

COVID-19 and pregnancy: a review of current knowledge

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SUMMARY

Background: Since December 2019, coronavirus disease 2019 (COVID-19) has become a major health problem that is spreading all over the world. Several viral infections such as SARS, MERS, and influenza have been associated with adverse pregnancy outcomes. The question arises whether pregnant women are at greater risk of complications related to COVID-19 compared to other people. What complications should we expect in the fetuses whose mothers were infected?

Aims: This review aims to provide a summary of studies on symptoms of COVID-19 and the possible risks of COVID-19 among pregnant women, as well as complications in fetuses and neonates whose mothers were infected with COVID-19.

Methods: The included data were provided from Web of Science, Cochrane, PubMed, and Scopus which are extracted from the published studies in English until April 2nd, 2020 that contained data on the risk of COVID-19 in pregnancy.

Results: The early symptoms of patients with COVID-19 were fever, cough, dyspnea, myalgia, and fatigue; while production of sputum, headache, hemoptysis, and diarrhea were other symptoms which were less common. There is no evidence of vertical maternal-fetal transmission in pregnant women with COVID-19.

Conclusions: The clinical findings in pregnant women with COVID-19 are not significantly different compared to other patients, and pregnant women with COVID-19 are not at a higher risk of developing critical pneumonia compared to non-pregnant women. Although, there has been no sign of vertical infection in infants, but maternal infection can cause serious problems such as preterm labour and fetal distress.

Keywords: COVID-19, pregnancy, SARS, neonates, coronavirus.

INTRODUCTION

Coronaviridae, Arteriviridae, and Roniviridae are the three families of the *Nidovirales* order [1]. The *Coronavirinae* family is divided into two subfamilies which include the *Coronaviridae* and the *Torovirinae*. The *Coronavirinae* is also divided into four categories by phylogenetic clustering which are comprising the alpha, beta, gamma

and delta coronaviruses [1]. The envelope and a non-segmented positive-sense RNA are the characteristics of viruses in *Nidovirales* order. While all of these viruses possess large genomes, *Coronavirinae* is considered to contain the largest RNA genome that is identified [1]. Family of coronaviruses consists of viruses which can lead to several symptoms including fever, dyspnea, and pneumonia [2]. Coronavirus is responsible for important public health problems that led to the global epidemics including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and coronavirus disease 2019 (COVID-19) [3]. Rather than SARS-CoV-1 and MERS-

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CoV, genetic features of SARS-CoV-2 is found to be more similar to bat-SL-CoVZC45 and bat-SL-CoVZXC21 which are SARS-like coronaviruses derived from the bat [4].

First identified in December 2019, COVID-19 became an epidemic in Wuhan, Hubei Province, China [5]. Based on the World Health Organization, 159 countries and regions have been affected between 31 December 2019 and 17 March 2020 [6]. Moreover, 184,976 cases were confirmed within this period with 7,529 deaths [6]. Since there are suggestions regarding similarity about the pathogenesis of COVID-19 and SARS-CoV-1, the potential risk of vertical maternal-fetal transmission of COVID-19 may be as low as SARS-CoV-1 [7]. Viral infections such as SARS, MERS, and influenza have been related to the adverse pregnancy outcomes [8-10]. To reduce fetal rejection, some physiological changes happen in pregnant women for reducing immune responses [11]. Therefore, pregnant women may be at a higher risk of complications after COVID-19 infection.

Multiple studies concerned about the effects of COVID-19 on pregnancy. Thus, this review aims to summarize the symptoms and possible risks of COVID-19 infection in pregnant women. We also provide a summary of studies as of April-2nd, 2020 on complications in fetuses or neonates whose mothers were infected with COVID-19.

Data sources

The included data were provided from Web of Science, Cochrane, PubMed, and Scopus which were extracted from the published studies in English until 2 April 2020 that contained data on the risk of COVID-19 in pregnancy with the following medical cases heading terms and/or text words: pregnancy, pregnancy outcomes, pregnant women, COVID-19, vertical transmission, and 2019-nCoV.

