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A Systematic Review of Obstetrical Outcomes in COVID-19 Positive Pregnant Women

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become a major public health issue worldwide since Dec 2019. With the rising number of infected cases daily, concerns have been raised to generate comprehensive and extensive evidence about the effects of COVID-19 infection during pregnancy on maternal obstetric outcomes; this would provide guidance in obstetrician clinical management to reduce maternal mortality and morbidity. The aim is to evaluate the effects of COVID-19 on pregnancy and its maternal obstetrical outcomes. We searched four databases (PubMed, Embase, Scopus and Web of Science) by using medical subject heading and keywords under the PECO concept (P = Pregnant woman, E = COVID-19 infection, O = Obstetric outcome). The search was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method to identify relevant articles based on inclusion and exclusion criteria published from January 1st 2020 to June 20th 2021. The risk of bias of the selected articles was also assessed. We found that though most pregnant women experienced mild to moderate COVID-19 symptoms, the severity development was considered multifactorial, which included issues like maternal pre-gestational comorbidity and health status. The severe form of COVID-19 was linked to an increased BMI in women. Caesarean rates were higher in the COVID-19 positive cohort, especially if the women are experiencing severe COVID-19. An increased miscarriage rate was found in women infected with COVID-19 in the first trimester of pregnancy as compared to the second trimester. The rate of preterm delivery was also elevated among pregnant women who were suffering from severe-to-critical COVID-19 disease. There were reports on maternal death secondary to acute respiratory distress syndrome from COVID-19 disease, but the percentage was low. We did not find any significant link between COVID-19 and intrauterine death and infection, hypertension in pregnancy, stillbirth and post- partum

haemorrhage. COVID-19 positive pregnant women are at enhanced risk of preterm birth, obstetric complications and caesarean section delivery. This systematic review provided a comprehensive guide to obstetricians when managing a COVID-19 positive pregnancy.

Subject Areas

Infectious Disease, Obstetrics and Gynaecology

Keywords

COVID-19, SARS-CoV-2, Pregnancy, Maternal Outcome, Obstetrics Outcome

1. Introduction

Coronavirus Disease 19 (COVID-19), also known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is caused by a novel coronavirus that belongs to the *Coronaviridae* family [1] [2] [3] [4]. COVID-19 has transmitted rapidly across the globe after being first erupted in Wuhan, China during the late December of 2019; it was shortly declared as a worldwide pandemic on the March 11th of 2020 by the World Health Organization (WHO), calling attention to the immensity of the viral outbreak [1] [2] [5] [6]. Up till September 25th 2021, there is an accumulated 230 million cases worldwide, resulting in deaths of over 4.7 million [7]. Meanwhile, COVID-19 is estimated to affect 13.9 per 1000 deliveries in pregnant women [8].

While such viral outbreaks are not new in this recent two decades with the emergence of the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) in the years 2002 and 2012, respectively, COVID-19 has spread faster and caused higher mortality than that of SARS, and MERS combined, which is approximately 10,000 deaths [1] [6] [9]. Looking back in history, the pregnant population has been seriously affected by various adverse pregnancy events following the outbreaks of SARS and MERS. Also, the severity of a respiratory infection is likely to be increased for a pregnant woman due to ineffective airway clearance secondary to anatomical and physiological changes during pregnancy [10]. Considering that the COVID-19 virus is from the same human coronavirus family as the previous SARS-CoV-1 and MERS-CoV outbreaks, there are emerging worries that the pregnant population who are infected with COVID-19 will have potential similar adverse outcomes as the previous two outbreaks [1] [11] [12]. This review paper aims to appraise the currently available evidence through a systematic approach to identify the factors influencing the maternal obstetrics outcomes of COVID-19 infected pregnant women. The review findings will contribute to developing a comprehensive maternal care modality and appropriate preventive strategies for COVID-19 related pregnancy complications.

2. Methods

2.1. Search Strategy

We conducted this systematic review in the databases including PubMed, Embase, Scopus and Web of Science. The primary reviewers' institution subscribes these four electronic databases; hence, it was convenient to get access to full-text resources. The search was performed from January 1st 2020 to June 20th 2021 following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method to identify relevant articles on COVID-19 infected pregnancies and maternal outcomes. We searched all databases using keywords and MeSH terms related to COVID-19 disease (Table 1), pregnant women and maternal outcomes. We used search string across all databases, which included [("Covid" OR "SARS-CoV-2" OR "Covid-19" OR "Coronavirus disease 2019" OR "2019-nCoV") AND ("Pregnancy" OR "Pregnant" OR "Pregnant woman") AND ("Maternal outcomes" OR "Pregnancy outcomes" OR "Obstetrics outcomes")]. To refine the search results further, we also applied a filter including "only articles in English language and females with age ranging from 19 to 44 years as the research population".

2.2. Selection Criteria

1) Inclusion criteria: Following inclusion criteria were considered before including any study in this review:

- Study types: Cohort studies, randomized controlled trials, database analysis;
- Study sample size: More than 150 COVID-19 infected pregnant women;
- Reported outcomes of COVID-19 infected pregnancies;
- If the full text is available;
- English language.

2) Exclusion criteria: Following criteria were considered before excluding

Table 1. Keywords and subject headings according to PECO concept.

