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REVIEW ARTICLE

Obstetrics

Consequences and implications of the coronavirus disease (COVID-19) on pregnancy and newborns: A comprehensive systematic review and meta-analysis

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Abstract

Background: Pregnant patients are potentially vulnerable to COVID-19.

Objectives: To clarify the clinical features of COVID-19 and analyze maternal/fetal morbidity and mortality and the obstetric and neonatal outcomes of pregnant patients.

Search strategy: Embase, PubMed, Web of Science, CINAHAL, LILACS, Google Scholar, and Scopus.

Selection criteria: Articles published from December 2019 to February 2021.

Data collection and analysis: The reviewers extracted relevant data from the full-text. Data synthesis was performed using the R-4.1.0 Project for Statistical Computing for Windows. The meta-analysis of the included studies was carried out using the random-effects model (DerSimonian and Laird). Heterogeneity was measured using I^2 analysis.

Results: A total of 70 studies included 10 047 pregnant women with COVID-19, of whom 71.6% were in their third trimester. The most common symptoms were fever, cough, chest pain, dyspnea, and fatigue. Most newborns were delivered preterm (24%, 95% confidence interval [CI] 0.17–0.34, $I^2 = 93\%$) and via cesarean delivery (42%, 95% CI 0.38–0.47, $I^2 = 92\%$). There were 108 maternal mortalities (2%, 95% CI 0.01–0.03, $I^2 = 54\%$) and 50 abortions (5%, 95% CI 0.03–0.09, $I^2 = 73\%$). The neonatal outcomes included fetal distress (11%, 95% CI 0.06–0.19, $I^2 = 91\%$), birth weight (15%, 95% CI 0.10–0.21, $I^2 = 76\%$), APGAR <7 (19%, 95% CI 0.12–0.28, $I^2 = 43\%$), admission to the neonatal intensive care unit (28%, 95% CI 0.17–0.43, $I^2 = 90\%$), and fetal mortality (2%, 95% CI 0.01–0.03, $I^2 = 46\%$).

Conclusion: There was no evidence of severe acute respiratory syndrome coronavirus-2 in the placenta, breast milk, umbilical cord, and amniotic fluid of pregnant patients.

PROSPERO registration number: CRD42020181519.

KEYWORDS
coronavirus disease 2019, COVID-19, obstetrics, pregnancy

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) has spread worldwide, becoming one of humanity's most critical public health challenges. The disease is transmitted from person to person and its presentation may range from a common cold to severe respiratory disease, ultimately leading to death.[1–4]

It is recognized that symptoms become more aggressive and fatal in more vulnerable patients, including the elderly, patients with chronic diseases, patients on immunosuppression treatment, and pregnant women.[3,4]

Pregnant patients are potentially vulnerable to COVID-19. Among the other physiological adaptations during pregnancy, decreased functional residual capacity and changes in cellular immunity can increase the risk of serious illness in response to viral infections and the potential harm of vertical transmission.[3,4] Additionally, maternal organism adaptations predispose pregnant women to a more severe course of pneumonia, subsequently leading to higher maternal and fetal morbidity and mortality.[5]

Vertical transmission is no longer controversial as previous studies have revealed the absence of the virus in the placenta and newborns from pregnant women with COVID-19.[6–8] However, some studies have confirmed vertical transmission in a minority of cases during the third trimester, though these were associated with other congenital infections.[2]

Analyses of serum samples from newborns whose mothers were seropositive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) showed that most newborns acquired IgG antibodies against the virus, indicating a transplacental transfer of these antibodies and neonatal protection from the disease.[9]

Pregnant women with symptomatic SARS-CoV-2 infection, mainly those with a severe course, are more likely to exhibit an adverse fetal outcome, with slightly more frequent histopathologic findings (low placental weight, accelerated villous maturation, decidual vasculopathy, infarcts, thrombosis of fetal placental vessels, and chronic histiocytic intervillositis) of maternal and fetal vascular malperfusion.[10] In addition, several studies have suggested the importance of thromboembolic factors in the pathogenesis of COVID-19 infection.[11,12]

Furthermore, the third trimester's physiological prothrombotic state could increase critical outcomes, such as placental abruption and placental insufficiency. Furthermore, due to insufficient information, the course of the disease is not entirely known.

Some systematic reviews and meta-analyses have already been published.[13–15] However, to date, there has been insufficient evidence to support the latter studies. As evidence has been accumulating rapidly, these data need to be updated.

Additionally, scientific information concerning COVID-19 in pregnant women must be shared concisely and practically. The aim of the present systematic review was to clarify the clinical features of COVID-19 and analyze maternal/fetal morbidity and mortality, as well as obstetric and neonatal outcomes, of pregnant patients with COVID-19.

2 | MATERIALS AND METHODS

The present systematic review and meta-analysis was designed and reported according to the Meta-analyses of Observational Studies in Epidemiology Checklist[16] and PRISMA[17] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[18] Since this study was based on previously published studies, no ethical approval or patient consent was required.

The protocol of the present study had been previously published[1] and registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42020181519).

The search of bibliographic databases and gray literature was based on the guidelines designed for systematic review and meta-analyses under the supervision of an experienced librarian (DMSS - UFRN, Natal, Brazil). The literature searches were conducted in the following electronic databases: PubMed, Web of Science, Embase, Cumulative Index to Nursing and Allied Health, Latin American and Caribbean Health Sciences Literature, ClinicalTrials.gov, SCOPUS, Google Scholar, and the Cochrane Central Controlled Trials Registry. Articles published from December 2019 to February 2021 were included. The main search was performed in PubMed using the Medical Subject Headings (MeSH) terms and equivalent keywords and phrases. The MeSH terms were evaluated for accordance, and the final search was conducted on February 5, 2021. These MeSH terms were then converted into EMBASE on February 13, 2021, CINAHL on February 14, 2021, and SCOPUS on February 15, 2021. The keyword details and the complete search strategy used are provided in Appendix 1.

