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Neonatal Outcomes of COVID-19 Positive Pregnant Women: A Systematic Review

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Abstract

Pregnant women experience physiological changes such as pulmonary adaptation due to an elevated diaphragm and altered cell immunity. These factors can predispose pregnant women to enhanced susceptibility to severe viral pneumonia infection, leading to adverse pregnancy outcomes associated with increased mortality and morbidity in neonates. Currently, the COVID-19 pandemic has reported over 230 million cases reported globally and generated evidence on raising concerns about maternal infection on the added risk of adverse neonatal outcomes. The review aims to evaluate the effects of COVID-19 on neonatal outcomes of infected pregnant women. We conducted the systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. To identify relevant articles based on the inclusion and exclusion criteria on COVID-19 infected pregnancies and the neonatal outcomes, we searched four databases (PubMed, Embase, Scopus and Web of Science) from January 01, 2020 to June 20, 2021 by using medical subject heading and keywords under the PECO concept (P = pregnant women, E = COVID-19, O = neonatal outcome). We also assessed the risk of bias of the selected articles. We found that newborns of COVID-19 positive mothers are more likely to be born prematurely and by caesarean section. They need NICU admissions mainly due to prematurity related to maternal COVID-19 status at delivery. We did not find any evidence linking maternal COVID-19 status to low Apgar score, low birthweight, neonatal resuscitation at birth and neonatal death. Neonatal SARS-CoV-2 positive status was infrequently reported. The possibility of vertical transmission was raised, which may contribute to a large number of preterm births and caesarean deliveries in the COVID-19 positive mothers, but there is a paucity of evidence on vertical transmission. There is a shift in focus from vertical to horizontal transmission in the case of neonatal COVID-19 infection, thereby emphasizing the implementation of safety precautions while balancing the need to al-low breastfeeding and mother-to-infant skin contact. This systematic review provides evidence on the necessity of close monitoring of neonates of COVID-19 positive mothers and taking preventive measures against the acquisition of COVID-19 in neonates.

Subject Areas

Infectious Disease, Obstetrics and Gynaecology, Neonatology

Keywords

Systematic Review, Pregnant Women, COVID-19, Neonatal Outcomes

1. Introduction

The COVID-19 disease was identified in late 2019 [1] [2] [3] [4], leading to severe respiratory consequences. It was caused by a new mutation of the coronavirus and is now known as SARS-CoV-2 [1] [5]. Worldwide, the viral outbreak has led to an accumulation of 230 million cases as of September 25, 2021 [6]. An estimation of 1 in 200 pregnant women was affected with COVID-19 during their pregnancy [7].

This novel coronavirus shares a similarity of 80% and 50%, respectively, in terms of the viral genome with two other well-known coronaviruses that were responsible for causing the severe acute respiratory syndrome (SARS) and middle-east respiratory syndrome (MERS), namely the SARS-CoV and MERS-CoV [1] [5] [8] [9]. Previous studies have linked maternal infection and systemic inflammation to a risk of progression into undesirable obstetrical and neonatal outcomes like pre-eclampsia, preterm birth, stillbirth, small-for-gestational-age, and low birth weight due to disruption in the placental hemodynamics [10]. Moreover, during pregnancy, women experience physiological changes such as an elevated diaphragm in response to the accommodation of the developing foetus, leading to decreased pulmonary functional residual volume and respiratory tract mucosal oedema and friability due to high levels of oestrogen. These pulmonary changes and altered cell immunity can predispose pregnant women to enhanced susceptibility to severe viral pneumonia infections and lead to adverse pregnancy outcomes [11] [12] [13] [14].

To date, the possibility of mother-child vertical transmission remains controversial. The incidence of COVID-19 infection in newborns to mothers with SARS-CoV-2 positive status has been reported in many studies. The angiotensin-converting enzyme 2 (ACE-2) receptors, where SARS-CoV 2 binds to for cell entry, are also abundantly detected in the placenta, supporting the biological plausibility of intrauterine transplacental vertical transmission [15]. However, several studies challenged the feasibility of vertical transmission, be it through the placenta, during vaginal delivery or breastfeeding, as SARS-CoV-2 was not discovered in the samples of amniotic fluid, cord blood and breast milk [16].

Thus, this study aims to identify the potential neonatal outcomes associated with a COVID-19 infected pregnancy by critically appraising the latest available evidence. In addition, it aims to summarise the incidence rates of the interested neonatal outcome and provide a comprehensive logical discussion based on previously established scientific facts. Thus, this review finding will contribute to providing a consensus on the management of neonates of COVID-19 positive mothers, including isolation precautions and the safety for breastfeeding after birth.

2. Methods

2.1. Search Strategy

We conducted this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method to identify relevant articles on COVID-19 infected pregnancies and the neonatal outcomes. We searched the relevant articles in four databases (PubMed, Embase, Scopus and Web of Science) published from January 01, 2020 to June 20, 2021. The primary reviewers' institution subscribes to these four electronic databases; hence, it was convenient to get access to full-text resources. It did not limit the scope of the study as we need full text to extract data. All databases were searched using subject headings and keywords related to COVID-19 infection, pregnant women and neonatal outcomes (Table 1).

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: Neonatal outcomes	• Infant, Newborn • Pregnancy outcome • Neonatal outcome • Newborn outcome • Infant outcome • Perinatal outcome	• Neonates • Neonatal outcome • Newborn outcome • Infant outcome • Birth outcome • Pregnancy outcome • Obstetric outcome • Perinatal outcome

The typical search string, which was used across all databases, is [("Covid" OR "SARS-CoV-2" OR "Covid-19" OR "Coronavirus disease 2019" OR "2019-nCoV") AND ("Pregnancy" OR "Pregnant" OR "Pregnant woman") AND ("Neonatal outcomes" OR "Newborn outcomes" OR "Infant outcomes" OR "Perinatal outcomes")]. We further refined the search results by applying filters including "only English language articles, females with ages ranging from 19 to 44 years and newborns of 0 to 12 months as the research population".

2.2. Selection Criteria

1) Inclusion criteria: We identified the following criteria to include the relevant studies in this review:

- Study types: Cohort study, randomized controlled trials, database analysis;
- Study sample size: More than 100 newborns whose mothers were COVID-19 positive during pregnancy;
- Neonatal outcomes of COVID-19 infected pregnancies are reported;
- If the full text is available;
- English language.

2) Exclusion criteria: Following criteria were considered before excluding any study from this review:

- Study types: Case reports, case series, cross-sectional studies, protocol papers, review articles;
- Study sample size: Less than 100 newborns whose mothers were COVID-19 positive during pregnancy;
- Incomplete trials or duplicate publications of the same study that yield similar results;
- If the specific neonatal outcomes are not mentioned;
- If the language is not in English.

2.3. Screening

We decided to screen the articles published from January 01 2020 onwards, as Covid-19 became pandemic on March 11, 2020. Primarily, we identified 2504 articles from the four databases and exported them to Endnote, a citation manager, where we identified the duplicated and removed them. Primary reviewers concurrently screened all the prospective articles by title and abstract based on the inclusion and exclusion criteria and went through the full text of the shortlisted eligible articles. Finally, they included 13 articles in this review based on their consensus (Figure 1).

2.4. Data Extraction

To extract data, two primary reviewers (JK and JT[1]) developed a standardized form, which includes: study design, sample size, main study findings and conclusion, and pull out all the potential data independently from 13 finally selected

[1]JT: Jiexi Teoh; JK: Junwen Khong.