Concept	Subject Headings (MeSH/Emtree)	Keywords/Entry Terms
Population: Pregnant women	• Pregnant women • Pregnancy • Gravidity	• Pregnant woman • Pregnancy • Gestation • Gravidity • Childbearing
Exposure: COVID-19	• COVID-19 • SARS-CoV-2 • Coronavirus disease 2019 • Severe acute respiratory syndrome coronavirus 2	• COVID-19 • 2019-nCoV • 2019 Novel Coronavirus • Coronavirus Disease 2019 • SARS Coronavirus 2
Outcome: Obstetrics outcome	• Pregnancy outcome • Delivery, Obstetric • Birth	• Maternal outcome • Pregnancy outcome • Birth • Perinatal outcome • Obstetric delivery • Labour outcome

any study from this review:

- Study types: Review articles, case reports, case series, protocol papers, cross-sectional studies;
- Study sample size: Less than 150 COVID-19 infected pregnant women;
- Occurring of COVID-19 infection before the pregnant period;
- If the specific outcomes of pregnancy are not mentioned;
- If the language is not in English;
- Incomplete trials or duplicate publications of the same study that yield similar results.

2.3. Screening

We aimed to screen the articles published from January 1st 2020 onwards. Initially, we identified 2389 articles from the four databases: Pubmed (448 articles), Embase (867 articles), Scopus (768 articles), and Web of Science (306 articles). Thereafter, we exported all articles to the citation manager Endnote and identified the duplicates using the EndNote software before removing them. Two reviewers simultaneously screened all the potential articles by title and abstract based on the inclusion and exclusion criteria. Lastly, we selected 13 articles (**Figure 1**) after full-text screening and included those for data extraction under this review. Out of 13 articles, the majority articles were available in PubMed (**Table 2**).

2.4. Data Extraction

Two primary reviewers (JT and JK[1]) used a standardized form, which included: study design, sample size, main study findings and conclusion, to extract all the potential data independently from 13 finally selected articles. Thereafter, they compared their individual data and reached a consensus before including the data for analysis by NVivo software. They invited the 3rd reviewer, either SSSH or NKJ[2], when they could not resolve any discrepancies.

2.5. Quality Assessment

We assessed the quality of each study using the Newcastle-Ottawa Scale (NOS) (**Table 3**), which is a tool to assess the quality of both cohort and case-control studies included in a systematic review. We selected this NOS tool as most of our included studies were cohort studies, either prospective or retrospective. The NOS tool has three parameters: selection = 4, comparability = 2 and outcome = 3; based on that we conducted the quality assessment of all 13 studies. Two primary reviewers conducted the quality assessment independently and invited the third reviewer to resolve any disagreement.

3. Results

We identified 7030 pregnant women with COVID-19 positive status from the

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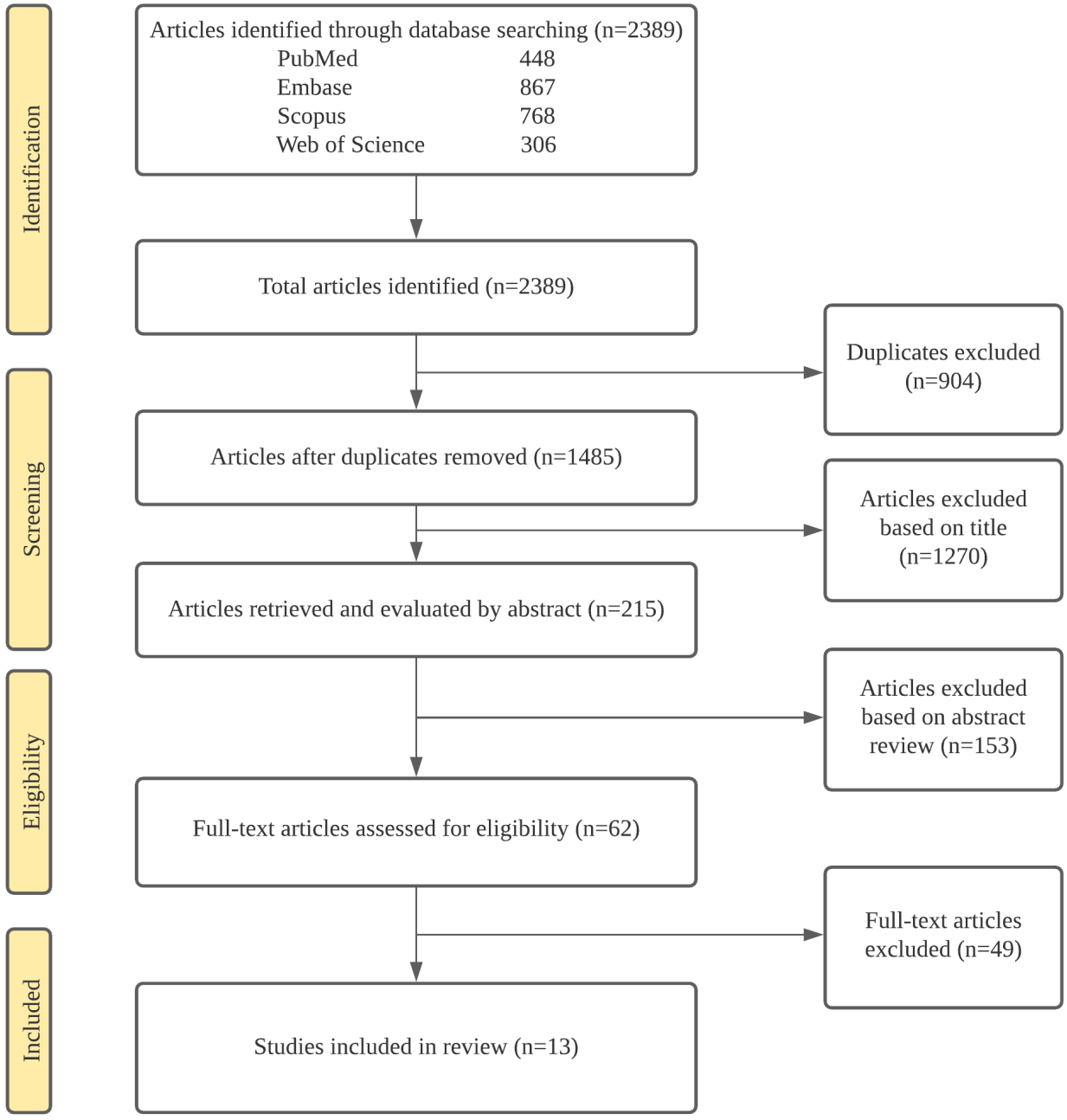

