Received: 25 September 2020 | Revised: 16 November 2020 | Accepted: 9 December 2020

DOI: 10.1002/ijgo.13533

REVIEW ARTICLE

Obstetrics

COVID-19 infection in pregnant women: Review of maternal and fetal outcomes

Deemah Salem[1,2] | Fawzi Katranji[3] | Talah Bakdash[4]

[1]Department of Obstetrics and Gynecology, Mohammad Bin Rashid University of Medicine and Health Sciences, Dubai, UAE

[2]Department of Obstetrics and Gynecology, Genesis Healthcare Center, Dubai, UAE

[3]Department of Pulmonary Medicine, Michigan State University School of Osteopathic Medicine, East Lansing, MI, USA

[4]School of Medicine, University of Kansas, Kansas City, KS, USA

***Correspondence**
Deemah Salem, Genesis Healthcare Center, Office 205, Building 49, Dubai Healthcare City, Dubai, United Arab Emirates.
Email: Drdeemah@genesis-dubai.com

Abstract

Pregnant women, their fetuses, and newborns are likely to represent a high-risk population during the current coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Literature on the outcomes of COVID-19 infections during pregnancy is slowly building up. The aim of the present review was to gather evidence from relevant articles published in English from January to August 2020 in Medline and Google Scholar. The review revealed that pregnant women who become COVID-19-positive are usually either asymptomatic or mild-to-moderately symptomatic, similar to non-pregnant women. Pneumonia is one of the most common outcomes in pregnant women with COVID-19. However, it cannot be conclusively said that SARS-CoV-2 infection increases the risk of maternal, fetal, and neonatal complications. Pregnant women with COVID-19 with co-morbidities have increased risks of complications: there are regional variations in the rates of adverse outcomes reported. Though uncommon, the review shows that vertical transmission is possible. Additionally, the third trimester seems to be the most vulnerable period of infection. This aspect needs to be researched further to activate surveillance programs at the end of second trimester. Overall, it is necessary to monitor pregnant women before and after delivery, and their infants, during this pandemic.

KEYWORDS
adverse effects, COVID-19, fetal outcome, hospital admission, maternal outcome, pregnant women, SARS-CoV-2, vertical transmission

1 | INTRODUCTION

In December 2019, a viral outbreak emerged from Wuhan in the Hubei province of China, reportedly being caused by a novel coronavirus. It has now spread worldwide and is one of the most severe public health threats.[1] The virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease was called coronavirus disease 2019 (COVID-19).[1] On March 11, 2020, WHO announced COVID-19 as a "pandemic".[2] Previously, a total of six coronavirus species belonging to the genus Alphacoronavirus (HCoV-229E and HCoV- NL63) and Betacoronavirus (HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome CoV [SARS-CoV], and Middle East respiratory syndrome [MERS-CoV]) were known to infect humans.[3] With the emergence of SARS-Cov-2, there are now seven species of coronavirus infecting humans.[4]

The physiologic and immunologic changes during pregnancy may result in systemic effects that predispose women towards complications from respiratory infections leading to maternal and fetal mortality and morbidity.[5,6] Both SARS-CoV and MERS-CoV were known to be associated with adverse outcomes in pregnant women with greater mortality rates than the general population.[3,7] With SARS-CoV-2 rapidly spreading, it is reasonable to contemplate that pregnant women are likely to get infected.[4]

Worldwide concerns have been raised about the risk of intrauterine transmission of this virus from the mother to the fetus.[8,9] The clinical characteristics and possibility of transmission of COVID-19 in pregnant women vertically or during delivery are still unclear.[8-10]

The questions that require immediate attention include the following: whether the symptoms of the disease in pregnant women with COVID-19 differ from symptoms in non-pregnant women; whether complications of the disease and mortality rate are higher in pregnant women than in non-pregnant women; and whether there is a chance of premature delivery or fetal mortality, or even vertical transmission of the disease.[11,12] Finding answers to these questions are crucial for planning effective obstetrical management for pregnant women with COVID-19.

Given the importance of the issue, the present narrative review collates the literature assessing the effect of COVID-19 infection in pregnancy, including the maternal and fetal outcomes of COVID-19, vertical transmission, as well as the benefits of screening for COVID-19 in pregnant women.

