

# COVID-19 and Pregnancy

## A narrative review of maternal and perinatal outcomes

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**ABSTRACT:** As of August 11, 2021, approximately 206 million people worldwide had been infected with SARS-CoV-2. However, limited data are available regarding the effects of COVID-19 infection on pregnancy and maternal and perinatal outcomes. This review aimed to resolve this gap in literature. The MEDLINE®, SCOPUS and Cumulative Index to Nursing and Allied Health Literature databases were searched to identify relevant English-language articles published between January 2020 and February 2021. A total of 17 articles describing the outcomes of 762 pregnancies were identified. There were 613 babies born, including 16 sets of twins. Within the cases studied, 12 (1.6%) maternal deaths and eight (1.3%) stillbirths were reported. A small proportion of mothers (3.9%) required admission to the intensive care unit, usually due to associated comorbidities. Rates of caesarean and preterm delivery ranged from 27–100% and 4–50%, respectively. Further research is necessary to determine the effect of COVID-19 infection on early pregnancy.

**Keywords:** COVID-19; Pregnancy; Maternal Death; Perinatal Death; Pregnancy Outcome; Stillbirth; Preterm Birth; Review.

COVID-19 IS A SEVERE RESPIRATORY ILLNESS caused by a novel strain of single-stranded RNA betacoronavirus—known as severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2).<sup>1</sup> The disease was first reported in December 2019 in Wuhan, China, and has since spread rapidly worldwide, resulting in 206,273,369 cases and more than 4,347,832 deaths in August 2021.<sup>2</sup> The main route of transmission is direct transmission from close contact (i.e. within 2 m) with an infected person through aerosol/droplet spread.<sup>3</sup> The average incubation period is five days (range: 2–14 days), and the illness varies in severity from very mild, with flu-like symptoms, to severe respiratory illness and death. The World Health Organization (WHO)–China Joint Mission comprising 25 national and international experts, headed by the WHO, reported the following common symptoms in 75,465 COVID-19 patients: fever (87.9%), dry cough (67.7%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%) and myalgia (14.8%).<sup>4</sup> However, some patients were asymptomatic.<sup>5,6</sup>

To date, limited data are available regarding the effect of COVID-19 on pregnancy.<sup>4</sup> It can be postulated that the anatomical and physiological changes inherent to pregnancy—such as diaphragmatic elevation by the gravid uterus leading to reduced functional residual capacity, increased oxygen consumption and airway oedema—might increase susceptibility to severe respiratory infections and decrease tolerance to hypoxia, as was found by a study conducted in Hong Kong on patients with SARS-CoV-1.<sup>7</sup> The effects of

other coronaviruses such as SARS-CoV-1 and Middle East respiratory syndrome (MERS) on pregnant women might also provide insight into the possible impact of COVID-19 on this population.<sup>1</sup>

In the largest series of pregnancy outcomes in SARS-CoV-1 cases, Wong *et al.* reported 12 pregnancies resulting in a 25% fatality rate.<sup>7</sup> Maternal complications included acute respiratory distress syndrome (ARDS; 33.3%), renal failure (25%), disseminated intravascular coagulopathy (DIC; 25%), sepsis (16.7%) and secondary bacterial pneumonia (16.7%). Four out of seven women (57.1%) experienced spontaneous miscarriages in the first trimester, and four out of five (80%) had preterm deliveries at 24–32 gestational weeks.<sup>7</sup> A total of 13 case reports on pregnancy outcomes in MERS revealed a 23% fatality rate, including three deaths due to ARDS.<sup>8–13</sup> In addition, there were two cases of intrauterine fetal death and two preterm births.<sup>10,11,13</sup> However, no evidence of vertical transmission has been reported in either SARS-CoV-1 or MERS patients in 2016 and 2014, respectively.

This review aimed to evaluate available evidence from the beginning of the COVID-19 pandemic in January 2020 to February 2021 regarding maternal and perinatal outcomes in pregnant women infected with SARS-CoV-2.

## Methods

This narrative review was conducted in March 2021 to identify articles reporting maternal and

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perinatal outcomes in pregnant women diagnosed with COVID-19. The MEDLINE® (National Library of Medicine, Bethesda, Maryland, USA), SCOPUS (Elsevier, Amsterdam, Netherlands) and Cumulative Index to Nursing and Allied Health Literature (EBSCO Information Services, Ipswich, Massachusetts, USA) databases were searched electronically utilising appropriate medical terminology related to the topic. The following search terms were used both individually and in combination: 'COVID-19 infection', 'coronavirus' and 'pregnancy'.

The search was restricted to English-language articles published between January 2020 and February 2021. All full-text articles investigating pregnancy and perinatal outcomes in women with COVID-19, such as case reports, case series and original studies, were included. Review articles were excluded due to the possibility of duplication of data. Articles related to other types of coronavirus infections such as MERS and SARS-CoV-1 were excluded. The initial search revealed 24 articles, of which seven were excluded due to duplication of data already incorporated in other articles. Subsequently, a total of 17 articles (case series and case reports) were included in the final analysis.

Each article was reviewed to determine the maternal and perinatal outcomes. The pregnancy or maternal outcomes of interest in this review included maternal age, maternal comorbidity, major presenting symptom, relevant investigation, miscarriage, preterm delivery (defined as birth before 37 gestational weeks), fetal growth restriction (FGR), mode of delivery, complication related to COVID-19 infection, intensive care unit (ICU) admission and death. Perinatal outcomes included gestational age at delivery, neonatal admission to the ICU, perinatal asphyxia, stillbirth, neonatal death and any evidence of vertical transmission. In addition, data related to investigations and treatment modalities used in the included articles were extracted and tabulated.

