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REVIEW

COVID-19 in pregnancy: What do we really know? [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to escalate worldwide and has become a pressing global health concern. This article comprehensively reviews the current knowledge on the impact of COVID-19 over pregnant women and neonates, as well as current recommendations for their management. We also analyse previous evidences from viral respiratory diseases such as SARS, Middle East respiratory syndrome, and influenza that may help to guide clinical practice during the current pandemic. We collected 23 case reports, case series, and case-control studies (18 from China) comprising 174 pregnant women with COVID-19. The majority of mothers showed a clinical presentation of the disease similar to that of non-infected adults. Preliminary evidences point towards a potentially increased risk of pregnancy adverse outcomes in women with COVID-19, with preterm delivery the most frequently observed (16.7%) followed by fetal distress (9.77%). The most commonly reported adverse neonatal outcomes included respiratory symptoms (7.95%) and low birth weight (6.81%). A few studies reported other maternal comorbidities that can influence these outcomes. Mothers with other comorbidities may be at higher risk of infection. Mother-to-child transmission of SARS-CoV-2 appears unlikely, with no study observing intrauterine transmission, and a few cases of neonatal infection reported a few hours after birth. Although the WHO and other health authorities have published interim recommendations for care and management of pregnant women and infants during COVID-19 pandemic, many questions remain open. Pregnant women should be considered in prevention and control efforts, including the development of drugs and vaccines against SARS-CoV-2. Further research is needed to confirm the exact impact of COVID-19 infection during pregnancy. To fully quantify this impact, we urgently need to integrate the current knowledge about viral characteristics,

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epidemiology, disease immunopathology, and potential therapeutic strategies with data from the clinical practice.

Keywords

coronavirus disease, covid, infection, pregnancy, neonate, outcomes, vertical transmission

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Introduction

Coronavirus disease 2019 (COVID-19) has emerged as the most pressing current global health issue. Since the identification of the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causing COVID-2019 in Wuhan, China, in December 2019¹, the virus has spread almost to every country in the world. Local transmission of SARS-CoV-2 is occurring in most countries². The World Health Organization (WHO) declared COVID-19 a 'public health emergency of international concern' on 30th January 2020, and characterized the situation as pandemic on 11th March 2020. According to WHO situation report from 7th April 2020, there were around 1,280,000 COVID-19 confirmed cases and over 72,600 deaths worldwide, with Europe and North America being the current epicentres of the pandemic². The numbers continue to grow at staggering speed.

SARS-CoV-2 is the seventh known coronavirus that infects humans, and several studies support its probable zoonotic origin^{3,4}. SARS-CoV-2 belongs to the betacoronaviridae and, similarly to other members of this genus such as severe acute respiratory syndrome coronavirus (SARS-CoV), binds to angiotensin-converting enzyme 2 (ACE2) as the host receptor for entering the cell to cause infection^{5,6}. Although current data suggest that the majority of infections with SARS-CoV-2 cause a mild presentation of COVID-19, older adults and people with comorbidities, including cardiovascular and respiratory diseases and diabetes, are at increased risk of severity and death, with men potentially at higher risk than women^{7,8}.

Pregnant women are particularly vulnerable to infectious diseases that can cause both maternal and fetal adverse outcomes, compared to their non-pregnant counterparts. Infections caused by influenza virus^{9,10}, hepatitis E virus¹¹, herpes simplex virus¹², cytomegalovirus¹², human papilloma virus¹³, and malaria parasites¹⁴, among others, more severely affect women during gestation. During pregnancy, women experience a series of immunological transformations that allow the immune system to tolerate and support the growing fetus while still maintaining antimicrobial defence and tissue repair¹⁵. These transformations, together with mechanical or anatomical changes, may explain the increased severity or susceptibility to some infectious diseases observed in pregnant women¹⁶.

In particular, the physiological and immunological changes associated with gestation make pregnant women at increased risk for serious viral respiratory illness¹⁷. In view of the urgent threat that COVID-19 pandemic is posing worldwide, obstetricians and future mothers are wondering whether SARS-CoV-2 infection could be associated with adverse fetal and maternal outcomes and/or be transmitted to the fetus. Although current evidences are scarce, several case reports, case series, and case-control studies have already been published reporting clinical manifestations and evaluating the possibility of vertical transmission, as well as maternal and fetal outcomes in pregnant women with COVID-19.

This review collects up-to-date information from the existing literature about the presentation and outcomes of COVID-19 in pregnant women; and discusses current recommendations for their care and management. Moreover, since current knowledge about COVID-19 in pregnancy is scarce, we summarize previous evidences from the impact of other viral respiratory infections, including SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and influenza virus on maternal and fetal outcomes to get insights that may help to better understand COVID-19 and guide the clinical practice. We also discuss challenges that pregnant women may face in the context of the pandemic, including the access to safe therapeutic strategies and mental health issues, and the particularly difficult situation of those in low-resource settings.

The scientific community is intensively working to elucidate the impact of this global health concern over pregnant mothers and their newborns, but still many questions remain unanswered. Since new data are being collected everyday, it is essential to provide healthcare workers with the most updated information about COVID-19 in pregnant women. This information will help to answer the numerous questions that future mothers may have in the current situation and to prevent obstetrical complications.

Methods

After defining the research questions and objectives, we conducted a literature review using [PubMed](#) and [Google Scholar](#). A first search was conducted on 27th March 2020, and a second search was conducted on 8th April 2020 to include the most recently published articles. We searched for articles including the terms 'COVID-19', 'SARS-CoV-2' or 'ncov-2019', and 'pregnancy', 'pregnant', 'gestation', 'newborn', 'neonatal', 'neonate' or 'perinatal' without limits. On 8th April 2020, this search produced 104 results. All abstracts were screened and relevant articles were further inspected. The bibliographic reference lists of the included articles were screened for additional publications. In total, 23 studies comprising case reports, case series, and case-control studies (reporting a total of 174 pregnant women with COVID-19) were included. Relevant information was extracted from the full-text articles, with the exception of one case series and one case-control study that were originally published in Mandarin Chinese (relevant data were extracted from the published English version of the abstract). Publications in Chinese without an English version of the abstract available were discarded. We also reviewed letters, perspectives, and reviews to obtain additional information. We searched for information about COVID-19, SARS-CoV-2, and other viral diseases in pregnancy in PubMed database and [WHO](#) webpage.

What do we know about COVID-19 in pregnancy?

This section reviews the reported cases of pregnant women with COVID-19 since the beginning of the pandemic until 8th April 2020 (summarized in [Table 1](#) and [Table 2](#)).

Table 1. Summary of reported cases of coronavirus disease 2019 (COVID-2019) in pregnant women.

