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Review article

Effect of the severity of SARS-CoV-2 on pregnancy and delivery: A narrative review

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ABSTRACT

Background: Pregnant women with the novel coronavirus disease (COVID-19) are more likely than non-pregnant women to develop severe COVID-19 complications. In addition, COVID-19 is linked to unfavorable pregnancy outcomes. Due to the lack of effective COVID-19 treatment, it is critical to assess geographic differences and trends in current clinical care and the effect of COVID-19 on pregnant women. This review aims to evaluate maternal and neonatal outcomes in COVID-19 pregnancies. We searched the Medline database for research papers from January 2019 to December 31, 2021. Eleven studies of systematic, meta-analysis, review, and cohort designs were included with searched keywords {Pregnancy AND COVID [MeSH Terms]}. This study summarizes the maternal characteristics, vertical Transmission, maternal and neonatal outcomes, the rate of cesarean section, comorbidities, mechanical ventilation, ICU admission rate, mode of delivery, type of anesthesia, the average hospital length of stay (HLOS), the extracorporeal membrane oxygenation (ECMO), preeclampsia, pregnancy-induced hypertension, chest x-ray and CT scan findings, treatments, and outcomes over time.

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Introduction

In December 2019, the novel coronavirus disease (COVID-19) was discovered in Wuhan, China [1], caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [2]. In addition, SARS-CoV-2 is a single-stranded RNA virus of the subgenus Salvecovirus beta coronavirus genus derived from bats [2]. COVID-19 soon issued a global health emergency alert and spread to many countries, with WHO announcing the start of a new pandemic on March 12, 2020 [2]. According to the Worldometers dated January 2, 2022, there were 289,713,814 confirmed cases and 5,457,330 deaths worldwide [3]. The symptoms of COVID-19 include fever, cough, malaise, and severe cases are defined by the development of pneumonia with hypoxia, which occurs in approximately 14% of infections [4]. Subsequently, this results in serious illness in 5% of cases, with acute respiratory distress syndrome, septic shock, or other systemic complications, and usually needs automated ventilation [4]. The earliest reports reveal that older people are more vulnerable to COVID-19.

Furthermore, men are more susceptible to the virus than females, and men are more likely to become seriously ill or die due to the virus [1]. Besides, severe types of COVID-19 have been reported in young women [1]. Correspondingly, pregnant women with COVID-19 are more likely to experience severe COVID-19 complications than non-pregnant women with COVID-19 of similar age [1]. Still, symptoms and clinical symptoms are common [5] due to the anatomical structure and physiological adaptation modifications of the respiratory system that change during pregnancy, such as increased oxygen consumption and edema of the respiratory tract [6]. In addition, pregnancy is a specific immune tolerance condition that makes women more susceptible to viral infections [1]. According to extensive population-based cohort studies, seasonal influenza epidemics increase the risk of severe complications in pregnant women [1].

In pregnant women, severe acquired respiratory syndrome (SARS-CoV-1) has a mortality rate of about 25%, and up to 50% of infected pregnant women require intensive care [4]. Moreover, fetal death in utero happened at a rate of 30% in gestations with Middle East Respiratory Syndrome (MERS) complications, while 33% of current pregnancies were premature [4]. There is no evidence of SARS-CoV-1 or MERS infection in utero [4]. Nevertheless, SARS-CoV-1 is associated with complications associated with severe conditions and a higher mortality rate in pregnant women than in non-pregnant patients [7]. Correspondingly, pregnant women are at increased risk of severe COVID-19 than non-pregnant women [7]. Besides, SARS-CoV-1 has also been reported to cause obstetric complications such as spontaneous abortion, preterm birth, and intrauterine growth retardation [7]. Furthermore, SARS-CoV-1 and MERS had worse clinical outcomes in pregnant women than in non-pregnant women [8].