## Results

A total of 24 articles were documented, but only 17 articles related to pregnancy and COVID-19 were included in the analysis as they fit the inclusion criteria.<sup>14–30</sup> In terms of article type, six case reports and 11 case series were identified. In total, the articles described the outcomes of 762 pregnancies and 613 babies, including 16 sets of twins.<sup>14–30</sup>

The maternal age ranged from 20–49 years. Pregnant women most commonly presented in the third trimester with symptoms of fever.<sup>14,16–22,25–26,28</sup> Common laboratory findings included leukopaenia, lymphopaenia, elevated C-reactive protein levels and chest X-ray changes suggestive of viral pneumonia.<sup>14–22,24,25,29</sup> Although

maternal comorbidities were not specified in many articles, the most commonly reported was obesity (n = 131, 17.2%).<sup>15,16,18</sup> A total of 30 (3.9%) women required ICU admission and mechanical ventilation for respiratory support due to ARDS.<sup>14–18,24,26</sup> In the cases studied, 12 (1.6%) maternal deaths occurred, of which seven were reported in a case series of nine women with severe disease in Iran.<sup>18</sup> The rate of caesarean section delivery was high in the studied cohort, ranging from 27–100%, due to the mother and physician's preferences.<sup>14–30</sup> However, other indications included fetal distress, preterm premature rupture of the membranes, placenta previa, failure to progress and COVID-19 pneumonia [Table 1].<sup>16</sup>

Out of the 17 articles, only six reported pre-eclampsia investigations.<sup>14,15,17,20,23,25</sup> Eight articles mentioned the use of anti-viral medications, but only two articles specified remdesivir use.<sup>15,23</sup> Four articles did not mention the use of corticosteroids, and in the remaining articles, the use of corticosteroids ranged from 12.5–100%.<sup>14,16,18,22</sup> Maternal thromboprophylaxis was given in only three instances,<sup>14,18,24</sup> and was not given in eight series.<sup>17,21,22,25,27,28–30</sup> Moreover, data about thromboprophylaxis were not available in the remaining five articles [Table 2].<sup>15,16,19,20,23,26</sup>

There was no evidence that COVID-19 infection increased the risk of miscarriage, early pregnancy loss, teratogenicity or FGR. However, 10 out of the 17 articles reported preterm delivery (83 babies) occurring in 24–37 gestational weeks (4–50%).<sup>15–20,22,23,25,28</sup> In addition, eight (1.3%) intrauterine fetal deaths or stillbirths and four (0.7%) neonatal deaths were reported.<sup>15,17,18,22,24,28</sup> Of the 524 neonates who were tested for SARS-CoV-2, seven babies tested positive.<sup>23,28</sup> Six of these neonates were reported from the series published by Adhikari *et al.* wherein four neonates were positive at 24 hours and two at 48 hours.<sup>23</sup> Only one of these (preterm birth at 34 weeks with prelabour rupture of membranes) was suspected to be intra-uterine transmission, as electron microscopy of the placental tissue revealed SARS-CoV-2 viral particles. No specific route of SARS-CoV-2 transmission could be determined in the remaining cases. No samples were obtained from the amniotic fluid. Although one (0.2%) case of neonatal infection with COVID-19 was confirmed at 36 hours after birth via pharyngeal swab, there was no evidence of vertical transmission as samples from the placenta, cord blood and breast milk tested negative [Table 3].<sup>21</sup>

## Discussion

There is limited information regarding the effect of COVID-19 infection on pregnancy and childbirth due to the short time-frame since the start of the