The maternal, obstetric, and perinatal outcomes were extracted. Specifically, the maternal outcomes included the clinical features (signs and symptoms), laboratory and imaging examinations, mortality and morbidity, complications, and treatment (respiratory support and admission to the intensive care unit [ICU]). The obstetric outcomes included the rates of operative vaginal delivery and cesarean delivery stratified by indication. The perinatal outcomes included the clinical features (APGAR scores, birth weights, complications, signs of vertical transmission, and breast milk positivity for SARS-CoV-2) and treatment.

Two authors (KSM and ACAS) independently reviewed all abstracts to minimize the effects of information bias. Agreement regarding potential relevance or inconsistencies was reached by consensus or resolved by discussion with a third reviewer (APFC).

The same reviewers independently extracted relevant data from the full-text copies of relevant articles, compared findings, and resolved inconsistencies by discussing them with the third reviewer. Data synthesis was performed using the R-4.1.0 Project for Statistical Computing for Windows (R Foundation, Vienna, Austria). The quantitative synthesis (meta-analysis) of the included studies was carried out using the random-effects model (DerSimonian and Laird, assuming that the analyzed data were drawn from a hierarchy of different populations). Owing to the small number of cases and outcomes explored, univariate comparisons of dichotomous data

were performed using the Peto method. Heterogeneity was measured using I^2 analysis (Higgins I^2).

2.1 | Study selection

For the selection of the papers, the following inclusion criteria were defined: articles focused on pregnancy and perinatal outcomes of COVID-19; articles with observational designs (control case and cohort); studies that described pregnant women with COVID-19; and studies published since December 2019. There were no language restrictions. Studies regarding other viruses in the coronavirus family (i.e. severe acute respiratory syndrome coronavirus-1, Middle East respiratory syndrome) were excluded.

Three authors, KSM, ACAS and APFC, screened the search results using the titles and abstracts. The articles were included in Google Sheets. Duplicates and reviews were removed from the database. The same authors reviewed the full text to determine whether the studies met the inclusion criteria. The fourth reviewer, AKG, resolved any discrepancies. The selection of studies is summarized in a PRISMA flow diagram (Figure 1).

3 | RESULTS

3.1 | Study selection

Database searches identified 2138 articles (Figure 1). From these initial articles, 158 were excluded due to duplication, 1887 were excluded after reviewing their titles and abstracts, and 23 were excluded because these did not meet the eligibility criteria. Case reports and case series were excluded from the study. Ultimately, 70 studies met the eligibility criteria and were included in the final review (Table 1).

3.2 | Study characteristics

The 70 articles identified included 10 047 pregnancies with laboratory-confirmed COVID-19 from December 11, 2019, to February 1, 2021. Of these, there were 23 in the United States, 10 in China, seven in Italy, six in Spain, four each in Turkey and Iran, two each in the United Kingdom, France, Mexico, and Israel, and one each in Russia, Chile, Canada, Nepal, Singapore, and Kuwait.

