



## Case Report

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# Recurrent Miscarriage in the Context of COVID-19 Pandemic: Is There An Association?

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## Abstract

Corona virus disease 2019 (COVID-19) is considered a worldwide pandemic. COVID-19 patients had profound immune dysregulation, so they could be susceptible for adverse pregnancy outcomes as preeclampsia and miscarriage. In this mini-review, we tried to explain the link between recurrent miscarriage and COVID-19.

The ongoing corona virus disease-2019 (COVID-19) is a global public health emergency. Little is known about the effect of COVID-19 on pregnancy [1]. Data are mostly limited to small case series and controversies exist about its impact on pregnancy outcomes. A multicenter study included 116 pregnant women with COVID-19 from 25 hospitals in China reported that infection during pregnancy is not associated with an increased risk of spontaneous miscarriage or preterm birth (PTB) [2]. Additionally, they reported no evidence of vertical transmission of infection during pregnancy [2]. On the contrary, in a meta-analysis combining data from pooled proportions in 19 studies, > 90% of them also had pneumonia, PTB was the most frequent adverse pregnancy outcome. Miscarriage, cesarean sections, preeclampsia and perinatal death (7-11%) were also higher than in the general population, with no evidence of vertical transmission of the virus [1].

It is well established that pregnant women are more harshly affected by some viral infections [3]. Since the COVID-19 is most probably not transmitted to the growing embryo, and our aim in this review is to find an explanation of the possible cause of this potential risk. The immunological influences play a pivotal role in embryonic development, and implantation [4]. Endometrial receptiveness is linked to multiple immunological factors including cytokines [5].

Several studies agreed that COVID-19 patients had profound immune dysregulation including marked reduction in the level of lymphocytes, especially natural killer (NK) cells, which is clearly manifest in severe cases [6-10]. Both uterine NK cells and regulatory-T cells (Tregs) have been shown to be potent sources of anti-inflammatory molecules that play a key role in the maintenance of pregnancy [11]. NK cells are critical for the development of the placenta and prevent semi-Allogeneic fetus rejection [12]. Patients with COVID-19 had lower levels of Tregs, and NK cells and even undetectable in severe cases, whether this reduction affects pregnancy or

not needs further investigations [13].

In severe COVID-19, although patients have lymphocytopenia, the lymphocytes were activated [14]. The expression of CD8 on the cytolytic T lymphocytes, which is important for T-cell activity, raised significantly [15], and the cytotoxic particles as perforin and granulysin were greatly expressed in CD8+ T cells [16]. T lymphocytes may be trying to raise their cytotoxic activity [17]. Disturbances in NK cells are largely implicated in recurrent spontaneous miscarriages (RSM) [18], could the cytotoxic activity by these cells be up regulated as well to the level causing poor pregnancy outcomes is a matter that necessitates future studying.

A common feature in COVID-19 patients is having extremely high inflammatory parameters, including high levels of cytokines resembling cytokine storm (CS) in SARS and MERS (including IL-6, TNF $\alpha$ , IL-8, IL-2, IL-7, IL-8, IL-9, IL-10, G-CSF, IP10, MCP1, MIP1A, IFN $\gamma$ ...etc.) [7,9,19]. In one study [9], in most of the severe COVID-19 patients, this CS was associated with hypercoagulability and disseminated intravascular coagulopathy (DIC). Local and systemic inflammatory processes exaggerate the cascade of inflammatory cytokine production with coagulation and ischemia that may lead to adverse pregnancy outcomes including implantation failure,

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pregnancy loss, PTB, fetal inflammatory syndrome, and even RSM [20,21]. These assumptions need further studies to validate them in the future.

In conclusion, we still have limited knowledge about the effect of COVID-19 on early pregnancy. Further studies are recommended to show the association between COVID-19 and RSM. Until further research is available, we suggest that obstetricians should be aware of the risk of RSM among pregnant women contagious to a positive COVID-19 patient or had a history of suggestive symptoms in early pregnancy.

## Conflict of Interest

The authors state that there are no conflicts of interest.

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