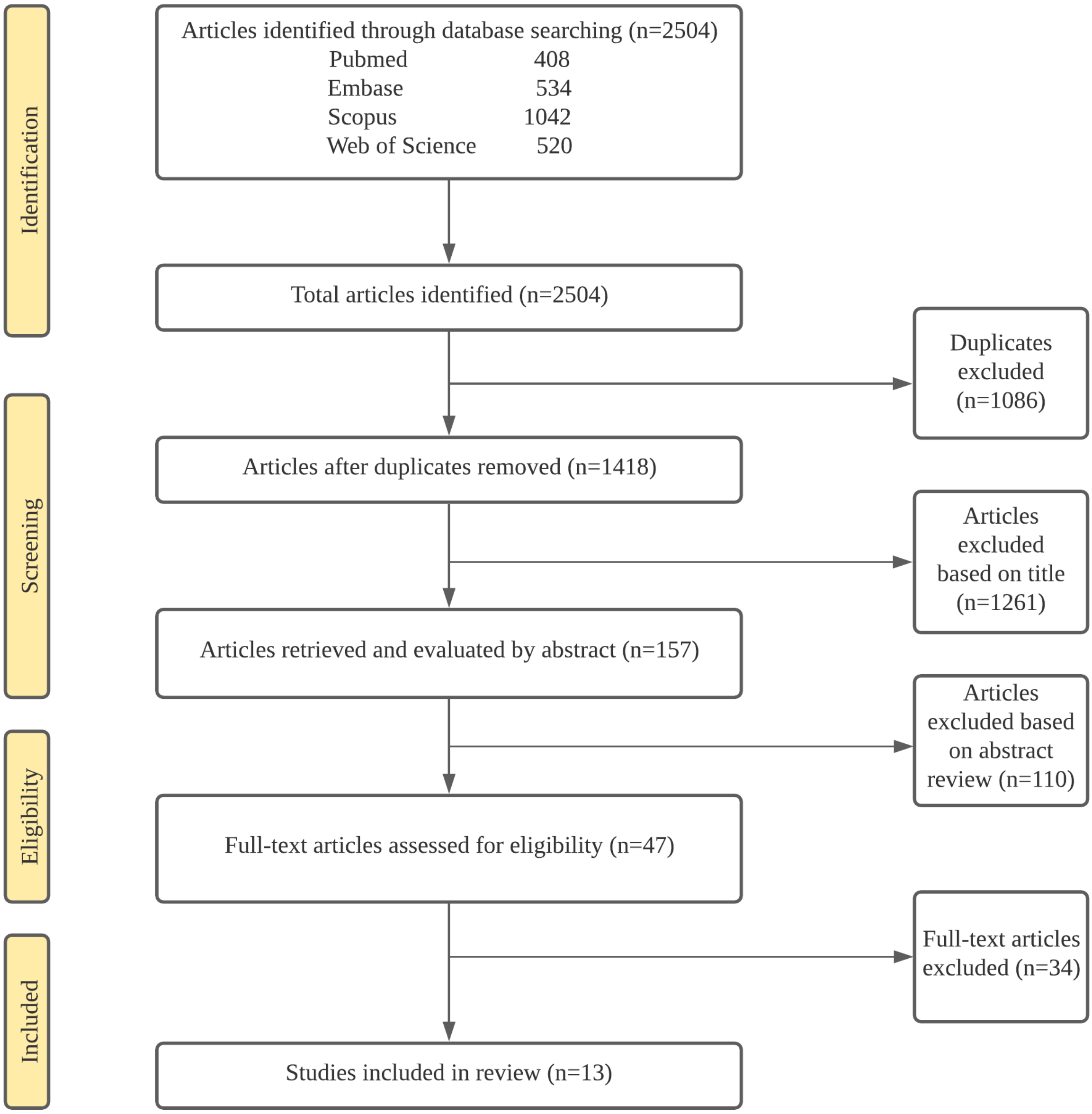

Figure 1. PRISMA chart used for the selection of articles.

articles. Thereafter, they compared their individual data and reached a consensus before exporting the data into Nvivo for analysis. In the data analysis, the neonatal outcomes of interest were: APGAR scores at 1 and 5 minutes; neonatal intensive care unit (NICU) admission; neonatal investigations for COVID-19; neonatal mortality rate. They invited the 3rd reviewer, either SSSH or NKJ[2], when they could not resolve any raised disagreement between them.

2.5. Quality Assessment:

We employed the Newcastle-Ottawa Scale (NOS), a quality assessment tool for both cohort and case-control studies included in a systematic review, to assess the quality of the selected studies (Table 2). We decided to use this NOS tool as

[2]SSSH: Sharifah Shahirah Syed Hashim; NKJ: Nowrozy Kamar Jahan.

Table 2. Risk of bias assessment of the selected cohort studies using the newcastle-ottawa scale.

First author; Country; 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.*; Saudi Arabia; 2021	★		★	★	★	★	★	★		7
Angelidou *et al.*; USA; 2021	★		★	★	★	★	★	★	★	8
Gabriel *et al.*; Spain; 2020	★		★	★	★	★	★	★	★	8
Gupta *et al.*; India; 2021	★	★	★	★	★	★	★			7
Hcini *et al.*; France; 2020	★	★	★	★	★	★	★	★	★	9
Khoury *et al.*; USA; 2020	★		★	★	★	★	★	★	★	8
Maraschini *et al.*; Italy; 2020	★	★	★	★	★	★	★			7
Norman *et al.*; Sweden; 2021	★	★	★	★	★	★	★	★	★	9
Oncel *et al.*; Turkey; 2021	★	★	★	★	★	★	★	★	★	9
Saccone *et al.*; Multinational; 2021	★	★	★	★	★	★	★	★	★	9
Sánchez-Luna *et al.*; Spain; 2021	★		★	★	★	★	★	★		7
Singh *et al.*; India; 2021	★	★	★	★	★	★	★			8

most of our included studies were cohort studies, either prospective or retrospective. While assessing the selected studies' quality using the NOS tool, we had to consider three parameters: selection = 4, comparability = 2 and outcome = 3. Two primary reviewers assessed the quality independently and invited the third reviewer to resolve any disagreement.

3. Results

In this systematic review, we included 5183 neonates who were born to the COVID-19 positive mothers [17]-[29]. The median gestational age at birth ranged from 38 to 39 weeks, while the mean gestational age at birth ranged from 36.6 to 39.2 weeks [17] [18] [20] [22] [25] [26] [27] [28]. The main study findings and conclusion are summarized in Appendix **Table S1**.

3.1. Pregnancy Characteristics and Exposure

The median age of COVID-19 positive mothers included in this review ranged from 25 to 33 years [17] [21] [22] [24] [28], while the mean age was from 24.7 to

32.2 years [18] [20] [25] [27]. A majority of the mothers were diagnosed with COVID-19 in the third trimester of pregnancy (69.8% to 92.1%) [17] [19] [27]. The percentage range of asymptomatic COVID-19 positive mothers was extensive, from 24.2% to 86.1%. [18] [19] [20] [21] [22] [24] [27] [28] [29]. As for the symptomatic women, 26.5% to 34.29% of them presented with mild-to-moderate COVID-19 symptoms [21] [22] [28] [29]. The majority (61.1%) of the symptomatic mothers do not require any form of respiratory support [17]. Meanwhile, a lesser percentage (0.76% to 26.1%) of pregnant women were classified as having severe or critical COVID-19 disease [21] [22] [28] [29]. We found that 1.4% to 19.2% of mothers required some form of respiratory support, which included nasal cannula, face mask, high flow nasal cannula, continuous positive airway pressure (CPAP), mechanical ventilation, and intubation [17] [21] [22] [24] [27] [28].

3.2. Maternal Comorbidities

Overweight or obesity was the most commonly reported maternal pre-existing comorbidities in eight studies, recording 55.1% as the highest incidence rate [17] [21] [22] [24] [25] [27] [28] [29]. It was reported that a maternal BMI of more than 30 kg/m^2 had an impact on the disease severity of COVID-19 [22]. We found that 0.6% to 4.1% mothers had a diagnosis of type 2 diabetes mellitus [17] [24] [28], while 0.6% to 3.4% of them had pregestational hypertension [17] [21] [24] [26] [28]. The rates of gestational diabetes ranged from 4.6% to 14.8% [20] [21] [25] [26] [28] [29]. We also found that 2% to 13.64% of the COVID-19 positive mothers experienced hypertensive disorders of pregnancy, which included gestational hypertension and pre-eclampsia [17] [20] [21] [26] [28] [29].

3.3. Neonatal Outcomes

The median Apgar score at 1 min was 8 - 9 (IQR: 7 - 9) [19] [26] [28], and 87.1% to 89% of the neonates achieved a 1 min Apgar score of >7 for those who were born to symptomatic COVID-19 mothers [21] [24]. As for the 5-min Apgar score, 93.52% to 97.9% of the newborns had a score of >7 [20] [21] [24] [25], and the median score achieved was 9 - 10 (IQR: 9 - 10) [19] [22] [28]. One study found that newborns with a positive SARS-CoV-2 infection had significantly lower 5th minute Apgar score than those who were negative [8 (7 - 9) vs. 9 (9 - 10), p = 0.039, 95% CI: 0.263 - 0.998] [26]. We also found that 76% to 85% of the newborns of COVID-19 positive mothers had a birthweight of more than 2500 g [17] [23] [24]. The mean birthweight ranged from 2590 g to 3436 g [18] [19] [20] [21] [25] [27] [28] [29]. Neonates from symptomatic COVID-19 mothers had a lower birthweight compared to those born to asymptomatic mothers (2821 ± 846 g vs. 3149 ± 496, p = 0.004) [27]. The percentage of newborns who were identified as small for gestational age (SGA) or intrauterine growth restriction (IUGR) ranged from 1.5% to 11.3% [17] [18] [21] [23] [25] [27] [29]. The rate of perinatal losses, inclusive of miscarriage, termination of pregnancy, and stillbirth, varied from 0.8% to 5.1% [17] [20] [21] [22] [24] [27] [29]. There were 30 neonatal deaths reported from six studies [18] [23] [25] [27] [28] [29].

We found that 4.8% to 28.7% of the neonates were premature [17]-[29], and 15% to 71.2% of the newborns were delivered via caesarean section [17]-[22] [24]-[29]. Up to 23.8% of the caesarean deliveries were indicated due to maternal COVID-19 status and severity [19] [22] [24] [28]. There was a huge variability observed between the studies for the rate of neonatal intensive care unit (NICU) admission (2.3% - 86.4%) [17]-[29]. The reasons for high rates of NICU admission were linked to maternal COVID-19 status and severity, neonatal complications, requirements for isolation from the COVID-19 infected mothers, and hospital management difficulties in organizing rooming-in for the newborns [17] [25] [26] [28] [29].