Reference	Country	Infected pregnant women, n	Mode of delivery (n)	Vertical transmission	Adverse pregnancy/neonatal outcomes (n)
Liu <i>et al.</i> ¹⁸	China	15 (4 still pregnant at the end of the study period)	- Caesarean section (10) - Vaginal delivery (1) - Unknown (4, discharged before delivery)	No	Not reported
Chen <i>et al.</i> ¹⁹	China	3	Emergency caesarean section (3)	No	- Preterm delivery (1) - LBW (1)
Chen <i>et al.</i> ²⁰	China	5	- Vaginal delivery (3) - Caesarean section (2; 1 emergency due to fetal tachycardia, 1 elective due to gestational diabetes)	No	Fetal tachycardia (1)
Wang <i>et al.</i> ²¹	China	1	Emergency caesarean section (1)	No	- Preterm delivery (1) - LBW (1)
Liu <i>et al.</i> ²²	China	13	- Caesarean section (10, of which 5 were emergency) - Unknown (3, discharged before delivery)	No	- Maternal MODS including ARDS, acute hepatic and renal failure, and septic shock (1) - Preterm delivery (6) - Fetal distress (3) - PROM (1) - Stillbirth (1)
Chen <i>et al.</i> ²³	China	9	Caesarean section (9)	No	- Preterm delivery (4) ^a - PROM (2) - Fetal distress (2) - LBW (2)
Chen <i>et al.</i> ²⁴	China	17	Caesarean section (14 epidural anesthesia, 3 general anesthesia)	No	- Intraoperative hypotension in women undergoing epidural anesthesia (12) - Preterm delivery (3)
Zhang <i>et al.</i> ²⁵	China	1	Emergency caesarean section (1)	Not reported	- Maternal severe ARDS, multiple organ dysfunction syndrome, and septic shock (1) - Fetal death (endouterine asphyxia) (1)
Zhu <i>et al.</i> ²⁶	China	9	- Caesarean section (7) - Vaginal delivery (2)	No	- Fetal distress (6) - Preterm delivery (6) - SGA (2) - PCIS<90 (6) - Shortness of breath (6) - Fever (2) - Thrombopenia accompanied by abnormal liver function (2) - Rapid heart rate (1) - Vomiting (1) - Pneumothorax (1) - Infant death (1)
Fan <i>et al.</i> ²⁷	China	2	Caesarean section (2)	No	- Lymphopenia (2) - Low-grade fever (1) - Mild neonatal pneumonia (1) - Diffuse haziness in both lung fields without patchy consolidation (1)
Yu <i>et al.</i> ²⁸	China	7	Caesarean section (7)	? (1 neonate positive 36 h after birth)	Not reported
Li <i>et al.</i> ²⁹	China	1	Emergency caesarean section (1)	No	Preterm delivery (1)
Xia <i>et al.</i> ³⁰	China	1	Emergency caesarean section (1)	No	Not reported

Reference	Country	Infected pregnant women, n	Mode of delivery (n)	Vertical transmission	Adverse pregnancy/neonatal outcomes (n)
Wang <i>et al.</i> ³¹	China	1	Emergency caesarean section (1)	? (1 neonate positive 36 h after birth)	Neonatal swallowing syndrome (1)
Zeng <i>et al.</i> ³²	China	33	Caesarean section (33)	? (3 neonates positive on day 2 after birth)	<ul style="list-style-type: none"> - Shortness of breath (4) Positive neonates at day 2: <ul style="list-style-type: none"> - Pneumonia (3) - Fever (2) - Lethargy (2) - Respiratory distress syndrome (1) - Leukocytosis (1) - Lymphopenia (1) - Elevated CK-MB fraction (1) - Bacterial sepsis (1)
Dong <i>et al.</i> ³³	China	1	Caesarean section (1)	? (neonate positive for SARS-CoV-2 IgG and IgM 2 h after delivery)	Laboratory analysis (elevated cytokines and white cell blood counts) suggestive of neonatal inflammation and liver injury (1)
Alonso <i>et al.</i> ³⁴	Spain	1	Emergency caesarean section (severe preeclampsia) (1)	No	<ul style="list-style-type: none"> - Severe preeclampsia (1) - LBW (1) - Neonatal respiratory distress (1)
Kalafat <i>et al.</i> ³⁵	Turkey	1	Caesarean section (1)	No	Not reported
Lee <i>et al.</i> ³⁶	Korea	1	Emergency caesarean section (1)	No	Not reported
Gidlöf <i>et al.</i> ³⁷	Sweden	1 (twins)	Emergency caesarean section (severe preeclampsia, gestational diabetes) (1)	No	<ul style="list-style-type: none"> - Breathing problems (1) - Vomiting (1) - LBW (1)
Zambrano <i>et al.</i> ³⁸	Honduras	1	Vaginal delivery (1)	No	<ul style="list-style-type: none"> - Preterm delivery (1) - LBW (1)
Total women		124			

Abbreviations: LBW, low birth weight; PROM, premature rupture of membranes; ARDS, acute respiratory distress syndrome; SGA, small for gestational age; MODS, multiple organ dysfunction syndrome; ARDS, acute respiratory distress syndrome; PCIS, Pediatric Critical Illness Score; CK-MB, creatine kinase myocardial band; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IgG, immunoglobulin G; IgM, immunoglobulin M.

^a Not directly related with COVID-19.

Table 2. Summary of case-control studies of coronavirus disease 2019 (COVID-2019) in pregnant women.

Reference	Country	Infected pregnant women		Control pregnant women		Vertical transmission	Adverse pregnancy/neonatal outcomes in infected women (n)
		n	Mode of delivery	n	Mode of delivery		
Zhang <i>et al.</i> ³⁹	China	16	Caesarean section	45	Caesarean section	No	Not reported
Li <i>et al.</i> ⁴⁰	China	34 (18 confirmed, 16 suspected)	<ul style="list-style-type: none"> - Caesarean section (30 of which 22 emergency)^a - Vaginal delivery (4) 	242 (121 from 2019 cohort, and 121 from 2020 cohort)	<ul style="list-style-type: none"> - Caesarean section (n=101) - Vaginal delivery (n=141) 	No	<ul style="list-style-type: none"> - Preterm delivery (6)^a - LBW (5)^a - Fetal distress (3)
Total women		50		287			

Abbreviation: LBW, low birth weight.

^a Significantly higher in comparison with control pregnant women.

Disease presentation in infected mothers

A previous review including 108 infected pregnant women in the third trimester described fever (68%) and coughing (34%) as the most frequent symptoms of COVID-19, and elevated C-reactive protein (70%) and lymphopenia (59%) as the most commonly altered maternal parameters⁴¹.