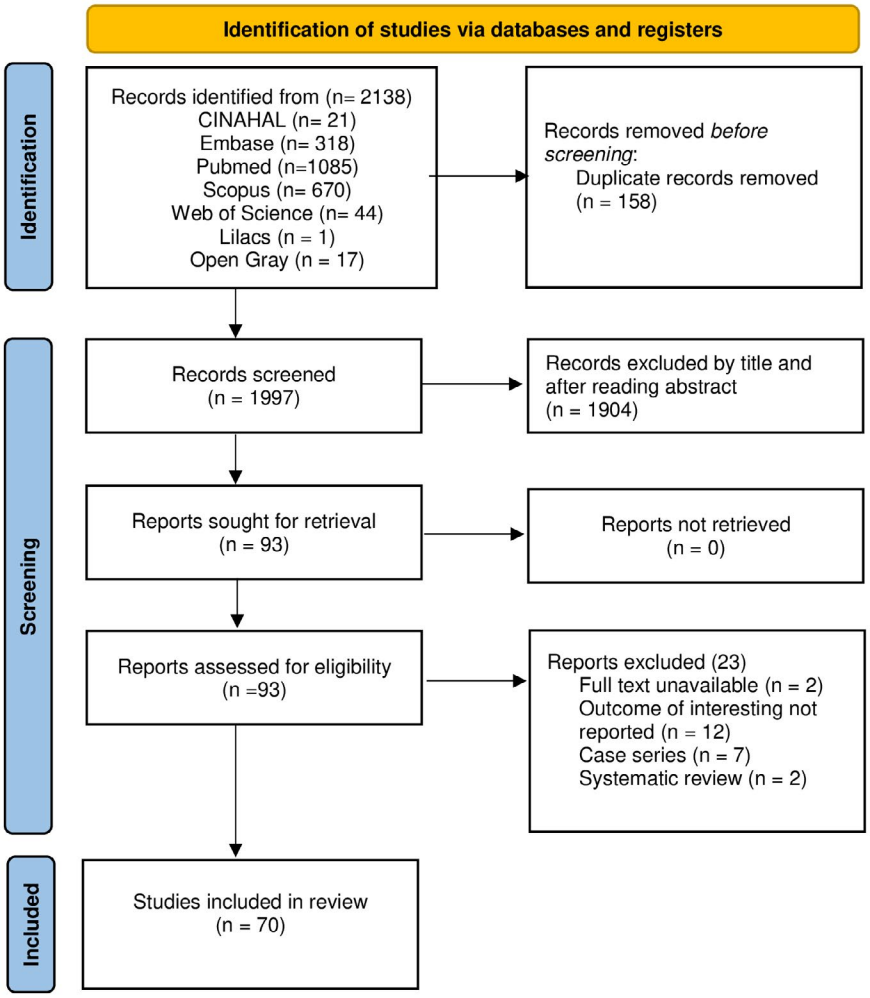


FIGURE 1 PRISMA flow diagram

TABLE 1 Characteristics of the studies included in the systematic review

Author/Year	Country	Study design	Sample (n)	Mean age (years)	Gestational age (weeks)	Diagnostic methods
Sahin (2020)	Turkey	Cohort	100	26.38	37.7	RT-PCR and CT
Sun (2020)	China	Case-control	60	30.97	37.87	RT-PCR
Farghaly et al. (2020)	USA	Cohort	79	30.81	38.03	CXR, head ultrasound, MRI and EEG
Grechukhina et al. (2020)	USA	Cohort	141	30	35	RT-PCR
McLaren Jr et al. (2020)	USA	Cohort	125	31.83	30.93	RT-PCR
Bertino et al. (2020)	Italy	Cohort	14	31.36	NA	RT-PCR
Ashish et al. (2020)	Nepal	Cohort	907	24.3	NA	NA
Gulersen et al. (2020)	USA	Cohort	100	30	39.3	RT-PCR
Popofsky et al. (2020)	USA	Cohort	160	30.8	38.8	RT-PCR
MohrSasson et al. (2020)	Israel	Cohort	26	34	36.4	RT-PCR
Pirjani et al. (2020)	Iran	Cohort	43	29.85	32.64	RT-PCR and CT
Cuñarro-López et al. (2020)	Spain	Cohort	111	27.1	28.6	RT-PCR
WAPM (2021)	Multicenter	Cohort	388	32.2	30.6	RT-PCR
Yassa et al. (2020)	Turkey	Cohort	296	26.8	35.18	RT-PCR and lung ultrasound
Prabhu et al. (2020)	USA	Cohort	70	27.6	39	RT-PCR
Pineles et al. (2020)	USA	Cohort	935	35	≥20	RT-PCR
Di Mascio et al. (2020)	Italy	Cohort	388	34.1	30.6	RT-PCR
Sakowicz et al. (2020)	USA	Cohort	1418	30.6	NA	RT-PCR
Cour Freiesleben et al. (2020)	Multicenter	Cohort	1055	32.96	13	IgM and IgG
Nuray et al. (2020)	Turkey	Case-control	187	29	NA	RT-PCR
Shmakov et al. (2020)	Russia	Cohort	66	30.3	31.3	Blood test and CT
Ensiyeh et al. (2020)	Iran	Case-control	45	29.47	37.13	RT-PCR
Brandt et al. (2020)	USA	Case-control	61	30.3	41	RT-PCR
Cosma et al. (2020)	Italy	Case-control	225	35.5	11–13	RT-PCR and IgG and IgM
Moreno et al. (2020)	USA	Cohort	37	31.7	37.2	RT-PCR
DeBolt et al. (2020)	USA	Case-control	38	34.7	NA	RT-PCR
Trahan et al. (2020)	Canada	Cohort	41	29.4	≥37	RT-PCR
Hu et al. (2020)	China	Cohort	6	30.3	28–36	RT-PCR and chest CT
Na Li et al. (2020)	China	Case-Control	29	30.9	38	Chest CT and RT-PCR
Adhikari et al. (2020)	USA	Cohort	3280	27.6	37	RT-PCR
Maraschini et al. (2020)	Italy	Cohort	146	32	NA	RT-PCR and CXR or CT
Ríos-Silva et al. (2020)	Mexico	Cohort	1664	33	NA	RT-PCR
Badr et al. (2020)	France, Belgium	Cohort	107	34.17	≤20	RT-PCR
Bender (2020)	USA	Cohort	318	30.1	39.14	RT-PCR
Maru (2020)	USA	Cohort	124	30.2	35	RT-PCR
Barbero et al. (2020)	Spain	Cohort	91	23	28	RT-PCR and CXR
Blitz et al. (2020)	USA	Cohort	382	32.9	39.2	RT-PCR
Gabriel et al. (2020)	Spain	Cohort	7	33.4	40.1	RT-PCR
Goldfarb et al. (2020)	Spain	Cohort	136	32	23	RT-PCR
He et al. (2020)	USA	Case-control	21	30	33–40	RT-PCR
Khoury et al. (2020)	USA	Cohort	241	32	NA	RT-PCR
Knight et al. (2020)	UK	Cohort	427	35	29–38	RT-PCR and CXR
Liu et al. (2020)	China	Case-control	30	31	37	RT-PCR and CT
London et al. (2020)	USA	Cohort	68	30	25–26	RT-PCR

(Continues)

TABLE 1 (Continued)

Author/Year	Country	Study design	Sample (n)	Mean age (years)	Gestational age (weeks)	Diagnostic methods
Lucarelli et al. (2020)	USA	Cohort	3	NA	26.67	RT-PCR, CXR, and CT
Martínez-Perez et al. (2020)	Spain	Cohort	82	36	NA	RT-PCR
Oncel et al. (2020)	Turkey	Cohort	125	35	NA	RT-PCR
Pariente et al. (2020)	Israel	Cohort	346	29.1	29.1	NA
Pierce-Williams et al. (2020)	USA	Cohort	64	33	29.9	Bronchoalveolar lavage and RT-PCR
Qiancheng et al. (2020)	China	Cohort	82	30	38	RT-PCR
San-Juan et al. (2020)	Spain	Cohort	52	32	NA	RT-PCR, CXR, and CT
Sattari et al. (2020)	Iran	Cohort	50	29.2	NA	NA
Savasi et al. (2020)	Italy	Cohort	77	30	27.75	RT-PCR
Schwartz et al. (2020)	Iran	Cohort	19	30	NA	RT-PCR
Wu et al. (2020)	China	Cohort	13	30	38	RT-PCR and CT
Xu et al. (2020)	China	Cohort	64	30	>28	RT-PCR
Zeng et al. (2020)	China	Cohort	33	NA	31–40	RT-PCR
Buonsenso et al. (2020)	Italy	Cohort	2	40	36.5	RT-PCR
Verma et al. (2020)	USA	Cohort	149	31.4	<37	RT-PCR
Popofsky et al. (2020)	USA	Cohort	85	30.8	38.8	RT-PCR
Mattar (2020)	Singapore	Cohort	16	29.7	36	RT-PCR
Ayed (2020)	Kuwait	Cohort	185	31	29	RT-PCR
Fenizia (2020)	Italy	Cohort	31	30	32	RT-PCR and IgG and IgM
Rojas (2020)	Chile	Cohort	9	30	33	RT-PCR
Griffin (2020)	USA	Cohort	78	NA	39	RT-PCR
Knight (2020)	UK	Cohort	427	30	34	RT-PCR and CT
Zhang (2020)	China	Case-control	4	29.3	NA	RT-PCR and CT
Hcini (2020)	France	Cohort	507	25	37	RT-PCR
Martinez-Portilla (2021)	Mexico	Cohort	5183	28.5	NA	RT-PCR
Wang (2020)	China	Cohort	72	31	NA	RT-PCR

Abbreviations: CT, computed tomography; CXR, chest radiography; MRI, magnetic resonance imaging; NA, not applicable; RT-PCR, transcriptase-polymerase chain reaction.

