



Review Article

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Coronavirus Disease 2019 (COVID-19) and Pregnancy: A Review of the Current Knowledge

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ABSTRACT

The vaccination process in most countries is expediting, and the world is moving into the terminal stage of the third wave of COVID-19. Many articles have been published on COVID-19 and pregnancy addressing the different features of the disease in this population. Therefore, the present study aims to explore the salient features of COVID-19 in pregnancy and how it has affected maternal mortality and morbidity as published in the literature. Articles were searched using MeSH words in PubMed, Medline, Google Scholar, and Scopus from 20th May 2021 to 24th May 2021. Fever, cough, fatigue, and dyspnea were the most commonly reported presentation in these females; the disease severity ranged from mild to moderate to severe in patients with co-morbidities, especially obesity and asthma. Evidence of mother to fetus transmission is scarce, and intrauterine transmission of COVID-19 is not supported by evidence. Hospitalization with careful monitoring should be done in patients with lymphopenia, and class III obesity, and stringent adherence to the SOPs should be ensured for safe delivery in this pandemic.

Key words: SARS-CoV-2 virus, Vertical transmission, Pregnancy, Complications, Placenta

INTRODUCTION

The pandemic of coronavirus (COVID-19) was first highlighted in Wuhan city of China when people in the last weeks of 2019 were presented with the symptoms of respiratory tract infection and pneumonia caused by an unknown agent [1]. Later on, it was discovered that the causative agent of the disease was a novel virus from a group of coronaviruses named “SARS-CoV-2 i.e., severe acute respiratory syndrome coronavirus 2” [2]. The disease quickly spread to all parts of the globe and was declared a “global pandemic” by the WHO on 11th March 2020 [3]. COVID-19 has a high reproduction rate (Ro factor) reported from 2.28 to 5.27, which means each case can infect two to five patients showing a high rate of transmission that may be the contributing factor behind its rapid spread [4]. COVID-19 presents acute onset of fever, occasionally productive cough, myalgia, dyspnea, and gastrointestinal disturbances, e.g., diarrhea and vomiting. Ground-glass opacities, lymphopenia, and C-reactive protein are the main inflammatory markers elevated in COVID-19 as reported in lab and imaging findings [5]. Also, consistently these features have been observed in pregnant females diagnosed with COVID-19 [6]. Pregnancy is known to make females prone to respiratory diseases due to increased demand for oxygen and concurrent dyspnea, changes in the environment of the respiratory tract, edema, and mucous secretion in the respiratory passages. These factors make pregnant females more susceptible to pneumonia caused by respiratory tract infections of viral origin [6], and it is the very common non-obstetric cause of maternal death [7].

Various case series conducted on pregnant females diagnosed with COVID-19 have shown that the presentation is usually apparent in the last trimester. Many undiagnosed cases remain in the first and second trimesters [8]. Moreover, the rate of cesarean section in these females is as high as 85% [9]. However, vertical transmission does

not occur, and the birth weight of the neonates born to these mothers is normal in most cases [10]. A previous systematic review had shown that SARS and MERS infection increase the risk of prenatal death, miscarriage, abortion, and preeclampsia [11]. In another case series of 13 females, cesarean section was the preferred mode of delivery; one female suffered from severe “acute respiratory distress syndrome” (ARDS) and progressed to multiorgan failure, whereas fetal distress was common, and one stillbirth was also reported [12]. The studies conducted on SARS-CoV-1 in the past have shown a very high risk of maternal mortality, growth restriction in neonates, and a rise in the number of preterm deliveries in pregnant females; however, the vertical transmission was not reported in these cases too [13]. It shows that our knowledge of COVID-19 is still far from the conclusion, and there is conflicting evidence on this matter. Several studies are being published on pregnancy and COVID-19 regarding the complications in the mother, risk of vertical transmission, and development of congenital disabilities in the fetus. Still, only a few papers have addressed and reviewed all these features together so this study attempted to fill the gap. There is a need to describe the clinical characteristic of COVID-19 pregnant patients, the most common complications encountered in this process, and the risk of vertical transmission. Therefore, this article aims to explore these salient features of COVID-19 in pregnancy and how it has affected maternal mortality and morbidity as published in the literature.