Several authors suggested that pregnancy did not aggravate the symptoms or computed tomography (CT) features of COVID-19 pneumonia^{18,42}. The most common early finding on chest CT was ground-glass opacity, which progressed to 'crazy paving' pattern and consolidations¹⁸. The most frequent symptoms at onset of COVID-19 were fever (13/15 patients) and cough (9/15), while the most common abnormal laboratory finding was lymphopenia (12/15). Pneumonia was not aggravated after delivery in these women. The results of a point-of-care lung-ultrasound examination were found to correlate with CT findings in one pregnant woman; and therefore, this technique has been proposed as a tool to facilitate the triage of mothers with suspected COVID-19^{35,43}.

Liu H. *et al.* evaluated clinical and CT imaging on 41 COVID-19 infected pregnant women (16 laboratory-confirmed and 25 clinically-diagnosed), in comparison with 14 infected non-pregnant adults⁴⁴. Both laboratory-confirmed and clinically-diagnosed COVID-19 pregnant groups more frequently presented leukocytosis, elevated neutrophil ratio, and lymphopenia than non-pregnant adults. Mixed and complete consolidation were more commonly observed in the pregnant groups than in non-pregnant adults. Ground-glass opacity with reticulation was less common in the two pregnant groups than in non-pregnant adults. Moreover, the clinically-diagnosed cases showed more pulmonary involvement than the laboratory-confirmed cases. In view of these results, researchers warned that the atypical clinical findings observed in pregnant women with COVID-19 could complicate the initial identification of the disease⁴⁴.

Placental pathology

In a case series including three pregnant women infected by SARS-CoV-2, all placental histopathological findings included various degrees of fibrin deposition within and around the villi with increased local syncytial nodules, but without villitis or chorioamnionitis¹⁹. One placenta also showed chorionic hemangioma, and another presented massive placental infarction. However, Chen S. *et al.* found no placental complications, including placenta infarction or chorionic amniotic inflammation, in five infected pregnant women from Hubei province, in China²⁰. Further histopathological studies of placenta samples are urgently needed.

Maternal, fetal, and neonatal outcomes

A vast majority of available publications refers to Chinese pregnant women. In a case series including three pregnant women infected by SARS-CoV-2, one of the infants was born preterm with low birth weight (LBW)¹⁹. Other publication presented the case of a 30-week pregnant woman with COVID-19 that gave birth to a LBW but healthy baby²¹.

Liu *et al.* presented 13 pregnant women infected with SARS-CoV-2, two with less than 28 weeks of gestation and 11 in the third trimester²². Three patients improved after hospitalization, were discharged from the hospital, and had an uncomplicated pregnancy. The other ten patients underwent caesarean section, of which five were emergency sections because of fetal distress (n=3), premature rupture of membranes (PROM) (n=1), and stillbirth (n=1). Six patients (46%) had preterm labour from 32 to 36 weeks of gestation. The condition of one of the mothers deteriorated during hospitalization, requiring ICU admission with intubation and mechanical ventilation. This woman presented multiple organ dysfunction syndrome (MODS) that comprised of acute respiratory distress syndrome (ARDS), acute hepatic failure, acute renal failure, and septic shock, and was under extracorporeal membrane oxygenation at the time of the study²².

Chen H. *et al.* reported two cases of fetal distress, four cases of preterm delivery (one mother with preeclampsia, one case of PROM and two with previous history of caesarean sections or stillbirth), and two of LBW (the mother with preeclampsia and the case of PROM) among nine pregnant women infected with COVID-19²³. Chen R. *et al.* included 17 infected pregnant women, three of the neonates were prematurely born²⁴. One case of newborn death due to endouterine asphyxia was reported in a critically ill pregnant woman with SARS-CoV-2 (who developed severe acute respiratory distress syndrome, multiple organ dysfunction syndrome, and septic shock)²⁵. The mother successfully recovered after treatment with convalescent plasma.

Zhu H. *et al.* found several adverse pregnancy outcomes among nine infected women (clinical symptoms beginning before delivery in four cases, on the day of delivery in two mothers, and after delivery in other three)²⁶. Of ten newborns (eight singletons and two twins), six were born premature and two were small for gestational age (SGA) infants. Six of the newborns had a Pediatric Critical Illness Score (PCIS) lower than 90, and showed clinical symptoms including shortness of breath (n=6), fever (n=2), thrombopenia accompanied by abnormal liver function (n=2), rapid heart rate (n=1), and vomiting (n=1). Four neonates presented gastrointestinal symptoms including bloating, refusing milk, feeding intolerance, and gastric bleeding, and seven showed radiography abnormalities (infections, n=4; neonatal respiratory distress syndrome, n=2; and pneumothorax, n=1). One infant presented multiple organ failure, refractory shock, and disseminated intravascular coagulation at day 8 after delivery, received a transfusion, and died on day 9²⁶.

Fan C. *et al.* reported two cases of COVID-19 during the third trimester of pregnancy showing good outcomes in general²⁷. One infant developed low grade fever and abdominal distension with lymphopenia (16.9%) on day 3, and diffuse haziness in both lung fields without patchy consolidation was observed in a chest radiograph on day 4. The fever and lung infection responded to antibiotics, and was discharged on day 9. The second newborn developed mild neonatal pneumonia and

lymphopenia (10.5%), and was treated with antibiotics with good response in two days²⁷. Chen S. *et al.* and Yu N. *et al.* observed good maternal, fetal, and neonatal outcomes in 12 infected pregnant women^{20,28}.

Only a few cases of COVID-19 in pregnancy have been reported outside from China. An infected pregnant women in Spain delivered through an urgent caesarean section due to severe preeclampsia³⁴. The newborn presented LBW, required resuscitation and was transferred to the neonatal unit due to immediate respiratory distress. The neonate received respiratory support for 2 h post birth, showing normal findings on the physical examination at 9 h post birth. The neonate tested negative for SARS-CoV-2 at day 6 post birth, but positive at day 8, showing respiratory symptoms until day 13, while the mother required ICU care with mechanical ventilation³⁴. Kalafat *et al.* reported the case of a pregnant women in Turkey with lung ultrasound findings consistent with COVID-19, but an initial negative real time PCR (RT-PCR) result that subsequently became positive; the woman delivered a healthy newborn³⁵. One Korean mother with COVID-19 delivered a healthy infant through emergency caesarean section due to obstructed labour³⁶. In Sweden, one SARS-CoV-2-positive woman with severe preeclampsia and gestational diabetes delivered twins, one was LBW and the other showed respiratory problems and vomiting after birth³⁷. In Honduras, a woman with gestational hypertension and hypothyroidism prematurely delivered a LBW infant³⁸. Although general media have reported the birth of healthy non-infected infants from SARS-CoV-2 infected mothers in Italy, there is no published scientific literature on the topic yet.