**Table 1:** Maternal outcomes of pregnant women infected with SARS-CoV-2

| No. | Author and year of publication [type of study]                 | Number of pregnant women/ pregnancies                         | Purpose of study  | Age range or mean in years | n (%)  |  |                                 |               |                |
|-----|--|---|---|----------------------------|--|--|---------------------------------|---------------|----------------|
|     |  |   |   |                            | Symptom  | Comorbidities/laboratory findings  | ICU admission                   | CS            | Maternal death |
| 1   | Federici <i>et al.</i> <sup>14</sup> (2020) [Case report]      | 1 woman   | To study the continuation of pregnancy in spite of ICU admission and mechanical ventilation   | 33                         | Fever: 39.2 °C<br>Dyspnoea   | Co-morbidity: 0<br>CXR/CT viral changes: Yes<br>Lymphocytopenia<br>Thrombocytopenia<br>↑Hepatic transaminases  | Yes                             | No            | 0              |
| 2   | Lokken <i>et al.</i> <sup>15</sup> (2021) [Case series]        | 240 women (85 undelivered)<br>24 hospitalised<br>1 postpartum | To describe disease severity and outcomes of SARS-CoV-2 infections during pregnancy across Washington State including pregnancy complications and outcomes, hospitalisation and case fatality | 20–39                      | Symptomatic: 185 (77.1) Details of symptoms including cough, fever and dyspnoea were not provided Severe: 18 (7.5) Critical: 4 (1.7) | Obesity: 102 (49.5) (BMI ≥30+ ≥40)<br>Asthma: 20 (8.3)<br>DM: 13 (5.4)<br>HTN: 11 (4.6)<br>Lymphopaenia: 10/23 (43.5)<br>↑CRP: 8/15 (53.3)<br>↑Hepatic transaminases: 17/22 (77.3) | 8 (3.3)                         | 55/155 (35.5) | 3 (1.3)        |
| 3   | Breslin <i>et al.</i> <sup>16</sup> (2020) [Case series]       | 43 women (25 undelivered)                                     | To determine the clinical characteristics of SARS-CoV-2 infection in 29 symptomatic pregnant women (26 with mild disease and 3 severe)  | 20–39                      | Fever: 14 (48.3)<br>Cough: 19 (65.6)<br>Myalgia: 11 (37.9)<br>Dyspnoea: 7 (24.1)   | Obesity: 26 (60.5)<br>Asthma: 8 (18.6)<br>DM: 3 (7)<br>HTN: 3 (7)<br>CXR/CT viral changes: 3/3 (100) with severe disease   | 2 (4.7)                         | 8/18 (44.4)   | 0              |
| 4   | Yan <i>et al.</i> <sup>17</sup> (2020) [Case series]           | 116 women (17 undelivered)                                    | To report the maternal and neonatal outcomes of COVID-19 patients   | 24–41                      | Fever: 59 (50.9)<br>Cough: 33 (28.4)<br>Myalgia: 6 (5.2)<br>Dyspnoea: 3 (2.6)  | Lymphopaenia: 51 (44)<br>↑CRP: 51 (44)<br>CXR/CT viral changes: 104 (96.3)<br>GDM: 9 (7.8)<br>HTN: 5 (4.3)<br>Preeclampsia: 4 (3.4)  | 8 (6.9)                         | 85/99 (85.9)  | 0              |
| 5   | Hantoushzadeh <i>et al.</i> <sup>18</sup> (2020) [Case series] | 9 women   | To describe maternal and perinatal outcomes and death in a case series of pregnant women with COVID-19 disease  | 25–49                      | Fever: 9 (100)<br>Cough: 9 (100)<br>Dyspnoea: 6 (66.7)<br>Myalgia: 4 (44.4)  | Obesity: 3 (33)<br>Age: >40yrs (22)<br>Lymphopaenia: 100%<br>↑CRP: 100%<br>CXR/CT viral changes: 100%  | 9 (100)<br>1 with renal failure | 6 (67)        | 7 (78)         |
| 6   | Zheng <i>et al.</i> <sup>19</sup> (2020) [2 case reports]      | 2 women   | Maternal and neonatal outcomes  | 29–33                      | Fever: 1 (50)<br>Dyspnoea: 1 (50)  | Lymphopaenia: 100%<br>↑CRP: 50%<br>CXR/CT viral changes: 100%  | N/A                             | 100%          | 0              |
| 7   | Wu <i>et al.</i> <sup>20</sup> (2020) [Case series]            | 13 women (8 undelivered)                                      | To assess if vaginal secretions and breast milk of women with COVID-19 contain SARS-CoV-2   | 26–40                      | Fever: 8 (61.5)<br>Cough: 5 (38.5)<br>Dyspnoea: 1 (7.6)<br>Myalgia: 1 (7.6)  | Lymphopaenia: 2 (15.4)<br>↑CRP: 5 (38.5)<br>↑Hepatic transaminases: 2 (15.4%)<br>CT chest changes: 8 (61.5)  | 0                               | 4/5 (80)      | 0              |
| 8   | Wang <i>et al.</i> <sup>21</sup> (2020) [Case report]          | 1 woman   | To report the first case of neonatal SARS-CoV-2 infection in China where the mother was diagnosed with COVID-19   | 34                         | Fever: 100%  | CXR/CT viral changes: 100%   | 0                               | 100%          | 0              |
| 9   | Zhu <i>et al.</i> <sup>22</sup> (2020) [Case series]           | 9 women (1 set of twins)                                      | To report the clinical features and outcomes of 10 neonates (including 2 twins) born to 9 mothers with confirmed 2019-nCoV infection in 5 hospitals that were retrospectively analysed        | -25–35                     | Fever: 9 (88.9)<br>Cough: 4 (44.5)   | CXR/CT viral changes: 100%   | 0                               | 7 (78)        | 0              |

ICU = intensive care unit; CXR = chest X-ray; CT = computed tomography; BMI = body mass index; DM = diabetes mellitus; HTN = hypertension; CRP = C-reactive protein; GDM = gestational diabetes mellitus; N/A = not available; Hep = hepatitis; SOB = shortness of breath; B/L = bilateral.