Furthermore, there were two multicenter studies. Of the articles, 60 were cohort studies, while 10 were case-control studies. Most studies described the clinical course of COVID-19, laboratory trends, and pregnancy and neonatal outcomes. The mean age of the study participants was 31.3 years. Although chest radiography and computed tomography (CT) were performed, the gold method for detecting SARV-COV-2 was reverse transcriptase-polymerase chain reaction (RT-PCR, SARS-CoV-2 nasopharyngeal swab testing) (63 of 70 articles, 90%). The characteristics of the included studies are summarized in Table 1.

3.3 | Risk of bias of the included studies

Among the included papers, the risk of bias assessment showed that 12 (17%) studies fulfilled all the items in the Newcastle-Ottawa Scale and were therefore considered excellent. Meanwhile, 32 (45.7%) were good, 21 (30%) were fair, and 5 (7.1%) were poor.

3.4 | Assessment of quality

The quality of the 70 included documents was evaluated according to Grading of Recommendations Assessment, Development, and Evaluation. Of them, 17 (38%) were of a very low quality, while 27 (38.5%) and 22 (31.4%) were graded as low- and middle-quality, respectively. Only 4 (5.7%) articles were graded high-quality. These articles were considered low-quality because these were all observational studies with few cases and without control groups, interventions, or blind methods. The literature quality assessments are presented in Table 2.

3.5 | Maternal outcomes

3.5.1 | Clinical characteristics

The clinical features of the pregnant women with COVID-19 are shown in Figure 2. All pregnant women were hospitalized during the course of delivery and treatment. The most common symptoms were fever on admission (42%, 95% confidence interval [CI] 0.35–0.50, I^2 = 86%), followed by cough (52%, 95% CI 0.42–0.63, I^2 = 88%) and fatigue (29%, 95% CI 0.20–0.40, I^2 = 75%). Other symptoms were presented in a pooled proportion of less than 25%, including dyspnea (26%, 95% CI 0.16–0.38, I^2 = 87), myalgia (21%, 95% CI 0.12–0.33, I^2 = 88%), tachycardia (19%, 95% CI 0.10–0.31, I^2 = 73%), and desaturation (18%, 95% CI 0.10–0.30, I^2 = 83%). Other symptoms were also observed, including tachypnea, diarrhea, nausea or vomiting, headache, ageusia, anosmia, sore throat, and chest pain. However, some pregnant women were asymptomatic in some studies (Figure 2).

Most infants were delivered via cesarean delivery (42%, 95% CI 0.36–0.47, I^2 = 92%). Oxygen therapy (nasal cannula, face mask, intubation, and mechanical ventilation or extracorporeal machine oxygenation) was used in 501 patients (19%, 95% CI 0.10–0.32, I^2 = 95%). Specifically, four patients required extracorporeal machine oxygenation because of multiorgan failure. Pre-eclampsia was present in 85 patients (6%, 95% CI 0.04–0.09, I^2 = 62%). A total of 108 pregnant patients died (2%, 95% CI 0.01–0.03, I^2 = 54%) and 50 patients experienced miscarriage (5%, 95% CI 0.03–0.09, I^2 = 46%). The most common complications during pregnancy were pneumonia (65%, 95% CI 0.64–0.66, I^2 = 97%), admission to the ICU (8% 95% CI 0.05–0.15, I^2 = 92%), and preterm delivery (15%, 95% CI 0.11–0.21, I^2 = 73%) (Figure 2).

3.6 | Laboratory and radiological findings

Lymphocytopenia was present in 265 patients, with a pooled proportion of 25% (95% CI 0.15–0.38, I^2 = 92%). More than one-third of the pregnant women had elevated concentrations of C-reactive protein (CRP; >10 mg/L) (43%, 95% CI 0.34–0.51, I^2 = 84%). Another important finding was the elevated levels of D-dimer (45%, 95% CI 0.37–0.51, I^2 = 9%). Among the 1071 chest CT scans performed, 65% revealed bilateral or unilateral pneumonia. The most common pattern seen on chest CT scans was ground-glass opacity, seen in 31% of patients (95% CI 0.11–0.61, I^2 = 90%).

3.7 | Neonatal outcomes

Many of the neonatal outcomes of the infants born to mothers positive for COVID-19 were unfavorable. Admission to the neonatal intensive care unit (NICU) was the most prevalent outcome (28%, 95% CI 0.17–0.43, I^2 = 90%), with 576 of 2430 neonates having clinical indications that justified admission to the NICU. In addition, low birth weight was also observed in 148 of 1093 neonates (15%, 95% CI 0.10–0.21, I^2 = 76%). Mortality (2%, 95% CI 0.01–0.03, I^2 = 46%), APGAR score below 7 (19%, 95% CI 0.12–0.28, I^2 = 43%), and fetal distress (11%, 95% CI 0.06–0.19; I^2 = 91%) were the outcomes found in the respective combined proportions. Although there was no evidence of vertical transmission in the studies found, there was a combined prevalence of 25% of COVID-19 infection (95% CI 0.05–0.66, I^2 = 76%) when neonates were investigated within 48 h of birth by RT-PCR. There was no evidence of transmission via breastfeeding. However, the combined prevalence of breastfeeding was low (40%, 95% CI 0.14–0.73, I^2 = 80%) (Figure 3).