Until now, two case-control studies have been conducted in China (Table 2). Zhang L. *et al.* compared the pregnancy outcomes of 16 women with COVID-19 (one severe case) and 45 non-infected women, all delivering by caesarean section³⁹. Researchers did not observe significant differences in the intraoperative blood loss, meconium-stained amniotic fluid, fetal distress, preterm birth, neonatal asphyxia, or birth weight between infected and non-infected mothers. A second case-control study by Li N. *et al.* compared 16 pregnant women with confirmed COVID-19 pneumonia and 18 suspected cases, all with mild symptoms who were admitted to labour in the third trimester, with two cohorts of 121 age-matched control pregnant women each (one from 2019 and one from 2020)⁴⁰. Around 70% of the two cases groups presented other maternal complications (mostly gestational diabetes mellitus, gestational hypertension, and hypothyroidism), a percentage significantly higher than in the control groups (33%). Three confirmed cases (18.8%, two caused by PROM and one by placental bleeding) and three suspected cases (16.7%, one due to gestational hypertension/preeclampsia and one due to placenta previa) delivered prematurely, compared with a 5.8% of the controls. LBW also occurred more often in infants of the two cases groups (17.6% for confirmed and 10.5% for suspected cases) than in those of controls (2.5%). Two newborns from COVID-19 confirmed mothers and one from a suspected case had intrauterine fetal distress, but this percentage was not significantly different from the control groups⁴⁰.

Delivery

In the great majority of COVID-19 cases reported, mothers delivered by caesarean section (Table 1 and Table 2). Of them, several emergency caesarean sections were performed because the condition of the mother deteriorated, or due to fetal risk (including fetal distress or PROM). Only 11 out of 174 mothers had a vaginal delivery (6.32%).

Chen R. *et al.* evaluated 17 infected patients undergoing caesarean delivery, and found that a significant majority of women with COVID-19 receiving continuous epidural anesthesia presented significant intraoperative hypotension²⁴. The team reported an increased use of carbetocin or carboprost tromethamine for the treatment of uterine contraction fatigue in caesarean sections in pregnant women with COVID-19, compared with a non-COVID-19 group³⁹.

Mother-to-child transmission

None of the studies reported vertical transmission of SARS-CoV-2 when fetal samples, amniotic fluid, cord blood, or breast milk where tested by RT-PCR^{18–23,26,27,29,30,34,35,36,39}. A neonate born to a pregnant woman with SARS-CoV-2 pneumonia tested positive for the infection in pharyngeal swabs 36 h after birth, but maternal breast milk was negative³¹. Yu N. *et al.* found that one out of three neonates tested in throat swabs was positive for SARS-CoV-2 infection 36 h after birth²⁸. Zeng L. *et al.* reported three neonates born from SARS-CoV-2-positive mothers (out of 33 neonates from infected women investigated) that tested positive for viral infection in nasopharyngeal and anal swabs on days 2 and 4 after birth³². In this study, the babies were all born by caesarean section under strict infection control conditions and were immediately separated from their mothers. The outcomes were favourable, and infected neonates only showed a mild presentation with shortness of breath and non-specific radiographic findings (with the exception of a seriously ill probably due to prematurity, asphyxia, and sepsis, rather than SARS-CoV-2 infection). One case report presented a 2 h newborn with elevated immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies to SARS-CoV-2 born to a mother with COVID-19³³. Infant's nasopharyngeal swabs, maternal vaginal secretions at delivery, and breast milk were negative for SARS-CoV-2. Laboratory analysis suggested inflammation and liver injury in the newborn. Since IgM antibodies cannot cross the placenta, further research is needed to confirm this observation, and whether intrauterine or perinatal SARS-CoV-2 infection occurred in these studies.

Zheng Q.L. *et al.* found that ACE2 expression is minimal in almost all cell types of the early maternal-fetal interface in humans, with the exception of decidual perivascular cells cluster⁴⁵. This observation may suggest that the susceptibility of cells in the maternal-fetal interface to COVID-19 could be low, limiting the probabilities of transplacental vertical transmission of SARS-CoV-2. On the contrary, Levy *et al.* found that ACE2 expression and activity are increased during pregnancy in rat models, in particular in the placenta but also in the uterus⁴⁶. Reduced expression of ACE2 has been linked to fetal growth

restriction, both in humans and rats^{47,48}. Further experimental studies are needed to discern the link between ACE2 expression, SARS-CoV-2 susceptibility, and pregnancy outcomes.

Pooled data

A WHO joint mission recently investigated 147 pregnant women (64 confirmed, 82 suspected and 1 asymptomatic; 8% with severe disease and 1% critical) and suggested that pregnancy does not appear as a risk factor for severe COVID-19 disease, as opposed to pandemic influenza A (H1N1)pdm09⁴⁹. The report concluded that having COVID-19 during pregnancy may have an impact on fetal outcomes.

A previous review about COVID-19 in pregnancy included published studies until the 25th February 2020, and was used to inform the UK Royal College of Obstetricians and Gynaecologists guidance⁵⁰. This review found that preterm delivery affected 47% of women (n = 32) hospitalized with COVID-19. There were no maternal deaths and serious morbidity requiring intensive care unit (ICU) admission occurred in two out of 32 (6.25%) reviewed cases. A second review including 37 mothers reported 6 cases (16.2%) of preterm labour, 6 (16.2%) of PROM, 2 (5.40%) with abnormal amniotic fluid, and 2 (5.40%) with abnormal umbilical cord⁵¹. A review published on 17th March 2020 reported preterm birth in 39% of cases, intrauterine growth restriction in 10%, and miscarriage in 2%⁵². A review published on 7th April including 108 women noted three cases of maternal ICU admissions, one neonatal death and one intrauterine death, with 91% of deliveries by caesarean section⁴¹.

Since the publication of these reviews, several new cases of infected pregnant women have been reported, a great majority of them including Chinese pregnant women and only a few case reports from other settings. Among the 174 cases included in this review, a majority of the mothers did not show severe complications related with COVID-19 infection, in particular from mid-trimester onwards. The predominant presentation of COVID-19 in pregnancy included fever, cough, dyspnea, and lymphopenia, as previously reported⁵². Data on first-trimester COVID-19 infection and subsequent follow-up are lacking. It is unknown whether pregnant women have an increased susceptibility to SARS-CoV-2 infection, and there is no evidence from SARS or MERS about an increased susceptibility during pregnancy. However, several publications reported adverse pregnancy and neonatal outcomes in pregnant women infected by SARS-CoV-2.

