

# COVID-19 in pregnancy: A review

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## ABSTRACT

COVID-19 has led on to a global healthcare crisis, similar to none in the recent past. Special emphasis must be laid on the status of pregnant women amid this outbreak, considering the vulnerability seen in pregnant women toward previous coronavirus diseases. In this review, we will try to elicit the correlation between the complications of previous coronavirus diseases (Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome) and COVID-19, the possibility of materno-fetal vertical transmission and the obstetric management protocol.

**Keywords:** COVID 19, pregnancy, outcome

## Introduction

An array of atypical pneumonia cases, caused by the novel mutated  $\beta$ -coronavirus, were reported in Wuhan, China in December 2019. This novel virus was primarily cleped by World Health Organization (WHO) as the 2019 novel coronavirus (2019-nCoV) and later as coronavirus disease 2019 (COVID-19). Also, the Coronavirus Study Group (CSG) of the International Committee proposed to call it the SARS-CoV-2.

SARS-CoV-2 was isolated from a patient on 7 January 2020 and scientists came out with its genome sequencing.<sup>[1]</sup> As of 14<sup>th</sup> April 2020, COVID-19 had a total of 1,844,863 confirmed cases including 117,021 deaths.<sup>[2]</sup> The reproduction number ( $R_0$ ) value of SARS-CoV-2 was precisely derived in one study (as 2.2),<sup>[3]</sup> and as a range in another (from 1.4 to 6.5).<sup>[4]</sup> The steady growth of the COVID-19 pandemic is evident by the flared familial clusters of pneumonia and human-to-human transmission.<sup>[5]</sup>

Since there is a paucity of data available about effects of COVID-19 in pregnancy, we must trace back to other highly pathogenic coronavirus infections [i.e., severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS)] to gain astuteness into COVID-19's effect on pregnancy.

Recent viral infections have elicited consequential impact on pregnant women and their fetuses,<sup>[6]</sup> with the aggravated complications in pregnant women with H1N1 influenza virus<sup>[7]</sup> and the severe fetal effects of Zika virus, as recent examples.<sup>[8,9]</sup>

In this review, we'll be highlighting the correlation of complications from previous coronavirus infections in pregnant women, discuss the complications of COVID-19 in pregnant women and the possible materno-fetal vertical transmission of COVID-19.

## Prior Coronavirus Infections in Pregnancy

Pregnancy is a known indicatory condition for aggravated risk of adverse obstetrical and neonatal outcomes from many viral infections. A whole cluster of systemic effects, which propagate the risk of complications from respiratory infections, arise due to the altered physiological and immunological state that is a typical component of pregnancy. The cardiovascular and respiratory components of these changes, along with the development of an immunological adaptation that allows the maternal body to

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tolerate the antigenically diverse fetus; inflate the risk towards development of severe respiratory diseases.<sup>[10]</sup> A marked risk of maternal morbidity and mortality was observed in a meta-analyses of influenza infections, when compared with non-pregnant women.<sup>[10,11]</sup> Similar trend was associated with pregnant women who were infected with either of the two severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).<sup>[12]</sup>

**Severe acute respiratory syndrome (SARS)**

The SARS epidemic afflicted more than 8,000 people with close to 10% fatalities, in 26 different countries.<sup>[13]</sup> The causative agent, SARS-CoV, a coronavirus, was being transmitted via human-to-human contact, aerosolized droplets, and environmental contamination.<sup>[12,14]</sup>

Twelve cases were reported of pregnant women with respiratory distress, among whom 3 died during gestation (fatality rate-25%).<sup>[12]</sup> SARS was evident in materno-fetal complications, like first trimester miscarriages (4/7 women); intrauterine growth restriction (IUGR) (2/5), and pre-term birth (4/5) in 2<sup>nd</sup> and 3<sup>rd</sup> trimesters.<sup>[15]</sup> It can be analyzed that in terms of clinical outcomes, pregnant women were worse hit than non-pregnant women.<sup>[12,15-18]</sup>

Several studies highlighted preventive approach of obstetric protocols during the SARS epidemic to curb transmission to pregnant women.<sup>[19,20]</sup> Although the significance of these mediations was not quantifiably assessed, there definitely were valuable lessons that can be utilized in the approach to COVID-19.