Figure 1. PRISMA chart used for the selection of articles.

cohort studies conducted in different parts of the world, including the USA, UK, Europe like Spain, South America like Peru, Chili and Middle-east countries like Kuwait and Saudi-Arabia [13]-[25]. The COVID-19 positive status was confirmed among most of the pregnant women (90% and above) by laboratory SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) assay, SARS-CoV-2 antibody testing, or radiological findings. In the INTERCOVID Multinational Cohort Study, a small proportion (7.1%) of pregnant women was clinically diagnosed with COVID-19 without laboratory confirmation [24]. The main study findings and conclusion are summarized in **Table 4**.

Table 2. Selected articles and their source.

Author	Year of publication	Database
Al-Matary *et al.*	2021	PubMed
Ayed *et al.*	2020	PubMed
Crovetto *et al.*	2021	Embase
Cruz-Melguizo *et al.*	2021	Scopus
Haye *et al.*	2021	Web of Science
Khoury *et al.*	2020	PubMed
Lokken *et al.*	2021	Embase
Martinez-Perez *et al.*	2021	PubMed
Metz *et al.*	2021	PubMed
Saccone *et al.*	2021	Web of Science
Taya *et al.*	2020	Web of Science
Villar *et al.*	2021	Embase
Vousden *et al.*	2021	PubMed

3.1. Socio-Demographic Status

The maternal age ranged from 18 to 49 years [13]-[20] [22] [23] [25]. With regards to the median age, the range was from 28 to 32 years [13] [14] [18] [19]. Seven studies included the ethnic backgrounds of the patients [15] [16] [18] [19] [20] [21] [25]. Non-Hispanic whites or Hispanics made up the majority (up to 64.2%) of the research population [15] [16] [18] [19] [20] [21] [25]. Other ethnicities included were non-Hispanic Blacks, Asians, and others [15] [16] [18] [19] [20] [21] [25]. Low socioeconomic status, defined as having no educational background, no employment history or being unemployed for more than two years, was found to be 33.3% among the COVID-19 positive pregnant women in one study [15].

3.2. Pregnancy Characteristics

The percentage of nulliparous women ranged from 19.5% to 53% [14] [15] [16] [17] [18] [20], while up to 80.5% of women were multiparous [14] [17] [25]. In one study, multiparity was associated with higher rates of moderate and severe COVID-19 as compared to nulliparous pregnant women who were infected with the virus (87.5% vs. 12.5%; 62.5% vs. 37.5%) [23]. Most of the pregnancy was a singleton, and only 1.1% to 2.5% were of multiple pregnancies [14] [16] [17] [18] [20] [23] [25].

3.3. Pre-Existing Comorbidities

Obesity, defined as body mass index (BMI) more than 30 kg/m^2, was the most common pre-gestational comorbidities identified, with the highest prevalence of 55.1% [13] [15]-[22] [24] [25]. Pregnant women who were overweight or obese

Table 3. Risk of bias assessment of the selected articles.

First author; Year	Selection				Comparability		Outcome			Total
	Representation of COVID-19 infected pregnant women	Selection of non-COVID-19 exposed pregnant women	Confirmation of COVID-19 infection through nasopharyngeal swab or RT-PCR	Maternal outcomes of interest were not present at the beginning of the study	Adjustments of important risk factors	Adjustments for additional risk factors	Assessment of maternal outcomes	Follow up until end of pregnancy	All patients were followed up adequately	
Al-Matary *et al.*; 2021	★		★	★	★	★	★	★		7
Ayed *et al.*; 2020	★	★	★	★	★	★	★	★	★	9
Crovetto *et al.*; 2021	★	★	★	★	★		★			6
Cruz-Melguizo *et al.*; 2021	★	★	★	★	★	★	★	★	★	9
Khoury *et al.*; 2020	★		★	★	★	★	★		★	7
Lokken *et al.*; 2021	★	★	★	★	★	★	★	★	★	9
Martinez-Perez *et al.*; 2021	★	★	★	★	★	★	★	★	★	9
Metz *et al.*; 2021	★		★	★	★	★	★	★	★	8
Haye *et al.*; 2021	★		★	★	★	★	★		★	7
Saccone *et al.*; 2021	★	★	★	★	★	★	★	★	★	9
Taya *et al.*; 2020	★		★	★	★	★	★			6
Villar *et al.*; 2021	★	★	★	★	★	★	★		★	8
Vousden *et al.*; 2021	★	★	★	★	★	★	★	★	★	9

were more likely to be hospitalized due to symptomatic COVID-19 and are at risk of higher maternal morbidity and mortality [24] [25]. In the group of patients admitted for critical-severe COVID-19, there was a higher proportion of women with a BMI of 30 kg/m^2 or more (58.4%) [21]. Pre-pregnancy asthma had affected up to 8.3% of women [13] [14] [15] [16] [17] [19] [20] [25]. Chronic lung disease was only found in 0.2% to 0.4% of COVID-19 infected pregnant women [13] [16] [20]. While most of the infected pregnant women were non-smokers, up to 14.2% of them had a smoking history [15] [16] [18] [20] [21] [22] [25].