MATERIALS AND METHODS

Study design

This article is qualitatively in nature and explores the features of COVID-19 in pregnancy.

Search strategy

The databases searched were PubMed, Google Scholar, Medline, and Scopus. Further records were retrieved from the WHO database and the website of the centers for disease control (CDC). The MeSH words used in searching the database were "COVID-19", "pregnancy", "coronavirus", "neonate", and "vertical transmission", which were edited as per the database requirement. The literature search was carried out from 20th May 2021 to 24th May 2021.

Inclusion and exclusion criteria

Articles considered eligible were only those in which the diagnosis of COVID-19 was confirmed by nasopharyngeal swab using “reverse transcriptase-polymerase chain reaction” (rt-PCR), and was published in the English language until 30th April 2021. Articles that lacked data, case reports, short communications, letters to the editors, and unpublished articles were excluded from the review. In cases of overlapping data, the study with a larger sample size was given preference to avoid duplicating the data. No restriction of country or region was applied. Relevant articles were defined as the articles that included the data on either of the following; clinical features of COVID-19 in pregnancy, complications encountered during pregnancy, evidence of vertical transmission, and fetal abnormalities.

Selection strategy and analysis of data

After searching the databases, the selected articles were de-duplicated and their title and abstract were read and accessed based on eligibility criteria. The full text of the qualified articles was retrieved and they were again accessed based on the same eligibility criteria. The reference lists of the selected articles were also read through as not to miss any relevant articles. The results from the selected articles were organized and arranged based on the separate topics and headings for narrative analysis. The initial searches yielded 861 articles in total. Records were reviewed for their relevance using “title and abstract” and then retrieving the article's full length.

RESULTS AND DISCUSSION

The findings obtained from the relevant articles are synthesized below in narrative form and are grouped under the following subsections:

Clinical features of COVID-19 in pregnancy

The most prominent features of COVID-19 in pregnant females correspond with those observed in the general population, i.e., fever, cough, dyspnea, myalgias, etc. Similarly, laboratory findings and radiological features

most commonly observed include elevated lymphocytes, elevated ESR, elevated CRP, and ground-glass opacities [6]. An article published on 41 Chinese pregnant women and the pediatric population suffering from COVID-19 reported that fever was the most common finding in the patients, along with cough, fatigue, and leukocytosis with an elevated neutrophil ratio was. Fever resolved in the post-partum period within three days in most cases [14]. The study also reported the radiological features of the affected females; bilateral lung opacities, consolidation, and ground-glass opacities were observed in most cases [14]. The study concludes that due to atypical clinical symptoms in pregnant women, early detection of COVID-19 is difficult. However, the study was limited by its small sample size. In another study done on 10 pregnant women in Wuhan, lung abnormalities were the most common finding; meanwhile, fever was the only symptom reported in most patients, whereas other less common symptoms included cough and chest tightness [15]. One case in this study was reported to have a high fever which later on progressed to preeclampsia. The notable lab findings included lymphopenia, elevated LDH, and coinfection, and the most common radiological findings were pleural effusion (6/10), and patchy infiltrates on CT (5/10). Although two premature births took place, no fetal or maternal deaths were reported [15]. However, this could be due to the study setting not being a COVID-19 designed center and the severe COVID-19 cases were not referred here. Duffy *et al.* [16]. evaluated lymphopenia as a prominent finding in confirmed and suspected patients of COVID-19 and posit that decreased absolute lymphocyte count was reported in 48% (15/31) PCR positive cases of COVID-19. In contrast, lymphopenia was found in a majority of the severe cases at presentation, and lymphopenia was reported as a risk factor for severe prognosis [16]. However, this study was limited in its sample size. Another retrospective study from the USA showed that the outcome of most patients was favorable [17]. Obesity was found to be a predictor of poor outcomes among the patients as there were 16% (7/46) cases categorized as severe, and all of these occurred in obese or females with significant co-morbidities [17]. Moreover, there was one stillbirth and one preterm birth, both of which occurred in class III obese females [17]. These clinical features make COVID-19 a high risk for complexities in pregnant women.