Among the neonatal complications reported, prematurity and low birth weight were the most common [22]. For neonates who were admitted to the NICU due to clinical symptoms, their median length of hospital stay was longer than those under normal care (2.5 days, IQR: 2.5 - 7 days vs. 2 days, IQR: 2 - 2.33 days) [28]. While a big proportion (89.5%) of the neonates born to COVID-19 positive mothers do not require any form of respiratory support [19], it is found that in other studies, the need for respiratory support in the form of mechanical ventilation, continuous positive airway pressure (CPAP), or intubation ranged from 1.0% to 15.7% [17] [18] [23] [25] [29]. The demand for CPAP and mechanical ventilation was also found to be higher in neonates born to mothers infected with COVID-19 (4.9% vs. 3.8%; OR, 1.32; 95% CI, 1.06 - 1.64; 1.6% vs. 0.5%; OR, 3.51; 95% CI, 1.856.65) [25]. The percentage of neonates requiring any form of resuscitation at birth ranged from 3.6% to 30% [18] [19] [22] [23] [25] [28]. Newborns from COVID-19 positive mothers were more likely to receive resuscitation in the form of assisted ventilation (CPAP or face mask) and intubation at birth compared to those who were born to non-COVID positive mothers (6.4% vs. 5.1%; OR, 1.28; 95% CI, 1.05 - 1.55; 0.6% vs. 0.3%; OR, 1.90; 95% CI, 1.002 - 3.59) [25].

SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) testing was done for most of the neonates from mothers who were positive for COVID-19 disease [17]-[29]. Among the 5052 (97.5% of 5183) neonates who tested for COVID-19 infection, 116 of them (2.3%) were found to have a positive SARS-CoV-2 RT-PCR test result within 96-hour of post-birth (**Table 3**) [17]-[29].

In particular, 101 of them were diagnosed with COVID-19 within 24-hours of life [18] [19] [22]-[29], and 30.3% of the neonates who tested positive for COVID-19 were symptomatic of the disease [23]. It was reported that newborns with a positive SARS-CoV-2 status were at a higher risk of neonatal death (OR 4.8, 95% CI 1.25 - 18.36) [23]. All the placenta samples tested for SARS-CoV-2 infection were negative [21] [28]. COVID-19 infected newborns had a significantly lower neutrophil count than those who tested negative for the infection [3235 (2235 - 5500) vs. 8445 (4965 - 12,385), 95% CI: 1.002 - 1.005, p = 0.024]

Table 3. Number of neonatal COVID-19 infections with nasopharyngeal swab testing or RT-PCR from included articles in the review.

Article; Study country; Year of Publication	No. of neonates tested	No. of neonates with positive SARS-CoV-2 status within 96 hours of life	No. of neonates with positive SARS-CoV-2 status detected within 24 hours of life	No. of neonates with positive SARS-CoV-2 status detected after 24 hours of life
Al-Matary *et al.*; Saudi Arabia; 2021	200	N/A	N/A	N/A
Angelidou *et al.*; USA; 2021	225	5	5	N/A
Gabriel *et al.*; Spain; 2020	230	13	11	2
Gupta *et al.*; India; 2021	108	N/A	N/A	N/A
Hcini *et al.*; France; 2020	108	4	N/A	4
Khoury *et al.*; USA; 2020	236	6	6	N/A
Malik *et al.*; India; 2021	523	33	33	N/A
Maraschini *et al.*; Italy; 2020	138	9	5	4
Norman *et al.*; Sweden; 2021	2323	21	20	N/A
Oncel *et al.*; Turkey; 2021	120	4	4	N/A
Saccone *et al.*; Multinational; 2021	251	1	1	N/A
Sánchez-Luna *et al.*; Spain; 2021	469	18	14	4
Singh *et al.*; India; 2021	121	2	2	N/A
Total	5052	116	101	14

*1 case of positive SARS-CoV-2 was detected post-neonatal period (28 days). *N/A: Not available.

[26]. They also had a higher demand for mechanical ventilation or CPAP, and longer hospitalization compared to non-COVID-19 infected neonates (75% vs. 19%, 95% CI: 1.271 - 128.5, p = 0.028); [26 (15 - 48.5) vs. 7 (3 - 11) days, 95% CI: 1.018 - 1.148, p = 0.033] [26]. The same study also reported that mothers who gave birth to SARS-CoV-2 positive newborns, compared to those who had non-infected newborns, were diagnosed with COVID-19 at an earlier stage of pregnancy, which warrants further evaluation to establish a link (35 weeks vs. 37 weeks, p = 0.306) [26].

We found that 40.2% to 59.6% of COVID-19 positive mothers breastfeed their children. [18] [19] [26] [27] [28]. At discharge, as high as 94.4% of the mothers were breastfeeding [25]. The rates of maternal-neonate separation after birth varied greatly between different studies, ranging from 8% to 92% [18] [19] [23] [26] [28] [29], and there was even one study that did not practice any isolation at all [21]. For studies that promoted separation between the mother and neonate, the rationales given were isolation from the infected mother and organizational limitations such as the mother being in a COVID-19 ward instead of an isolated room [19] [23] [26].

4. Discussion

We found that a majority of the newborns of COVID-19 positive mothers had a birthweight of more than 2500 g, with the mean birth weight ranging from 2590 g to 3436 g. This finding was consistent with the findings from other systematic reviews, with the median and mean birth weight at 3120 g and 3144.71 g, respectively [30] [31]. Despite the reassuring results, it was suggested that women who were infected with COVID-19 early in pregnancy or who suffered from chronic hypoxia require more frequent monitoring of the foetal growth to assess for intrauterine growth restriction or retardation [32]. However, Tadas *et al.* demonstrated a statistically significant higher mean birthweight in newborns of COVID-19 positive mothers compared to the controls. The difference was attributed to the baseline nutritional and socioeconomic status variability, where most cases originated from urban areas with adequate nutrition [33]. Low birthweight was reported to be associated with a higher rate of perinatal death, while IUGR was speculated to be common in SARS-CoV-2-infected pregnancies according to previous experience from other SARS pandemics [34] [35]. However, our rate of perinatal losses in COVID-19 affected pregnancies ranged from 0.8% to 5.1%, a mean rate similar to that of a systematic review by Chamseddine *et al.* [35]. The rate of stillbirth was higher than in the pre-COVID-19 era, but the further evaluation has to be explored to identify a link between COVID-19 and stillbirth rates [36].

Low 5-minute Apgar scores have been reported to have a 20- to 100-fold increase in relative risk for cerebral palsy compared with neonates with good scores of 7 to 10 [37] [38] [39]. From our findings, most of the neonates born to COVID-19 positive mothers have a good Apgar score of more than 7 at 1-minute and 5-minute, which is a trend supported by other systematic reviews [40] [41]. Verma *et al.* added that APGAR scores were similar between asymptomatic and symptomatic COVID-19 positive pregnant women [42]. It was thought that a low Apgar score in babies of COVID-19 positive mothers was likely to be secondary to pulmonary immaturity if the neonates were born preterm [43]. Our review found that NICU admission rates were not uniform across included studies, in which neonatal complications and implementation of maternal-infant isolation contributed to the higher rates. Similar reasons were demonstrated in the study by Dube *et al*., where the main indications for NICU admission were for isolation and prematurity-related complications [43].

Premature babies face an increased risk of short-term and long-term morbidities and mortality. In fact, prematurity is the leading cause of death in children under the age of 5 [12]. Complications that are commonly associated with preterm infants include higher rates of respiratory distress syndrome, bronchopulmonary dysplasia, infections (inclusive of sepsis), necrotising enterocolitis, periventricular leukomalacia, seizures, cerebral palsies, intraventricular haemorrhage, hypoxic-ischaemic encephalopathy, feeding issues, and problems with vision and hearing [44] [45] [46]. It was found that maternal pneumonia can result in adverse maternal and neonatal outcomes. Preterm labour, intrauterine foetal death, intrauterine growth restriction, and neonatal death are common adverse outcomes associated with pneumonia during pregnancies [47] [48] [49] [50].

In our review, it was found that up to one-third of the newborns were premature. Theories have proposed that maternal COVID-19 may lead to hypoxemia, leading to an increased risk of foetal distress, causing birth asphyxia or meconium-stained amniotic fluid [51]. The increased demand for oxygen in the COVID-19 affected mother secondary to severe foetal hypoxemia and acidemia may indicate an early delivery [52]. COVID-19 infection during pregnancy leads to an increased rate of medically indicated preterm delivery, as described by a systematic review by Allotey *et al*., stating that the rates of spontaneous preterm births in COVID-19 affected mothers were mainly similar to the pre-pandemic rates [53]. However, whether preterm births were secondary to iatrogenic causes linked to maternal or foetal compromise, or other etiologies, will need to be explored further before coming to a conclusion [54].