**Middle East Respiratory Syndrome (MERS)**

MERS was first identified in Saudi Arabia during 2012 and spread to over 27 countries both within and outside of the Arabian Peninsula.<sup>[12,21]</sup> MERS-CoV was associated with possible zoonotic transmission, along with intra-familial transmission, with camels as primary source.

It was reported in 13 pregnant women and was associated with a medley of adverse clinical outcomes among 10 (77%) of them. Postnatal maternal mortality, premature delivery, and perinatal fetal death were among some of the most severe outcomes. Among the three deaths, the mothers expired within 2–3 weeks post-delivery. Among the babies, there was one intrauterine fetal demise, one stillbirth and one premature delivery at 25 weeks (where the neonate died 4 h post birth).<sup>[22-29]</sup> Yet, vertical transmission of MERS-CoV had not been confirmed.<sup>[12]</sup>

**Complications of COVID-19**

The SARS-CoV-2, a non-segmented enveloped positive-sense RNA virus, is a  $\beta$ -coronavirus.<sup>[30]</sup> In a research project, the scientists isolated the genome of a strain of SARS-CoV-2, Wuhan-Hu-1 coronavirus (WHCV), and it was found to be 29.9 kb and reported to contain 16 non-structural proteins (NSP).<sup>[31]</sup> Another study suggested that genome of CoVs elicit varying number of open reading frames (ORFs).<sup>[32]</sup> To link with this, it has been reported that the virulence and differentiation mechanism of SARS-CoV-2 are attributed to particular mutations in NSP2 and NSP3.<sup>[33]</sup>

It is an expeditiously disseminating outbreak that has proven to have compelling effects on global health and medical groundwork. Thus, exquisite requirements of pregnant women ought to be incorporated in formulation of any plan of action. COVID-19 principally transmits through the respiratory tract via aerosolized droplets and respiratory secretions; and direct contact,<sup>[34]</sup> for a low minimal infectious dose.<sup>[35]</sup> However, Table 1 summarizes the findings in multiple contemporary studies, which are suggestive of the complications of COVID-19 on pregnant women.

Here, we analyzed the findings of 9 contemporary studies, out of which 3 claimed that there were no fetal complications of COVID-19 and it affected pregnant women and non-pregnant