SARS-CoV-1 and pregnancy

Wong *et al.* [10] reported that the SARS tests on neonates who were born to mothers with SARS were negative; however, out of seven pregnant women with SARS who were in the first trimester, four patients had a spontaneous miscarriage. In addition, out of five pregnant women with SARS who were after 24 weeks, four patients underwent preterm delivery, and intrauterine growth restriction was observed despite women's recovery before delivery [10]. Another investigation on

the effect of SARS-associated coronavirus among five neonates who were born to pregnant women with SARS during the outbreak in Hong Kong showed that all performed tests, including viral cultures, reverse transcriptase-polymerase chain reaction, and paired serologic titers were negative in those infants [12]. However, one preterm neonates developed jejunal perforation shortly after birth, and another one suffered from ileal perforation and necrotizing enterocolitis [12]. Five pregnant women who were infected with SARS in their second or third trimester delivered their neonates with no evidence of SARS infection [13]. Stockman *et al.* also reported that samples of cord blood and placenta of one patient were negative for antibodies to SARS-CoV while her serum samples were positive at the time of delivery [14]. Furthermore, breast milk samples, that were tested on days 12 and 30 of postpartum, were negative for the antibodies. The reverse transcription-polymerase chain reaction was also negative for viral RNA in stool samples of the neonates [14].

MERS-CoV and pregnancy

MERS-CoV infection clinical presentations vary from asymptomatic infection to more serious forms such as, acute respiratory distress syndrome, multi-organ failure, septic shock, and even death [15-18]. The disease shows nonspecific symptoms at the early stages, including headaches, malaise, low-grade fever, chills, myalgia, nonproductive cough, and dyspnea [19, 20]. Similar to SARS-CoV, patients infected by MERS-CoV may also suffer from some gastrointestinal symptoms which include abdominal pain, anorexia, nausea, vomiting, and diarrhea [18]. Since acute respiratory distress syndrome occurs more frequently in MERS patients rather than patients with SARS, the mortality rate of MERS-CoV patients was higher (~36%) than SARS patients (~10%) [21].

A study indicated that one pregnant woman infected by MERS-CoV presented with respiratory failure and admitted to ICU, delivered a healthy infant [22]. Another investigation demonstrated that all five pregnant women with MERS-CoV required ICU care; one women delivered a stillborn infant at 34 weeks and another infant died 4 hours after delivery [8]. One pregnant woman whose polymerase chain reaction test was positive for MERS-CoV presented an abrupt vaginal

bleeding; results of several tests were all negative for MERS-CoV, indicating that this woman fully recovered from MERS without transmitting the infection to her baby [23].

Clinical and laboratory characteristics of pregnant women with COVID-19 infection

Huang *et al.* reported that the early symptoms of patients with COVID-19 were fever, cough, dyspnea, myalgia, and fatigue [24]. Production of sputum, headache, hemoptysis, and diarrhea were other less common symptoms [24]. However, some patients did not show at first any signs of fever [24, 25]. Another study also reported that fever and cough were the most common symptoms of pneumonia onset in patients with COVID-19 [26]. Wan *et al.* study on 135 patients with COVID-19 have indicated that fever, cough, and fatigue were the most common symptoms and chest CT images of all patients showed bilateral ground-glass opacity or patchy shadows in the lungs [25]. Ground-glass opacity has been reported to be the most frequent early finding in chest CT images of 15 pregnant women with COVID-19 [26].