We also found that 1.2% to 4.6% of pregnant women had chronic hypertension [13] [15] [16] [17] [19] [20] [25]. When compared to non-hospitalized pregnant women with COVID-19 disease, it was found that those with obesity,

Table 4. List of selected articles which are included in review with the main findings and conclusion.

Author; Study country; Year of Publication [Reference number]	Type of study	Sample size	Main findings	Conclusion
Al-Matary *et al*.; Saudi Arabia; 2021 [13]	Cohort study	288	• A majority of pregnant women were symptomatic with cough being the most frequent COVID-19 symptom. • Caesarean section made up 35.8% of the deliveries. • Prematurity (15.5%) was the most common adverse pregnancy outcome, followed by foetal distress (6.5%) and pre-eclampsia (2.0%). • Less than half (43%) of neonates of COVID-19 positive mothers were admitted into the neonatal intensive care unit (NICU) for respiratory support. • None of the newborns were positive for COVID-19 infection.	• The majority of the pregnant women with COVID-19 infection experienced mild or moderate disease symptoms. • No evidence was found to suggest vertical transmission of COVID-19 infection from mothers to their newborns.
Ayed *et al*.; Kuwait; 2020 [14]	Cohort study	185	• The majority of the pregnant women experienced mild symptoms of COVID-19, with fever (58.6%) being the most common presenting symptom. • 1.6% of the pregnant women had a miscarriage and 8.6% had ongoing pregnancies, while 89% had a live birth. • The median gestational age at birth for newborns was 38 (IQR: 36 - 39) weeks. • Only 2 newborns were tested positive for COVID-19 on day 5 by nasopharyngeal swab testing.	• Most pregnant women infected with COVID-19 had mild symptoms. • While there is a possibility of mother-to-child vertical transmission when a pregnant woman is infected with COVID-19, it may not lead to unfavourable maternal and neonatal outcomes.
Crovetto *et al*.; Spain; 2021 [15]	Cohort study	317	• A majority of the COVID-19 positive pregnant women were asymptomatic (68.5%) or had mild symptoms (29.3%). • Symptomatic women had higher rates of preterm delivery (16.9% vs 7.2%; P = 0.03) and intrapartum foetal distress (19.2% vs 9.1%, P = 0.004) when compared to non-infected women, however, the rates for asymptomatic women were similar to those of non-infected cases. • None of the newborns of COVID-19 positive mothers had anti-SARS-CoV-2 IgM/IgA in cord blood.	• In general, there was little difference in the rates of pregnancy complications between infected and non-infected women. • An increase in preterm delivery and intrapartum foetal distress was associated with symptomatic COVID-19 infection.
Cruz-Melguizo *et al*.; Spain; 2021 [16]	Cohort study	1347	• There were higher rates of premature rupture of membranes, venous thrombotic events and severe pre-eclampsia incidence in COVID-19 positive pregnancies compared to non-infected pregnancies, which could have been overestimated in the infected cohort due to the shared clinical signs of the hypertensive disorders and COVID-19. • More infected patients delivered preterm mainly due to a higher rate of iatrogenic preterm births. • Prematurity in COVID-19 affected pregnancies results from a predisposition to terminate the pregnancy due to maternal disease.	• Pregnant women with COVID-19 are at risk of preterm deliveries, mainly due to iatrogenic deliveries secondary to pneumonia and/or pre-eclampsia. • A higher proportion of infected women reported venous thromboembolism and disseminated intravascular coagulation.

Continued

Haye *et al*.; Chile, 2021 [17]	Cohort study	458	• A majority (74.4%) of the COVID-19 positive women presented with mild symptoms and 25.5% of them experienced severe COVID-19 symptoms. • 5.6% women were admitted into the ICU and 2.8% of them required mechanical ventilation. • Adverse maternal outcomes were linked to severe COVID-19 presentation, infection over 24 weeks, and comorbidities. • 16.5% of the deliveries were preterm.	• Maternal compromise resulted from women with severe COVID-19 and the occurrence of disease in the second half of the pregnancy. • The high perinatal morbidity and mortality in severe COVID-19 positive women warrants attention. • Outpatient management was safe for mild cases.
Khoury *et al*.; USA; 2020 [18]	Cohort study	241	• A majority of women were asymptomatic for COVID-19 at the time of admission. • 52.4% of women with severe and 91.7% with critical COVID-19 underwent caesarean delivery. • The rate of preterm delivery was 14.6%. • Body mass index (BMI) of 30 or higher was associated with COVID-19 severity (P = 0.001). • 97.5% of newborns were tested negative for SARS-CoV-2 infection immediately after birth.	• Obesity was associated with COVID-19 severity. • Disease severity was associated with higher rates of caesarean and preterm deliveries.
Lokken *et al*.; USA; 2021 [19]	Cohort study	240	• Disease severity was linked to comorbidities or underlying conditions including asthma, hypertension, type 2 diabetes mellitus, autoimmune disease, and class III obesity. • The case fatality for COVID-19 was 13.6-fold higher in the pregnant population compared to individuals of a similar age. • Higher rates of preterm delivery were observed in women with severe or critical COVID-19 compared to women who had recovered from the infection.	• Pregnant women are at risk of developing severe or critical disease and mortality from COVID-19 infection, compared to non-pregnant adults of similar age, as well as preterm birth.
Martinez-Perez *et al*.; 2021 [20]	Cohort study	246	• Being SARS-CoV-2 positive increased the odds of preterm deliveries compared to non-infected mothers. • Infected women more commonly reported iatrogenic preterm births, but the occurrence of spontaneous preterm deliveries was similar statistically. • There was an increased risk of premature rupture of membranes at term and neonatal intensive care unit admissions in positive mothers.	• Pregnant women who were COVID-19 positive demonstrated more infection-related obstetric morbidity.
Metz *et al*.; USA; 2021 [21]	Cohort study	1219	• Disease severity was associated with older mean age, higher median body-mass-index, and pre-existing medical comorbidities. • Women with severe-critical COVID-19 had an increased risk of adverse perinatal outcomes like caesarean birth, hypertensive disorders of pregnancy and preterm deliveries compared to asymptomatic women. • Compared with asymptomatic patients, mild-moderate COVID-19 was not associated with adverse perinatal outcomes.	• Pregnant women with severe-critical COVID-19, but not those with mild-moderate COVID-19 were at an increased risk of perinatal complications compared with asymptomatic pregnant patients.

