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The role of a cytokine storm in severe COVID-19 disease in pregnancy

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Details of Ethics Approval:

This case report, including its publication, was approved by the Ethics Committee of Xiaolan Affiliated Hospital of Southern Medical University, Zhongshan, Guangdong Province, China. The patient's family members gave written consent on behalf of the patient for the permission to the publication of her clinical data (including the images).

Contribution to authorship

XW and DW drafted the first version of the manuscript. XW and SH were involved in conception, planning and carrying out of the case report and the present follow-up study and reviewed the manuscript. XW, DW and SH edited the manuscript, read and approved the final version.

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TO THE EDITOR:

We read with great interest the recent article by Sedigheh et al on maternal death due to coronavirus disease 2019 (COVID-19).[1] As noted by the authors, the 7 maternal deaths due to severe COVID-19 should prompt reexamination of any current guidelines and recommendations by professional societies.[1] We agree with their views, and meanwhile, we would like to draw readers' attention to the cytokine storm in COVID-19 pregnant women.

As a uniquely vulnerable group, pregnant women may be predisposed to a higher risk of SARS-CoV-2 infection and more complicated clinical events than the general population. There have been case reports of pregnant women with severe COVID-19 requiring mechanical ventilation and extracorporeal membrane oxygenation (ECMO),[2, 3] and reports of maternal and intrauterine fetal death.[1, 4] Accumulating evidence suggests that a cytokine storm syndrome, an over-active immune response triggered by SARS-CoV-2 infection, rather than the virus itself, is responsible for severe symptoms in COVID-19 patients and deaths. However, there is little information on this hyperinflammatory response in pregnant women with COVID-19. We would like to present a COVID-19-infected pregnant woman, although she was previously presented by Liu and colleagues in the Journal of Infection,[2] who developed a severe systemic inflammatory response syndrome (SIRS), cytokine storm with acute respiratory distress syndrome (ARDS) and multiple organ failure requiring the use of continuous renal replacement therapy (CRRT), ECMO and fortunately survived and recovered.

On Feb 1, 2020, a 31-year-old woman at 35 and 2/7 week's gestation in her third pregnancy was referred to our hospital with fever and dry cough. Pertinent laboratory results on admission showed leucopenia (white blood cell count 1.8×10^9/L, normal range $3.5\sim9.5\times10^9$/L) and lymphopenia (lymphocytes 0.223×10^9/L, normal range $1.1\sim3.2\times10^9$/L), impaired liver function as well as remarkably elevated levels of C-reactive protein (CRP 60.8mg/L, normal range <10.0mg/L), procalcitonin (PCT 18.19ng/ml, normal range <0.05ng/ml), interleukin-6 (IL-6 >5000pg/ml, normal range <7.0pg/ml, other cytokine measurements were unavailable in our hospital), and D-dimer (4743ug/L, normal range <256ug/L). Unenhanced chest CT showed a large opaque patchy shadow in the lower lobe of the left lung. (Figure 1. A-B) Due to a rapid deterioration in clinical status and a concurrent surge in inflammatory biomarkers triggered by COVID-19, she developed a severe SIRS, septic shock, ARDS, and multiple organ failure, requiring an emergency cesarean delivery and mechanical ventilation. The male fetus was born with Apgar score of 1 and did not respond to neonatal cardiopulmonary resuscitation protocol and died 2 hours after birth. RT-PCR testing of amniotic fluid or placenta or the neonate for SARS-CoV-2 infection was not performed, and the family refused autopsy for the neonate. Later,

the blood culture obtained on the admission day revealed the patient had a co-infection with Streptococcus parasanguinis. The patient continued to deteriorate, requiring the combined supportive treatment of CRRT, ECMO, antibiotics and antiviral treatment, immunoglobulin, and steroids. Fortunately, she responded to the treatment, survived and subsequently recovered, and she was discharged on Mar 17, 2020. (Figure 1. C-F)

The surge in IL-6 and remarkably elevated levels of CRP, PCT and D-dimer, accompanied with severe leucopenia, lymphopenia, and a rapid deterioration in clinical status suggested the presence of a cytokine storm syndrome on this patient. This case highlights the need to be vigilant for clinical and laboratory evidence of a cytokine storm triggered by COVID-19 in pregnant women. All pregnant women with COVID-19 should be closely observed and screened for hyperinflammation. The key to this severe COVID-19-infected pregnant woman's clinical improvement and survival was the rapid identification and control of the hyperinflammatory response and the reduction of inflammatory mediators by using a combination of CRRT, ECMO and these other therapies.

Figure and legend.

Figure. 1. Imaging findings of the patient. A and B: Unenhanced chest CT showing large opaque and ground consolidation (indicated in white arrow) in the lower lobe of the left lung. C-F: Shown are the serial anteroposterior chest X-ray about the development and outcomes of pulmonary inflammation after hospitalization. C: on day 2, after the caesarean section, D: on day 21, before withdrew the ECMO support, E: on day 38, before withdrew the mechanical ventilation, and F: on day 50, before discharged.

REFERENCES

1. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19. Am. J. Obstet. Gynecol., 2020, undefined: undefined. doi:10.1016/j.ajog.2020.04.030
2. Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. J. Infect. 2020; undefined(undefined), undefined. doi:10.1016/j.jinf.2020.02.028
3. Hirshberg A, Kern-Goldberger AR, Levine LD, et al. Care of critically ill pregnant patients with coronavirus disease 2019: a case series. Am. J. Obstet. Gynecol., 2020, undefined: undefined. doi:10.1016/j.ajog.2020.04.029
4. Amorim MMR, Soligo Takemoto ML, Fonseca EBD. Maternal deaths with coronavirus disease 2019: a different outcome from low- to middle-resource countries? Am. J. Obstet. Gynecol., 2020, undefined: undefined. doi:10.1016/j.ajog.2020.04.023