Complications and outcomes of COVID-19 in pregnant women

We now report both the maternal and fetal complications that have been shown to arise in pregnant females suffering COVID-19 and undergoing delivery. Chen *et al.* [12] reported a premature rupture of membranes in two (22%) cases; preeclampsia and gestational hypertension were also reported in one case (11%). In a case series by Li *et al.* [18] involving 16 females that gave birth to 17 neonates, hypothyroidism (2/16), gestational diabetes (3/16), and gestational hypertension (3/16) were reported to be the major complications found in COVID-19 infected pregnant females. One of the morbid conditions in pregnant women with COVID-19 pneumonia was preeclampsia as reported by Mendoza *et al.* [19] but overall, the finding was reported in only 11% of all cases in this study, and only one patient had confirmed angiogenic abnormality and increased LDH. Whereas, in neonates, Yan *et al.* [20] reported 50 confirmed cases of COVID-19 pneumonia and neonatal complications included fetal distress (7/50), failure to progress (3/50), preterm delivery (17/50), preeclampsia (1/50), and one neonatal death. Neonatal encephalopathy has also been reported in rare cases of babies born to COVID-19 pregnant patients [21]. Moreover, preterm delivery has also done very commonly observed in critical cases [22]. Another study in the early part of the pandemic showed a high frequency of maternal and fetal complications, including fetal distress, abnormal umbilical cord, and preterm delivery, which was reported in up to 60% of the cases [23]. Not all the studies reported complications. Some studies reported normal deliveries with no harmful outcomes on the fetuses, or mothers [10, 24]. However, the sample size of these two studies is also small. This significantly shows that COVID-19 infected female individuals are prone to have complications related to pregnancy.

A study reported clinical experience in managing pregnant women infected with SARS-CoV-2 during the initial 30 days of the COVID-19 pandemic [25]. The majority of pregnant women infected with COVID-19 had a positive clinical outcome. However, one-third of patients had pneumonia, with 5% having a serious clinical state. CRP and D-dimer levels were shown to be positively connected with severe pneumonia, and the neutrophil/lymphocyte ratio dropped as the patients' clinical conditions improved. Seventy-eight percent of the women gave birth vaginally. There were no vertical or horizontal transmissions detected in the newborns during birth or nursing [25].

To illustrate the specific factors, a case of fast clinical decompensation and the development of severe acute respiratory distress syndrome was presented in a woman at 31 weeks' gestation [26]. This case emphasized important physiologic and treatment issues for the care of critically sick pregnant women with

COVID-19. There are few current tools to help the multidisciplinary team make judgments about optimal maternal-fetal monitoring, intensive care techniques, and delivery timing [26]. This thorough example examines the conceptual process, team-based strategy, and analytical method to diagnosing and managing this new disease. Another study characterized the clinical course of COVID-19, the impact of comorbidities on disease severity, laboratory trends, and pregnancy outcomes in symptomatic and asymptomatic COVID-19 positive pregnant women [27]. The case in this study was tested positive for the coronavirus that causes severe acute respiratory syndrome. The results depicted that COVID-19 in pregnancy can cause serious illness and even death. Hispanic women were more likely than other ethnic groups to get a positive test result for severe acute respiratory syndrome 2. Moreover, obesity and Hispanic ethnicity are risk factors for mild and severe illnesses, respectively [27].