In a study on three pregnant patients with confirmed COVID-19 infection, fever has been observed as a symptom; while, there were no signs of significant lymphocytopenia or leukopenia [27]. Chen *et al.* observed that patients had decreased lymphocyte count and increased hyper-

sensitive C reactive protein [28]. Consolidations and crazy paving pattern are two other findings which were observed with the progression of COVID-19 infection [26]. Zhu *et al.* observed that, in addition to cough and fever, diarrhea occurred in one patient out of nine patients [29]. Notable, in Liu *et al.* study, lymphocytopenia has been considered as the most frequent abnormal findings in laboratory tests [26]. Some other clinical characteristics have been observed in pregnant women with COVID-19 infection, including myalgia, sore throat, malaise, lymphocytopenia, and increased concentrations of aminotransferase [30]. Liu *et al.* found that leukocytosis, lymphopenia, increased neutrophil ratio, and initial normal body temperature were more common in 41 pregnant women with COVID-19 who were clinically-diagnosed or laboratory-confirmed compared to non-pregnant patients [31]. They indicated that it is more common for some pregnant women to have mixed or complete consolidations compared to non-pregnant patients. Whereas, ground-glass opacity occurred less frequently in the pregnant group compared to non-pregnant group [31]. Interestingly, Liu *et al.* noted that the initial identification of pregnant women with COVID-19 infection may be more challenging due to their atypical clinical findings [31]. Collectively, these studies have suggested that clinical characteristics of pregnant women with COVID-19 infection are similar to non-pregnant patients [27, 30, 32].

Table 1 - Clinical and laboratory characteristics of pregnant women with COVID-19.

Cases	Age (range/average)	Gestational week (range + days)	Cough	Fever (before delivery/postpartum)	Fatigue/malaise	Myalgia	Diarrhea	Dyspnea	Sore throat	Lymphopenia	Elevated C-reactive protein	Reference
15	23-40	12-38	9	13 / 1	4	3	1	1	1	12	10	[26]
17	29.5/28.7*	≥ 37**	4	4	1	-	1	1	-	5	7	[32]
9	26-40	36 - 39+4	4	7 / 6	2	3	1	1	2	5	6	[30]
9***	30	31-39	5	9	-	-	1	-	1	-	-	[29]
3	-	-	-	1 / 2	-	-	-	-	-	0	-	[27]
16	-	37.9 ± 1.6	-	-	-	-	-	-	-	-	-	[33]
41****	22-42	-	15	16 / 14	5	-	0	-	-	25	27	[31]
7	29-34	37- 41+2	1	6	-	-	1	-	-	-	7	[38]

* Age ranges belong to pregnant women who received epidural anesthesia and general anesthesia, respectively.

** Gestational ages belong to 14 patients out of 17 pregnant women. The three other women gestational age was less than 37 weeks.

*** The authors reported the first symptoms in pregnant women and some symptoms probably haven't been reported.

**** The number of cases include both laboratory-confirmed and clinically-diagnosed patients.

Table 2 - Neonatal outcomes in infants who were born to women with COVID-19.

Cases	Severe asphyxia	Death	1-min/5-min Apgar scores	Low birth weight	Premature delivery	Reference
11	0	0	8 / 9	-	-	[26]
17	0	0	9 / 10	0	3	[32]
9	0	0	8-9 / 9-10	2	4	[30]
7	0	0	8-9 / 9-10	0	-	[38]
3	-	0	-	1 *	1	[27]
10	-	1	7-10 / 8-10	2**	6	[29]

*Authors reported that one premature infant was transferred to the neonatology department due to the low birth weight but we are not aware whether the rest of the neonates had a low birth weight or not.

**Two infants were small-for-gestational-age and 1 was a large-for-gestational-age.

What problems do the COVID-19 cause for pregnant women and their delivery?