2 | MATERIALS AND METHODS

A detailed literature search was carried out using databases such as Medline and Google Scholar. The following search terms were combined using Boolean operators "AND/OR": "COVID-19"; "SARS-CoV-2"; "Maternal effect"; "Maternal outcome"; "Fetal effect"; "Fetal outcome"; "Vertical transmission"; "Pregnancy outcome"; "Antenatal"; "Perinatal"; and "Screening." Relevant literature reporting both maternal and fetal outcomes of COVID-19 during pregnancy and published in English from January 1, 2020, to August 31, 2020, was retrieved. The retrieved literature was filtered to include only systematic reviews, meta-analyses, clinical trials, retrospective real-world studies, case series, and narrative reviews. No randomized trials were retrieved. Publications covering only maternal or fetal outcomes and those for which full text was not available were not included. In addition, publications covering the treatment and/or management of COVID-19 and/or its outcomes in pregnancy were not included in the narrative review. Of the remaining publications, the authors have tried to present a mix of different types of publications reporting unique data.

3 | TRANSMISSION OF SARS-COV-2

The principal transmission routes for SARS-CoV-2 include droplets and aerosols, mainly through inhalation of respiratory droplets produced by coughing or sneezing by infected persons. Moreover, transmission also occurs via hand to mouth/nose route from infected droplets deposited on different surfaces and objects.[13,14] The virus transmission could potentially occur in individuals at a distance of 1 meter from the infected person.[14]

4 | PREGNANCY AND SUSCEPTIBILITY TOWARDS SARS-COV-2 INFECTION COMPARED TO NON-PREGNANT WOMEN

Pregnancy causes physiological changes in the respiratory and circulatory systems as well as alterations in immunological reactions. These are the primary factors that are likely to make pregnant women more vulnerable to viral infections.[15] The common changes in the respiratory system that are likely to increase the susceptibility of a pregnant woman to respiratory infections include reduced functional residual volumes, elevation of the diaphragm, relaxation of ligaments in the ribs, increased pulmonary hypertension resulting in hyperventilation, and even hypoxic respiratory failure.[15,16] Altered cell immunity increases pregnant women's risk of an immunocompromised state, thereby making them more prone to develop worst outcomes.[15,16] Moreover, viral infection in pregnancy can result in modification of the cardiovascular system, increased metabolic rate and consumption of oxygen, higher pulmonary vascular resistance, and even heart failure.[15] Additionally, during the third trimester of pregnancy, the probability of physical dyspnea is high (due to increased maternal oxygen demands, gestational anemia, and consumption of fetal oxygen) leading to further worsening of breathing difficulties.[16]

It is important to note that pregnant women are susceptible to SARS-CoV-2 infection.[4] However, despite there being many respiratory, circulatory, and immunological factors that could increase a pregnant woman's risk of SARS-CoV-2 infection, the data available so far do not reflect an increased risk. In their literature review, Selim et al. [17] report very small absolute risks of SARS-CoV-2 infection in pregnancy. Also, there is no evidence to date that pregnant women are more susceptible to SARS-CoV-2 infection than non-pregnant women.[17] In general, the unique immunologic changes of pregnancy are thought to suppress the virulence of the virus.[17]

The symptoms of COVID-19 in pregnant women are thought to be due to the direct effect of the virus on the mothers.[17] The disease course of SARS-CoV-2 in pregnant women seems to be either asymptomatic or with mild to moderate symptoms (fever and cough), similar to non-pregnant women.[16,18,19] In pregnant women presenting with severe symptoms (e.g. hypoxia, pneumonia, etc.), enhanced angiotensin-converting enzyme 2 (ACE-2) expression is thought to be linked to severity of symptoms.[17] A recent meta-analysis reported that less than 20% of pregnant women need admission to the intensive care unit (ICU).[20]

In a Chinese study on hospitalized pregnant women with COVID-19, 77% had fever and 23% reported dyspnea. Of these cases, 23% improved with treatment and discharged with ongoing pregnancy, while 46% had preterm labor at 32–36 weeks of pregnancy. Only 7.6% developed severe pneumonia and even multi-organ dysfunction, requiring ICU care and extracorporeal membrane oxygenation.[4] The rate of critical care in pregnant women with COVID-19 was similar to that reported in the general population (7.6% vs 5%).[4]

Chen et al.[21] reported epidemiological, clinical, and laboratory characteristics and outcomes of 118 pregnant women with confirmed

SARS-CoV-2 infection in China. Among them, 92% had mild disease and 8% had severe disease with hypoxemia. The condition of one patient was critical, requiring non-invasive mechanical ventilation, which was continued even after delivery. Six women developed severe disease after delivery; 94% were discharged without any complications and no death was reported.[21] The risk of severe disease among pregnant women was comparable with the risk reported in the general population suffering from COVID-19 across mainland China.[21]