Regarding pregnancy outcomes in the 174 women with COVID-19, there were 29 cases of preterm delivery (16.7%), 17 cases of fetal distress (9.77%), three cases of PROM (1.72%), two cases of SGA (1.15%), one stillbirth (0.57%), and one fetal death (0.57%). Regarding neonatal outcomes (n=176 since there were two births of twins), there were 14 newborns with respiratory problems (including shortness of breath and pneumonia, 7.95%), 12 with LBW (6.81%), five with fever (2.84%), three with gastrointestinal problems (1.70%), three with lymphopenia (1.70%), three with thrombopenia (1.70%),

two with tachycardia (1.14%), and one infant death (0.57%) (Table 1 and Table 2). These percentages should be interpreted cautiously, since at this point we cannot exclude that some women have been included in more than one publication. Similarly, we cannot exclude that other maternal conditions may potentially confound the results, or even interact with COVID-19. A few cases of preeclampsia and gestational diabetes, among others, were reported in the pregnant women included in this calculations. Interestingly, a case-control study in China found that other maternal complications, such as gestational diabetes mellitus, gestational hypertension, and hypothyroidism, were more frequent in women with COVID-19 than in control women. Further research is needed to understand whether pregnant women with other comorbidities are more susceptible to SARS-CoV-2 infection.

Until more evidences are collected in larger studies and in different settings, the current observations suggest that COVID-19 may be potentially associated with adverse pregnancy outcomes, including preterm delivery and fetal distress, and adverse neonatal outcomes including respiratory problems and LBW. Therefore, special attention should be paid to infected women along the gestational period and at the time of delivery, or to those pregnant women that may be eventually exposed to SARS-CoV-2 virus.

Can we learn something from other viral respiratory infections in pregnancy?

Acute lower respiratory tract illness caused by viral infection, mostly human rhinovirus, respiratory syncytial virus, and influenza virus, is common during pregnancy and associated with significant morbidity¹⁷. In particular, infection is a relevant cause of morbidity and mortality among future mothers⁵³. Pneumonia during pregnancy is related with a higher risk of maternal death and pregnancy-related complications; including preterm delivery, caesarean section, preeclampsia/eclampsia, and LBW and SGA newborns⁵³. The consequences of influenza on pregnant women and fetuses have been widely studied, but less is known about the impact of other viral acute respiratory illnesses in this population. In this section we summarize previous studies about infections with SARS-CoV, MERS-CoV, other coronaviruses, and influenza virus during pregnancy (Table 3).

SARS-CoV

SARS-CoV is a zoonotic virus from the betacoronaviridae genus first identified in 2003⁵⁴. SARS-CoV and SARS-CoV-2 are closely related (around 79% of genome sequence identity) and originated in bats, which have been proposed as a reservoir host for the two viruses³. Between 2002 and 2003, SARS-CoV caused an epidemics that affected more than 8000 people and resulted in around 1000 deaths in 29 countries, mostly in China and Hong Kong, as reported by the WHO. The illness caused by SARS-CoV frequently initiated with fever and mild respiratory symptoms, but progressed to pneumonia within a few days, and eventually led to respiratory distress requiring intensive care. The WHO estimated an overall case fatality rate of 14–15%⁵⁵.

Table 3. Summary of the impact of several viral respiratory infections during pregnancy.

Virus	Increased maternal disease severity	Adverse maternal outcomes	Adverse fetal outcomes	Vertical transmission
SARS-CoV	++	++	++	-
MERS-CoV	+	++	++	-
Other CoV ^a	-	-	-	+?
Influenza ^b	++	++	+	+
SARS-CoV2	-?	+	+	-?

Symbols indicate: frequently reported (++), reported in some cases (+), not reported (-), presumable in view of the currently limited evidences (?).

Abbreviations: SARS, severe acute respiratory syndrome; CoV, coronavirus; MERS, Middle East respiratory syndrome.

^a Limited evidence available.

^b A majority of studies analysed pandemic influenza, not seasonal influenza. Maternal severe infections, but not mild, seem to have a stronger impact on pregnancy.

Several case reports and small clinical studies documented relatively few cases of SARS occurring during pregnancy, with estimations forecasting around 100 pregnant women infected during the 2003 epidemics⁵⁵. Although vertical transmission was not observed, SARS-CoV infection was associated with severe maternal illness or even maternal death, spontaneous abortion, severe intrauterine growth retardation, preterm delivery, and life-threatening gastrointestinal complications in the newborn^{18,56,57}. A case-control study investigating the effects of SARS on pregnancy found a higher mortality rate (30% maternal mortality vs. no deaths in non-pregnant), more frequent renal failure and disseminated intravascular coagulopathy, more frequent admission to the ICU, and higher intubation rate in pregnant SARS patients compared with a non-pregnant infected cohort⁵⁸.

Ng W.F. *et al.* evaluated the placental pathology of SARS-CoV infection in seven women⁵⁹. The placentas from women with SARS infection detected along the first trimester of pregnancy were normal. On the contrary, the placentas from women convalescent from SARS during the third trimester showed increased intervillous or subchorionic fibrin, probably associated with disturbances in placental blood flow due to the hypoxic respiratory disease. The delivery outcomes of women convalescent during the third trimester included intrauterine growth retardation and SGA newborns. The placentas from women with acute SARS infection were also highly abnormal, showing extensive fetal thrombotic vasculopathy, probably caused by placental hypoxia, with sharply demarcated zones of avascular fibrotic villi at delivery⁵⁹. Clinical guidelines have been published for the management of obstetric patients and neonates born to mothers with suspected or probable SARS⁶⁰. The WHO declared SARS epidemics as contained in July 2003, and the latest outbreak in China was contained in May 2004.

MERS-CoV. MERS-CoV is a betacoronavirus causing respiratory disease, which was first identified in Saudi Arabia

in 2012⁶¹. From 2012 until the end of January 2020, the total number of laboratory-confirmed MERS-CoV cases reported globally to the WHO were 2519, with 866 associated deaths (around 35% estimated mortality). Since 2012, 27 countries have reported cases of MERS, although 80% of them occurred in Saudi Arabia, according to the WHO. Humans can be infected with MERS-CoV from direct or indirect contact with dromedaries, although the virus can also be transmitted between humans in close contact. The clinical presentation of MERS-CoV infection widely ranges from absence of symptoms or mild respiratory symptoms to severe acute respiratory disease, and even death. Pneumonia is frequent, and gastrointestinal symptoms have also been described. Severe illness can lead to respiratory failure that requires ICU support with mechanical ventilation. The severity of the disease increases with age, in immunosuppressed people, and in those with chronic conditions such as renal or respiratory diseases, cancer, and diabetes.