Continued

Saccone *et al*.; Multinational (22 countries); 2020 [22]	Cohort study	388	• 12.1% of women with a positive SARS-CoV-2 status had composite adverse maternal outcomes; 11.1% were admitted to the ICU, 9.3% required mechanical ventilation and 0.8% died. • Excluding the 122 women who were still pregnant at the time of data analysis, six had miscarriage, three had termination of pregnancy, six had stillbirth and 251 delivered a liveborn infant. • The preterm delivery rate was 26.3%. • Only one (0.4%) infant was found to be SARS-CoV-2 positive on RT-PCR.	• SARS-CoV-2 infection during pregnancy was associated with a low maternal mortality rate, but an 11.1% rate of ICU admission. • The risk of vertical transmission may be negligible.
Taya *et al*.; Peru; 2020 [23]	Cohort study	247	• 83% of the SARS-CoV-2 positive pregnancies were asymptomatic, with only 3.2% of them being severe. • Rates for caesarean deliveries were high (60%), while vaginal delivery rates had doubled over time. • Severe cases had higher rates of caesarean section and iatrogenic preterm delivery.	• There is a higher possibility of caesarean and iatrogenic preterm deliveries in severe cases. • COVID-19 infection was not found to be linked to perinatal complications.
Villar *et al*.; Multinational (18 countries); 2021 [24]	Cohort study	706	• Women infected with COVID-19 were at a higher risk for pre-eclampsia/eclampsia, severe infections, intensive care unit admission, maternal mortality, preterm birth, severe neonatal morbidity index, and severe perinatal morbidity and mortality index. • Any duration of fever and shortness of breath was associated with increased risk of severe maternal and neonatal complications • 13% of the neonates of COVID-19 positive mothers tested positive. • Caesarean deliveries but not breastfeeding was linked to an increased risk for neonatal test positivity.	• When comparing pregnant women with and without COVID-19 diagnosis, a positive infection status was linked with increases in severe maternal morbidity and mortality and neonatal complications.
Vousden *et al*.; UK; 2021 [25]	Cohort study	1148	• Women who were overweight or obese, of Black, Asian or other minority ethnic group, and having a relevant medical comorbidity, were more likely to be symptomatic for SARS-CoV-2 requiring hospitalisation, when compared to non-infected pregnant women. • Regardless of symptom status, there were increased rates of caesarean deliveries and neonatal unit admission.	• Factors that increase the risk of symptomatic and asymptomatic SARS-CoV-2 in pregnancy have been identified. • The majority of women do not experience severe complications of SARS-CoV-2 in pregnancy.

asthma, and hypertension were more likely to be hospitalized due to COVID-19 symptoms or concerns (21.1% vs. 6.3%, $p = 0.01$; 20.8% vs. 6.9%, $p = 0.02$; 20.8% vs. 2.8%, $p < 0.001$) [19]. The prevalence of cardiovascular diseases before pregnancy (excluding hypertension) was found to be low (0.3% to 2%) [13] [16] [20] [25].

Pre-gestational type 2 diabetes mellitus was also uncommon among the infected pregnant women (0.5% to 5.4%) [13] [14] [15] [16] [17] [19] [20] [25].

However, in the study by Metz *et al*., critical or severe COVID-19 diseases were more likely to develop in pregnant women with pre-existing asthma, chronic obstructive pulmonary disease, chronic hypertension, and diabetes [21].

Other comorbidities such as thyroid dysfunctions, liver and renal diseases, haematological diseases, autoimmune diseases, and psychological disorders were infrequently reported [13] [14] [16] [17] [19] [20] [21].

3.4. Exposure

The median gestational age at maternal diagnosis of COVID-19 ranged from 29 to 38 weeks [13] [14] [21]. Half or more (51.3% to 56.3%) of the SARS-CoV-2 diagnoses were confirmed during the third trimester [14] [19]. The rates of asymptomatic and symptomatic pregnant women showed a huge variability among the studies, ranging from 22.9% to 88.6% and 11.4% to 88.6% for both categories, respectively [13]-[25]. The commonly reported symptoms were fever, cough, sore throat and shortness of breath [13] [14] [18] [20] [21] [22] [23] [24]. It was found that pregnant women presenting with any duration of fever and dyspnoea were more likely to develop severe maternal complications (RR: 2.56; 95% CI: 1.92 - 3.40) [24].