5 | PREGNANCY OUTCOMES IN COVID-19

COVID-19 infection is very new. Data on clinical outcomes of pregnant women suffering from COVID-19 are therefore relatively scarce.[22] Selim et al.[17] report that SARS infection (but not SARS-CoV-2 infection) has been associated with a higher risk for intrauterine growth retardation, premature births, and spontaneous abortion. This is also reflected in a publication that shows that compared to maternal outcomes in SARS-CoV and MERS-CoV infections, the maternal outcomes in SARS-CoV-2 are more favorable, with lower morbidity and mortality, with case fatality rates of 18%, 25%, and 0%, respectively.[16] However, recently a meta-analysis of 13 publications (n = 114) reported preterm births, neonatal pneumonia, and respiratory distress syndrome in infants born of COVID-19-positive mothers.[20] There are also regional variations in the rate of maternal and neonatal complications. A meta-analysis by Dubey et al. [23] reported that the rates of cesarean deliveries and adverse pregnancy outcomes were substantially higher in Chinese studies (91% and 21%) compared to American (40% and 15%) and European studies (38% and 19%). Similarly, the rates of preterm births were lower in American studies (12%) compared to Chinese and European studies (17% and 19%, respectively).

Therefore, since the infection is new, care should be taken to monitor COVID-19-positive pregnant women to prevent adverse maternal and fetal outcomes.

The reported maternal and fetal outcomes in pregnant women infected with COVID-19 are outlined in Table 1.

6 | MATERNAL OUTCOMES IN COVID-19

As more and more data become available, it is becoming clear that maternal complications are common in pregnant women infected with SARS-CoV-2.[20,23] Maternal complications in mothers positive for COVID-19 mostly included pneumonia.[4,24-26] Other reported complications are premature rupture of membranes (PROM), pre-term deliveries, fetal distress, increased cesarean deliveries, lymphopenia, elevated C-reactive protein, gestational hypertension, diabetes, pre-eclampsia, placenta previa, oligohydramnios, polyhydramnios, hypothyroidism, abnormal umbilical cord, and sinus tachycardia.[4,12,20,23,26-31] In the past, SARS infection was found to increase the risk of fetal distress, and gestational diabetes and pre-eclampsia are known to be higher in MERS infection, but no such correlation can be established for SARS-CoV-2.[31] However, morbidity and mortality were found to be quite low in pregnant patients with COVID-19.[11,12,21,24,28,30,32,33] In general, a systematic review of the literature shows that pregnant women positive for COVID-19 with co-morbidities are more likely to develop complications than those without.[34]

6.1 | Pneumonia

Pneumonia is one of the most common outcomes in pregnant women infected with COVID-19.[4,24-26] Severe cases of pneumonia and respiratory conditions requiring ventilation support are one of the main causes of admission to hospital.[4,25,26]

However, a meta-analysis of data from nine publications including 87 pregnant women with SARS-CoV-2 infection concluded that most pregnant women had mild to moderate COVID-19 pneumonia, similar in clinical characteristics to that seen in an adult population.[35]

A retrospective study reported pneumonia among 96.3% of the pregnant patients with confirmed COVID-19, with 3.7% of patients having severe pneumonia.[24] In a case-control study in China, 94% of the pregnant women with confirmed COVID-19 showed typical chest computed tomography (CT) images of COVID-19 pneumonia. However, the majority were asymptomatic upon admission to hospital, and none experienced severe respiratory failure during hospital stay and none died.[26] In another single-center Chinese study, mild pneumonia was diagnosed in all pregnant patients with COVID-19 at the time of admission to hospital for delivery. However, no acute respiratory distress syndrome and aggravation of pneumonia were observed in the whole course.[22] Even though all parturient patients required oxygen support, none required mechanical ventilation and the recovery was good.[22] In their single-center case-control study (n = 55; 13 cases, 42 controls), Yang et al. [36] reported that pregnant women with confirmed SARS-CoV-2 infection did not have expectoration, myalgia, or dyspnea; however, their pulmonary CT scan images resembled COVID-19 pneumonia with ground-glass opacity (46.2%), patch-like shadow (23.1%), pleural effusion (38.5%), and pleural thickening (7.7%). Although the pleural effusion was significantly higher in pregnant women than non-pregnant women, none showed any adverse effects.[36]