Information about the pathophysiology of MERS-CoV infection during pregnancy is scarce, but pregnant women are thought to develop severe disease and adverse maternal and fetal outcomes. A retrospective study conducted in Saudi Arabia between 2012 and 2016 included five pregnant women infected with MERS-CoV during the second or third trimester of pregnancy, all requiring ICU care and showing adverse pregnancy outcomes⁶². Among them, two women died, and two pregnancies resulted in perinatal death. A case report presented a stillbirth, while a second one reported the delivery of a healthy infant, with both women requiring ICU care^{63,64}. One mother died in Abu-Dhabi after delivering a healthy baby by caesarean section⁶⁵. One asymptomatic woman delivered a healthy infant⁶⁶. In South Korea, a MERS-CoV-infected mother had abrupt vaginal bleeding with membranes rupture, and delivered a healthy baby by caesarean section⁶⁷. About 10% placental abruption was found in this patient. Considering all these cases, the estimated maternal case fatality rate in pregnant women is not significantly different than the overall case

fatality rate by MERS-CoV infection, while the disease has resulted in 27% of fetal/infant deaths⁶⁶.

In view of the available information, maternal outcomes in COVID-19 appear less concerning compared to those of SARS and MERS. Pooled data found a case fatality rate of 0% for COVID-19, 18% for SARS, and 25% for MERS, being severe sepsis and respiratory failure the most frequent causes of maternal death in the last two infections⁵².

Other coronaviruses. At least four other types of coronaviruses (alphacoronaviruses HCoV-229E and HCoV-NL63 and betacoronaviruses HCoV-OC43 and HCoV-HKU1) are known to infect humans causing mild, self-limiting respiratory infections. These viruses cause around 15–30% of respiratory tract infections each year, with more severe presentation in neonates, the elderly, or individuals with underlying conditions⁶⁸. A prospective pilot study evaluated the potential maternal-fetal transmission of these coronaviruses⁶⁹. The results suggested the possibility of vertical transmission of human coronaviruses, in particular HCoV-229E, which was detected in three out of four newborn gastric samples whose mothers tested positive in vaginal samples collected at delivery. Two of these mothers were also positive in respiratory samples, and none of the infants showed clinical symptoms. Further studies are needed to understand the potential intrauterine transmission, as well as the effect over pregnancy outcomes, of these coronavirus infections.

A detailed discussion of the epidemiological and clinical impact of SARS, MERS, and other coronavirus infections on pregnant women and newborns can be found in a recently published perspective article⁷⁰.

Influenza virus. Influenza viruses are enveloped viruses with segmented negative-sense single-strand RNA genome, members of the family Orthomyxoviridae. This family comprises several genera, including influenza A viruses infecting humans and several animals with pandemic potential; influenza B viruses that circulate among humans and cause seasonal epidemics; influenza C viruses that can infect humans with mild presentation, as well as pigs; and influenza D viruses that primarily affect cattle (see [WHO influenza page](#)). Influenza A virus infections can cause human diseases ranging from mild upper respiratory tract infection with fever and cough to severe pneumonia, sepsis with shock, acute respiratory distress syndrome, and even death. Seasonal influenza caused by influenza A or B virus subtypes is characterized by a fast onset of fever, cough, headache, severe malaise, muscle and joint pain, sore throat, and rhinorrhea, which can cause severe illness or death especially in high-risk populations (children under five, the elderly, or individuals with chronic diseases or immunosuppressive conditions).

Influenza infection in pregnant women has been associated with increased severity, adverse maternal and fetal outcomes, and a higher risk of death. Moreover, women also have an increased risk of death from pandemic influenza during the four weeks post-partum⁷¹. Substantial evidences were obtained from

the influenza pandemic of 1918 to 1919, 1957 to 1958, and 2009 to 2010, and many studies have been published on this topic. For example, the mortality rate of the 1918 influenza pandemic in Iceland reached 37% among pregnant women, while it was around 2.6% in the general population⁷². In 2009, pregnant women were 1% of patients in the US infected with influenza A H1N1 virus, accounting for 5% of deaths⁷³. The increased severity of influenza during pregnancy and postpartum is thought to be related to the normal physiologic changes occurring during pregnancy, including the hormone-regulated shift in immune responses, decreased lung capacity, and augmented heart rate and oxygen consumption^{74,75}. The WHO recommends the inactivated influenza vaccine for all pregnant women independently of the trimester of pregnancy⁷⁶.

A few systematic reviews and meta-analyses have been conducted to summarize the results of the abundant literature about influenza infection in pregnancy. A meta-analysis published in 2017 found that influenza during pregnancy resulted in a 2.5-fold higher risk of hospital admission compared with non-pregnant adults, but the risk of mortality was similar in both groups¹⁰. Similar results were found in a meta-analysis published in 2019 including 36,498 women, although the risk of hospital admission was almost seven-fold higher in pregnant women than in non-pregnant individuals, and they observed an association between pregnancy and a reduced risk of ICU admission⁷⁷.

Several clinical studies reported complications related to pandemic influenza infection in fetuses and neonates, particularly those born from mothers with severe infection, including miscarriage, preterm birth, stillbirth, neonatal death, and LBW^{78–80}. A systematic review of comparative studies from 2017 confirmed the increased risk of preterm birth following severe pandemic H1N1 influenza illness, but not in mild-to-moderate pandemic H1N1 or seasonal influenza infections⁸¹. This study found that evidences for the increased risk of SGA birth and fetal death were limited. Littauer E.Q. *et al.* suggested that H1N1 virus infection during pregnancy results in dysregulated inflammatory responses leading to preterm labour, impairment of fetal growth, and increased fetal mortality and maternal morbidity in animal models⁸².

A meta-analysis including 22 studies showed that first trimester maternal influenza exposure is associated with an augmented risk of several non-chromosomal congenital anomalies, including neural tube defects, hydrocephaly, congenital heart defects, among others, although exposure to influenza-related medication was not assessed⁸³. Previous work suggested a link between influenza infection during pregnancy and psychotic disorders in the offspring, particularly in mothers with psychiatric disorders^{84,85}, but the evidences are currently insufficient to draw a conclusion⁸⁶. Transplacental transmission of influenza virus has been rarely reported in the literature, but evidence exists that suggests that the virus can cross the placenta⁸⁷.

A WHO technical consultation identified several quality issues (potential confound biases, methodological limitations,

inconsistent definitions, etc.) and evidence gaps in the current knowledge about the risks of severe influenza outcomes among pregnant women, the risks to the fetus, and the effects of maternal immunization⁸⁸. In particular, evidence is lacking for seasonal influenza, for the impact of other contextual factors such as malnutrition or co-infections, as well as evidence from low-resource settings and long-term safety data regarding vaccination in pregnant women⁸⁸. As this report suggests, even in the case of influenza infection in pregnant women where numerous studies have been conducted, many questions remain unanswered.