A high proportion of the newborns in our review were born via caesarean section. The rationale behind the increased rate of caesarean deliveries was to reduce the risk of infection from the COVID-19 positive mothers and reduce the burden of maternal effort during labour [55] [56]. However, current recommendations indicate that COVID-19 infection should not be the sole indication for caesarean delivery and preterm births [52] [54] [57]. A Spanish study with a 6.9% (5/72) of neonatal COVID-19 infection rates mentioned no difference between vaginal and caesarean deliveries [58]. The decision for caesarean section should take into account the maternal disease severity and comorbidities, maternal and foetal status, and gestational age [52] [59] [60]. Studies have supported the safety of vaginal delivery as none of the vaginal secretions samples from COVID-19 positive pregnant women were tested positive for SARS-CoV-2 [61] [62]. In addition, maternal vaginal secretions exposure was found to be associated with the development of immunogenic response in neonates [63].

A huge concern arises when pregnant women are infected with COVID-19, as the risk of cross-infection to the in-utero foetus cannot be neglected. It also contributes to the decision of perinatal management with the priority to prevent maternal and neonatal adverse outcomes, be it short-term or long-term. Neonatal SARS-CoV-2 may be acquired from the vertical transmission, either during the intrauterine period through the placenta or amniotic fluid, or the intrapartum period from exposure to infected maternal vaginal secretions, urine and faeces, or via postpartum contact with infected mothers or healthcare workers [64]. In our review, we reported a rate of 2.3% for neonatal COVID-19 infections, which accounted for 116 cases. In particular, 87.9% (102/116) of those infected were detected with SARS-CoV-2 within the first day of life. Similar findings (2.0%; 208/10188) of neonatal SARS-CoV-2 test positivity were reported in the National Perinatal COVID-19 (NPC-19) Registry by the American Academy of Paediatrics [65]. Pooled data from other systematic reviews also reported a rate of 2% for the newborns who tested positive for SARS-CoV-2 virus via nasopharyngeal swab [66] [67]. To date, there was unclear evidence to confirm the absolute risk of vertical transmission [59]. Samples of amniotic fluid, umbilical cord blood and breastmilk were explored for SARS-CoV-2 using RT-PCR in the study by Chen *et al*., with all nine results returning as negative [68].

In contrast to our findings, another study by Penfield *et al*., identified three placental samples with positive SARS-CoV-2 test results among the 11 tested [56]. However, there was no neonatal COVID-19 infection detected. Theories support the role of the placenta as a physical barrier to viral entry and mediation of antiviral immune response by the placental immune cells [11] [69] [70]. In addition, 14 among the total of 16 infected infants in the study by Woodworth et al. were born to mothers who were diagnosed with COVID-19 within the period of 14 days before birth, thereby suggesting the possibility of intrapartum or postpartum vertical transmission [71]. There may be a role for SARS-CoV-2 specific IgM antibodies as a better detection tool for in-utero infections as IgM antibodies do not cross the placenta [72] [73].

Early postpartum neonatal SARS-CoV-2 acquisition has gained more attention, with Raschetti *et al*. attributing 70% of the 176 neonatal COVID-19 infections to horizontal transmission by exposure to infected mothers or healthcare personnel during the care immediately after birth [74]. In view of mitigating the risk of horizontal transmission, studies have looked into the implementation of maternal-infant separation, which includes social distancing measures and the safety of immediate breastfeeding. The practice of maternal-newborn separation varied distinctively in our paper. To date, skin-to-skin contact has been recommended as a consequence of shared decisions between individual mothers and healthcare teams after weighing the risks and benefits as no clear evidence exists to support the increased risk of COVID-19 transmission by allowing skin-to-skin contact [75] [76] [77].

A systematic review which included a total of 82 breast milk samples analysis found that 13% (9/68) of breast milk samples tested positive for SARS-CoV-2, and one sample (7%, from another 14 samples tested for antibodies) had identified SARS-CoV-2 IgG antibodies [78]. Sahin *et al*. has reported 1 case of positive test result for SARS-CoV-2 in breast milk samples among the 533 mothers tested [79]. Nonetheless, breastfeeding has not been shown to be a vector of SARS-

CoV-2 transmission [63] [64]. Instead, breastfeeding provides passive immunity for the infants against COVID-19 as breast milk contains anti-SARS-CoV-2 antibodies [63] [80] [81]. In our review, breastfeeding rates among COVID-19 infected mothers were not optimum (40.2% to 59.6%).

For COVID-19 infected mothers, breastfeeding is not contraindicated but should be practised with safety precautions to minimize postpartum horizontal transmission, where infants are exposed to infectious respiratory droplets from mothers or care providers and environmental sources of infection [82]. Infected mothers are recommended to wear surgical masks, maintain hand and breast hygiene during breastfeeding, and keep social distance with infants between feedings while staying in the same room [64] [82] [83]. Overall, breastfeeding offered nutritional, immunological and developmental benefits, which outweigh the relatively small potential risk of transmission [84] [85].

Our review concluded low rates of SARS-CoV-2 acquisition among neonates. Literature has suggested possible aetiologies of lower infection rates and milder presentation in newborns to be associated with the passive protection from maternal transfer of IgG antibodies and the immature immune system, while further research is needed to bridge the gap [86] [87] [88] [89]. Reduced ACE2 expression in newborns and younger children compared to adults was also found to have contributed to less inflammation, dampened immune response, milder symptoms and subsequent quicker recovery in infants [86] [90] [91]. Interestingly, we found data reporting significantly lower neutrophil counts in COVID-19 infected neonates when compared to those non-infected [26]. While age-related ACE2 expression was linked to COVID-19 presentations and severity, placental expression of ACE2 seemed to be elevated with the advancement of pregnancy [59] [92]. ACE2 receptors in the placenta were found to be at an exceptionally low level in the first-trimester of gestation, thereby making first- trimester vertical transmission unlikely [59]. In contrast, we found that COVID-19 positive neonates were more likely to be born to mothers diagnosed with COVID-19 at the earlier stage of pregnancy [26].

5. Conclusions

The outlook of neonates born to COVID-19 positive mothers seems to be relatively reassuring as most newborns had a 5-min Apgar score of more than 7 and minimal symptoms despite increased caesarean and preterm deliveries rates in the infected pregnancies. Current evidence suggests that iatrogenic preterm births should not be indicated due to the sole reason of maternal COVID-19 status or the prevention of vertical transmission. Instead, it should take into account the maternal and foetal compromise on a case-to-case basis.

While the risk of vertical transmission cannot be safely excluded from currently available evidence, horizontal transmission during intrapartum and postpartum periods has been speculated to cause higher rates of neonatal SARS-CoV-2 acquisition. However, the possibility of cross-infection should not restrict breastfeeding, and skin-to-skin contact after delivery as both of them offer greater benefits for the overall development of the infants over the potential risk of SARS-CoV-2 infection. Nonetheless, disease prevention strategies including social distancing, use of surgical masks and hand hygiene along with close monitoring should continue to be undertaken to minimize neonatal exposure to SARS-CoV-2 through close contact with the mother and the hospital environment. This systematic review provides a new focus on the potential of horizontal transmission being the main culprit for neonatal SARS-CoV-2 infection, which warrants further research to develop a link between the two factors.

Nonetheless, our study has a few identifiable limitations. We could not conduct a meta-analysis due to the lack of a sufficient number of homogenous studies that can generate more accurate pooled data for comparisons and conclusion-making. We also could not search other databases like MedRxiv and Cochrane databases in order to identify additional potentially eligible articles; as those are not subscribed by the primary reviewer's institution.

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Conflicts of Interest

The authors also declare no conflicts of interest regarding the publication of this paper.

References

[1] Wang, C.L., Liu, Y.Y., Wu, C.H., Wang, C.Y., Wang, C.H. and Long, C.Y. (2021) Impact of COVID-19 on Pregnancy. *International Journal of Medical Sciences*, **18**, 763-767. https://doi.org/10.7150/ijms.49923

[2] Ahn, D.G., Shin, H.J., Kim, M.H., Lee, S., Kim, H.S., Myoung, J., *et al*. (2020) Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). *Journal of Microbiolog and Biotechnology*, **30**, 313-324. https://doi.org/10.4014/jmb.2003.03011

[3] Di Mascio, D., Khalil, A., Saccone, G., Rizzo, G., Buca, D., Liberati, M., *et al*. (2020) Outcome of Coronavirus Spectrum Infections (SARS, MERS, COVID-19) during Pregnancy: A Systematic Review and Meta-Analysis. *American Journal of Obstetrics & Gynecology MFM*, **2**, Article ID: 100107. https://doi.org/10.1016/j.ajogmf.2020.100107

[4] Maleki Dana, P., Kolahdooz, F., Sadoughi, F., Moazzami, B., Chaichian, S. and Asemi, Z. (2020) COVID-19 and Pregnancy: A Review of Current Knowledge. *Le infezioni in Medicina*, **28**, 46-51.