**Table 1 (cont'd.):** Maternal outcomes of pregnant women infected with SARS-CoV-2

| No. | Author and year of publication [type of study]                | Number of pregnant women/ pregnancies        | Purpose of study  | Age range or mean in years | n (%)  |   |               |                    |                |
|-----|---|--|---|----------------------------|--|---|---------------|--------------------|----------------|
|     |   |  |   |                            | Symptom  | Comorbidities/laboratory findings   | ICU admission | CS                 | Maternal death |
| 10  | Adhikari <i>et al.</i> <sup>23</sup> (2020) [Case series]     | 252 women (245 delivered, 7 aborted)         | To evaluate adverse outcomes associated with severe SARS-CoV-2 infection in pregnancy and to describe clinical management, disease progression, hospital admission, placental abnormalities and neonatal outcomes | 27                         | Details not available  | DM (GDM + DM): 15 (6%)<br>HTN: 12 (5%)<br>BMI mean: 30.5 (7.2%)<br>Investigation details not available  | 0             | 65/245 (27)        | 0              |
| 11  | Rawat <i>et al.</i> <sup>24</sup> (2021) [Case reports]       | 4 women                                      | To report maternal death in Sagar city of central India   | 25–31                      | Fever (n = 2), cough (n = 2), sore throat (n = 1), loss of smell and taste (n = 1) No symptoms (1) Vomiting and breathless (n = 1) | Co-morbidity: 0 CRP high in 1 (25)<br>CXR: prominent bronchovascular marking in 1 woman, but recovered<br>Patchy ground glass changes in 1 (25) woman   | 1             | 1/3 (33)           | 1              |
| 12  | Qiancheng <i>et al.</i> <sup>25</sup> (2020) [Case series]    | 28 women (2 undelivered, 4 medical abortion) | To compare clinical course and outcomes between pregnant (28) and non-pregnant (54) women with COVID-19 and assess the vertical transmission  | 30 (26.75–32)              | Fever: 5 (17.9)<br>Malaise: 1 (3.6)<br>Cough: 7 (25)<br>Dyspnoea: 2 (7.1)<br>Abdominal pain: 5 (17.9)                              | HTN: 1 (3.6)<br>Diabetes: 2 (7.1)<br>Chronic Hep B infection: 2 (7.1)<br>Hypothyroidism: 1 (3.6)<br>Lymphopaenia: 8 (28.6)<br>Thrombocytopaenia: 2 (7.1)<br>Radiological findings of pneumonia: 26 (92.9) | 0             | 17 (60.7)          | 0              |
| 13  | Chaudhary <i>et al.</i> <sup>26</sup> (2020) [Case series]    | 26 women (12 undelivered)                    | To examine the disease course in COVID-19-affected pregnant women   | 27 (19–35)                 | 16 symptomatic<br>Fever: 14 (87.5)<br>Cough: 11 (68.8)<br>Body ache: 3 (18.8)<br>SOB: 2 (12.5)                                     | Co-morbidity: 0<br>Lymphocytopenia: 1 (3.8)<br>CRP raised: 5 (19.2)<br>CXR: B/L<br>Peripheral opacities: 5 (19.2)   | 1             | 11/14 (78.5)       | 1              |
| 14  | Elkafrawi <i>et al.</i> <sup>27</sup> (2020) [Case report]    | 1 woman                                      | To present first case report of SARS-CoV-2 in pregnancy in the USA  | 34                         | Myalgia, fatigue and non-productive cough  | Co-morbidity: Type II diabetes, chronic hep B   | 0             | Yes                | 0              |
| 15  | Birindwa <i>et al.</i> <sup>28</sup> (2021) [Case report]     | 1 woman                                      | To study the possibility of vertical transmission to the neonate  | 25                         | Fever  | 0   | 0             | Yes (previous 2CS) | 0              |
| 16  | Gheysarzadeh <i>et al.</i> <sup>29</sup> (2020) [Case series] | 4 women (2 undelivered)                      | To describe the outcomes of 4 pregnant women with COVID-19  | 27–42                      | Fever: 4 (100)<br>SOB: 2 (50)<br>Cough: 1 (25)<br>Abdominal pain: 1 (25)   | Co-morbidity: 0 CRP raised: 2 (50%)   | 0             | 1 (50)             | 0              |
| 17  | Doria <i>et al.</i> <sup>30</sup> (2020) [Case series]        | 12 women (10 delivered, 1 set of twins)      | To study the outcome of COVID-19-infected pregnant women in one region of Portugal  | 22–41                      | Headache: 1 (8.3)  | Co-morbidity: ulcerative colitis and psoriasis, severe scoliosis, Behcet's disease, severe myopia, Asthma and Raynaud syndrome, chronic HTN (in different women) 7 women with no co-morbidities           | 0             | 6 (60)             | 0              |

ICU = intensive care unit; CXR = chest X-ray; CT = computed tomography; BMI = body mass index; DM = diabetes mellitus; HTN = hypertension; CRP = C-reactive protein; GDM = gestational diabetes mellitus; N/A = not available; Hep = hepatitis; SOB = shortness of breath; B/L = bilateral.

**Table 2: Maternal treatment modalities of pregnant women infected with SARS-CoV-2**

| No | Author and year of publication [type of study]  | n (%)  |   |
|----|---|--|---|
|    |   | Maternal treatment   | Preeclampsia investigations   |
| 1  | Federici <i>et al.</i> <sup>14</sup> (2020)<br>[Case report]  | Corticosteroids: No<br>Hydroxychloroquine: No<br>Thromboprophylaxis: Yes<br>Antibiotics: Yes<br>Antiviral: No<br>Convalescent plasma: No<br>Mechanical ventilation: Yes  | Minimal haemolysis, thrombocytopenia: 86 × 10 <sup>9</sup> /L<br>Proteinuria (creatininuria): 0.14 g/mmol<br>Liver enzymes: Raised (ALT & AST)<br>sFlt-1 to PlGF ratio: Low (neg) |
| 2  | Lokken <i>et al.</i> <sup>15</sup> (2021)<br>[Case series; 24 hospitalised patients]                    | Corticosteroids: 3 (12.5)<br>Hydroxychloroquine: 2 (8.3)<br>Thromboprophylaxis: N/A<br>Antibiotics: N/A<br>Antiviral (remdesivir): 9 (37.5)<br>Convalescent plasma: 2 (8.3)<br>Mechanical ventilation: 4 (16.7)        | ↑Liver transaminases: 17 (77.3)<br>Rest N/A   |
| 3  | Breslin <i>et al.</i> <sup>16</sup> (2020)<br>[Case series; 4 symptomatic patients requiring admission] | Corticosteroids: No<br>Hydroxychloroquine: 2 (50)<br>Thromboprophylaxis: N/A<br>Antibiotics: 2 (50)<br>Antiviral: No<br>Convalescent plasma: No<br>Mechanical ventilation: No  | Data not available  |
| 4  | Yan <i>et al.</i> <sup>17</sup> (2020)<br>[Case series]   | Corticosteroids: 37 (31.9)<br>Hydroxychloroquine: No<br>Thromboprophylaxis: No<br>Antibiotics: 104 (94)<br>Antiviral: 63 (54.3)<br>Convalescent plasma: No<br>Mechanical ventilation: 2 (1.7)<br>ECMO: 1 (0.9)         | 4 (3.4) with preeclampsia but the related investigations were not provided—including platelet count, liver enzymes and urine protein creatinine ratio                             |
| 5  | Hantoushzadeh <i>et al.</i> <sup>18</sup> (2020)<br>[Case series; 9 cases]                              | Corticosteroids: No<br>Hydroxychloroquine: 5 (55.6)<br>Thromboprophylaxis: 9 (100)<br>Antibiotics: 9 (100)<br>Antiviral (not remdesivir): 9 (100)<br>Convalescent plasma: 1 (11.1)<br>Mechanical ventilation: 7 (77.8) | 0   |
| 6  | Zheng <i>et al.</i> <sup>19</sup> (2020)<br>[2 case reports]  | Corticosteroids: 2 (100)<br>Hydroxychloroquine: 2 (100)<br>Thromboprophylaxis: N/A<br>Antibiotics: 2 (100)<br>Antiviral: 2 (100)<br>Convalescent plasma: No<br>Mechanical ventilation: No                              | 0   |
| 7  | Wu <i>et al.</i> <sup>20</sup> (2020)<br>[Case series]  | Corticosteroids: 32 (23.1)<br>Hydroxychloroquine: No<br>Thromboprophylaxis: N/A<br>Antibiotics: 8 (61.5)<br>Antiviral: 8 (61.5)<br>Convalescent plasma: No<br>Mechanical ventilation: No                               | ↑Liver transaminases: 5 (38.5)  |
| 8  | Wang <i>et al.</i> <sup>21</sup> (2020)<br>[Case report]  | Corticosteroids: Yes<br>Hydroxychloroquine: No<br>Thromboprophylaxis: No<br>Antibiotics: Yes<br>Antiviral: Yes<br>Convalescent plasma: No<br>Mechanical ventilation: No  | N/A   |
| 9  | Zhu <i>et al.</i> <sup>22</sup> (2020)<br>[Case series]   | Corticosteroids: No<br>Hydroxychloroquine: No<br>Thromboprophylaxis: No<br>Antibiotics: No<br>Antiviral: 5 (55.56)<br>Convalescent plasma: No<br>Mechanical ventilation: No  | N/A   |
| 10 | Adhikari <i>et al.</i> <sup>23</sup> (2020)<br>[Case series; 13 women with severe/critical disease]     | Corticosteroids: 5 (38)<br>Hydroxychloroquine: No<br>Thromboprophylaxis: No<br>Antibiotics: 3 (23)<br>Antiviral (remdesivir): 5 (38)<br>Convalescent plasma: 2 (15)<br>Mechanical ventilation: 2 (15)                  | 26 (11) Not significantly higher than in pregnant women negative for SARS-CoV-2   |