**Table 1: Complications of COVID-19 on pregnant women**

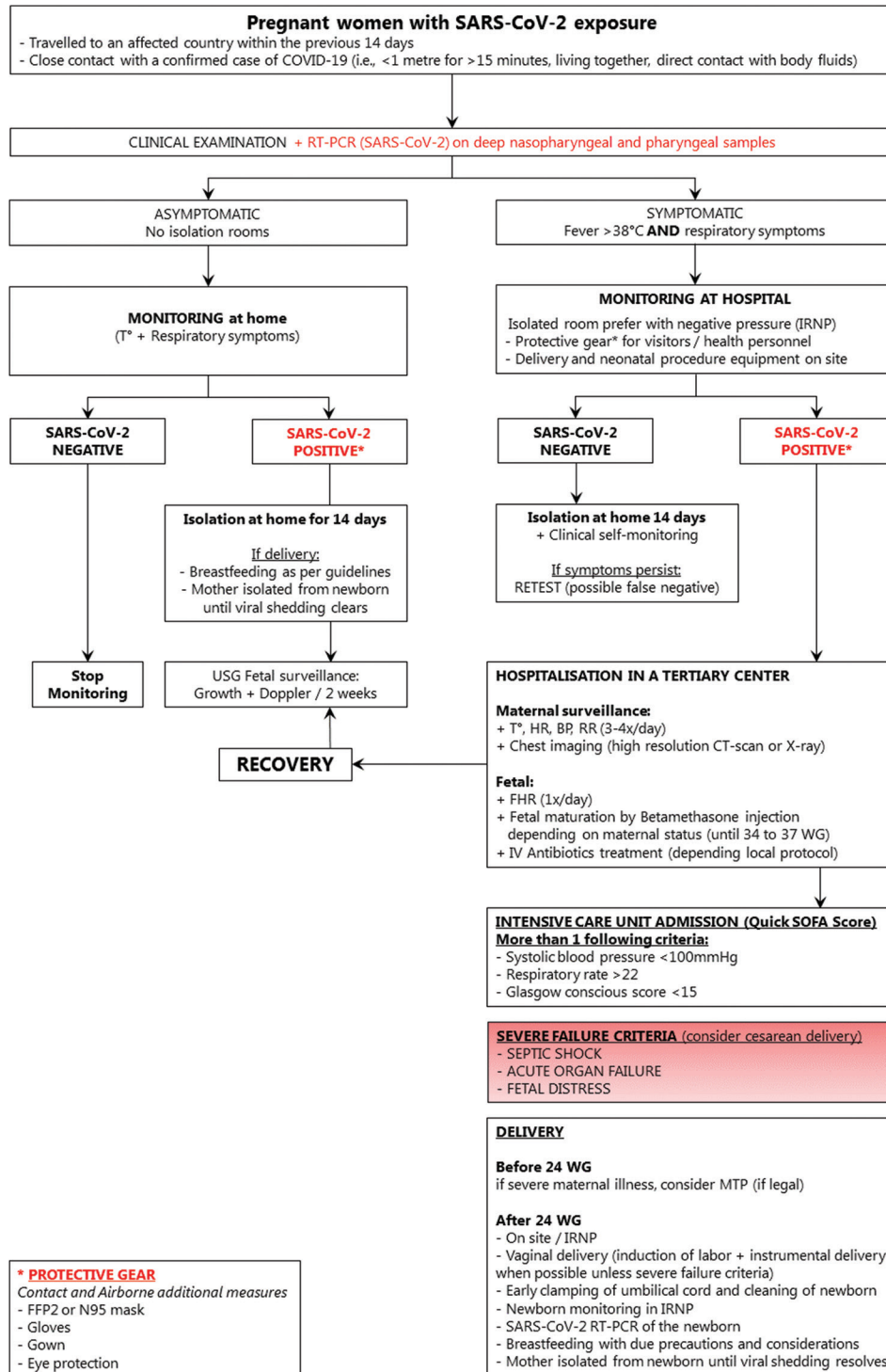
Authors	Key Findings
Chen et al. <sup>[36]</sup>	COVID-19 can lead to fetal distress during pregnancy, but doesn't affect neonates.
Chua et al. <sup>[37]</sup>	Non-evident intrauterine vertical transmission of COVID-19 infection. Breastfeeding should be refrained in cases of infected or suspected mothers. Mandatory perinatal monitoring should be brought in place for all COVID-19 positive mothers.
Liu et al. <sup>[38]</sup>	No significant aggravation of the course of symptoms or CT features of COVID-19 pneumonia have been observed in pregnancy women.
Mardani et al. <sup>[39]</sup>	Neonates born to COVID-19 positive mothers should be put under a two-week isolation and abstinence from breastfeeding. Extensive follow up of such patients is a must, since recurrence of symptoms is a possibility.
Rasmussen et al. <sup>[40]</sup>	Fetal distress and preterm delivery were seen in some newborns.
Wang et al. <sup>[41]</sup>	No report of fetal distress or neonatal infection with COVID-19. COVID-19 indicated for pre-term delivery in infected mothers.
Zhu et al. <sup>[42]</sup>	Perinatal COVID-19 infection produce adverse effects on neonates, causing a wide array of complications like- fetal distress, premature labor, respiratory distress, thrombocytopenia accompanied by abnormal liver function, and even death.
Faver et al. <sup>[43]</sup>	Miscarriage, fetal growth restriction, preterm birth and maternal mortality were the notable adverse effects reported in pregnant women with COVID-19.
Dong et al. <sup>[44]</sup>	Postpartum elevation of IgM levels in a neonate, delivered via caesarean section, born to a COVID-19 positive mother was reported. This indicated a possible intra-uterine vertical transmission of COVID-19.