Risk of vertical transmission

Vertical transmission is defined as viral, bacterial, or protozoal infections that follow mother to fetus/embryo transmission in intrauterine life or during the process of delivery [28]. Mother to fetus transmission of COVID-19 in IUL has not yet been reported widely [12]. While most studies have tested the placenta, cord, and nasopharynx using PCR and have ruled out the intrauterine transmission of the disease [29] some conflicting reports have surfaced. For example, a case report on the COVID-19 mother published in Iran showed that the RT-PCR test of amniotic fluid and second neonate throat and the nasal test were positive for the virus, whereas the initial neonate test, vaginal secretion, and umbilical cord blood were negative [30]. This finding suggests that the neonate contracted COVID through the intrauterine channel. This case study raises concerns related to the possibility of COVID-19 through vertical transmission in infected pregnant mothers. Regarding retrospective study on obstetric patients with COVID-19 shows that SARS-CoV-2 does not pass in the milk from the affected mother as milk was negative for the virus [10].

A study explained the clinical characteristics of COVID-19 in pregnancy and the newborn to explore the vertical transmission of SARS-CoV-2 [31]. The case series investigation included comprehensive testing process for SARS-CoV-2 infection was carried out utilizing oropharyngeal swabs, placenta tissue, vaginal mucus, and breast milk from mothers, as well as oropharyngeal swabs, umbilical cord blood, and serum from infants. All of the patients had a smooth prenatal course and a satisfactory outcome. There was no evidence in the case series to imply a risk of intrauterine vertical transfer [31]. Both the pregnant mother and her child had less negative maternal and neonatal outcomes.

Another study investigated the vertical transmission potential of COVID-19 in pregnancy [32]. The major goal was to analyze the severity of sickness, viral clearance time, and duration of hospital stay, while the vertical transmission potential of COVID-19 was also investigated. The results depicted that pregnant women had clinical courses and outcomes similar to reproductive-aged non-pregnant women, when infected with SARS-CoV-2. There was no evidence to support vertical transmission of COVID-19 in late pregnancy, including vaginal birth [32].

Treatment

Most cases of mild to moderate nature have been treated with supportive and symptomatic treatment with various agents. Several pharmacological agents have also been tried in moderate to severe cases. Antiviral like ritonavir with or without lopinavir has been used in the UK with acceptable results, and neonates with pulmonary compromise were treated with corticosteroids to expedite the lung maturation [21]. Moreover, remdesivir has also been used in a few women suffering from severe COVID-19 in the last trimester [21]. Hydroxychloroquine and anticoagulant therapy have also been employed in moderate to severe cases with variable outcomes [22]. Convalescent serum of the recovered patient has also been used to successfully treat pregnant mothers [33], with no apparent side effects or transfer of infection to new-born [34]. For severe cases, careful monitoring in ICU with supplemental oxygen has been done [35]. In all these studies the preferred mode of delivery remained the C-section, although there were different indications in some cases. Similarly, supplemental oxygen was invariably used in patients with ARDS [36]. This review highlighted the key features of COVID-19 occurring in pregnancy, the risk of vertical transmission, and the complications associated with it. There is a significant similarity in the clinical presentation and imaging features of COVID-19 pregnant patients and adult COVID-19 patients. Fever, cough, and SOB remain the most common presentation, whereas elevated inflammatory markers (e.g., CRP, ESR), lymphocytosis, and neutropenia were the prime laboratory findings, although few articles reported lymphopenia the prominent finding [15]. A similar incidence of clinical features has also been

described in another systematic review where fever, cough, and fatigue were reported to be the chief presenting complaints with mild to moderate severity [37]. Patients with lymphopenia need to be carefully monitored as lymphopenia is an indicator of the severity of the disease, especially when there are two lives at stake [38]. Our findings are consistent with the other reviews on the intrauterine transmission of COVID-19 in pregnancy [39, 40].