ALT = alanine transaminase; AST = aspartate aminotransferase; sFlt = soluble fms-like tyrosine kinase; PlGF = placental growth factor; ECMO = extra-corporeal membrane oxygenation; N/A = not applicable; LDH = lactate dehydrogenase.

**Table 2 (cont'd.): Maternal treatment modalities of pregnant women infected with SARS-CoV-2**

| No. | Author and year of publication<br>[type of study]   | n (%)  |   |
|-----|---|--|---|
|     |   | Maternal treatment   | Preeclampsia investigations   |
| 10  | Adhikari <i>et al.</i> <sup>23</sup> (2020)<br>[Case series; 13 women with severe/critical disease] | Corticosteroids: 5 (38)<br>Hydroxychloroquine: No<br>Thromboprophylaxis: No<br>Antibiotics: 3 (23)<br>Antiviral (remdesivir): 5 (38)<br>Convalescent plasma: 2 (15)<br>Mechanical ventilation: 2 (15)    | 26 (11) Not significantly higher than in pregnant women negative for SARS-CoV-2 |
| 11  | Rawat <i>et al.</i> <sup>24</sup> (2021)<br>[Case reports; 1 patient sick]                          | Corticosteroids: Yes<br>Hydroxychloroquine: N/A<br>Thromboprophylaxis: Yes<br>Antibiotics: N/A<br>Antiviral (remdesivir): No<br>Convalescent plasma: N/A<br>Mechanical Ventilation: Yes                  | Not mentioned   |
| 12  | Qiancheng <i>et al.</i> <sup>25</sup> (2020)<br>[Case series; 7 hospitalised]                       | Corticosteroids: 4 (14.3)<br>Hydroxychloroquine: No<br>Thromboprophylaxis: No<br>Antibiotics: 24 (85.7)<br>Antivirals (not remdesivir): 21 (75)<br>Convalescent plasma: No<br>Mechanical ventilation: No | Low platelets (<100): 2<br>↑LDH: 4  |
| 13  | Chaudhary <i>et al.</i> <sup>26</sup> (2020)<br>[Case series]                                       | Corticosteroids: N/A<br>Hydroxychloroquine: N/A<br>Thromboprophylaxis: N/A<br>Antibiotics: N/A<br>Antiviral (remdesivir): N/A<br>Convalescent plasma: N/A<br>Mechanical ventilation: 1                   |   |
| 14  | Elkafrawi <i>et al.</i> <sup>27</sup> (2020)<br>[Case report]                                       | Corticosteroids: No<br>Hydroxychloroquine: No<br>Thromboprophylaxis: No<br>Antibiotics: No<br>Antiviral (remdesivir): No<br>Convalescent plasma: No<br>Mechanical ventilation: No                        | N/A   |
| 15  | Birindwa <i>et al.</i> <sup>28</sup> (2021)<br>[Case report]  | Corticosteroids: Yes<br>Hydroxychloroquine: No<br>Thromboprophylaxis: No<br>Antibiotics: Yes<br>Antiviral (remdesivir): No<br>Convalescent plasma: No<br>Mechanical ventilation: No                      | N/A   |
| 16  | Gheysarzadeh <i>et al.</i> <sup>29</sup> (2020)<br>[Case series]                                    | Corticosteroids: N/A<br>Hydroxychloroquine: No<br>Thromboprophylaxis: No<br>Antibiotics: N/A<br>Antiviral (remdesivir): N/A<br>Convalescent plasma: No<br>Mechanical ventilation: No                     | N/A   |
| 17  | Doria <i>et al.</i> <sup>30</sup> (2020)<br>[Case series]   | Not described<br>Mechanical ventilation: No  | N/A   |

ALT = alanine transaminase; AST = aspartate aminotransferase; sFlt = soluble fms-like tyrosine kinase; PlGF = placental growth factor; ECMO = extra-corporeal membrane oxygenation; N/A = not applicable; LDH = lactate dehydrogenase.