[5] Mohamadian, M., Chiti, H., Shoghli, A., Biglari, S., Parsamanesh, N. and Esmaeilzadeh, A. (2021) COVID-19: Virology, Biology and Novel Laboratory Diagnosis. *The Journal of Gene Medicine*, **23**, Article No. e3303. https://doi.org/10.1002/jgm.3303

[6] World Health Organization (WHO) (2020) WHO Coronavirus (COVID-19) Dashboard. World Health Organization, Genava. https://covid19.who.int

[7] Abedzadeh-Kalahroudi, M., Sehat, M., Vahedpour, Z. and Talebian, P. (2021) Maternal and Neonatal Outcomes of Pregnant Patients with COVID-19: A Prospective Cohort Study. *International Journal of Gynecology & Obstetrics*, **153**, 449-456. https://doi.org/10.1002/ijgo.13661

[8] Figueiro-Filho, E.A., Yudin, M. and Farine, D. (2020) COVID-19 during Pregnancy: an Overview of Maternal Characteristics, Clinical Symptoms, Maternal and Neonatal Outcomes of 10,996 Cases Described in 15 Countries. *Journal of Perinatal Medicine*, **48**, 900-911. https://doi.org/10.1515/jpm-2020-0364

[9] Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., *et al*. (2020) Genomic Characterisation and Epidemiology of 2019 Novel Coronavirus: Implications for Virus Origins and Receptor Binding. *Lancet*, **395**, 565-574. https://doi.org/10.1016/S0140-6736(20)30251-8

[10] Yao, W.L., Qiu, J.C., Xiao, Z.R. and Ouyang, S. (2020) Pregnancy and COVID-19: Management and Challenges. *Revista do Instituto de Medicina Tropical de São Paulo*, **62**, Article No. e62. https://doi.org/10.1590/S1678-9946202062062

[11] Goldenberg, R.L., Culhane, J.F., Iams, J.D. and Romero, R. (2008) Epidemiology and Causes of Preterm Birth. *Lancet*, **371**, 75-84. https://doi.org/10.1016/S0140-6736(08)60074-4

[12] Chawanpaiboon, S., Vogel, J.P., Moller, A.B., Lumbiganon, P., Petzold, M., Hogan, D., *et al*. (2019) Global, regIonal, and National Estimates of Levels of Preterm Birth in 2014: A Systematic Review and Modelling Analysis. *The Lancet Global Health*, **7**, e37-e46. https://doi.org/10.1016/S2214-109X(18)30451-0

[13] Akhtar, H., Patel, C., Abuelgasim, E. and Harky, A. (2020) COVID-19 (SARS-CoV-2) Infection in Pregnancy: A Systematic Review. *Gynecologic and Obstetric Investigation*, **85**, 295-306. https://doi.org/10.1159/000509290

[14] Papapanou, M., Papaioannou, M., Petta, A., Routsi, E., Farmaki, M., Vlahos, N., *et al*. (2021) Maternal and Neonatal Characteristics and Outcomes of COVID-19 in Pregnancy: An Overview of Systematic Reviews. *International Journal of Environmental Research and Public Health*, **18**, Article No. 596. https://doi.org/10.3390/ijerph18020596

[15] Phoswa, W.N. and Khaliq, O.P. (2020) Is Pregnancy a Risk Factor of COVID-19? *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **252**, 605-609. https://doi.org/10.1016/j.ejogrb.2020.06.058

[16] Salem, D., Katranji, F. and Bakdash, T. (2021) COVID-19 Infection in Pregnant Women: Review of Maternal and Fetal Outcomes. *International Journal of Gynecology & Obstetrics*, **152**, 291-298. https://doi.org/10.1002/ijgo.13533

[17] Al-Matary, A., Almatari, F., Al-Matary, M., AlDhaefi, A., Alqahtani, M.H.S., Alhulaimi, E.A., *et al*. (2021) Clinical Outcomes of Maternal and Neonate with COVID-19 Infection—Multicenter Study in Saudi Arabia. *Journal of Infection and Public Health*, **14**, 702-708. https://doi.org/10.1016/j.jiph.2021.03.013

[18] Angelidou, A., Sullivan, K., Melvin, P.R., Shui, J.E., Goldfarb, I.T., Bartolome, R., *et al*. (2021) Association of Maternal Perinatal SARS-CoV-2 Infection with Neonatal Outcomes during the COVID-19 Pandemic in Massachusetts. *JAMA Network Open*, **4**, Article ID: e217523. https://doi.org/10.1001/jamanetworkopen.2021.7523

[19] Gabriel, M.A.M., Vergeli, M.R., Carbonero, S.C., Sole, L., Molina, T.C., Calle, I.R., *et al*. (2020) Maternal, Perinatal and Neonatal Outcomes with COVID-19: A Multicenter Study of 242 Pregnancies and Their 248 Infant Newborns during Their First Month of Life. *The Pediatric Infectious Disease Journal*, **39**, E393-E397.

https://doi.org/10.1097/INF.0000000000002902

[20] Gupta, P., Kumar, S. and Sharma, S.S. (2021) SARS-CoV-2 Prevalence and Maternal-Perinatal Outcomes among Pregnant Women Admitted for Delivery: Experience from COVID-19-Dedicated Maternity Hospital in Jammu, Jammu and Kashmir (India). *Journal of Medical Virology*, **93**, 5505-5514. https://doi.org/10.1002/jmv.27074

[21] Hcini, N., Maamri, F., Picone, O., Carod, J.F., Lambert, V., Mathieu, M., *et al*. (2021) Maternal, Fetal and Neonatal Outcomes of Large Series of SARS-CoV-2 Positive Pregnancies in Peripartum Period: A Single-Center Prospective Comparative Study. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **257**, 11-18. https://doi.org/10.1016/j.ejogrb.2020.11.068

[22] Khoury, R., Bernstein, P.S., Debolt, C., Stone, J., Sutton, D.M., Simpson, L.L., *et al*. (2020) Characteristics and Outcomes of 241 Births to Women with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection at Five New York City Medical Centers. *Obstetrics & Gynecology*, **136**, 273-282. https://doi.org/10.1097/AOG.0000000000004025

[23] Malik, S., Surve, S., Wade, P., Kondekar, S., Sawant, V., Shaikh, M., *et al*. (2021) Clinical Characteristics, Management, and Short Term Outcome of Neonates Born to Mothers with COVID-19 in a Tertiary Care Hospital in India. *Journal of Tropical Pediatrics*, **67**, Article No. fmab054. https://doi.org/10.1093/tropej/fmab054

[24] Maraschini, A., Corsi, E., Salvatore, M.A., Donati, S. and It OSSC-WG (2020) Coronavirus and Birth in Italy: Results of a National Population-Based Cohort Study. *Annali dell'Istituto Superiore di Sanità*, **56**, 378-389. https://doi.org/10.1101/2020.06.11.20128652

[25] Norman, M., Navér, L., Söderling, J., Ahlberg, M., Hervius Askling, H., Aronsson, B., *et al*. (2021) Association of Maternal SARS-CoV-2 Infection in Pregnancy with Neonatal Outcomes. *JAMA*, **325**, 2076-2086. https://doi.org/10.1001/jama.2021.5775

[26] Oncel, M.Y., Akin, I.M., Kanburoglu, M.K., Tayman, C., Coskun, S., Narter, F., *et al*. (2021) A Multicenter Study on Epidemiological and Clinical Characteristics of 125 Newborns Born to Women Infected with COVID-19 by Turkish Neonatal Society. *European Journal of Pediatrics*, **180**, 733-742. https://doi.org/10.1007/s00431-020-03767-5

[27] Saccone, G., Sen, C., Di Mascio, D., Galindo, A., Grunebaum, A., Yoshimatsu, J., *et al*. (2021) Maternal and Perinatal Outcomes of Pregnant Women with SARS-CoV-2 Infection. *Ultrasound in Obstetrics & Gynecology*, **57**, 232-241. https://doi.org/10.1002/uog.23107

[28] Sánchez-Luna, M., Fernández Colomer, B., de Alba Romero, C., Alarcón Allen, A., Baña Souto, A., Camba Longueira, F., *et al*. (2021) Neonates Born to Mothers with COVID-19: Data from the Spanish Society of Neonatology Registry. *Pediatrics*, **147**, Article ID: e2020015065. https://doi.org/10.1542/peds.2020-015065

[29] Singh, V., Choudhary, A., Datta, M.R. and Ray, A. (2021) Maternal and Neonatal Outcomes of COVID-19 in Pregnancy: A Single-Centre Observational Study. *Cureus*, **13**, Article ID: e13184. https://doi.org/10.7759/cureus.13184

[30] Bellos, I., Pandita, A. and Panza, R. (2021) Maternal and Perinatal Outcomes in Pregnant Women Infected by SARS-CoV-2: A Meta-Analysis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **256**, 194-204. https://doi.org/10.1016/j.ejogrb.2020.11.038

[31] Di Toro, F., Gjoka, M., Di Lorenzo, G., De Santo, D., De Seta, F., Maso, G., *et al*. (2021) Impact of COVID-19 on Maternal and Neonatal Outcomes: A Systematic

Review and Meta-Analysis. *Clinical Microbiology and Infection*, **27**, 36-46. https://doi.org/10.1016/j.cmi.2020.10.007