Most symptomatic pregnant mothers experienced mild to moderate COVID-19 disease, only requiring oxygen supplementation through nasal cannula or face mask, or none at all [13] [16] [18] [19] [20] [22] [23]. Severe COVID-19 disease occurred in 3.2% to 26.1%, while only 1.7% to 4% of pregnant women developed critical COVID-19 disease [16]-[21]. Among the severe and critical COVID-19 group, maternal hypoxia and acute respiratory failure were reported up to 61% and 67%, respectively [21].

Mechanical ventilation was required in 2.1% to 16.7% of the symptomatic pregnant population [13] [17] [19] [22]. Lymphopenia, elevated liver enzymes (ALT, AST), elevated CRP and procalcitonin, and chest imaging abnormalities consistent with COVID-19 pneumonia were the frequently encountered investigation findings [13] [14] [18]-[23]. Mothers of positive COVID-19 were commonly treated with antibiotics, antivirals, low molecular weight heparin (LMWH) and corticosteroids [13] [14] [21] [25].

3.5. Outcomes

We found that 1.4% to 4.6% of the pregnant mothers experienced a pregnancy loss before 24 weeks of gestation [14] [15] [17] [22] [25], and 19.4% of pregnancy loss occurred in mothers who were infected in the first-trimester [22]. In terms of hypertensive disorders during pregnancy, which includes gestational hypertension, pre-eclampsia, eclampsia and Haemolysis, Elevated Liver enzyme and Low Platelet Syndrome (HELLP), the incidence rate was from 1.3% to 40.4% [13] [14] [15] [16] [17] [19] [20] [21] [24] [25]. The risk of developing pre-eclampsia or eclampsia was increased for pregnant women infected with COVID-19 disease (RR: 1.76, 95% CI: 1.27 - 2.43), even for the asymptomatic

mothers (RR: 1.63, 95% CI: 1.01 - 2.63) [24]. It was also found that 89.5% of new-onset gestational hypertensive disorders were detected at or after the diagnosis of COVID-19 infection [19]. Pregnant women with gestational diabetes ranged from 5.24% to 11.0% [14] [16] [17] [19] [20] [25].

In general, 1.1% to 11.1% of women were admitted to the intensive care unit (ICU) [13]-[25]. Pregnant women diagnosed with COVID-19 infection had a higher tendency for ICU admission as compared with non-infected mothers (RR: 5.04, 95% CI: 3.13 - 8.10) [24]. Among the COVID-19 positive pregnant women, those who were symptomatic, especially with a severe form of the disease, were at a higher risk of ICU admission [15] [17] [22]. Maternal deaths were uncommon, with mortality rates of no more than 1.6%. However, despite a wide range of confidence intervals, it was worth noting that pregnant women with COVID-19 were at a 22 times higher risk of dying (RR: 22.3; 95% CI: 2.88 - 172) [24].

The prevalence of preterm birth among pregnant women diagnosed with COVID-19 ranged from 9.7% to 26.6% (**Table 5**) [13]-[25]. Comparing symptomatic COVID-19 positive mothers to those without the infection, there was a 10-fold increased risk of preterm births in the infected women (OR: 11.43, 95% CI: 5.07 - 25.75) [25]. However, the rates of preterm births were similar among the asymptomatic maternal COVID-19 infection and non-infected pregnant women [15]. Medically indicated or iatrogenic preterm labour was more likely to occur in COVID-19 positive mothers (RR: 1.97, 95% CI: 1.56 - 2.51) [24]. Up to 83% of the iatrogenic preterm births were indicated due to COVID-19 symptoms

Table 5. The rates of preterm birth among COVID-19 positive mothers across different studies and their characteristics.

Author; Year of Publication	Preterm birth (General)	Medically indicated/Iatrogenic	Spontaneous
Al-Matary *et al.*; 2021	15.5	NA	NA
Ayed *et al.*; 2020	26.6	1.2	NA
Crovetto *et al.*; 2021	11.4	NA	NA
Cruz-Melguizo *et al.*; 2021	11.1	47.7	38.9
Haye *et al.*; 2021	16.5	NA	NA
Khoury *et al.*; 2020	14.6	NA	NA
Lokken *et al.*; 2021	9.7	NA	NA
Martinez-Perez *et al.*; 2021	13.8	7.7	6.1
Metz *et al.*; 2021	16.7	10.6	6.2
Saccone *et al.*; 2020	26.3	80.0	20.0
Taya *et al.*; 2020	18.5	8.8	NA
Villar *et al.*; 2021	22.5	18.8	3.8
Vousden *et al.*; 2021	18.3	14	4

*All figures were given in percentage; *NA: Not available.

or pneumonia [16] [20] [23]. Among them, up to 63.6% of the cases were from mothers with severe or critical COVID-19 disease [18] [19]. In another study, more than half of the women with severe COVID-19 delivered preterm, all of them being iatrogenic [23].

On the other hand, non-COVID-related indications for preterm deliveries that were commonly reported in the COVID-19 positive pregnant women were as follows: hypertensive disorders of pregnancy (7% - 33%), stillbirth (16%), preterm prelabour rupture of membranes (PPROM) (13%), spontaneous rupture of membranes (20.0%), small for gestational age (SGA) (15.5%), and foetal distress (13.2%) [16] [20] [21] [22] [24].