Care and management of pregnant women and newborns during COVID-19 pandemic

Interim recommendations

In view of the scarce knowledge about COVID-19 in pregnancy and the similar pathogenic potential as SARS-CoV and MERS-CoV, several authors have highlighted in letters and perspectives the need for a systematic screening and careful follow-up of any suspected SARS-CoV-2 infection during pregnancy^{89,90}. Several organizations have issued interim guidance specific to pregnant women, and several individual expert opinions have been published giving recommendations based on their institutional experiences.

The WHO published on 13th March 2020 an interim guidance for the clinical management of severe acute respiratory infection when COVID-19 is suspected, which includes recommendations for pregnant women⁹¹. In this document, the WHO specifically states that pregnant women with suspected or confirmed COVID-19 should be treated with supportive and management therapies, considering the immunologic and physiologic adaptations during and after the gestational period⁹¹. It also emphasizes the need to prioritize COVID-19 testing of symptomatic pregnant women to enable access to specialized care. WHO recommends caesarean section to be only undertaken when medically justified, and highlights that the mode of delivery should be decided based on obstetric indications and the woman's preferences. Infants born to mothers with suspected or confirmed COVID-19 infection should be fed according to standard infant feeding guidelines, and thus breastfeeding is encouraged following strict hygienic practices. Moreover, this interim guidance mentions that mothers and infants should remain together and practice skin-to-skin contact, in particular immediately after birth during establishment of breastfeeding, also when they or their infants have suspected or confirmed SARS-CoV-2 infection. If the mother is severely or critically ill, separation could be needed, with attempts to express breast milk to maintain milk production⁹¹. Similarly, the Centers for Disease Control and Prevention (CDC) from the US have prepared some '*interim considerations for infection prevention and control of COVID-19 in inpatient obstetric healthcare settings*'. The International Society of Ultrasound in Obstetrics & Gynecology (ISUOG), the European Centre for Disease Prevention and Control (ECDC), and other national health authorities have also published interim recommendations for management of infection during pregnancy and puerperium⁹²⁻⁹⁴. In Italy, one of the countries most affected

by the pandemic, the health authorities state that caesarean section does not seem appropriate unless there are specific clinical indications. Moreover, they recommend health professionals and mothers to carefully consider together any temporary separation of the infant from the mother during hospitalization, evaluating the risks and benefits of this choice, and advises breastfeeding under strict measures of infection control⁹⁵. The International Federation of Gynecology and Obstetrics (FIGO) published on 4th April the most up-to-date interim guidance on COVID-19 during pregnancy and puerperium⁹⁶.

In the studies including Chinese pregnant women with COVID-19, the majority of patients delivered through caesarean section, the neonates were isolated immediately after birth for at least 14 days, and breastfeeding was not recommended. The National Health Commission of China, after expert consensus, issued recommendations on 8th February 2020 emphasizing that neonates of pregnant women with suspected or confirmed COVID-19 infection should be isolated in a designated unit for at least 14 days after birth, and not be directly breastfed^{97,98}. These recommendations generated some controversy^{99,100} and have been updated in some Chinese settings to promote breastfeeding and neonatal isolation only of newborns with confirmed SARS-CoV-2 infection¹⁰¹.

Special attention should be paid to pregnant healthcare workers, and some countries have already recommended to those after 28 weeks of pregnancy to avoid direct contact with SARS-CoV-2-infected patients¹⁰².

The existence of disseminated intravascular coagulation (DIC) is common in deaths of COVID-19 patients, and abnormal coagulation parameters have been associated with poor prognosis¹⁰³. During pregnancy, women are at increased risk for hemorrhagic events and obstetrical syndromes that may develop into DIC, usually associated with high mortality and morbidity rates¹⁰⁴. Additionally, women with SARS-CoV infection showed higher risk of DIC⁵⁸. Although alterations in coagulation processes have not been reported in pregnant women infected with SARS-CoV-2, obstetric teams should evaluate this risk and consequently adapt the anticoagulation therapeutic plan during and after the hospitalisation of pregnant women.

Diagnosis of SARS-CoV-2 in pregnant women. A CT scan of the chest is a primary tool to confirm or exclude SARS-CoV-2 pneumonia, complementing RT-PCR diagnosis¹⁰⁵. The majority of reported pregnant women with COVID-19 infection showed radiological signs of viral pneumonia²³. Chest CT scan has been recommended in suspected cases of COVID-19 in pregnant women, since the risk of radiation exposure to the fetus is small⁹². However, shared decision-making should be encouraged. In any case, informed consent is needed, and a radiation shield should be applied over the uterus⁹².

Recommendations for the obstetrics units. In the present emergency situation, the obstetrics units need to be reorganized without delay, and several recommendations have been made in

this sense¹⁰⁶. These recommendations include the preparation of a closed circuit for all COVID-19 positive patients separated from non-infected patients, whenever possible. The ISUOG has prepared a position statement to guide the safe performance of obstetric and gynecological scans and equipment cleaning in the context of COVID-19 pandemic¹⁰⁷. The document refers to ultrasound in particular, which places the patient and the caregiver at high risk because of the impossibility of maintaining the safety distance. Ultrasound is an essential tool of obstetric and gynecological care, and therefore what constitutes an elective or an emergency examination has to be decided locally¹⁰⁷. The expert-opinion-based guidance from the ISUOG focuses on two aspects: first, the preparation and cleaning of the room and the ultrasound equipment; and second, the protection of the patient and ultrasound operators (physicians, sonographers and other health professionals).

Drugs and vaccines against COVID-19: what happens with pregnant women? Currently, there are no specific treatments for COVID-19. More than 80 clinical trials are ongoing, some of them on repurposed drugs and, therefore, in more advanced clinical stages. WHO has recently launched the SOLIDARITY trial (ISRCTN83971151) of treatments for COVID-19 infection in hospitalized patients. The study treatments under evaluation are the experimental antiviral remdesivir, the antimalarials chloroquine or hydroxychloroquine, the combination of human immunodeficiency virus (HIV) drugs lopinavir/ritonavir, and interferon-beta. These drugs were selected based on the likelihood of being effective, previous safety data, and expected wide availability. Simultaneously, the DISCOVERY trial (NCT04315948) of treatments for COVID-19 in hospitalized adults will be conducted in several European countries to evaluate the safety and efficacy of the same drugs, with the exception of chloroquine. Similarly to all decisions regarding treatment during pregnancy, careful assessment of the risk-benefit ratio both for the mother and the fetus is indispensable. It seems reasonable not to exclude seriously ill pregnant women from trials of these experimental drugs for COVID-19⁵⁰.