The impact of COVID-19 on risky populations, especially pregnant women, is very problematic, as changes in cell-mediated immunity during pregnancy can increase susceptibility to intracellular pathogens such as viruses [8]. Additionally, anatomical and physiological changes during pregnancy, such as increased chest diameter, increased transverse diameter of the thorax, diaphragm elevation, lung volume changes, vasodilation, and mucosal edema, may lower maternal hypoxia tolerance and lead to undesirable outcomes [8]. Furthermore, during the pandemic, it has been observed that the severity of the disease is kept in the pregnant population [8]. For example, during the 1918 influenza pandemic, a 27% maternal mortality rate was observed in people affected by the disease [8].

The clinical manifestations during pregnancy and the effects of COVID-19 infection on the mother and newborn are not yet fully understood. In addition, the possibility of vertical transmission of SARS-CoV-2 is currently unknown [4]. Furthermore, adverse pregnancy outcomes include preterm birth and maternal death, and when pregnant women with COVID-19 are compared to disease-free women, hospitalization in the intensive care unit (ICU) is observed [5]. Although many pharmacological interventions have been used to treat COVID-19, few are practical, such as Remdesivir or systemic steroids for the disease, and pregnancy outcomes are unknown in this group [5]. Moreover, specific pregnancy-specific interventions apply only to pregnant women, such as the type of childbirth and the type of anesthesia [5]. Several therapies have been used to treat pregnant COVID-19 patients, although their effects on COVID-19 and pregnancy outcomes are unknown [5].

This study summarizes maternal characteristics, vertical transmission, maternal and

neonatal outcomes, cesarean section rates, comorbidities, symptomatic symptoms, ventilators, ICU admission rates, delivery modes, types of anesthesia, and hospital length of stay (HLOS), extracorporeal membrane oxygenation (ECMO), preeclampsia, chest X-ray, CT findings, treatment options, and the long-term outlook.

Methods

The MEDLINE database was searched from January 2019 to December 31, 2021. Using specific keywords {Pregnancy AND COVID [MeSH Terms]}, we searched for COVID-19 and SARS-CoV-2 infections during pregnancy. A systematic review and meta-analysis study was included to examine pregnant patients with COVID-19/SARS-CoV-2 infection at any time during pregnancy. Review and observational studies of COVID-19/SARSCoV2 infection in non-pregnant patients were excluded. In addition, screening of abstracts from the first literature search was performed.

The regional variations in maternal characteristics, treatment profile, and outcomes

The average age of pregnant COVID-19 patients was 32.1 years in Europe, 30.8 years in the United States, and 28.4 years in Asia [9]. However, when compared to Asian studies (34.8 weeks), the average gestational age at detection was lower in European research (29.3 weeks) and US studies (31.9 weeks) [9]. The majority of pregnant COVID-19 patients in Asian (100%) and European (92%) studies were symptomatic, while almost half of the patients in US trials were asymptomatic [9]. Obesity was the most reported comorbidity in US studies (20%) and European studies (11%) [9]. Antibiotics were the most usually observed therapies in Asia (78%), while oxygen support (33%) and Hydroxychloroquine HCQ (26%) were the most observed therapeutics in Europe [9]. Antibiotics (12%), HCQ (7%), and oxygen support (7%) were used more frequently in US pregnant COVID-19 patients than other treatments, despite their low quantities [9]. Except for HCQ, the US studies used the fewest medicines compared to other countries [9]. HCQ and corticosteroid use proportions in European studies were more significant than in the US and Asia [9]. Mechanical ventilation assistance (2, 4, and 6%) and ICU admission (6, 5, and 7%) were found to be comparable throughout the US, Asia, and Europe [9]. The average HLOS, however, was highest in Asian studies (11.8 days) and lowest in European studies (7.34 days) [9]. Preterm birth rates were more significant in Asian (35%) and European (29%) studies than in US studies (13%) [9]. Cesarean section rates were comparable in the United States (46%) and Europe (53%) but lower in Asian studies (80%) [9].