Vaginal birth accounted for 41.7% to 64.2% of all deliveries [13] [14] [16] [17] [18] [23] [25]. The overall caesarean section rates among the COVID-19 positive cohort ranged from 22.4% to 54.2% [13]-[25]. We observed a trend of Caesarean section for COVID-19 positive mothers who were symptomatic or experiencing severe forms of the disease [16] [17] [18] [21] [23] [25]. Vousden *et al*. showed a statistically significant increased risk of caesarean section delivery, as high as 1.5 -times, among pregnant women with symptomatic COVID-19 compared to those who were asymptomatic (OR = 1.51, 95% CI = 1.11 - 2.06) [25]. Severe and critical COVID-19 further increased the risk of caesarean section (RR: 1.62, 95% CI: 1.1 - 2.3, $p = 0.01$; RR: 2.8, 95% CI: 2.0 - 3.8, $p < 0.001$) [18]. Elective and maternal requests for caesarean delivery were as high as 44.3%, while other indications included hypertensive disorder of pregnancy, malpresentation, foetal distress, placental abnormalities and failed induction of labour [14] [16] [20] [21] [23] [25].

The incidence of perinatal losses (stillbirth and foetal death) remained low, accounting for 0.6% to 8.4% of deliveries [13]-[23] [25]. Up to 12.9% of neonates born to mothers with COVID-19 were tested positive for the disease [13] [14] [17]-[25]. Nearly half of the newborns were found to have IgG antibodies alone without any presentation of infection during the neonatal period [15].

4. Discussion

Obesity has always been a huge concern for women in the reproductive age range, and it is as common as affecting one-third of the pregnant women population in the West [26] [27]. Maternal obesity plays a role in disrupting maternal metabolism and predisposes pregnant women to a higher risk of gestational diabetes and pre-eclampsia, which can lead to adverse pregnancy outcomes such as preterm birth and perinatal mortality [26]. In our review, a BMI of more than 30 kg/m^2 was the most common pre-gestational comorbidities in the COVID-19 positive women. It was found that a higher proportion of pregnant women with severe COVID-19 disease were obese. A comparison with other studies identified a similar link between obesity and severe COVID-19 presentation among pregnant mothers [28] [29] [30].

There was a variability in the percentage of asymptomatic COVID-19 preg-

nant women in our systematic review. In part, the high proportion of COVID-19 pregnancies that were asymptomatic can be attributed to the universal screening of all pregnant women who were admitted to the hospital for deliveries [31]. We also observed that half or more (51.3% to 56.3%) of the COVID-19 diagnoses were made during the third trimester, which can be explained by the practice of conducting testing near term [31]. This situation has contributed to a higher proportion of women being tested positive in the 3rd trimester rather than in earlier stages of pregnancy, especially if they were asymptomatic.

Most symptomatic COVID-19 pregnancies in our study reported mild-to-moderate symptoms. This finding was consistent with the World Health Organization (WHO) report, which stated that pregnant women are not more vulnerable to a severe illness course [32]. Albeit the similar vulnerability between pregnant women and those of a similar reproductive age in terms of COVID-19 severity, the same cannot apply if the pregnancy is complicated with pulmonary comorbidities [aOR 4.3, 95% CI: 1.9 - 9.5], hypertensive disorders [aOR 2.7, 95% CI: 1.0 - 7.0] and diabetes [aOR2.2, 95% CI: 1.1 - 4.5] [33].

In this review, we did not identify any mention of the mutated SARS-CoV-2 strains and their impact on the COVID-19 severity in pregnant patients. However, a recent publication mentioned a potentially increased risk of developing severe COVID-19 if the mothers were infected with the delta variant, compared to the alpha variant [34].

Preterm birth can lead to higher neonatal and infant mortality rates, especially at lower gestational ages [35]. Babies born prematurely face issues like the requirement of intensive care services after birth, the need for ongoing health and developmental support, a higher risk of long-term neurological impairment and developmental delay, and increased mortality rates [36] [37]. We found that preterm birth was not more common (9.7% to 26.6%) for pregnant women with COVID-19 positive status per se, a finding supported by various other studies as well as global preterm birth rate estimations [37] [38] [39].

However, pregnancies with symptomatic or severe COVID-19 symptoms had a higher likelihood of preterm birth, mainly iatrogenic [40]. Delahoy *et al*. reported preterm birth rates for symptomatic and asymptomatic pregnant women with COVID-19 infection at 23.1% and 8%, respectively [41]. The dilemma to deliver prematurely stems from the need to balance between the benefit of improved maternal disease outcome and the risk of neonatal morbidity and mortality [42]. Still, it was inconclusive whether or not the delivery of infants showed significant improvement to the mothers' respiratory functions [43] [44] [45].

We reported that not more than half of the COVID-19 positive pregnant women underwent caesarean section. To date, no clear evidence has been found to support the indication of caesarean section for active COVID-19 infection [11] [46] [47]. Nonetheless, systematic reviews by Capobianco *et al*., Di Toro *et al*., and De Melo *et al*. have reported high rates of caesarean sections [11] [47] [48]. There are concerns on vertical transmission as vaginal delivery increases

the risk of cross-infection, and caesarean sections are performed to minimize maternal exertion during labour and improve maternal respiratory function as per local guidelines or recommendations [46] [48].