In a case series from Iran with nine pregnant women in the second or third trimester, the initial symptoms at the time of presentation in all of them were fever, dry cough, and dyspnea, and three patients later developed COVID-19 pneumonia. Seven women died and two survived: one was critically ill and dependent on a ventilator; and the other was cured after a prolonged hospital stay. Neither of them had pre-existing co-morbidities.[37]

6.2 | Other adverse outcomes of COVID-19 in pregnant women

Reports of worse clinical outcomes in pregnant women with COVID-19, and even death, are also reported from countries outside of

TABLE 1 Pregnancy outcomes in women with COVID-19 seen in various studies

Author and year	Country	Study design	Study population with COVID−19 infection (n)	Maternal effects	Fetal effects
Capobianco et al.,[20] July 2020	China	Systematic review and meta-analysis	13 publications (n = 114) (retrospective studies, cohort study, case series, and case reports)	• Most commonly reported symptoms: fever and cough • Maternal complications pooled prevalence: 45.0% (95% CI 24.0 −67.0) • Admission to ICU: <20% • Preterm infants pooled proportion: 23.0% (95% CI 11.0–39.0)	• Most frequent neonatal complications: pneumonia and respiratory distress syndrome • Infected infants pooled proportion: 6.0% (95% CI 2.0–12.0)
Dubey et al.,[23] July 2020	Global	Systematic review and meta-analysis	61 publications (790 COVID−19-positive women and 548 infants)	• Most common presentations: fever, cough, and dyspnea (not requiring mechanical ventilation) • Lymphopenia: 46% • Elevated CRP: 48% • Cesarean delivery: 72% • Adverse pregnancy outcomes (preterm births and death/stillbirth or early terminated pregnancies): 27%	• Low birth weight: 7% • Neonatal COVID-19 infection: 1%
Elshafeey et al.,[28] April 2020	Global	Systematic review	33 publications (385 COVID−19 positive pregnant women and 256 infants)	• Mild symptoms (95.6%), severe (3.6%), critical (0.8%) • Mechanically ventilated: 1.5% • Maternal mortality: 0.3% • Cesarean delivery: 69.4%	• RT-PCR positive: 1.6% • Neonatal death: 0.4%
Zaigham and Andersson,[29] April 2020	Global	Systematic review of case series and case reports	18 publications (n = 108)	• Most presented at third trimester: 68% • Most presenting symptoms: fever and cough • Lymphocytopenia: 59% • Elevated CRP: 70% • Cesarean delivery: 91% • Admission to ICU: 3 patients	• Intrauterine death: 1 • IUGR: 1
Smith et al.,[30] June 2020	Global	Systematic review	9 publications on COVID−19-positive pregnant women (n = 92)	• Symptomatic: 67.4% • RT-PCR inferior to CT-based diagnosis: 31.7% • Mechanical ventilation and ICU: 1 patient • Maternal mortality: 0% • Caesarean delivery: 80% • Preterm births: 63.8% • Fetal distress: 61.1%	• Admission to NICU: 76.92% • Low birth weight: 42.8%
Trocado et al.,[31] July 2020	China	Systematic review of case series and case reports	8 publications	• Most commonly reported symptoms: fever (55%), cough (38%), and fatigue (11%) • PROM: 5% • Fetal distress: 14% • Postpartum fever: 8%	• Neonatal death: 2% • Severe neonatal asphyxia: 0% • Positive for Sars-CoV-2: 2% • Pneumonia but negative for SARS-CoV-2: 13%

(Continues)

TABLE 1 (Continued)

Author and year	Country	Study design	Study population with COVID−19 infection (n)	Maternal effects	Fetal effects
Li et al.,[26] March 2020	China	Case-control study	16 confirmed, 18 suspected	• Fever and cough at the time of presentation in few patients • Most had COVID-19 pneumonia • None had respiratory failure • All had cesarean delivery apart from 2	• No infant with COVID-19 infection • None developed severe neonatal complications
Chen et al.,[12] February 2020	China	Retrospective study	9	• 7 patients had fever, sore throat, myalgia, and cough • None developed COVID-19 pneumonia • None died	• 9 live births; no neonatal asphyxia • 1 min Apgar score 8–9 and 5-min score 9–10 • No evidence of intrauterine transmission of disease
Liu et al.,[4] March 2020	China	Retrospective study	13	• Cesarean delivery: 77% • Pregnancy complications included preterm delivery (46%), fetal distress (30%), PROM (10%), and stillbirth (10%) • Admission to ICU: 1 patient	• No evidence suggested vertical transmission of disease
Yang et al.,[36] April 2020	China	Retrospective study	13 confirmed	• Mild symptoms with fever and dry cough, no expectoration • Cesarean delivery: 69%: vaginal delivery: 31% • No serious complications or death	• 57 newborns; all tested negative for SARS-CoV-2
Yang et al.,[24] May 2020	China	Retrospective study	27	• Viral pneumonia: 26 • Severe pneumonia after delivery: 1 patient • No maternal deaths • Pre-term delivery due to PROM: 1	• 24 live births, of which 23 were full-term with good Apgar score • 23 newborns tested negative for SARS-CoV-2 infection • 1 newborn had high IgG and IgM levels 2 h after birth but tested negative in repeated RT-PCR
Liu et al.,[22] July 2020	China	Retrospective study	15	• Mild symptoms in all patients with COVID-19 pneumonia • No adverse effects • Cesarean delivery: 67%; vaginal delivery: 7%	• No cases of neonatal death or asphyxia with normal Apgar scores at 1 min and 5 min • No neonates were infected