[32] Poon, L.C., Yang, H., Kapur, A., Melamed, N., Dao, B., Divakar, H., *et al.* (2020) Global Interim Guidance on Coronavirus Disease 2019 (COVID-19) during Pregnancy and Puerperium from FIGO and Allied Partners: Information for Healthcare Professionals. *International Journal of Gynecology & Obstetrics*, **149**, 273-286. https://doi.org/10.1002/ijgo.13156

[33] Tadas, M.P., Prashanthi, S. and Waikar, M. (2021) Maternal and Neonatal Outcomes of Pregnant Women with Covid-19: A Case-Control Study at a Tertiary Care Center in India. *Journal of South Asian Federation of Obstetrics and Gynaecolog*, **13**, 44-49. https://doi.org/10.5005/jp-journals-10006-1850a

[34] Mboya, I.B., Mahande, M.J., Obure, J. and Mwambi, H.G. (2020) Predictors of Perinatal Death in the Presence of Missing Data: A Birth Registry-Based Study in Northern Tanzania. *PLoS ONE*, **15**, Article ID: e0231636. https://doi.org/10.1371/journal.pone.0231636

[35] Chamseddine, R.S., Wahbeh, F., Chervenak, F., Salomon, L.J., Ahmed, B. and Rafii, A. (2020) Pregnancy and Neonatal Outcomes in SARS-CoV-2 Infection: A Systematic Review. *Journal of Pregnancy*, **2020**, Article ID: 4592450. https://doi.org/10.1155/2020/4592450

[36] Anand, P., Yadav, A., Debata, P., Bachani, S., Gupta, N. and Gera, R. (2021) Clinical Profile, Viral Load, Management and Outcome of Neonates Born to COVID 19 Positive Mothers: A Tertiary Care Centre Experience from India. *European Journal of Pediatrics*, **180**, 547-559. https://doi.org/10.1007/s00431-020-03800-7

[37] Ehrenstein, V. (2009) Association of Apgar Scores with Death and Neurologic Disability. *Clinical Epidemiology*, **1**, 45-53. https://doi.org/10.2147/CLEP.S4782

[38] Moster, D., Lie, R.T., Irgens, L.M., Bjerkedal, T. and Markestad, T. (2001) The Association of Apgar Score with Subsequent Death and Cerebral Palsy: A Population-Based Study in Term Infants. *The Journal of Pediatrics*, **138**, 798-803. https://doi.org/10.1067/mpd.2001.114694

[39] Lie, K.K., Grøholt, E.K. and Eskild, A. (2010) Association of Cerebral Palsy with Apgar Score in Low and Normal Birthweight Infants: Population Based Cohort Study. *BMJ*, **341**, Article No. c4990. https://doi.org/10.1136/bmj.c4990

[40] Dubey, P., Reddy, S.Y., Manuel, S. and Dwivedi, A.K. (2020) Maternal and Neonatal Characteristics and Outcomes among COVID-19 Infected Women: An Updated Systematic Review and Meta-Analysis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **252**, 490-501. https://doi.org/10.1016/j.ejogrb.2020.07.034

[41] Huntley, B.J.F., Mulder, I.A., Di Mascio, D., Vintzileos, W.S., Vintzileos, A.M., Berghella, V., *et al.* (2021) Adverse Pregnancy Outcomes among Individuals with and without Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Systematic Review and Meta-Analysis. *Obstetrics & Gynecology*, **137**, 585-596. https://doi.org/10.1097/AOG.0000000000004320

[42] Verma, S., Bradshaw, C., Auyeung, N.S.F., Lumba, R., Farkas, J.S., Sweeney, N.B., *et al.* (2020) Outcomes of Maternal-Newborn Dyads after Maternal SARS-CoV-2. *Pediatrics*, **146**, Article ID: e2020005637. https://doi.org/10.1542/peds.2020-005637

[43] Dube, R. and Kar, S.S. (2020) COVID-19 in Pregnancy: The Foetal Perspective—A Systematic Review. *BMJ Paediatrics Open*, **4**, Article ID: e000859. https://doi.org/10.1136/bmjpo-2020-000859

[44] Kinney, H.C. (2006) The Near-Term (Late Preterm) Human Brain and Risk for Periventricular Leukomalacia: A Review. *Seminars in Perinatology*, **30**, 81-88.

https://doi.org/10.1053/j.semperi.2006.02.006

[45] Mwaniki, M.K., Atieno, M., Lawn, J.E. and Newton, C.R. (2012) Long-Term Neurodevelopmental Outcomes after Intrauterine and Neonatal Insults: A Systematic Review. *Lancet*, **379**, 445-452. https://doi.org/10.1016/S0140-6736(11)61577-8

[46] Ramenghi, L.A. (2015) Late Preterm Babies and the Risk of Neurological Damage. *Acta Biomedica*, **86**, 36-40.

[47] Madinger, N.E., Greenspoon, J.S. and Ellrodt, A.G. (1989) Pneumonia during Pregnancy: Has Modern Technology Improved Maternal and Fetal Outcome? *American Journal of Obstetrics and Gynecology*, **161**, 657-662. https://doi.org/10.1016/0002-9378(89)90373-6

[48] Benedetti, T.J., Valle, R. and Ledger, W.J. (1982) Antepartum Pneumonia in Pregnancy. *American Journal of Obstetrics and Gynecology*, **144**, 413-417. https://doi.org/10.1016/0002-9378(82)90246-0

[49] Berkowitz, K. and LaSala, A. (1990) Risk Factors Associated with the Increasing Prevalence of Pneumonia during Pregnancy. *American Journal of Obstetrics and Gynecology*, **163**, 981-985. https://doi.org/10.1016/0002-9378(90)91109-P

[50] Schwartz, D.A. and Graham, A.L. (2020) Potential Maternal and Infant Outcomes from Coronavirus 2019-NCOV (SARS-CoV-2) Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections. *Viruses*, **12**, Article No. 194. https://doi.org/10.3390/v12020194

[51] Zhu, H., Wang, L., Fang, C., Peng, S., Zhang, L., Chang, G., *et al*. (2020) Clinical Analysis of 10 Neonates Born to Mothers with 2019-nCoV Pneumonia. *Translational Pediatrics*, **9**, 51-60. https://doi.org/10.21037/tp.2020.02.06

[52] Barrero-Castillero, A., Beam, K.S., Bernardini, L.B., Ramos, E.G.C., Davenport, P.E., Duncan, A.R., *et al*. (2021) COVID-19: Neonatal-Perinatal Perspectives. *Journal of Perinatology*, **41**, 940-951. https://doi.org/10.1038/s41372-020-00874-x

[53] Allotey, J., Stallings, E., Bonet, M., Yap, M., Chatterjee, S., Kew, T., *et al*. (2020) Clinical Manifestations, Risk Factors, and Maternal and Perinatal Outcomes of Coronavirus Disease 2019 in Pregnancy: Living Systematic Review and Meta-Analysis. *The BMJ*, **370**, Article No. m3320. https://doi.org/10.1136/bmj.m3320

[54] Royal College of Obstetricians and Gynaecologists (2021) Coronavirus (COVID-19) Infection in Pregnancy. https://www.rcog.org.uk/globalassets/documents/guidelines/2021-08-25-coronavirus-covid-19-infection-in-pregnancy-v14.pdf

[55] Qi, H., Luo, X., Zheng, Y., Zhang, H., Li, J., Zou, L., *et al*. (2020) Safe Delivery for Pregnancies Affected by COVID-19. *BJOG*: *An International Journal of Obstetrics & Gynaecology*, **127**, 927-929. https://doi.org/10.1111/1471-0528.16231

[56] Penfield, C.A., Brubaker, S.G., Limaye, M.A., Lighter, J., Ratner, A.J., Thomas, K.M., *et al*. (2020) Detection of Severe Acute Respiratory Syndrome Coronavirus 2 in Placental and Fetal Membrane Samples. *American Journal of Obstetrics & Gynecology MFM*, **2**, Article ID: 100133. https://doi.org/10.1016/j.ajogmf.2020.100133

[57] Boelig, R.C., Manuck, T., Oliver, E.A., Di Mascio, D., Saccone, G., Bellussi, F., *et al*. (2020) Labor and Delivery Guidance for COVID-19. *American Journal of Obstetrics & Gynecology MFM*, **2**, Article ID: 100110. https://doi.org/10.1016/j.ajogmf.2020.100110

[58] Martínez-Perez, O., Vouga, M., Cruz Melguizo, S., Forcen Acebal, L., Panchaud, A., Muñoz-Chápuli, M., *et al*. (2020) Association between Mode of Delivery among Pregnant Women with COVID-19 and Maternal and Neonatal Outcomes in Spain. *JAMA*, **324**, 296-299. https://doi.org/10.1001/jama.2020.10125

[59] Auriti, C., De Rose, D.U., Tzialla, C., Caforio, L., Ciccia, M., Manzoni, P., *et al*.