As a retrospective study reported, there have been no significant differences in blood loss during the delivery (cesarean section) of 16 pregnant women with COVID-19 infection and 45 pregnant women without COVID-19 infection [33]. CT images that were taken before and after delivery of 11 pregnant women with COVID-19 infection demonstrated that delivery did not lead to the pneumonia aggravation [26]. Moreover, other symptoms of the patients did not aggravate because of pregnancy or childbirth [26]. Liu et al. study indicated that all of 15 pregnant patients recovered from COVID-19 pneumonia; although, some of them did not receive antiviral agents [26]. Chen et al. demonstrated that 17 pregnant women with COVID-19 delivered their babies safely through cesarean section with epidural or general anesthesia [32]. They also reported that intraoperative hypotension has occurred in 12 patients out of 14 patients who received epidural anesthesia [32].

How COVID-19 affects the neonates who were born to women with COVID-19 infection?

There were no differences between birth weight, fetal distress, neonatal asphyxia, and preterm birth of the neonates who were born to women with or without COVID-19 [33]. Assessments of the placentas, that were delivered from pregnant women with confirmed COVID-19 infection, demonstrated different degrees of fibrin depositions both around and inside the villi, as well as increased local syncytial nodules. Data showed that one of the placentas had severe infarction and another one presented aconcurrent chorionic hemangioma morphology. Meanwhile, none of

the three placentas showed pathological changes in chorioamnionitis and villitis [27]. Records of 15 pregnant women with COVID-19 indicated that there were no neonatal death, neonatal asphyxia, and stillbirth [26]. Another study showed that three out of 17 neonates who were born to women with COVID-19 were premature; however, no death or neonatal asphyxia were reported [32]. Zhu et al. found that six out of ten neonates who were born to women with COVID-19 were premature and Pediatric Critical Illness Score (PCIS) of six neonates were less than 90 [29]. They reported that perinatal infection with COVID-19 may lead to some problems, including premature labour, thrombocytopenia, which is accompanied by abnormal liver function, fetal distress, respiratory distress, and death [29]. Chen et al. concluded that 1-min and 5-min Apgar scores of neonates born to women with COVID-19 were 8-9 and 9-10, respectively [30]. Wang et al. also reported that a pregnant woman with COVID-19 delivered an infant with an uneventful postpartum and neonatal course [34]. As studies investigated, all of the samples collected from neonates who were delivered by women infected with COVID-19 were negative for COVID-19 nucleic acid [34]. Altogether, these findings suggest that there is no evidence of vertical transmission in pregnant women with COVID-19.

What should be considered when administering medicines for pregnant women?

Based on interim guidance provided by the World Health Organization on 13 March 2020, no specific anti-COVID-19 treatments are recommended. However, several clinical trials are investigating potential antiviral medications to treat COV-

ID-19 [35]. Chloroquine and remdesivir (GS-5734) are two antiviral drugs that have shown promising inhibitory effects on SARS-CoV-2 replication in cell culture [36]. Chloroquine has shown adverse effects on the fetal development [37]. Meanwhile, Zhou *et al.* suggested that hydroxychloroquine is a better potential therapeutic agent compared to chloroquine because of its safety profile in pregnant women [37]. It is observed that a higher dose of carbetocin or carboprost tromethamine has been used during cesarean section of pregnant women with COVID-19 compared to women without COVID-19 for treating uterine contraction fatigue. Thus, it is suggested that prophylactic administration of uterotonic drugs may lead to the less postpartum hemorrhage in women [33].

■ CONCLUSIONS

There are a few studies concerning with the effects of COVID-19 on pregnant women and their neonates. However, there is not enough evidence to draw a definitive conclusion. As the COVID-19 is spreading further all over the world, more studies are needed to be performed on the pregnant patients and their neonates. We discussed the clinical, laboratory, and radiological characteristics of pregnant women with COVID-19 infection and concluded: (1) clinical findings in pregnant women with COVID-19 are not significantly different compared to other patients; (2) pregnant women with COVID-19 are not at a significantly higher risk of developing critical pneumonia compared to non-pregnant women; (3) and there has been no sign of vertical infection in infants, but maternal infection can cause serious problems such as preterm labour and fetal distress.

Competing interests

The authors declare that they have no competing interests.

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