SARS-CoV-2 vertical transmission

A systematic review found more than 54,413 pregnancies infected with SARS-CoV-2 and gave birth to more than 30,840 newborns born to infected mothers [10]. Subsequently, the results of the tested sample show that more than 800 newborns are positive for SARS-CoV-2, suggesting the validity of vertical transmission of SARS-CoV-2 by mothers infected with COVID-19 [10]. Additionally, about 70% of mother-to-child transmission by SARS-CoV-2 during pregnancy is expected to have been transmitted by environmental exposure to postpartum infection [10]. However, about 30% of diseases can be vertical transmission, parturition, or congenital [10]. However, it has been confirmed that about 9% of infections can be vertically transmitted [10].

Maternal and neonatal outcomes

In thirteen cohort studies, 18% of pregnant women who tested positive for SARS-CoV-2 also experienced severe sickness, severe COVID-19 pneumonia needing oxygenation or non-invasive ventilation [4]. In addition, acute respiratory distress syndrome, sepsis, or acute organ dysfunction was diagnosed in 5% of patients [4]. The only exception was COVID-19, found in 69% and 31% of cases, respectively [4]. Thirteen cohort studies reported 111 and 40 severe cases [4].

The rate of cesarean section, preterm birth, maternal death, fetal death, and admission to the ICU

The rate of cesarean section was comparable in US (46%) and European (53%) studies but higher in Asian studies (80%) [9]. Additionally, medical comorbidities are found in 33% of mothers, with a history of cesarean section in 17%, an average pregnancy rate of 4.3, childbirth in 864 pregnant women in 46%, and no birth in another group of 978 pregnant women [7]. Cesarean section, preterm birth, fetal mortality, and maternal death all occurred at a rate of 69, 50, 8, and 5%, respectively [9]. Moreover, a cesarean section is a clinical, surgical method to deliver birth through an incision in the abdomen and uterus [10]. Most newborns who tested positive for SARS-CoV-2 either gave birth by cesarean section or were not breastfed by an infected

mother [10]. For example, cesarean delivery was more common than vaginal delivery ranging from 38.8%-50.8% [10]. Maternal mortality ranged from 0% to 11% in 39 studies, whereas newborn death ranged from 0% to 11.7% in 50 studies [10]. In addition, 54% of babies with positive SARS-CoV-2 readings reported being separated from their mothers and not nursed during the isolation phase [10]. In 4 trial studies, 153 women had a cesarean section, which was significantly associated with ICU hospitalization (OR 4.99, 95% CI 1.24 to 20.12) [5]. Some reports also emphasized that the high or low risk of mother-to-child transmission does not depend on the type of delivery (i.e., either by cesarean section or virgin delivery) and the evidence contained therein [10]. Subsequently, cesarean section and preterm birth rates were expected at 62% and 26%, respectively [9]. Also, fetal death accounted for fewer than 1% of maternal deaths [9].

The most common comorbidities

Obesity (30%) and diabetes mellitus (23%), followed by hypertension and asthma (9%), were the most common comorbidities [9]. About 50% of the mother's average body mass index (BMI) was 32.1 kg / m2, and the average gestational age at admission was 36 weeks [7]. Obesity was the most often reported comorbidity in both US (20 %) and European research (11%) [9]. In addition, cesarean section 48%, vaginal delivery 26%, single birth 92%, twins 9%, preterm birth 14%, preterm birth 25%, preterm birth 21%, placenta previa 9.5%, placenta previa confirmed by COVID-19 during pregnancy of the cases, 7.5% had a preterm birth, 4% had delivery, and 54.5% had postpartum bleeding [7].

The mechanical ventilation and ICU admission rate

The ventilator rate of pregnant COVID-19 patients was calculated to be 3%, and the rate of ICU admission was 6% (95% confidence interval: 2, 10%) [9]. Over a third of the patients, 35%, required mechanical breathing, with a 43% ICU admission rate (95 % CI: 31%, 57%) [9]. Mechanical ventilation assistance (2%, 4%, and 6%), as well as ICU admission (6%, 5%, and 7%), were found to be similar in the United States, Asia, and Europe, respectively [9].