**Table 3: Perinatal outcomes of women infected with SARS-CoV-2**

| No. | Author and year of publication<br>[type of study]            | Number of babies     | n (%)                 |                |                |                 |                       | Comments |
|-----|--|----------------------|-----------------------|----------------|----------------|-----------------|-----------------------|----------|
|     |  |                      | Prematurity <37 weeks | NICU admission | Neonatal death | Stillbirth/IUFD | Vertical transmission |          |
| 1   | Federici <i>et al.</i> <sup>14</sup> (2020)<br>[Case report] | 1                    | -                     | -              | -              | -               | 0                     |          |
| 2   | Lokken <i>et al.</i> <sup>15</sup> (2021)<br>[Case series]   | 158 (3 set of twins) | 15 (9.7)              | 11 (7.1)       | 0              | 2 (1.3)         | 0 tested              |          |
| 3   | Breslin <i>et al.</i> <sup>16</sup> (2020)<br>[Case series]  | 18                   | 1 (6)                 | 3              | 0              | 0               | 0                     |          |

NICU = neonatal intensive care unit; IUFD = intrauterine fetal demise; DCDA = dichorionic diamniotic; CPAP = continuous positive airway pressure; LBW = low birth weight; RT = reverse transcriptase; PCR = polymerase chain reaction; rRT = real-time reverse-transcriptase; FGR = fetal growth restriction; PPRM = preterm premature rupture of membranes; GDM = gestational diabetes mellitus; HTN = hypertension.

Table 3 (cont'd.): Perinatal outcomes of women infected with SARS-CoV-2

| No. | Author and year of publication [type of study]                 | Number of babies   | n (%)  |  |                                   |                  |  | Comments   |
|-----|--|--|--|--|-----------------------------------|------------------|--|--|
|     |  |  | Prematurity <37 weeks  | NICU admission                                     | Neonatal death                    | Stillbirth/IUFD  | Vertical transmission  |  |
| 4   | Yan <i>et al.</i> <sup>17</sup> (2020) [Case series]           | 100 (1 pair of twins)  | 21 (21)  | 47 (47)  | 1                                 | 0                | 0  |  |
| 5   | Hantoushzadeh <i>et al.</i> <sup>18</sup> (2020) [Case series] | 12 (3 sets of twins)   | 24–28 weeks: 3 (25); all DCDA twins<br><32 weeks: 3 (25) <37 weeks: 2 (17) | 4 (1 set of twins at 28 weeks)                     | 2 (set of twins on day 3 of life) | 4                | 0  | 2 pregnancies with DCDA twins undelivered -maternal death  |
| 6   | Zheng <i>et al.</i> <sup>19</sup> (2020) [2 case reports]      | 2  | 1 (50)   | 2 (100)  | 0                                 | 0                | 0  |  |
| 7   | Wu <i>et al.</i> <sup>20</sup> (2020) [Case series]            | 5  | 2 (40)   | 2 (40)   | 0                                 | 0                | 0  |  |
| 8   | Wang <i>et al.</i> <sup>21</sup> (2020) [Case report]          | 1  | 0  | 1  | 0                                 | 0                | Pharyngeal swab +ve at 36 hours but the umbilical cord and placenta reported negative confirming that it was not a vertical transmission | postpartum neonatal infection possibly acquired through an infected contact as the neonate was not isolated in the neonatal unit |
| 9   | Zhu <i>et al.</i> <sup>22</sup> (2020) [Case series]           | 10 (1 set of twins)  | <32 weeks: 2 (20); set of twins) 34–36 weeks: 4 (40)                       | 6  | 1                                 | 0                | 0  |  |
| 10  | Adhikari <i>et al.</i> <sup>23</sup> (2020) [Case series]      | 248 outcomes assessed<br>Total: 251 (6 set of twins) (3 major malformations) | Total: 27 (11) < 34 weeks: 9 (4) < 37 weeks: 18 (7)                        | 9 (3.6) 1 with cord pH <7.8 requiring CPAP support | 0                                 | 0                | 6 (3) Only 188 neonates were tested  | 4 were positive at 24 hours and 2 at 48 hours. Only one suspected intra-uterine infection  |
| 11  | Rawat <i>et al.</i> <sup>24</sup> (2021) [Case reports]        | 3  | 0  | 0  | 0                                 | 1                | 0  | IUFD in a dead mother  |
| 12  | Qiancheng <i>et al.</i> <sup>25</sup> (2020) [Case series]     | 23 (1 set of twins)  | 35 weeks: 1 (4.4)  | 0  | 0                                 | 0                | 0 (2 SARS-CoV-2 infection RT-PCR tests 24–48 hours apart were negative for all neonates)   | 1 LBW for the set of twin = 2,350 g  |
| 13  | Chaudhary <i>et al.</i> <sup>26</sup> (2020) [Case series]     | 14   | 0  | 0  | 0                                 | 0                | 0 (Nasopharyngeal COVID-19 RT-PCR negative for all neonates who delivered during mother's hospital stay; n = 9)                          | 9 women delivered during their hospital stay   |
| 14  | Elkafrawi <i>et al.</i> <sup>27</sup> (2020) [Case report]     | 1  | 0  | 0  | 0                                 | 0                | 0  | Nasopharyngeal swab tested rRT-PCR negative at delivery  |
| 15  | Birindwa <i>et al.</i> <sup>28</sup> (2021) [Case report]      | 1  | 34 weeks   | 0  | 0                                 | Yes, from sepsis | Yes SARS-CoV-2 oropharyngeal swab positive on day 3 (neonate was doing well until day 3)   | Thrombotic vasculopathy in the placenta and umbilical cord vessels on histopathology   |
| 16  | Gheysarzadeh <i>et al.</i> <sup>29</sup> (2020) [Case series]  | 2  | 0  | 0  | 0                                 | 0                | 0  |  |
| 17  | Doria <i>et al.</i> <sup>30</sup> (2020) [Case series]         | 11 (1 set of twins)  | 0  | 0  | 0                                 | 0                | 0 (All tested negative for SARS-CoV-2 RT-PCR)  | FGR: 8 (72.7) with 1 discordant growth<br>PPROM: 1 (9.1) GDM: 1 (9.1) Gestational HTN: 1 (9.1)                                   |