A higher risk of caesarean births was reported for symptomatic pregnant women, a finding also supported by Vouga M *et al*. [33]. Furthermore, the risk of foetal distress may be increased during labour when the mother is symptomatic for COVID-19 [49] [50] [51] [52]. Possibly, the higher risk for foetal distress and potential maternal compromise led to higher rates of caesarean deliveries in symptomatic mothers, but a clear link between maternal COVID-19 severity and caesarean section was yet to be established. This finding implicated the value of a COVID-19 positive mother to deliver in an obstetrical unit where immediate access to emergency services can be provided if needed [40].

Pregnancies that were complicated with severe COVID-19 were at a higher risk of developing pre-eclampsia. Similar findings have been reported in a systematic review by Ghayda *et al*. [53]. It can be explained by the overexpression of proinflammatory cytokines (IL-6, TNF-alpha, IFN-gamma, etc.) during severe COVID-19, whose levels were also significantly raised in the preeclamptic placentas [54]. However, the coronavirus-provoked inflammatory cascade, better known as the "cytokine storm", was not found to influence the levels of specific pre-eclampsia-related angiogenic and anti-angiogenic markers like P1GF and sFLT-1 [55]. Nonetheless, placental inflammation serves as the linkage between COVID-19 and adverse foetal outcomes [56]. Another theory mentioned the downregulation of ACE2 as SARS-CoV-2 binds to it when entering host cells. With the lower level of ACE2, there is an increased plasmatic concentration of angiotensin II [57], whose primary function is to raise blood pressure through vasoconstriction [58].

While ICU admission rates remained low, both COVID-19 infections and their severity are associated with a higher risk of ICU admission. Consistent trends were observed by Huntley *et al.* and Elsaddig *et al*., which found that more pregnant women who were positive for COVID-19 required ICU admission compared to their non-infected counterparts [59] [60]. That being said, there is a possibility of a lower threshold for initiating treatment in pregnancies instead of more serious diseases [39] [59].

The most commonly encountered laboratory findings of COVID-19 infection in our reviewed studies include lymphopenia, elevated liver enzymes (ALT, AST), increased CRP, and procalcitonin, which can be useful as parameters to predict ICU admission [61]. We reported a small percentage of perinatal losses from our studies. Despite the low stillbirth rates, a positive COVID-19 diagnosis increases the risk for stillbirth by almost two-fold [28] [30] [62]. Studies examining the placental histopathology of COVID-19 infected mothers have found an increased frequency of vascular malperfusion and villitis, suggesting a plausible mechanism to explain the higher risk of stillbirth for COVID-19 mothers [63] [64] [65].

5. Conclusions

Despite the inclining rates of COVID-19 infection globally, most pregnant women expressed mild to moderate symptoms when infected with SARS-CoV-2. However, maternal pregestational comorbidity, in particular, an increased BMI, was shown to be associated with severe COVID-19 disease. Women with symptomatic COVID-19 had an increased risk for preterm birth compared to asymptomatic women, but the risk was not nearly as high as those with a severe or critical form of the COVID-19 disease. Another significant outcome was C-section, in which its incidence rate increased significantly, especially in the severe COVID-19 group. Other maternal outcomes, including maternal death, intrauterine death and infection, hypertensive disorders in pregnancy, stillbirth and post-partum haemorrhage, had lower incidence rates.

This review was consistent with previous studies on the increased pre-eclampsia, preterm birth, and caesarean delivery rates in COVID-19 positive pregnant women. This paper mainly contributes to identifying a potential link between COVID-19 severity and iatrogenic deliveries, including caesarean section, while establishing that COVID-19 itself may not be the chief offender in adverse maternal outcomes if the mother is asymptomatic or experiencing only mild COVID-19 symptoms.

This study has some limitations. We acknowledge that most of our study data are from a White or Middle-Eastern background, and thus, it may not be applicable to the Asian, south-east Asian, or Black communities. We also could not conduct a meta-analysis on the available data, which meant that we could not have pooled evidence to draw the conclusions on the summary estimate of the effect. While an effort was made to keep this review as updated as possible, it was understood that more research has to be done to maintain the validity of information as the COVID-19 situation keeps evolving and more papers emerge in the field. In addition, further studies are needed to evaluate the maternal management modality to induce a better prognosis among COVID-19 infected pregnant women in the future.

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Conflicts of Interest

There are no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this review. The authors also declare no conflicts of interest regarding the publication of this paper.

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List of Abbreviation

Abbreviation	Representation
2019-nCoV	2019 Novel Coronavirus
95% CI	95% Confidence Interval
aOR	Adjusted Odds Ratio
ACE2	Angiotensin Converting Enzyme 2
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
COVID-19	Coronavirus Disease 19
CPAP	Continuous Positive Airway Pressure
CRP	C-Reactive Protein
ECMO	Extracorporeal Membrane Oxygen
Emtree	Embase Subject Headings
HELLP	Haemolysis, Elevated Liver enzyme and Low Platelet Syndrome
ICU	Intensive Care Unit
IFN-gamma	Interferon Gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-6	Interleukin-6
LMWH	Low Molecular Weight Heparin
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MeSH	Medical Subject Headings
NICU	Neonatal Intensive Care Unit
NOS	Newcastle-Ottawa Scale
OR	Odds ratio
PECO	Population, Exposure, Comparison/Control, Outcome
PlGF	Placental Growth Factor
PPROM	Preterm prelabour rupture of membranes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RT-PCR	Real-time polymerase chain reaction
RR	Relative risk
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sFLT-1	Soluble Fms-Like Tyrosine Kinase-1
TNF-alpha	Tumour Necrosis Factor Alpha
WHO	World Health Organisation