Mode of delivery and preterm birth

There was a significant association between the mode of delivery and preterm birth [5]. In addition, adult women who had preterm birth were more likely to have the baby via cesarean section [5]. However, there were no associations between the mode of delivery and a low Apgar score, neonatal acidosis, neonatal COVID-19, neonatal death, NICU admission, or stillbirth [5]. Eighteen studies (1020 women) provided information on delivery and its relationship to maternal and neonatal outcomes [5].

Type of anesthesia and maternal or neonatal outcomes

Only three studies reported the type of anesthesia and maternal or neonatal outcomes of 89 COVID-19-positive women who underwent cesarean section with local or general anesthesia [5]. Of the 90 newborns, 11 were born by cesarean section under general anesthesia, and five had an Apgar score of less than eight after five minutes [5]. Conversely, 70 newborns were born by cesarean section under local anesthesia [5]. One had an Apgar score of less than eight after 5 minutes [5]. Forty-one women who underwent cesarean section under general anesthesia had more severe COVID-19 (2 of 7) than women who underwent local anesthesia (2 of 32) [5]. Of 17 cases, three women underwent general anesthesia with a cesarean section. Still, no associated maternal endpoint was reported [5]. In addition, there were no adverse neonatal outcomes such as neonatal death, neonatal acidosis, neonatal COVID-19-positive infants, and low Apgar scores [5].

The average hospital length of stay (HLOS)

The average length of stay in the hospital was 14.6 days [9]. On the other hand, Asian studies had the longest HLOS (11.8 days) and the smallest (7.34 days) [9].

Extracorporeal membrane oxygenation (ECMO), preeclampsia, or pregnancy-induced hypertension, and pneumonia

Most people with COVID-19-related acute respiratory distress syndrome were treated with intravenous extracorporeal membrane oxygenation (ECMO) [11]. In the first year of the pandemic, hospital mortality for patients receiving ECMO support for COVID-19 was 37.1 %, comparable to patients with ARDS unrelated to COVID-19 [11]. Death was associated with aging. In selected patients with COVID-19-related ARDS, intravenous ECMO appears to be an effective intervention [11]. In an international cohort study of the Extracorporeal Life Support Organization

registry, for COVID-19 patients who underwent ECMO, the estimated mortality rate after 90 days of ECMO and the mortality rate of patients with final death or discharge was less than 40% [12]. These data from 213 hospitals worldwide provide generalized estimates of ECMO mortality in COVID-19 [12].

On the other hand, pregnant women with preeclampsia or pregnancy-induced hypertension had a higher chance of becoming symptomatic (OR 1.84; 95% CI 1.01 to 3.38; 5 studies, 1465 participants) [8]. It was unclear if this was COVID-19 pneumonitis in one of the two studies reporting on pneumonia [5]. There were no links between the delivery route and severe COVID-19 infection [5].

Chest x-ray and CT scan findings

The study of chest X-ray and computed tomography (CT) findings in pregnant COVID-19 patients revealed aberrant radiation findings on chest X-ray or computed tomography (CT) [7]. Also, bilateral lesions are the most common radiation abnormalities in COVID-19 during pregnancy, accounting for 68% of all cases. In addition, 49% of neonates had chest x-ray results [7].

Laboratory findings

The laboratory findings showed that the average white blood cell count (WBC) for COVID-19 during pregnancy was 8×10^9 per L [7]. Furthermore, pregnant women's white blood cell count fell by 25.5% [7]. The average neutrophil count for COVID-19 during pregnancy in COVID-19 patients was 6.6×10^9 per L [7]. Platelet counts fell in 12.5% of pregnant women [7]. Pregnant women had higher D-dimer levels 3.5 mcg/ml C-reactive protein (CRP) levels were higher in 52% of pregnant women [7].