4 | DISCUSSION

Despite the devastating effects of the COVID-19 pandemic worldwide, scientific studies on SARS-CoV-2 are still developing, and knowledge about the behavior of the virus in the body is not explicit. As such, the shortage of data regarding COVID-19 in the neonatal age represents a further challenge for obstetricians and neonatologists, who are called to face an unknown entity.[19]

Regarding COVID-19 infection in pregnant women, although they belong to the risk group, the potential of the virus to cause severe complications for mothers and newborns requires rigorous pregnancy screening and long-term follow-up.[19,20]

The present meta-analysis showed that pregnant women hospitalized with COVID-19 infection had more common symptoms, such as fever, cough, and lymphopenia among others, in addition to the radiological signs suggestive of pneumonia on chest radiography and CT. Pregnancies affected by infection had combined rates and proportions of prematurity, pre-eclampsia, and cesarean delivery. The combined proportion of perinatal mortality was only 2%, while the most common adverse perinatal outcome was fetal distress in newborns admitted to the NICU.

Pregnant women with COVID-19 are more likely to develop a severe disease than non-pregnant women, with a high rate of admission to the ICU, need for supplemental oxygen and ventilation, and mortality.[21] Immunological changes from pregnancy favor the risk of emerging infections, leading to a slightly different immune reaction among pregnant women. Therefore, during the ongoing SARS-CoV-2 pandemic, it cannot be excluded that pregnant women with COVID-19 can have a more severe disease course.[22]

Although possible complications may occur, some authors, such as Dashraath et al.,[22] have highlighted that changes in the hormonal environment during pregnancy affect the immune response to viral pathogens. Furthermore, the expression of the anti-inflammatory effect of cytokines (e.g. IL-4 and IL-10), together with a Th2 profile and other mechanisms of immune adaptation, results in a lower intensity of symptoms of COVID-19 in pregnant women compared to that in non-pregnant women.[23]

The present meta-analysis showed that the levels of lymphocytes decreased, while the levels of CRP increased. Lymphocytes act as an immune barrier against viral infection, and low levels are observed

TABLE 2 Quality assessment of observational studies.

Newcastle-Ottawa[a]	Selection				Comparability	Outcome				
Study	1	2	3	4	1	1	2	3	Total	Grade[b]
Dilek Sahin et al. (2020)	b)*	c)	a)*	a)*	b)*	b)*	b)	d)	5	Low ⊕⊕oo
Sun et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	a)*	a)*	a)*	9	Middle o⊕⊕⊕
Farghaly et al. (2020)	b)*	a)*	a)*	a)*	a)* b)*	b)*	b)	a)*	8	Low ⊕⊕oo
Grechukhina et al. (2020)	b)	b)	a)*	a)*	a)* b)*	a)*	a)*	a)*	7	Very low ⊕ooo
McLaren Jr et al. (2020)	b)	b)	c)	a)*	a)* b)*	a)*	a)*	a)*	6	Very low ⊕ooo
Bertino et al. (2020)	a)*	a)*	c)	a)*	a)* b)*	a)*	b)	b)	6	Low ⊕⊕oo
Di Mascio et al. (2020)	a)*	c)	a)*	a)*	a)* b)*	b)*	b)	a)*	7	Middle o⊕⊕⊕
Cour Freiesleben et al. (2021)	a)*	a)*	a)*	a)*	a)* b)*	a)*	b)	a)*	8	Middle o⊕⊕⊕
Yazihan et al. (2021)	a)*	a)*	b)*	a)*	a)* b)*	a)*	a)*	a)*	9	High ⊕⊕⊕⊕
Shmakov et al. (2020)	a)*	a)*	c)	a)*	a)* b)*	a)*	b)	a)*	7	Low ⊕⊕oo
Ashish et al. (2020)	a)*	a)*	c)	b)	a)* b)*	a)*	b)	a)*	6	Very low ⊕ooo
Sakowicz et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	b)*	b)	d)	7	Middle o⊕⊕⊕
He et al. (2021)	a)*	a)*	a)*	a)*	b)*	a)*	a)*	a)*	8	Middle o⊕⊕⊕
Khoury et al. (2020)	a)*	c)	a)*	a)*	—	b)*	b)	a)*	5	Low ⊕⊕oo
Liu et al. (2020)	b)*	a)*	a)*	a)*	a)* b)*	a)*	b)	a)*	8	Middle o⊕⊕⊕
London et al. (2020)	b)*	a)*	a)*	a)*	a)* b)*	a)*	b)	a)*	8	Middle o⊕⊕⊕
Lucarelli et al. (2020)	b)*	c)	a)*	a)*	—	a)*	b)	a)*	5	Very low ⊕ooo
Martínez-Perez et al. (2020)	a)*	c)	a)*	a)*	—	a)*	b)	a)*	5	Low ⊕⊕oo
Oncel et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	a)*	b)	a)*	8	Middle o⊕⊕⊕
Pariente et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	a)*	b)	a)*	8	Middle o⊕⊕⊕
Pierce-Williams et al. (2020)	a)*	a)*	a)*	a)*	a)*	a)*	b)	a)*	7	Low ⊕⊕oo
Qiancheng et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	a)*	b)	a)*	8	Middle o⊕⊕⊕
Na Li et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	d)	a)*	b)*	8	Low ⊕⊕oo
Gulersen et al. (2020)	b)*	a)*	a)*	a)*	a)*	b)*	a)*	b)*	8	Low ⊕⊕oo
Popofsky et al. (2020)	b)*	a)*	b)*	a)*	a)* b)*	b)*	b)	b)*	8	Low ⊕⊕oo
MohrSasson et al. (2020)	b)*	b)	a)*	a)*	b)*	d)	b)	b)*	5	Low ⊕⊕oo
Pirjani et al. (2020)	b)*	a)*	a)*	a)*	a)* b)*	b)*	a)*	b)*	9	Low ⊕⊕oo
Cuñarro-López et al. (2021)	a)*	a)*	b)*	a)*	b)*	b)*	a)*	b)*	8	Middle o⊕⊕⊕
Yassa et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	b)*	a)*	a)*	9	Low ⊕⊕oo
WAPM (2021)	a)*	a)*	a)*	a)*	a)* b)*	b)*	a)*	a)*	9	Low ⊕⊕oo
Prabhu et al. (2020)	a)*	a)*	a)*	a)*	a)*	b)*	a)*	a)*	8	Low ⊕⊕oo
Pineles et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	b)*	a)*	b)*	9	Middle o⊕⊕⊕
Savassi (2020)	b)*	a)*	a)*	a)*	a) b)*	b)*	b)	a)*	7	Low ⊕⊕oo
Adhikari (2020)	a)*	a)*	a)*	a)*	a)* b)*	b)*	a)*	a)*	9	Middle o⊕⊕⊕
Maraschini et al. (2020)	a)*	a)*	a)*	b)	a) b)*	b)*	a)*	a)*	7	Low ⊕⊕oo
Ríos-Silva et al. (2020)	a)*	a)*	b)*	a)*	a) b)*	b)*	a)*	a)*	8	Low ⊕⊕oo
Badr et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	b)*	a)*	b)*	9	Middle o⊕⊕⊕
Barbero et al. (2020)	b)*	a)*	a)*	a)*	a)* b)*	b)*	b)	a)*	8	Middle o⊕⊕⊕
Verma et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	b)*	a)*	a)*	9	High ⊕⊕⊕⊕
Popofsky et al. (2020)	a)*	a)*	b)*	b)	a)* b)*	b)*	a)*	d)	7	Low ⊕⊕oo
Griffin et al. (2020)	b)*	a)*	a)*	a)*	a)* b)*	b)*	a)*	b)*	9	Middle o⊕⊕⊕
Knight et al. (2020)	a)*	c)	a)*	b)	—	b)*	a)*	b)*	5	Very low ⊕ooo

