born. If COVID-19 infection is confirmed while a woman is pregnant, both the mother and the fetus should be closely watched [33]. Another study in China suggest that There is no proof that COVID-19 causes fetal distress or infections in babies. COVID-19 can be mild or severe during pregnancy, and it can cause the baby to come early which may sometimes cause critical issues in newborn [34]. According to a 2020 Chinese study, infection with COVID-19 during pregnancy might result in adverse consequences such miscarriage, fetal development impairment, early delivery, and even maternal fatality [35]. But another study shows that there is no indication that pregnant women can transmit COVID-19 vertically [36].

According to a research paper done in the United States in 2020, some newborns showed signs of fetal distress and preterm delivery. After birth, SARS-CoV-2 testing was negative for all kids born to pregnant women with COVID-19 [37]. According to a study done in China in 2020, prenatal COVID-19 infection may have detrimental effects on newborns. These effects may include fetal discomfort, early labor, respiratory distress, thrombocytopenia followed by impaired liver function, and even death [38]. As per some studies neither the mother nor the infant have shown any signs of having contracted SARSCoV-2 during pregnancy [39-41]. According to research, being affected with SARS during the perinatal period is associated with a high prevalence of potentially harmful maternal and neonatal side effects, including disseminated intravascular coagulopathy, spontaneous abortion preterm birth, intrauterine growth retardation, neonatal, intubation and the need for the newborn to be admitted to a neonatal intensive care unit

UNDER PEER REVIEW

(ICU) and organ failure [42]. Because of physiological, immune, and anatomical changes, pregnant women are more susceptible to respiratory diseases. Some studies point to a significant shift to a T-helper lymphocyte type 2 (Th2) immune response during pregnancy as a potential contributor to the severity of COVID-19 cases. Furthermore, the cytokine storm that occurs in severe cases causes an increased inflammatory state, which may worsen the clinical prognosis in this population. As a result, pregnant women may be a vulnerable group to COVID-19 infection, owing to an immune imbalance at the maternal-fetal interface [43]. Therefore, there is a hypothesis that the hormone level and immunological condition differ at various phases of pregnancy. In early pregnancy, for instance, the author suggests that the immune balance is still unstable, which can lead to a severe immune system disorder and internal environment imbalance in the event of a viral infection, resulting in abortion or abnormal fetal growth, similar to that observed in other respiratory infections. According to this author, as the pregnancy proceeds, the mother is constantly changing this immunological balance, with presumably decreasing severity [44]. Recent research indicates that in severe cases of COVID-19 infection, a cytokine-storm occurs, which is characterized by increased concentrations of plasma mediators such as IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, and tumor necrosis factor alpha, most of which are associated with an inflammatory response [45]. Dashraath et al. hypothesized that the physiological change to a Th2-anti-inflammatory environment during pregnancy and other undisclosed immune adaptations may function as the major immune response to SARS-CoV-2, resulting in a less severe manifestation of COVID-19 in the pregnant women. These results are consistent with the scant literature that asserts that, despite being put in high-risk groups mostly due to preventive measures, cases of COVID-19 among pregnant women may not be more severe or have worse clinical outcomes than those in the general population. Due to the lack of relevant

UNDER PEER REVIEW

data about the effects of COVID-19 on the immune response during pregnancy, a number of issues remain unresolved until the publication of adequate, case-based, evidence-based studies [46].

According to Li et al., 2020 four of seven pregnant women with COVID-19 who presented in the first trimester experienced spontaneous miscarriages, while two had voluntary terminations. The sole newborn survivor was born at full term, and no birth defects were noted [47]. Yan et al. hypothesized that pregnant women with COVID-19 had a higher rate of maternal mortality, intubation, and ICU hospitalization than non-pregnant women with COVID-19, but that the virus was not transmitted to the newborn. In addition, more problems such as miscarriage, premature birth, and small-for-gestational-age newborns have been documented. One study, however, found no increase in the risk of spontaneous abortion or spontaneous preterm birth among pregnant COVID-19 carriers. Numerous systemic infections and inflammatory conditions are related with premature birth, and preterm births have been observed in women infected with COVID-19. However, the majority were recorded in China, which has a distinct medical system, and it is still unclear whether SARS-CoV-2 caused these premature births or whether they were iatrogenic as a result of maternal distress or other indicators [48]. In table 2, this review study attempted to compile data on the number of miscarriages caused by COVID-19 in various countries.

Conclusion

In summary, one of the mainstays of the healthcare system is the provision of safe care to expectant mothers who have COVID 19 infection. The lack of information about the epidemic among pregnant women is one of the study's inadequacies. This may be connected to pregnant moms' anxiety about receiving routine prenatal treatment in clinics during the COVID-19 epidemic. Additionally, because the mother's consent was not obtained, restricted sample of the

UNDER PEER REVIEW

aborted fetus or placenta and absence of pathology reports have kept the current statistics on these abortions to the cases reported. There is little information available from the pregnant women who had abortions during the pandemic. Further investigation is therefore required to determine the causes of pregnancy loss in COVID-19 infected mothers and whether there is any evidence that viral transmission to the fetus causes miscarriage due to the virus's direct impact on the fetal organs.

UNDER PEER REVIEW

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UNDER PEER REVIEW

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UNDER PEER REVIEW

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UNDER PEER REVIEW

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UNDER PEER REVIEW

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Tables

Table-1: Maternal symptoms during Covid-19

No. of pregnant patients	Asymptomatic (%)	Fever (%)	Cough (%)	Dyspnea (%)	Chest pain (%)	Myalgia (%)	Headache (%)	Diarrhea (%)	Fatigue (%)	Referenc
7	28.5	28.5	43	-	28.5	43	28.5	-	-	[13]
43	33	48	65	24	17	38	28	-	-	[14]
20	80	10	-	10	-	-	-	-	-	[15]
2	-	100	-	-	-	-	-	-	-	[16]
17	-	18	35	12	-	-	-	18	-	[17]
10	-	70%	10	-	10	-	-	-	10	[18]
8	-	62.5	87.5	37.5	-	37.5	-	-	37.5	[19]
42	-	48	43	19	-	17	-	5	-	[20]
9	-	44	89	44		56	-	-	67	[21]
3	67	-	-	-	-	-	-	-	33	[22]

UNDER PEER REVIEW

Table-2: Number of miscarriages due to COVID-19 in different countries

Location	No. of patients	No. of miscarriages	Gestational weeks	References
Italy	225	12	Approx. 12-13 weeks	[49]
China	116	1	38 weeks	[48]
Turkey	553	12	1st trimester (130) 2nd trimester (165), Third trimester (238)	[50]
Kuwait	185	3	29 weeks	[51]
Malaysia	2	2	10 weeks	[52]
Pakistan	1	1	10 weeks	[53]
Italy	7	1	37 Weeks	[54]
China	118	9 (3 spontaneous abortion)	Mostly 3rd trimester	[55]
France	54	1	37 weeks	[56]
22 countries	887	11	Approx. 20-20 weeks	[57]
Switzerland	1	1	19 weeks	[58]

UNDER PEER REVIEW