(2020) Vertical Transmission of SARS-CoV-2 (COVID-19): Are Hypotheses More than Evidences? *American Journal of Perinatology*, **37**, S31-S38. https://doi.org/10.1055/s-0040-1714346

[60] Dingom, M.A.N., Sobngwi, E., Essiben, F., Assiga, A.N., Wasnyo, Y.F., Ngate, A., *et al*. (2020) Maternal and Fetal Outcomes of COVID-19 Pregnant Women Followed Up at a Tertiary Care Unit: A Descriptive Study. *Open Journal of Obstetrics and Gynecology*, **10**, 1482-1491. https://doi.org/10.4236/ojog.2020.10100135

[61] Wu, Y., Liu, C., Dong, L., Zhang, C., Chen, Y., Liu, J., *et al*. (2020) Coronavirus Disease 2019 among Pregnant Chinese Women: Case Series Data on the Safety of Vaginal Birth and Breastfeeding. *BJOG: An International Journal of Obstetrics & Gynaecology*, **127**, 1109-1115. https://doi.org/10.1111/1471-0528.16276

[62] Aslan, M.M., Uslu Yuvacı, H., Köse, O., Toptan, H., Akdemir, N., Köroğlu, M., *et al*. (2020) SARS-CoV-2 Is Not Present in the Vaginal Fluid of Pregnant Women with COVID-19. *The Journal of Maternal-Fetal & Neonatal Medicined*. https://doi.org/10.1080/14767058.2020.1793318

[63] Dumitriu, D., Emeruwa, U.N., Hanft, E., Liao, G.V., Ludwig, E., Walzer, L., *et al*. (2021) Outcomes of Neonates Born to Mothers with Severe Acute Respiratory Syndrome Coronavirus 2 Infection at a Large Medical Center in New York City. *JAMA Pediatrics*, **175**, 157-167. https://doi.org/10.1001/jamapediatrics.2020.4298

[64] Sankaran, D., Nakra, N., Cheema, R., Blumberg, D. and Lakshminrusimha, S. (2021) Perinatal SARS-CoV-2 Infection and Neonatal COVID-19: A 2021 Update. *Neoreviews*, **22**, e284-e295. https://doi.org/10.1542/neo.22-5-e1001

[65] American Academy of Pediatrics (2020) SONPM National Registry for Surveillance and Epidemiology of Perinatal COVID-19 Infection: Section on Neonatal-Pernatal Medicine. https://my.visme.co/view/ojq9qq8e-npc-19-registry

[66] Kotlyar, A.M., Grechukhina, O., Chen, A., Popkhadze, S., Grimshaw, A., Tal, O., *et al*. (2021) Vertical Transmission of Coronavirus Disease 2019: A Systematic Review and Meta-Analysis. *American Journal of Obstetrics and Gynecology*, **224**, 35-53.e3. https://doi.org/10.1016/j.ajog.2020.07.049

[67] Pierce-Williams, R.A.M., Burd, J., Felder, L., Khoury, R., Bernstein, P.S., Avila, K., *et al*. (2020) Clinical Course of Severe and Critical Coronavirus Disease 2019 in Hospitalized Pregnancies: A United States Cohort Study. *American Journal of Obstetrics & Gynecology MFM*, **2**, Article ID: 100134. https://doi.org/10.1016/j.ajogmf.2020.100134

[68] Chen, H.J., Guo, J.J., Wang, C., Luo, F., Yu, X.C., Zhang, W., *et al*. (2020) Clinical Characteristics and Intrauterine Vertical Transmission Potential of COVID-19 Infection in Nine Pregnant Women: A Retrospective Review of Medical Records. *Lancet*, **395**, 809-815. https://doi.org/10.1016/S0140-6736(20)30360-3

[69] Yockey, L.J., Lucas, C. and Iwasaki, A. (2020) Contributions of Maternal and Fetal Antiviral Immunity in Congenital Disease. *Science*, **368**, 608-612. https://doi.org/10.1126/science.aaz1960

[70] Pereira, L. (2018) Congenital Viral Infection: Traversing the Uterine-Placental Interface. *Annual Review of Virology*, **5**, 273-299. https://doi.org/10.1146/annurev-virology-092917-043236

[71] Woodworth, K.R., O'Malley Olsen, E., Neelam, V., Lewis, E.L., Galang, R.R., Oduyebo, T., *et al*. (2020) Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy—SET-NET, 16 Jurisdictions, March 29-October 14, 2020. *Morbidity and Mortality Weekly Report*, **69**, 1635-1640. https://doi.org/10.15585/mmwr.mm6944e2

[72] Dong, L., Tian, J., He, S., Zhu, C., Wang, J., Liu, C., *et al*. (2020) Possible Vertical

Transmission of SARS-CoV-2 from an Infected Mother to Her Newborn. *JAMA*, **323**, 1846-1848. https://doi.org/10.1001/jama.2020.4621

[73] Kimberlin, D.W. and Stagno, S. (2020) Can SARS-CoV-2 Infection Be Acquired in Utero? More Definitive Evidence Is Needed. *JAMA*, **323**, 1788-1789. https://doi.org/10.1001/jama.2020.4868

[74] Raschetti, R., Vivanti, A.J., Vauloup-Fellous, C., Loi, B., Benachi, A. and De Luca, D. (2020) Synthesis and Systematic Review of Reported Neonatal SARS-CoV-2 Infections. *Nature Communications*, **11**, Article No. 5164.

[75] Wang, L., Shi, Y., Xiao, T., Fu, J., Feng, X., Mu, D., *et al.* (2020) Chinese Expert Consensus on the Perinatal and Neonatal Management for the Prevention and Control of the 2019 Novel Coronavirus Infection (First Edition). *Annals of Translational Medicined*, **8**, Article No. 47. https://doi.org/10.21037/atm.2020.02.20

[76] Centers for Disease Control and Prevention (2020) Interim Considerations for Infection Prevention and Control of Coronavirus Disease 2019 (COVID-19) in Inpatient Obstetric Healthcare Settings. [Updated 18 February 2020]. https://stacks.cdc.gov/view/cdc/85196

[77] World Health Organization (WHO) (2021) COVID-19 Clinical Management: Living Guidance [Updated 25 January 2021]. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1

[78] Centeno-Tablante, E., Medina-Rivera, M., Finkelstein, J.L., Rayco-Solon, P., Garcia-Casal, M.N., Rogers, L., *et al.* (2021) Transmission of SARS-CoV-2 through Breast Milk and Breastfeeding: A Living Systematic Review. *Annals of the New York Academy of Sciences*, **1484**, 32-54. https://doi.org/10.1111/nyas.14477

[79] Sahin, D., Tanacan, A., Erol, S.A., Anuk, A.T., Eyi, E.G.Y., Ozgu-Erdinc, A.S., *et al.* (2020) A Pandemic Center's Experience of Managing Pregnant Women with COVID-19 Infection in Turkey: A Prospective Cohort Study. *International Journal of Gynecology & Obstetrics*, **151**, 74-82. https://doi.org/10.1002/ijgo.13318

[80] Lackey, K.A., Pace, R.M., Williams, J.E., Bode, L., Donovan, S.M., Järvinen, K.M., *et al.* (2020) SARS-CoV-2 and Human Milk: What Is the Evidence? *Maternal & Child Nutrition*, **16**, Article No. e13032. https://doi.org/10.1111/mcn.13032

[81] Yang, N., Che, S., Zhang, J., Wang, X., Tang, Y., Wang, J., *et al.* (2020) Breastfeeding of Infants Born to Mothers with COVID-19: A Rapid Review. *Annals of Translational Medicine*, **8**, Article No. 618. https://doi.org/10.21037/atm-20-3299

[82] American Academy of Pediatrics (2021) Breastfeeding Guidance Post Hospital Discharge for Mothers or Infants with Suspected or Confirmed SARS-Co V-2 Infection. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/breastfeeding-guidance-post-hospital-discharge/

[83] Farghaly, M.A.A., Kupferman, F., Castillo, F. and Kim, R.M. (2020) Characteristics of Newborns Born to SARS-CoV-2-Positive Mothers: A Retrospective Cohort Study. *American Journal of Perinatology*, **37**, 1310-1316. https://doi.org/10.1055/s-0040-1715862

[84] Stuebe, A. (2020) Should Infants Be Separated from Mothers with COVID-19? First, Do No Harm. *Breastfeeding Medicine*, **15**, 351-352. https://doi.org/10.1089/bfm.2020.29153.ams

[85] Cheema, R., Partridge, E., Kair, L.R., Kuhn-Riordon, K.M., Silva, A.I., Bettinelli, M.E., *et al.* (2020) Protecting Breastfeeding during the COVID-19 Pandemic. *American Journal of Perinatology*, 1-7. https://doi.org/10.1055/s-0040-1714277

[86] Rawat, M., Chandrasekharan, P., Hicar, M.D. and Lakshminrusimha, S. (2020) COVID-19 in Newborns and Infants-Low Risk of Severe Disease: Silver Lining or

Dark Cloud? *American Journal of Perinatology*, **37**, 845-849. https://doi.org/10.1055/s-0040-1710512

[87] Molloy, E.J. and Bearer, C.F. (2020) COVID-19 in Children and Altered Inflammatory Responses. *Pediatric Research*, **88**, 340-341. https://doi.org/10.1038/s41390-020-0881-y