(Continues)

TABLE 2 (Continued)

Newcastle-Ottawa[a]	Selection				Comparability	Outcome				
Study	1	2	3	4	1	1	2	3	Total	Grade[b]
Bender et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	b)*	b)	b)*	8	Middle o⊕⊕⊕
Maru et al. (2020)	a)*	a)*	b)*	a)*	a)*	b)*	b)	b)*	7	Low ⊕⊕oo
Hcini et al. (2020)	a)*	a)*	a)*	b)	a)* b)*	b)*	a)*	b)*	8	Middle o⊕⊕⊕
Martinez-Portilla et al. (2021)	a)*	a)*	a)*	a)*	a)* b)*	b)*	a)*	b)*	9	High ⊕⊕⊕⊕
Jenabi et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	d)	a)*	a)*	8	Low ⊕⊕oo
Brandt et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	d)	a)*	a)*	8	Low ⊕⊕oo
Moreno et al. (2020)	b)*	c)	a)*	a)*	—	b)*	a)*	a)*	6	Very low ⊕ooo
DeBolt et al. (2020)	b)*	b)	a)*	b)	a)* b)*	d)	a)*	a)*	6	Very low ⊕ooo
Trahan et al. (2020)	b)*	c)	a)*	b)	—	b)*	a)*	a)*	5	Very low ⊕ooo
Hu et al. (2020)	c)	c)	a)*	b)	—	b)*	a)*	a)*	4	Very low ⊕ooo
San-Juan et al. (2020)	b)*	a)*	a)*	a)*	—	b)*	a)*	a)*	7	Middle o⊕⊕⊕
Sattari (2020)	b)*	a)*	a)*	a)*	—	a)*	b)	a)*	6	Low ⊕⊕oo
Schwartz et al. (2020)	c)	b)	a)*	b)	—	b)*	b)	b)*	3	Very low ⊕ooo
Wu et al. (2020)	c)	b)	a)*	b)	—	a)*	a)*	b)*	4	Low ⊕⊕oo
Xu et al. (2020)	b)*	a)*	a)*	a)*	a)* b)*	a)*	b)	b)*	8	Middle o⊕⊕⊕
Zeng et al. (2020)	b)*	a)*	a)*	b)	—	a)*	a)*	b)*	6	Very low ⊕ooo
Wang et al. (2020)	a)*	a)*	a)*	b)	—	a)*	a)*	b)*	6	Very low ⊕ooo
Blitz et al. (2020)	b)*	c)	b)*	b)	—	b)*	b)	c)	3	Very low ⊕ooo
Gabriel et al. (2020)	c)	c)	a)*	B	—	b)*	b)	d)	2	Very low ⊕ooo
Mattar et al. (2020)	b)*	c)	a)*	a)*	—	b)*	b)	d)	4	Low ⊕⊕oo
Ayed et al. (2020)	b)*	c)	a)*	a)*	—	b)*	b)	d)	4	Low ⊕⊕oo
Fenizia et al. (2020)	b)*	c)	a)*	a)*	—	b)*	b)	c)	4	Low ⊕⊕oo
Rojas et al. (2020)	b)*	c)	b)*	a)*	—	b)*	b)	b)	4	Very low ⊕ooo
Zhang et al. (2020)	c)	c)	a)*	a)*	—	b)*	b)	d)	3	Very low ⊕ooo
Buosenso et al. (2020)	c)	c)	b)*	b)	—	b)*	b)	d)	2	Very low ⊕ooo
Cosma et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	a)*	a)*	a)*	9	High ⊕⊕⊕⊕
Goldfarb et al. (2020)	a)*	a)*	a)*	a)*	a)* b)*	b)*	b)	d)	7	Middle o⊕⊕⊕
Savasi et al. (2020)	a)*	a)*	a)*	a)*	a)* b)	b)*	b)	a)*	7	Middle o⊕⊕⊕

*corresponds to the score obtained by each domain.