women alike. Four of them suggested that it does have adverse fetal and neonatal complications. Moreover, in their report, Dong *et al.* presented a case where intrauterine vertical transmission of COVID-19 was possible.<sup>[44]</sup> A point that must be stressed upon is that almost all of the mothers that have been included in these studies were in their third trimester, and vertical transmission as well as fetal and neonatal complications,

even in previous coronavirus infections, have been prevalent in the first two trimesters and not so much in the third trimester.

### Vertical Transmission of COVID-19

As reported by Dong *et al.*,<sup>[44]</sup> there has been a case where the possibility of vertical transmission has been elicited, where the neonate had an increased IgM level, which indicated involvement



Flowchart 1: Obstetric management of pregnant women with COVID-19

of innate immunity of the neonate. Also, reports suggest that 2 neonates, born to COVID-19 infected mothers, tested positive for SARS-CoV-2, postpartum.<sup>[45,46]</sup>

It is suggested that similar to SARS-CoV, SARS-CoV-2 could also be utilizing angiotensin-converting enzyme 2 (ACE2) receptors to infect humans hosts.<sup>[47]</sup> Moreover, the pathological findings of COVID-19, also similar to SARS, is diffuse alveolar damage with fibrin rich hyaline membranes and a few multi-nucleated giant cells.<sup>[48,49]</sup>

In their extensive research, Valdés *et al.* reported that ACE2 receptors were detected in abundance in the materno-fetal interface, throughout pregnancy.<sup>[50]</sup> This can be correlated to the possibility of SARS-CoV-2 utilizing the ACE2 receptors present on the materno-fetal interface to vertically transmit from the mother to the fetus. This hypothesis can also explain the neonatal complications as suggested by the above-mentioned studies, due to the immunopathogenesis, as a response to the viral encounter.

## Obstetric Management in COVID-19

As summarized in Flowchart 1 by Favre *et al.*,<sup>[51]</sup> the principal for obstetric management of COVID-19 include rapid detection, isolation, and testing, profound preventive measures, regular monitoring of fetus as well as of uterine contractions, peculiar case-to-case delivery planning based on severity of symptoms, and appropriate post-natal measures for preventing infection. Transmission during birth via contact with infectious vaginal secretions and after birth via respiratory secretions is a concern. Thus, a mother who has confirmed COVID-19 or is a person under investigation should be isolated from her baby until the mother is free from any possible transmission danger.

## Conclusion

COVID-19 has proven to be a deadlier infection as compared to the previous two coronavirus-caused infection, SARS and MERS. Pregnancy is a severe physiologically stressful condition and is an indicatory state for immunosuppression and thus renders a pregnant woman more susceptible for complications of COVID-19, as compared to a non-pregnant woman. COVID-19 has been found to have adverse effects on both mother and neonate. Considering the reported fetal complications, it can be hypothesized that vertical transmission of COVID-19 is possible across the materno-fetal interface, by utilization of ACE2 receptors. Obstetric management of COVID-19 positive pregnant women is a critical process, which is essential in procuring a good prognosis for the mother and preventing infection in the neonate. Further, extensive Research is required to determine the viability of the hypothesis for vertical transmission of COVID-19 via the materno-fetal interface.

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## Conflicts of interest

There are no conflicts of interest.

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