NICU = neonatal intensive care unit; IUFD = intrauterine fetal demise; DCDA = dichorionic diamniotic; CPAP = continuous positive airway pressure; LBW = low birth weight; RT = reverse transcriptase; PCR = polymerase chain reaction; rRT = real-time reverse-transcriptase; FGR = fetal growth restriction; PPRM = preterm premature rupture of membranes; GDM = gestational diabetes mellitus; HTN = hypertension.

pandemic.<sup>4</sup> Pregnant women do not appear to be more likely to contract the SARS-CoV-2 infection than the general population. However, pregnancy itself alters the body's immune system and response to viral infections, in addition to various anatomical and physiological changes, which can result in women experiencing more severe symptoms such as respiratory distress, especially towards the end of their term.<sup>3,31</sup> As such, it is crucial that healthcare workers understand how the SARS-CoV-2 virus affects pregnancy so that they can better tailor antenatal, intrapartum and postpartum care in order to optimise maternal and fetal outcomes. This review article provides an overview of the available evidence regarding the maternal and perinatal outcomes of pregnant women diagnosed with COVID-19. The most important finding was that pregnancy did not appear to aggravate symptoms or imaging features of COVID-19-associated pneumonia.<sup>14–30</sup>

The majority of pregnant women infected with SARS-CoV-2 presented in the third trimester with mild to moderate COVID-19 symptoms in the form of fever, cough and myalgia.<sup>14,16–22,25–28</sup> These rates are similar to those described in non-pregnant adults with COVID-19 infections in various reviews and case series.<sup>31–33</sup> In a case series of 43 pregnant women, Breslin *et al.* found that 32.6% were asymptomatic and were diagnosed only due to the development of symptoms after admission or as a result of the implementation of universal COVID-19 screening in their unit.<sup>16</sup>

There is growing evidence that severe COVID-19 infection during pregnancy leads to a preeclampsia-like syndrome or atypical haemolysis, elevated liver enzymes and low platelets syndrome.<sup>34,35</sup> However, in the current review, no overwhelming evidence of such an association was found, but this could be explained by the fact that not many of the case series and reports have addressed the specific investigations that look for preeclampsia in pregnancies diagnosed with COVID-19. Apart from the case report by Federici *et al.*, preeclampsia has been mentioned in the case series by Yan *et al.* and Adhikari *et al.* at the rate of 3.4% and 11%, respectively.<sup>14,17,23</sup> These rates are not significantly higher than the incidence of the condition in pregnant women without infection with SARS-CoV-2.<sup>36</sup>

In this review, there were 12 maternal deaths, seven of which were reported in a single case series of nine women from Iran.<sup>18</sup> The most common comorbidity reported was obesity.<sup>15,16,18</sup> In the general (non-pregnant) population, obesity similarly appears to increase the need for intubation and ventilatory support.<sup>37,38</sup> However, it should be acknowledged that

the pandemic is still ongoing and a number of cases are yet to be reported.

According to the current review, the average rate of preterm delivery in COVID-19 pregnancies was approximately 27%, with most cases representing late preterm births (i.e. at 34–37 gestational weeks).<sup>15–20,22,23,25,28</sup> A systematic review and meta-analysis of all coronavirus spectrum infections, including 19 studies from 79 hospitalised women and 41 (51.9%) pregnancies affected by COVID-19, 12 (15.2%) by MERS and 26 (32.9%) by SARS-CoV-1, reported a 24.3% preterm delivery rate, which is similar to this review.<sup>39</sup> In contrast, the global rate of preterm delivery at <37 gestational weeks was 10.6%.<sup>40</sup> Similarly, the frequency of caesarean section in COVID-19 pregnancies in this cohort was high compared to international rates (4–50% versus 10–15%, respectively).<sup>31,32,39–41</sup> However, this rate is comparable to SARS-CoV-1, where it was reported as 84%.<sup>40</sup> Although many researchers did not report indications for the caesarean section procedure, the most common were fetal distress and the mother and physician's preferences.<sup>16,17</sup> Nevertheless, the high rate of caesarean deliveries in the current review may be due to the fact that most of the cohorts were based in China. In 2014, Feng *et al.* expressed increasing concern about the rapidly rising rate of caesarean deliveries in China (~40%), most of which were performed due to nonclinical factors.<sup>42</sup>

COVID-19 has not shown significant effect on fetal growth.<sup>14–30</sup> In contrast, the rate of FGR in SARS-CoV-1 cases was found to be 13.3%.<sup>39</sup> However, it is too early to conclude definitively that COVID-19 does not impact fetal growth as the outcomes of early pregnancies during this pandemic are yet to be reported. Further confirmation of this finding may require assessment in the future once a greater number of women who contracted COVID-19 in their first or second trimester reach full term and deliver. Moreover, rates of stillbirth and neonatal death were low, with these adverse outcomes mainly related to the severity of the mother's condition.<sup>15,17,18,22,24,28</sup> Overall, the perinatal mortality rate was 2%, further decreasing to 0.7% if the Iranian case series were to be excluded as an outlier, as compared to a rate of 33.2% with MERS.<sup>39</sup> No case of perinatal death was reported with SARS-CoV-1.