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID-19, coronavirus disease 2019, CRP, C-reactive protein; ICU, intensive care unit; IgG, immunoglobulin G; IgM, immunoglobulin M; IUGR, intrauterine growth retardation; NICU, neonatal intensive care unit; PROM, premature rupture of membranes; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory symptom coronavirus 2.

China, mainly the United States.[38] In a study from the USA, out of 67.4% patients with symptoms of COVID-19, 15% required antenatal admission. Among them, 9.3% developed severe disease and 4.7% developed critical disease requiring admission to the ICU and oxygen supplementation 6 days postpartum after a successful induction of labor.[7] This was similar to the data for non-pregnant patients with COVID-19 (15% severe and 5% critical).[7] A case series from the USA reported adverse outcomes in 28.5% pregnant patients with COVID-19 including shortness of breath, dyspnea, cardiomyopathy, and moderately reduced left ventricular ejection fractions and hypokinesis, leading to admission to the ICU.[39] However, another case series of pregnant women with confirmed COVID-19 from the U.S.A reported no pregnancy complications or maternal deaths but reported one fetal demise at 14 weeks of gestation.[33] Recently, the U.S. Centers for Disease Control and Prevention (CDC) presented a surveillance report of women (pregnant and non-pregnant) with laboratory-confirmed COVID-19. The pregnant women are found to have a higher probability of hospitalization than non-pregnant women (1.5% vs 0.9%), particularly admission to the ICU for mechanical ventilation (0.5% vs 0.3%). However, the risk of mortality was similar in both groups.[40]

6.3 | Fetal outcomes in pregnant women with COVID-19

Neonatal outcomes of COVID-19 mostly included preterm birth (39%), fetal distress (43%), intrauterine growth retardation (10%), miscarriage (2%), and perinatal death (7%).[16] A systematic review by Yang et al. [8] reported the following adverse fetal and neonatal outcomes of COVID-19: preterm birth (21.3%); fetal distress (10.7%); stillbirth (1.2%); neonatal death (1.2%); and neonatal asphyxia (1.2%). Other studies reported 46%, 44.4%, 33.3%, 23.5%, 21%, and 4% cases of preterm delivery.[4,12,21,25,26,36] In contrast, a case series reported full-term delivery in 100% of patients with COVID-19.[41] Fetal distress and PROM were reported in 22.2% of cases in a review,[42] and neonatal distress in 5.3% cases of a single-center study from China.[36] Two other studies respectively mentioned fetal distress in 30% and 19% as well as PROM in 10% and 13% of patients with confirmed COVID-19.[4,26] Chen et al. [21] reported the incidence of abortions (spontaneous and induced) among 6% of pregnant women with COVID-19 infection. The current data do not suggest a high risk of abortion or premature gestational loss, amniotic fluid abnormality, cyanosis, and congenital defects in neonates in mothers infected with COVID-19.[11]