Remdesivir and lopinavir/ritonavir appear to be safe in pregnancy⁵². Chloroquine phosphate has shown apparent efficacy and an acceptable safety profile against COVID-19-associated pneumonia in multicentre clinical trials conducted in China¹⁰⁸. However, special attention should be put to the use of the antimalarial chloroquine in pregnant women. Previous pharmacokinetic studies of chloroquine and its active metabolite observed differences in the elimination half-lives and in the volumes of distribution and clearance when compared with age-matched non-pregnant women¹⁰⁹. This translates in a reduced plasma concentration of chloroquine in pregnant women that could compromise the antiviral effect, while higher doses may increase the risk of adverse hemodynamic effects. Hydroxychloroquine (with a maximum tolerable dose of 1200 mg), also used in women with rheumatic diseases, could be a therapeutic alternative to chloroquine (with a maximum tolerable dose of 500 mg) in pregnant women because of its safety profile, with the potential to be administered at a higher dosage¹¹⁰.

If the deleterious effect of COVID-19 in pregnancy is confirmed, maternal immunization must constitute a priority and pregnant women should be considered in any prevention effort. As some researchers have highlighted, pregnant women should be included in the design, evaluation, and implementation of vaccine candidates for SARS-CoV-2¹¹¹.

Physical and mental health of pregnant women during COVID-19 pandemic. The mental challenges that the pandemic may pose in pregnant women should be carefully considered, and health authorities should implement programs to provide counselling and psychological support to future mothers. Stress and anxiety during pregnancy seem to be related with side effects such as depression, preeclampsia, preterm labour, LBW, and others^{112,113}. Ng J. *et al.* revealed the pivotal role of midwives in providing care, health education, and counselling to pregnant women during and after the crisis posed by the 2003 SARS epidemics in Hong Kong¹¹⁴.

In addition to an adequate management of stress and anxiety, a lifestyle including appropriate nutrition, moderate physical activity, and plenty of sleep could help pregnant women to stay healthy during COVID-19 pandemic. Emphasis should be put on the practice of regular exercise at home or away from other people if no contraindications exist. Moderate physical exercise during pregnancy has previously demonstrated benefits both for the mother and the fetus, including the reduction of back pain, the promotion of healthy weight gain, and the reduction of the risk of gestational diabetes, preeclampsia, and caesarean delivery (for example, [recommendations from The American College of Obstetricians and Gynecologists](#))¹¹⁵.

Pregnant women in low-resource settings. Maternal mortality remains unacceptably high (around 295000 deaths in 2017), with 94% of deaths occurring in low- and middle-income countries¹¹⁶. Infections remain one of the main causes of maternal death and adverse pregnancy outcomes in these settings. With SARS-CoV-2 present in every country of the world and the number of cases escalating, it is unclear how fragile health systems will be able to confront the pandemic. In this context, pregnant women and neonates in low-resource areas, as well as refugees and those in conflict zones, emerge as one of the most vulnerable populations. Moreover, we have no clues on the potential impact of comorbidities, such as tuberculosis or HIV infections, obstetric complications or malnutrition, on pregnant women with COVID-19. Experience from previous disease outbreaks revealed the disruptive effect on health service delivery and the consequences for diseases such as malaria, which mostly affects children and pregnant women. The [WHO has already urged countries to continue to guarantee the delivery of malaria services in the context of the pandemic](#), including chemopreventive treatment in pregnant women and infants. Similarly, other current efforts regarding women's, infant's, and children's health and healthcare should be guaranteed. Effective coordination, collaboration, and communication are more necessary than ever to protect pregnant women and their infants globally.

Conclusions

Although pregnant women do not seem to present an increased susceptibility to COVID-19 or more severe complications than non-pregnant adults, the available studies suggest that they may be at risk of adverse pregnancy outcomes, mostly preterm delivery, fetal distress, respiratory symptoms and LBW in the newborns. Analysis of the impact of COVID-19 on pregnancy regarding the ongoing trimester is needed in detail. Further research is urgently needed to understand the real effect of COVID-19 on pregnant women and neonates, and to guide the most appropriate recommendations for obstetricians. Only an integrated multiangle assessment of the current knowledge about viral characteristics, COVID-19 epidemiology, disease

immunopathology, and potential preventive and therapeutic strategies, together with clinical observations, will help to understand the exact impact of COVID-19 infection during pregnancy.

Data availability

Underlying data

No data are associated with this article.

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Caterina Montagnoli

Department of Midwifery, Geneva School of Health Sciences, HES-SO University of Applied Sciences and Arts of Western Switzerland, Geneva, Switzerland

I congratulate the authors for the extensive work on the review on COVID-19 effects upon pregnancy and maternal and neonatal outcomes.

I have few but essential comments for improving the text.

In the abstract: "a clinical presentation of the disease" is used. Please rephrase this sentence to make it more accessible.

Why describing the impact of other viral respiratory infections? Please add a sentence to justify your choice beside the lack of COVID-19 knowledge also in this part of the text.

This insight on other coronaviruses and pregnancy is very interesting. Nevertheless, it adds little information about the management of the current COVID-19 disease.

Were letters, perspectives, and reviews included in your data extraction/shortlisted papers?

You write: "The results of a point-of-care lung-ultrasound examination were found to correlate with CT findings in one pregnant women; and therefore, this technique has been proposed as a tool to facilitate the triage of mothers with suspected COVID-19" but were the articles case reports or studies? Were there statistical analysis?

In the conclusions you could discuss more recent literature and evidence regarding the administration of vaccines to pregnant women.

I also advice an update with more recent case studies and other databases for the search.

Is the topic of the review discussed comprehensively in the context of the current

literature?

Partly

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Partly

Are the conclusions drawn appropriate in the context of the current research literature?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Midwifery, Obstetrics, education, simulation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 10 August 2020

<https://doi.org/10.5256/f1000research.25980.r68159>

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Alfonso J. Rodriguez-Morales

Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Colombia

This is a very interesting review, addressing a relevant topic in the context of the coronavirus disease 2019 (COVID-19), its impact on pregnancy. Although I congratulate the authors for the efforts, before it can be fully acceptable it deserves some improvements, including an update of the review. This review is based on two searches in the literature in two databases. The last review was on April 8, 2020. Then, this means, more than four months have passed. For COVID-19 this is a lot. Multiple case reports, studies, and even reviews, and systematic reviews have come out. Then, this needs to be updated, including other additional databases, such as Scopus, and Web of Sciences. The section of Mother-to-Child transmission should be reviewed carefully, as new evidence suggested, that although sporadically, some cases ended in vertical transmission.

Finally, I would suggest to extend more the Conclusions, specially to better discuss the current and future implications of the COVID-19 on pregnancy.

Is the topic of the review discussed comprehensively in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Partly

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a Senior Researcher in Tropical and Emerging Infectious Diseases, currently Chair of the Latin American Network of Coronavirus Disease 2019 (COVID-19) Research (LANCOVID), <http://www.lancovid.org/>.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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