The highest preterm delivery rate was reported as 50%, but this was in a report of two cases.<sup>19</sup> The largest case series by Adhikari *et al.* reported the perinatal outcomes of 248 babies with a preterm rate of 21.8%.<sup>23</sup> Among nine pregnant Chinese patients with SARS-CoV-2 infections, Zhu *et al.* found that six



(60%) births occurred at 31–34 gestational weeks.<sup>22</sup> Neonatal morbidities were more marked in this series, probably due to greater prematurity. In particular, there were two cases of disseminated intravascular coagulation, of which one born at 34 gestational weeks subsequently developed multi-organ failure and died on day nine of life.<sup>22</sup>

Panigada *et al.* suggested that COVID-19 infection might increase the risk of micro and macrothrombi.<sup>43</sup> Given that the placenta is an organ fundamentally affected by hypercoagulable states, as reported by Greer *et al.*, it can be extrapolated that COVID-19 carries possible increased risks for embryonic or fetal death due to its placental effects.<sup>44</sup> In addition, the presence of high fever in the first trimester could lead to a higher incidence of miscarriage, as seen with SARS-CoV-1 cases.<sup>7</sup> However, more research is needed to confirm this hypothesis. Until then, greater attention should be given to ensuring adequate thromboprophylaxis in pregnant women contracting COVID-19 as pregnancy is a known hypercoagulable state, which increases risk of venous thrombosis.<sup>44</sup>

In their latest guideline, the Royal College of Obstetricians and Gynaecology, UK, recommends thromboprophylaxis for all pregnant women diagnosed with SARS-CoV-2 infection while they are self-isolating or hospitalised due to the disease and for 10 days following discharge from the hospital.<sup>3</sup> However, this review revealed that maternal thromboprophylaxis was given in only three instances.<sup>14,18,24</sup> This dearth could be explained by the fact that the association of pro-thrombotic state with SARS-CoV-2 infection was realised late into the progression of the pandemic.

Treatment guidelines for SARS-CoV-2 infection have been evolving over time and might continue to change. At the time of writing, chloroquine or hydroxychloroquine with or without azithromycin are not recommended for the treatment of COVID-19.<sup>45</sup> At present, remdesivir is the only Food and Drug Administration-approved broad spectrum anti-viral drug approved for the treatment of COVID-19. It is recommended for use in hospitalised patients who require supplemental oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation.<sup>46</sup> In addition, bamlanivimab and etesevimab were approved to treat people with elevated risk for severe disease, including adults over 65 years and those with relevant comorbidities.<sup>47,48</sup> Remdesivir was the only drug recommended for pregnant women during the study period, though it is not recommended by the WHO anymore.

In this review, eight articles mentioned the use of anti-viral medications, but only two articles specified remdesivir use.<sup>15,23</sup> There is a case report of a pregnant

woman with COVID-19 who required ICU care in the third trimester and received remdesivir. Her pregnancy continued after discharge from the ICU and she delivered at term without any complications.<sup>49</sup> Another case series reported 86 pregnant and postpartum women who received remdesivir for severe COVID-19 with an oxygen saturation of less than 94% on room air and had high recovery rates with low rate of adverse effects.<sup>50</sup>

Corticosteroids, specifically dexamethasone, have been found to reduce mortality in hospitalised patients who require supplemental oxygen; the greatest effect was observed in patients requiring mechanical ventilation. In pregnant women with COVID-19, dexamethasone is recommended for fetal lung maturity if preterm delivery is anticipated. Once the course of four doses of 6 mg over 48 hours is completed, if the patient still requires steroids due to severe COVID-19 disease, the course is recommended to be changed to prednisolone 40 mg once daily if oral intake is possible or hydrocortisone 80 mg intravenous twice daily. Prednisolone and hydrocortisone are extensively metabolised in the placenta and do not cross over to the fetus, thus reducing any concerns about detrimental effects of prolonged steroid exposure on the fetus.<sup>3</sup> In this review, four articles did not mention the use of corticosteroids, and in the remaining articles, the use of corticosteroids ranged from 12.5–100%.<sup>14,16,18,22</sup> This variation could be because the pregnant women did not require hospitalisation, supplemental oxygen or mechanical ventilation, which are indications for steroid use.

Antibiotics use in the treatment of SARS-CoV-2 infection has not been proven to be beneficial, although it is being widely used empirically to prevent secondary bacterial infection. This raises the concerns of antibiotic resistance in the long term and whether its use is justifiable.<sup>51</sup> In this review, eight articles documented the use of antibiotics. Antibiotics were not used in the case series by Zhu *et al.* and data were not available in the case series by Lokken *et al.*<sup>15,22</sup>

Convalescent plasma use is not recommended anymore in the treatment of SARS-CoV-2 infection and it was used minimally in the studied case series. The use of plasma was reported in two (8%) cases by Lokken *et al.*, in one (11%) case in the series by Hantoushadeh *et al.* and in two (15%) cases in the series by Adhikari *et al.*<sup>15,18,23</sup>

To date, there is low incidence of vertical transmission of the SARS-CoV-2 virus. A review of the literature indicated that of the approximately 55 neonatal samples taken from the amniotic fluid, umbilical cord, breast milk and throat immediately after birth, all were found to be negative.<sup>16,22,24,30,52,53</sup>

Dong *et al.* reported a neonate born to a mother with COVID-19 who was found to have raised serum levels of immunoglobulin (Ig)M antibodies to SARS-CoV-2 at birth.<sup>54</sup> Since IgM does not cross the placenta, this could be due to a neonatal immune response to an intrauterine infection.

The current review is subject to certain limitations. As the literature search was conducted using specific databases, it is possible that some relevant studies and articles were missed from the analysis, leading to potential bias. Finally, it is important to recognise that these findings are preliminary and may change as the number of cases reported increases.

## Conclusion

As of August 2021, COVID-19 pregnancies resulted in 12 maternal deaths and eight stillbirths as reported in the literature. Although limited data are available regarding the effect of the disease in early pregnancy, rates of preterm birth and caesarean delivery appear to be high. Healthcare practitioners in conjunction with infectious disease specialists should develop and review protocols for the management of COVID-19 in pregnancy. Despite promising reports regarding the outcomes of COVID-19 infections during pregnancy, it would be prudent to remain vigilant. As such, the authors recommend close monitoring of all pregnant women.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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## AUTHORS' CONTRIBUTION

Both authors reviewed and analysed the data and drafted and edited the manuscript. Both authors approved the final version of the manuscript.

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