7 | CHANCES OF INTRAUTERINE VERTICAL TRANSMISSION OF SARS-COV-2 INFECTION

The risk of vertical transmission can theoretically exist in COVID-19 since angiotensin-converting enzyme 2 (ACE-2) receptors are significantly expressed in the placenta with which SARS-CoV-2 may bind and enter. Intrauterine vertical transmission may typically occur through trans-placenta, or ingestion or aspiration of cervicovaginal secretions.[32,43] Multiple studies confirmed the absence of SARS-CoV-2 isolates in the amniotic fluid, cord blood, breast milk sample, and neonatal throat swabs of the infected mother, indicating that intrauterine transmission, transmission during vaginal delivery, or through lactation was not possible.[11,12,16,32,42] In the majority of the cases, the infected women gave birth to healthy babies with an Apgar score above 7 and negative reverse transcription polymerase chain reaction (RT-PCR) test results.[11,22,32] Furthermore, the placental pathology of three pregnant patients with COVID-19 showed no morphological changes linked with the infection; all three placentas tested negative to RT-PCR and there was no maternal-fetal transmission.[44] However, a systematic review and meta-analysis of the available data provide no conclusive evidence of vertical transmisison of SARS-CoV-2 to date, except for a small risk in the third trimester.[45] Therefore, actual risk of intrauterine vertical transmission can only be ascertained through RT-PCR tests on amniotic fluid, placenta, and cord blood.[45]

7.1 | Benefits of screening of pregnant women during COVID-19 pandemic

The diagnosis of COVID-19 is based on comprehensive contact, travel history, and precise laboratory tests. According to WHO recommendations, RT-PCR testing of samples from the respiratory tract should be performed for the identification and laboratory confirmation of cases of COVID-19.[14] Moreover, WHO has suggested the use of antibody-detecting rapid tests for surveillance of the disease rather than for patient care.[14]

SARS-CoV-2 is highly contagious and can spread from both symptomatic and pre-symptomatic patients.[14] A high proportion of pre-symptomatic patients with COVID-19 exist worldwide.[7] Due to a large number of pre-symptomatic pregnant patients with COVID-19, universal screening of pregnant women and implementing strict infection control measures to manage suspected or confirmed patients are essential to provide safety to both mothers and neonates as well as healthcare workers.[40] According to the guidelines of the American College of Obstetricians and Gynecologists (ACOG) and the Royal College of Obstetricians and Gynaecologists (RCOG), every pregnant woman is at high risk and should take preventive measures including wearing masks, washing hands, and strictly maintaining social distancing when interacting with others.[46,47]

ACOG and RCOG guidelines stated that COVID-19 testing is critical for pregnant women to prevent transmission of the disease.[46,47] All pregnant women admitted to the hospital for maternity care should be asked for SARS-CoV-2 testing, irrespective of whether they have symptoms. For women who tested negative on admission, repeat testing should be offered 5–7 days later if they remain as inpatients.[46] Pregnant women with suspected COVID-19 or with symptoms suggestive of COVID-19 should be tested on priority.[47]

Moreover, for pregnant women from areas of high prevalence, universal testing is strongly recommended due to an increased probability of presentation of asymptomatic patients to labor and delivery units from these areas.[47] It is important to note that RT-PCR is often not able to detect SARS-CoV-2 infection and therefore some pregnant women with COVID-19 pneumonia may be missed unless a CT scan is performed.[30]

8 | STRENGTHS AND LIMITATIONS

The present narrative review has several limitations. Most of the studies included in the systematic reviews and meta-analyses are from China. Thus, there is regional bias due to genetic and environmental factors and the level of medical care available in China. The majority of the literature is case reports, case series, or retrospective studies where the methodology is poor, and the evidence cannot be considered high level. There are very few case-control studies and no large randomized trials comparing pregnant women positive for COVID-19 with matched pregnant women without COVID-19 infection. Additionally, like most narrative reviews, the present review also has a selection bias.

However, the present narrative review does highlight the fact that COVID-19 infection occurs in pregnant women and can be associated with poor maternal and fetal outcomes. Neonates born of pregnant women with COVID-19 can get infected and therefore vertical transmission is possible. Additionally, RT-PCR may not be a conclusive test to diagnose SARS-CoV-2 infection in pregnant women as some pregnant women with CT-confirmed COVID-19 infection are RT-PCR negative. The present review also highlights that the majority of pregnant women get infected in the third trimester.

9 | CONCLUSION

There is currently limited knowledge about SARS-CoV-2 infections in pregnancy. Based on the available data, the clinical characteristics of pregnant women with COVID-19 seem to resemble those of non-pregnant women. It cannot be conclusively said that SARS-CoV-2 infection increases the risk of maternal, fetal, and neonatal complications. Increased risks of maternal, fetal, and neonatal complications are noted in pregnant women positive for COVID-19 with co-morbidities. There are regional variations in the rates of adverse outcomes reported. Though vertical transmission is noted in very few cases, the review shows that it is possible. Additionally, the third trimester seems to be the most vulnerable period of infection and this aspect needs to be researched further to activate surveillance programs at the end of the second trimester. Further studies are warranted to assess whether the higher rates of adverse outcomes reported in mothers with COVID-19 with co-morbidities are due to the co-morbidities or whether the SARS-CoV-2 infection worsens the disease course in these mothers. Multicenter global trials are required to look into the reasons for regional variations and understand why some regions report very few adverse outcomes. This would be helpful in developing a screening, diagnostic, and management algorithm to reduce adverse outcomes in mothers with COVID-19.