Treatments and outcomes over time

Antibiotics (36%) are the most used treatment of pregnant COVID-19 patients, followed by oxygen supplements (33%), antivirals (33%), HCQ (10%), anticoagulants (3%), and plasma supplements (2%) [9]. Except for HCQ and corticosteroid use, most treatments have decreased utilization over time [9]. Antibiotics were the most usually observed therapies in Asia (78%), while oxygen support (33%) and HCQ (26%) were the most reported therapeutics in Europe. Antibiotics (12%), HCQ (7%), and oxygen assistance (7%) were all utilized more frequently in US patients than other treatments, despite their low amounts [9]. Compared to other countries, the US research found the least utilization of all treatments except HCQ [9]. European studies reported enormous HCQ and corticosteroid use [9]. Asymptomatic pregnant COVID-19 patients comprised most of the group (89%). Antibiotics, oxygen support, antivirals, steroids, HCQ, zinc/magnesium, plasma treatment, anticoagulants, and immunosuppressants were prescribed in 64 %, 53%, 45%, 44%, 26%, 21%, 14%, 12%, and 10% of the time, respectively [9].

Six studies of (599 women) reported antiviral treatment, (systemic) corticosteroids, antibiotics, and immunotherapy for COVID-19 during pregnancy; however, the types and doses of the drugs were not described [5]. Despite the large denominators, the number of pregnant women exposed to intervention was limited, making a meta-analysis and drawing conclusions about pharmaceutical interventions for the COVID-19 treatment of pregnant women impossible [5]. Non-pharmacological therapies were reported in eleven investigations, with six mechanical ventilation and eight oxygen administration [5]. One thousand seven hundred thirty-eight women were enrolled in these investigations, with 240 receiving interventions, including 28 patients receiving mechanical ventilation and 212 receiving oxygen [5].

Conclusion

This review shows that COVID-19 in pregnant women reveals a potentially high risk of pregnancy complications. On the other hand, COVID-19 should not be associated with the development of preterm birth or the birth weight of a pregnant newborn. Due to the high frequency of preterm births and cesarean sections and the low breastfeeding rate, the severity of maternal illness and fetal dysfunction cannot be fully explained. In addition, the maternal mortality rate of pregnant women infected with COVID-19 was significantly higher than that of pregnant women without this disease. ICU admission, preterm birth, and average HLOS rates are relatively high in pregnant women with COVID-19 worldwide and are estimated to vary by geographic location. Maternal and neonatal COVID-19 infections are associated with various clinical manifestations, but asymptomatic and mild cases are most common in late pregnancy. The incidence of the neonatal disease is low and thought to be independent of the severity of maternal illness. Currently, most approaches to managing suspicious or confirmed COVID-19 mothers and their offspring are based on evidence and expert opinion. During

pregnancy, maternal and perinatal outcomes of COVID-19 are generally good and are not characterized by severe clinical consequences. The rate of preterm birth and cesarean sections appears to be high, but it is unclear how this is related to the clinical course of the disease and whether it is iatrogenic. It has been observed that the use of antibiotics, antivirals, oxygen support, and immunosuppressants has been significantly reduced. Still, these treatments are minimized through risk stratification and careful consideration. They can be further improved by limiting them to maternal and clinical outcomes. Rare but severe complications of infection are recognized in both mothers and newborns. Currently, there is no clear evidence of vertical transmission of COVID-19. Therefore, COVID-19 should not be considered an indicator of an elective cesarean section. SARS-CoV-2 can be vertically transmitted. However, the time of infection (intrauterine, during delivery, and postpartum) and infection rate are unknown.

As shown in this article, interventions and outcomes appear to be related to the severity of the disease. However, the evidence so far is very uncertain. Some reports suggest that vertical transmission of SARS-CoV-2 to newborns is possible, but the evidence remains debatable. Pregnant women with symptoms were more likely to require a maternal ICU and ventilator, and newborns were more likely to be admitted to the ICU. Prospective studies are needed to determine the actual risk of COVID-19 during pregnancy and to define its optimal treatment. In addition, there is little data on pregnant and postnatal females to clarify the risk of vertical transmission and identify factors that may predispose them to develop severe neonatal infections. Therefore, pregnant women should be included in clinical trials.

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