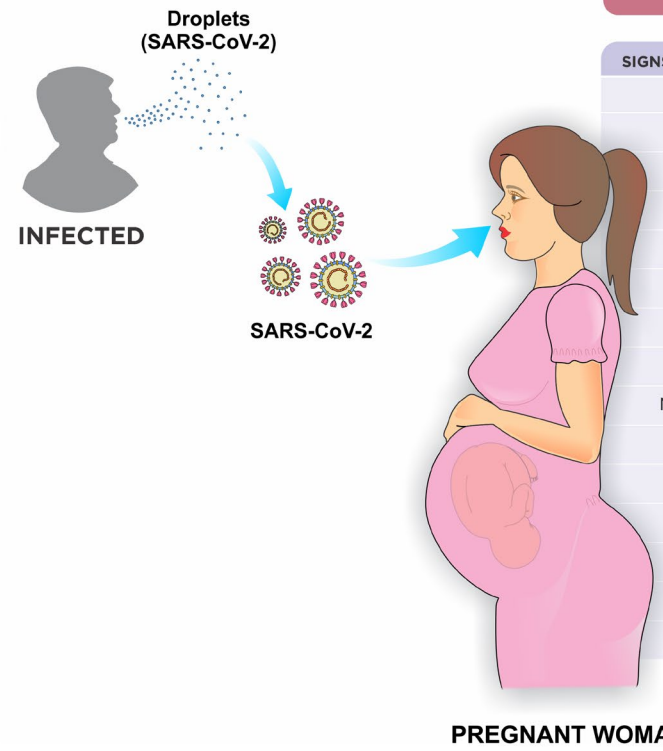
[a]Newcastle-Ottawa Quality Assessment Scale: 0–3 = poor; >3–6 = fair; >6–8 = good; >8–9 = excellent.

[b]Evaluated using the Grading of Recommendations Assessment, Development and Evaluation system: Very low ⊕ooo, Low ⊕⊕oo, Middle o⊕⊕⊕, High ⊕⊕⊕⊕.

when the body is infected. Although the level of lymphocytes can vary during pregnancy, this can be indicative of a poor prognosis.[24] For this reason, CRP can be used as a biomarker of bacterial infection and may be associated with the risk of puerperal infection (data not evaluated).[24,25] Increased levels of CRP are associated with mild symptoms.

Another laboratory data analyzed was the D-dimer, an indicator of fibrinolysis, which is widely used as a criterion for thromboembolism. Elevated levels of D-dimer are characteristic manifestations of COVID-19 and are associated with a worse prognosis of the disease.[26] Disseminated intravascular coagulation can occur in the most severe conditions and may be aggravated by prolonged bed rest and concomitant infections, which can increase the risk of venous thromboembolism.[27] Although the present study showed that pregnant patients with COVID-19 had higher levels of D-dimer, this interpretation may be limited since the levels physiologically increase throughout pregnancy.

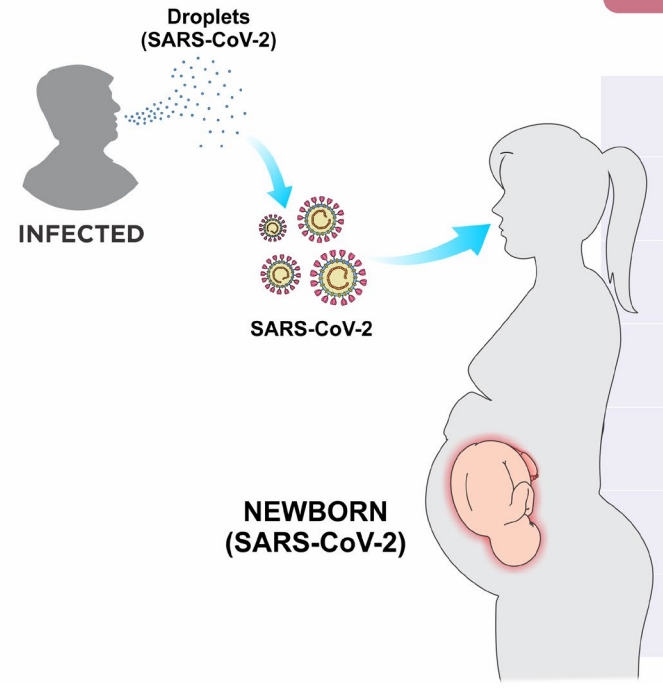
The present study showed a combined proportion of 65% for bilateral or unilateral pneumonia in pregnant women with COVID-19. Although observed during the active infection period, these data may be associated with lower immunity during pregnancy. Immunological changes, physiological changes in chest shape, and elevation of the diaphragm by the pregnant uterus alter the respiratory function. Occurring during the beginning of pregnancy, the reduction in chest volume leads to decreased functional residual capacity and expiratory volume. As such, the decreased lung capacity



15 SYMPTOMS WITH ENOUGH EVIDENCE FOR META-ANALYSIS

SIGNS AND SYMPTOMS	COHORT (95% CI)	CASE - CONTROL (IC 95%)
Fever	0.42 [0.35; 0.50]	0.20 [0.06; 0.50]
Cough	0.52 [0.42; 0.63]	0.09 [0.01; 0.50]
Chest Pain	0.13 [0.04; 0.32]	—
Myalgia	0.21 [0.12; 0.33]	0.02 [0.0; 0.08]
Sore Throat	0.20 [0.10; 0.35]	0.08 [0.01; 0.58]
Anosmia	0.15 [0.09; 0.24]	—
Ageusia	0.15 [0.06; 0.34]	—
Headache	0.16 [0.10; 0.25]	0.20 [0.08; 0.41]
Nausea or Vomiting	0.14 [0.09; 0.20]	0.11 [0.04; 0.27]
Diarrhea	0.08 [0.05; 0.13]	—
Tachypnea	0.18 [0.06; 0.43]	—
Tachycardia	0.19 [0.10; 0.31]	—
Fatigue	0.29 [0.20; 0.40]	0.16 [0.03; 0.55]
Dyspnea	0.26 [0.16; 0.38]	0.08 [0.02; 0.29]
Desaturation	0.18 [0.10; 0.30]	—

FIGURE 2 Signs and symptoms of a pregnant woman with COVID-19. Abbreviation: CI, confidence interval