ACKNOWLEDGMENTS

TheauthorsacknowledgeTuracozHealthcareSolutions(www.turacoz.com) for assistance with the manuscript writing.

AUTHOR CONTRIBUTIONS

DS was responsible for the design, planning, and writing of the manuscript. FK and TB were responsible for the literature data analysis for the review.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

ORCID

Deemah Salem https://orcid.org/0000-0002-7986-1780

REFERENCES

1. Rasmussen SA, Smulian JC, Lednicky JA, et al. (COVID-19) and pregnancy: what obstetricians need to know. *Am J Obstet Gynecol*. 2019;2020:13.
2. WHO Director-General's opening remarks at the Mission briefing on COVID-19 - 12 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-mission-briefing-on-covid-19---12-march-2020. Accessed 29 May 2020.
3. Della Gatta AN, Rizzo R, Pilu G, et al. Coronavirus disease 2019 during pregnancy: a systematic review of reported cases. *Am J Obstet Gynecol*. 2020:1-7.
4. Liu Y, Chen H, Tang K, et al. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. *J Infect*. 2020.
5. Da S. An analysis of 38 pregnant women with 2 COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. *Arch Pathol Lab Med*. 2020:1-25.
6. Mascio DD, Khalil A, Saccone G, et al. Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1–19) during pregnancy: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020.
7. Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. *Am J Obstet Gynecol*. 2020.
8. Yang Z, Wang M, Zhu Z, et al. Coronavirus disease 2019 (COVID-19) and pregnancy: a systematic review. *J Matern Fetal Neonatal Med*. 2020:1-4.
9. Kotlyar AM, Grechukhina O, Chen A, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020.
10. Walker KF, O'Donoghue K, Grace N, et al. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: a systematic review and critical analysis. *BJOG: An Int J Obstet Gynaecol*. 2020;127(11):1324-1336.
11. Panahi L, Amiri M,Pouy S. Risks of novel coronavirus disease (COVID-19) in pregnancy; a narrative review. *Arch Acad Emerg Mede*. 2020;8(1):1-5.
12. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine

pregnant women: a retrospective review of medical records. *The Lancet*. 2020;395(10226):809-815.
13. Lu Q,Shi Y. Coronavirus disease (COVID-19) and neonate: What neonatologist need to know. *J Med Virol*. 2020;92:564-567.
14. World Health Organization Q&A on coronaviruses (COVID-19)- April 12, 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses. Accessed on July 2020. In: WHO, editor.
15. Zhao X, Jiang Y, Zhao Y, et al. Analysis of the susceptibility to COVID-19 in pregnancy and recommendations on potential drug screening. *Eur J Clin Microbiol Infect Dis*. 2020;39(7):1209-1220.
16. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol*. 2020;222(6):521-531.
17. Selim M, Mohamed S, Abdo M, Abdelhaffez A. Is COVID-19 similar in pregnant and non-pregnant women? *Cureus*. 2020;12(6):e8888.
18. Matar R, Alrahmani L, Monzer N, et al. Clinical presentation and outcomes of pregnant women with COVID-19: a systematic review and meta-analysis. *Clin Infect Dis*. 2020.
19. Hirshberg JS, Stout MJ, Raghuraman N. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. *Am J Obstet Gynecol Mfm*. 2020;2(3).
20. Capobianco G, Saderi L, Aliberti S, et al. COVID-19 in pregnant women: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2020;252:543-558.
21. Chen L, Li Q, Zheng D, et al. Clinical characteristics of pregnant women with Covid-19 in Wuhan, China. *N Engl J Med*. 2020;382(25):e100.
22. Liu D, Li L, Wu X, et al. Pregnancy and perinatal outcomes of women with coronavirus disease (COVID-19) pneumonia: a preliminary analysis. *AJR*. 2020;215:1-6.
23. Dubey P, Reddy SY, Manuel S, Dwivedi AK. Maternal and neonatal characteristics and outcomes among COVID-19 infected women: an updated systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2020;252:490-501.
24. Yang H, Hu B, Zhan S, et al. Effects of SARS-CoV-2 infection on pregnant women and their infants: a retrospective study in Wuhan, China. *Arch Pathol Lab Med*. 2020.
25. Khan S, Peng L, Siddique R, et al. Impact of COVID-19 infection on pregnancy outcomes and the risk of maternal-to-neonatal intrapartum transmission of COVID-19 during natural birth. *Infect Control Hosp Epidemiol*. 2020;1-3.
26. Li N, Han L, Peng M, et al. Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study. *Clin Infect Dis*. 2020;71(16):2035-2041.
27. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. *Pediatr Infect Dis J*. 2020;39(6):469-477.
28. Elshafeey F, Magdi R, Hindi N, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. *Int J Gynecol Obstet*. 2020;150(1):47-52.
29. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: a systematic review of 108 pregnancies. *Acta Obstet Gynecol Scand*. 2020;99(7):823-829.
30. Smith V, Seo D, Warty R, et al. Maternal and neonatal outcomes associated with COVID-19 infection: a systematic review. *PLoS One*. 2020;15(6):e0234187.
31. Trocado V, Silvestre-Machado J, Azevedo L, Miranda A, Nogueira-Silva C. Pregnancy and COVID-19: a systematic review of maternal, obstetric and neonatal outcomes. *J Maternal-Fetal Neonatal Med*. 2020;1-13.
32. Fan C, Lei D, Fang C, et al. Perinatal transmission of COVID-19 associated SARS-CoV-2: should we worry? *Clin Infect Dis*. 2020.
33. Fox NS, Melka S. COVID-19 in pregnant women: case series from one large New York City obstetrical practice. *Am J perinatol*. 2020;37(10):1002-1004.
34. Hessami K, Homayoon N, Hashemi A, Vafaei H, Kasraeian M, Asadi N. COVID-19 and maternal, fetal and neonatal mortality: a systematic review. *J Matern Fetal Neonatal Med*. 2020;1-6.
35. Kasraeian M, Zare M, Vafaei H, et al. COVID-19 pneumonia and pregnancy; a systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. 2020;1-8.
36. Yang H, Sun G, Tang F, et al. Clinical features and outcomes of pregnant women suspected of coronavirus disease 2019. *J Infect*. 2020;16(3):1-5.
37. Hantoushzadeh S, Shamshirsaz AS, Aleyasin A, et al. Maternal death due to COVID-19 disease. *Am J Obstet Gynecol*. 2020;223(1):109.e1-109.e16.
38. Da S. The effects of pregnancy on women with COVID-19: maternal and infant outcomes. *Clin Infect Dis*. 2020;71(16):2042-2044.
39. Juusela A, Nazir M, Martin G. Two cases of COVID-19 related cardiomyopathy in pregnancy. *Am J Obstet Gynecol MFM*. 2020;2(2):100113.
40. Ellington S, Strud P, Tong VT, et al.Morbidity and Mortality Weekly Report (MMWR). In: Prevention CfDCa, editor. CDC; 2020:769-75.
41. Chen Y, Peng H, Wang L, et al. Infants born to mothers with a new coronavirus (COVID-19). *Front Pediatr*. 2020;1-5.
42. Karimi-Zarchi M, Neamatzadeh H, Dastgheib SA, et al. Vertical transmission of coronavirus disease 19 (COVID-19) from infected pregnant mothers to neonates. A review. *Fetal and Pediatr Pathol*. 2020.
43. Alzamora MC, Paredes T, Caceres D, et al. Severe COVID-19 during pregnancy and possible vertical transmission. *Am J Perinatol*. 2020.
44. Chen S, Huang B, Luo DJ, et al. Pregnancy with new coronavirus infection: clinical characteristics and placental pathological analysis of three cases. *Zhonghua Bing Li Xue Za Zhi*. 2020;49(5):418-423.
45. Yang Z, Liu Y. Vertical transmission of severe acute respiratory syndrome Coronavirus 2: a systematic review. *Am J Perinatol*. 2020;37(10):1055-1060.
46. (RCOG) RCoOaG. Coronavirus (COVID-19) Infection in Pregnancy June 2020. https://www.rcog.org.uk/coronavirus-pregnancy. Accessed 25 August 2020.
47. (ACOG) TACoOaG. Novel Coronavirus 2019 (COVID-19) July 2020. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/03/novel-coronavirus-2019. Accessed 25 August 2020.

How to cite this article: Salem D, Katranji F, Bakdash T. COVID-19 infection in pregnant women: Review of maternal and fetal outcomes. *Int J Gynecol Obstet*. 2021;152:291–298. https://doi.org/10.1002/ijgo.13533