Although most of the features are the same as reported in the adult population severity of the disease varies significantly, with multiple reports citing miscarriages, preterm delivery, and fetal distress. This may be explained by the changes in the immune system that normally take place in pregnancy that make pregnant females susceptible to viral infections. In pregnancy, the T-helper cell 1 (Th1) response wanes and is shifted to the Th2 response to protect the fetus [41]. The pathogenesis of SARS-COV-2 seems to involve “angiotensin-converting enzyme” subclass 2 (ACE2), which is present abundantly in the alveolar epithelium, endothelium of the blood vessels, and smooth muscles of the gut, veins, and arterioles, and the spike protein on the virus binds with this receptor [42]. Similarly, in theory, there is a chance of COVID-19 occurring via the transplacental route as the placenta possesses numerous ACE-2 receptors which can bind the SARS-CoV-2 [43]. However, we did not find any concrete evidence that the vertical transmission of COVID-19 occurs except few case reports which only reported one or two individual cases [30, 44]. This is consistent with the other articles published in the literature however, conclusive evidence is still needed, and the exact mechanism by which the vertical transmission does not occur is also unknown. Pregnancy is a hyperdynamic state of the body, increasing the demand for oxygen in the pregnancy.

According to the latest guidelines issued by the CDC in the USA, breastfeeding is not contraindicated, and newborn should be breastfed if there is no contraindication otherwise. We thus recommend that breastfeeding should be continued after birth even if the mother is positive for COVID-19 as it is beneficial in providing post-natal care to both the child and mother. Although several complications have been reported to occur in such pregnancies, “there is no convincing evidence that COVID-19 infection significantly predisposes the pregnant females to these complications”, a finding similar to the influenza pandemic [45]. One study comparing COVID-19 positive pregnant females with normal pregnant females reported that COVID-19 does not significantly increase the rate of occurrence of PROM, preeclampsia, fetal distress, placental rupture, gestational diabetes [44], Whereas another review article showed that the occurrence of premature delivery in the COVID-19 is higher than the normal population (23% vs 15%) [46]. It shows that there still exists a significant knowledge gap on this issue which warrants further research on this matter.

Convalescent plasma therapy was effective in pregnant women. Convalescent plasma is a short-term strategy of passive immunity, where the antibodies from a treated person are injected into the infected person. Although, a rich pool of donors is available due to the high number of infected patients with COVID-19 and relatively low mortality rate [45]. However, it has a limitation, as the potential donors need to be screened to be free from other infections and they should meet all other eligibility criteria [5]. Also, as its success is dependent on the high concentration of antibodies in the plasma and recently convalesced individuals COVID-19 has shown to cause high neutralizing antibody titers [44]. Further control group studies on the large sample are needed for the conclusive decision. Finally, the study suggests adopting maximum protection during the process of childbirth in COVID-19 cases as well as normal circumstances of delivery until the pandemic resolves because there may be a lot of asymptomatic cases that do not get tested in peripheral centers. In cases of the mother being COVID-19 positive during the natal period, we suggest that the neonate, placenta, and umbilical cord should be tested for COVID-19. Despite reviewing several articles published, our review has some significant limitations. We conducted a scoping review rather than a systematic one without using specific guidelines viz. PRISMA, STROBE, etc., and it was not registered in any database. Moreover, the study did not assess the grey literature, and no quantitative synthesis of data i.e., meta-analysis, was done. However, this article aims to provide useful insight into the various features of COVID-19 in pregnancy and gives rise to logical questions that can be useful in conducting further research.

CONCLUSION

COVID-19 in pregnant women shares some of the features observed in the general population; however, the severity of the respiratory illness is more. Moreover, there is no significant evidence that “vertical transmission” occurs during gestation or at the delivery time. COVID-19 can pose significant complications for the mother and

the infant and warrants great measures to be adopted in delivery. Further research should address the risk of developing congenital disabilities and perinatal complications, especially during the early phases of pregnancy.

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