NEONATAL OUTCOMES OF PREGNANT WOMEN WITH COVID-19

	COHORT (95% CI)	STUDY (n)	I^2 (%)
APGAR Score >7	0.19 [0.12; 0.28]	8	43%
Birth weights	0.15 [0.10; 0.21]	11	76%
Admission NICU	0.28 [0.17; 0.43]	25	90%
Fetal Distress	0.11 [0.06; 0.19]	10	91%
Mortality	0.02 [0.01; 0.03]	15	46%
Vertical transmission*	0.25 [0.05; 0.66]	7	76%
Breast-feeding	0.40 [0.14; 0.73]	6	80%

FIGURE 3 Neonatal outcomes of pregnant women with COVID-19. Abbreviation: CI, confidence interval; NICU, neonatal intensive care unit

and the inability to clear secretions can increase the susceptibility of pregnant women to severe respiratory infections.[28]

Regarding the increased risk of miscarriage, preterm birth, preeclampsia, and cesarean delivery, their prevalence did not show a statistical association with COVID-19 in the analyses. However, some studies have shown an increased risk of these outcomes in pregnant women with COVID-19, especially if they are hospitalized with pneumonia.[28] It is well known that the maternal physiological adaptations during pregnancy predispose pregnant women to a more severe course of pneumonia, with subsequently higher maternal and fetal morbidity and mortality. Furthermore, there is a lack of data in the literature on the effects of coronavirus infections during pregnancy, limiting the counseling and management of these patients.[4,29]

Neonatal SARS-CoV-2 infection is uncommon in infants admitted to hospitals. Infection during neonatal admission after birth to a mother with perinatal SARS-CoV-2 infection and the possibility of vertical transmission were unlikely, supporting international recommendations to avoid the separation of the mother and the infant. The high proportion of infants from black, Asian, or minority ethnic groups requires investigation.[30] In the present study, a high prevalence of newborn admission to the NICU was observed. Though the factors for admission to the ICU differ between hospitals, the findings suggest that the infants born to mothers positive for COVID-19 were transferred to the ICU to monitor the clinical status of the newborns and prevent vertical transmission.[31] Thus, the results presented in the sample could not allow for the determination whether COVID-19 was a direct cause of preterm birth or if viral/bacterial infections could result in complications that increase the risk of preterm labor.

APGAR score under 7 in the first minute of life had no significant relationship with neonatal health in the present study. However, regarding low birth weight, which had a prevalence of 15% in the sample, Di Toro et al.[31] suggests that infection with COVID-19 at the beginning of the gestational period increases the risk of intrauterine growth restriction. When infection occurs close to delivery, the birth weight is unlikely to be affected.

In the present study, vertical transmission showed a relevant prevalence, but no study mentioned RT-PCR collection soon after birth. Therefore, the possibility of contamination of the newborn by the mother, health professionals, or others cannot be ruled out. Concerning the rate of breastfeeding, previous studies, such as those by Di Toro et al.[31] and Smith et al.,[32] concluded that there is no evidence favoring transmission via breastfeeding despite the significant values. Therefore, the relative prevalence of 2% demonstrates that fetal and neonatal mortality was extremely low and could not be confirmed as a direct effect of the infection under study.

4.1 | Strengths and limitations of the study

The present review has some limitations. Some studies included a small number of cases. In addition, pregnant women may have been counted twice, although the authors independently reviewed all the included studies since many were American and Chinese. Moreover, the reported data are intuitively limited to a short-term follow-up period. Another significant limitation was the study design. Observational studies presented a higher risk of publication bias, which could affect the estimated outcomes. The lack of comparative data to assess the risk of pregnancy complications in women with and without COVID-19 also compromised the results. Furthermore, the lack of standardization for evaluating the outcomes in the studies in the review resulted in high heterogeneity, which was another major factor affecting the estimated outcome.

To reduce these limitations, several strategies were adopted. To minimize the risk of bias, the meta-analysis was restricted to cohort studies and case-control studies, and the quality of the included studies was reported using a validated scale. The authors were contacted and reports not published in PubMed were obtained to minimize the risk of missing relevant studies. To ensure better certainty of the outcomes, a large sample size was used in the present systematic review.

4.2 | Implications for future research

Many questions regarding the impact of the novel coronavirus, SARS-CoV-2, are still to be addressed, especially with the emergence of its new variants of (Delta, Gamma, Beta, Alpha). As such, presentation of the clinical disease, transmissibility, effectiveness of vaccines, and therapeutics need to be continually studied. Another issue that needs to be studied is the clinical outcomes in pregnant women who were vaccinated and the serological results in neonates of these vaccinated mothers. The present review suggests that obstetricians should request serological tests to help in the early identification of infected but asymptomatic women during prenatal consultations. It is also important to improve perinatal management before delivery.

5 | CONCLUSION

Physiological changes during pregnancy have a significant impact on the immune system, respiratory system, and coagulation. The impact of SARS-CoV-2 on pregnancy remains unknown, and a concerted global effort is needed to determine its effects on implantation, fetal growth and development, labor, and neonatal health. Asymptomatic infection presents an additional challenge in service delivery, prevention, and management. In addition to the direct impacts of the disease, many indirect consequences of the pandemic adversely affect maternal health, including reduced access to reproductive health services, increased pressure on mental health, and increased socioeconomic deprivation.

Pneumonia, admission to the ICU, use of ventilatory support, and death were the observed outcomes. However, the course of

the disease in pregnant women appears to be similar to that in non-pregnant women. The diagnosis of COVID-19 may have influenced the increase in premature and cesarean deliveries. Vertical transmission and breast milk were not explicitly highlighted.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

KSM conceived the study. KSM and AKG designed the study. ACAS, APFC, LTAM, LASS, and CLF screened the abstracts for inclusion in the study. KSM, ACAS, APFC, and CLF analyzed the data. AKG coordinated the discussions and helped in data interpretation. KSM, ACAS, APFC, and CLF drafted the manuscript, which was then critically revised by all authors. All authors approved the final manuscript.

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SUPPORTING INFORMATION

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