[88] Carsetti, R., Quintarelli, C., Quinti, I., Piano Mortari, E., Zumla, A., Ippolito, G., *et al*. (2020) The Immune System of Children: The Key to Understanding SARS-CoV-2 Susceptibility? *The Lancet Child & Adolescent Health*, **4**, 414-416. https://doi.org/10.1016/S2352-4642(20)30135-8

[89] Dhochak, N, Singhal, T., Kabra, S.K. and Lodha, R. (2020) Pathophysiology of COVID-19: Why Children Fare Better than Adults? *The Indian Journal of Pediatrics*, **87**, 537-546. https://doi.org/10.1007/s12098-020-03322-y

[90] Song, R., Preston, G. and Yosypiv, I.V. (2012) Ontogeny of Angiotensin-Converting Enzyme 2. *Pediatric Research*, **71**, 13-19. https://doi.org/10.1038/pr.2011.7

[91] Bunyavanich, S., Do, A. and Vicencio, A. (2020) Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults. *JAMA*, **323**, 2427-2429. https://doi.org/10.1001/jama.2020.8707

[92] Li, M., Chen, L., Zhang, J., Xiong, C. and Li, X. (2020) The SARS-CoV-2 Receptor ACE2 Expression of Maternal-Fetal Interface and Fetal Organs by Single-Cell Transcriptome Study. *PLoS ONE*, **15**, Article ID: e0230295. https://doi.org/10.1371/journal.pone.0230295

List of Abbreviation

95% CI	95% Confidence Interval
ACE-2	Angiotensin-converting enzyme 2
BMI	Body Mass Index
COVID-19	Coronavirus Disease 19
CPAP	Continuous Positive Airway Pressure
EMCO	Extracorporeal Membrane Oxygenation
ICU	Intensive Care Unit
IUGR	Intra-uterine Growth Restriction
MERS	Middle East Respiratory Syndrome
MeSH	Medical Subject Headings
NICU	Neonatal Intensive Care Unit
NOS	Newcastle-Ottawa Scale
OR	Odds Ratio
RT-PCR	Real Time Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SGA	Small for Gestational Age
WHO	World Health Organization

Appendix

Table S1. List of included articles in this review with main study findings and conclusion.

Article; Study country; Year of Publication [Reference no.]	Type of study	Sample size (No. of neonates)	Main Findings	Conclusion
Al-Matary *et al*.; Saudi Arabia; 2021 [17]	Retrospective Cohort Study	204	• Mean gestational age at delivery was 39 weeks (IQR 35 - 40). • The majority of neonates had normal laboratory results. • 43% of neonates admitted to NICU. • 7% of neonates required mechanical ventilation. • None of neonatal COVID-19 infections was detected. • 4 neonatal deaths were reported.	There was no evidence of vertical transmission of COVID-19 infection.
Angelidou *et al*.; USA; 2021 [18]	Retrospective Cohort Study	255	• 225 (88.2%) neonates were tested for COVID-19 infection and 2.2% were tested positive. • High maternal social vulnerability increased the likelihood of neonatal COVID-19 test positivity (adjusted odds ratio, 4.95; 95% CI, 1.53 - 16.01; p = 0.008). • Adverse neonatal outcomes were observed among preterm deliveries due to worsening maternal COVID-19 symptoms. • 1 positive result of COVID-19 testing was reported from the follow-up data of 151 newborns.	Maternal biological and social factors affect the perinatal outcomes of COVID-19 infections.
Gabriel *et al*.; Spain; 2020 [19]	Retrospective Cohort Study	248	• Maternal admission for COVID-19 infection increased the risk of premature delivery (p = 0.006). • 115 (46.3%) neonates were admitted to the neonatal unit with 87 admissions due to organizational difficulties. • None of neonatal COVID-19 infections nor neonatal deaths was detected. • Exclusive breastfeeding rate at discharge and 1-month was 41.7% and 40.4% respectively.	Vertical transmission of COVID-19 was not detected during delivery and up to the newborns' first month of life. Exclusive breastfeeding was less frequent than expected.
Gupta *et al*.; India; 2021 [20]	Retrospective Cohort Study	108	• Mothers with positive RT-PCR test results for COVID-19 were associated with statistically significant higher rates of prematurity, lower mean birth weight, lower Apgar score and increased prevalence of foetal distress when compared to pregnant women with negative test results. • None of neonatal COVID-19 infections was detected.	COVID-19 infection can lead to adverse maternal and perinatal outcomes. Mother-to-child vertical transmission of COVID-19 infection may be possible.

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Hcini *et al*.; France; 2020 [21]	Prospective Cohort Study	127	• Infected mothers were associated with higher rates of intrauterine foetal demise as compared to controls (5.1% vs. 1.1%, RR 4.7 [95% CI: 1.4 - 45.9). • None of neonatal COVID-19 infections was detected at birth (0/108). • Among 29 neonates who were tested again between 25 to 42 hours of life, 4 had positive test results for COVID-19 and remained asymptomatic.	Infected pregnant women were at higher risk of intrauterine foetal demise than those uninfected mothers.
Khoury *et al*.; USA; 2020 [22]	Prospective Cohort Study	245	• 2.5% of neonates had positive test results for COVID-19 infection immediately after birth. • Maternal COVID-19 severity was linked to BMI 30 or higher (p = 0.001). • Cesarean delivery was done for 52.4% of women with severe and 91.7% with critical COVID-19.	Disease severity was associated with obesity and higher cesarean birth rates.
Malik *et al*.; India; 2021 [23]	Database Analysis	524	• 6.3% of the neonates to mothers with COVID-19 were tested positive for SARS-CoV-2. • Infected neonates had a 4.09 [95% CI 1.28 - 13.00] fold higher risk to develop sepsis as compared to the non-infected newborns (p = 0.031). • Infected neonates were significantly more likely to experience poor feeding as compared to the non-infected newborns (p = 0.017). • A total of 13 neonatal deaths was reported with 3 deaths from the COVID-19 infected group.	There is an increased risk of adverse neonatal outcomes, including sepsis and death for the newborns infected with COVID-19 as compared to the non-infected.
Maraschini *et al*.; Italy; 2020 [24]	Prospective Cohort Study	149	• 6% of neonates had positive test results for COVID-19 infection at birth. • Neonatal mortality was not reported.	Clinical features and outcomes of COVID-19 in pregnant women had similar clinical features and outcomes of COVID-19 as the general population
Norman *et al*.; Sweden; 2021 [25]	Prospective Cohort Study	2323	• Maternal SARS-CoV-2 test positivity was significantly associated with higher rates of neonatal care admission, neonatal morbidities such as respiratory distress syndrome, any neonatal respiratory disorder, and hyperbilirubinemia. • 0.9% of the newborns to mothers with COVID-19 were tested positive for SARS-CoV-2 in the neonatal period, of those 9 had diagnoses with unclear relation to COVID-19.	Pregnant women with COVID-19 infection had a significant but slightly increased risk for some neonatal morbidities.

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Oncel *et al*.; Turkey; 2021 [26]	Prospective Cohort Study	125	• Cesarean delivery, prematurity, and low birthweight rates were 71.2%, 26.4%, and 12.8%, respectively. • Most newborns (86.4%) were admitted to the isolation rooms in NICU. • 3.3% of neonates had positive test results for COVID-19 infection at birth, including one sampling of deep tracheal aspirate from an intubated newborn. • A total of 3 neonates were detected for SARS-CoV-2 after negative test results on the first day of life.	Maternal COVID-19 infection was associated with maternal mortality, increased rates of cesarean delivery and preterm birth, suspected possibility of vertical transmission, and low breastfeeding rate.
Saccone *et al*.; Multinational; 2021 [27]	Retrospective Cohort Study	251	• Neonatal ICU admission rate was 27.5%. • Five (2.0%) neonatal deaths were reported. • The overall perinatal mortality rate was 4.1%. • Only one (0.4%) infant, born to a mother with COVID-19 diagnosed during the third trimester, had positive RT-PCR test results for SARS-CoV-2.	There is negligible risk for vertical transmission of COVID-19.
Sánchez-Luna *et al*.; Spain; 2021 [28]	Prospective Cohort Study	503	• The most frequently performed diagnostic test for neonatal COVID-19 infection was RT-PCR test at a median age of 3 hours after birth. • Almost one-half of neonates had skin-to-skin contact with mothers after delivery. • Delayed umbilical cord clamping was performed in 43% of newborns. • Rooming-in was allowed in 62.3% of asymptomatic neonates. • 76.5% of neonates received maternal milk, with 204 of them exclusively breastfed.	There is no role of mothers-newborn separation. Delayed cord clamping, skin-to-skin contact and breastfeeding were allowed in the majority of newborns to COVID-19 infected mothers.
Singh *et al*.; India; 2021 [29]	Retrospective Cohort Study	121	• The mean birth weight was reported as 2.59 kg. • Forty (33.05%) newborns were admitted to NICU. • Two neonates (1.65%) were detected for SARS-CoV-2 infection within the first day of life.	COVID-19 in pregnancy is associated with increased rates of prematurity and NICU admission. Perinatal mortality remains uncommon. The incidence of neonatal SARS-CoV-2 infection is low and most cases were asymptomatic, yet suggesting the possibility of vertical transmission.