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Labor Could Increase Systemic Inflammation and Cause/Deteriorate Cytokine Storm inCOVID-19

Amir Hossein Norooznezhad[1], MD; Alireza A. Shamshirsaz[2], MD; Sedigheh Hantoushzadeh[3*], MD

[1]Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran; [2]Maternal Fetal Care Center, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA; [3]Maternal, Fetal and Neonatal Research Center, Vali-asr Hospital, Tehran University of Medical Sciences Tehran, Iran

ABSTRACT

Pregnant women with coronavirus disease 2019 (COVID-19) have a higher risk of morbidity and mortality compared with the general population. Possible pathways are: I) in patients with COVID-19, cytokine storm defined as the excess release of pro-inflammatory cytokines such as interleukin 1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) has been associated with morbidities and an even higher rate of mortality. II) Labor, despite being a term/preterm, has an inflammatory nature, although, inflammation is more prominent in preterm delivery. During labor, different pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are involved which as mentioned, all are crucial role players in the cytokine storm. III) Tissue injury, and during labor, (especially cesarean section) is shown to cause inflammation via pro-inflammatory cytokines release including those involved in the cytokine storm through the activation of nuclear factor κB (NFκB). IV) post-partum hemorrhage with a notable amount of blood loss which can cause significant hypoxemia. In this condition, hypoxia-inducible factor 1α which has a cross-talk with NFκB, leads to the expression of IL-1β, IL-6, and TNF-α as both angiogenic and pro-inflammatory factors. Considering all the mentioned issues and pathways, we suggest that clinicians be careful about the escalation of the inflammatory status in their pregnant COVID-19 patients during/following labor.

Keywords: COVID-19, Pregnancy, Inflammation, Cytokine storm, Labor

*Corresponding author:
Sedigheh Hantoushzadeh, MD; Department of Obstetrics and Gynecology, Valiasr Hospital, Keshavarz Blvd, P.O. Box: 14197-33141, Tehran, Iran
Tel: +98 21 66591316
Fax: +98 21 66591315
Email: hantoushzadeh@tums.ac.ir

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INTRODUCTION

It has been more than a year that humankind has been involved in the coronavirus disease 2019 (COVID-19) pandemic (1). Despite notable growing data, many pathophysiological aspects of this disease still are unclear, especially in some populations such as pregnant women. As mentioned in the studies and similar to the general population, the clinical status of COVID-19 in pregnant women ranges from asymptomatic (2) to critically ill (3). Though, as different official organizations such as the Center

for Disease Control and Prevention (CDC) have declared pregnant women should be considered a more vulnerable population for poor disease outcomes (4). As shown, some morbidities such as acute respiratory distress syndrome (ARDS) are common in the general and pregnant populations. However, investigations have shown that pregnant women could experience other different pregnancy-related complications and/or morbidities due to COVDI-19 such as preterm labor and stillbirth (3).

The excess release of pro-inflammatory cytokines known as cytokine storm is a crucial pathway in the pathogenesis of severe COVID-19. This inflammatory condition is associated with the severity of the disease as well as many morbidities (5, 6). According to the studies, cytokine storm is mainly due to increased levels of interleukin 1β (IL-1β), IL-6, and tumor necrosis factor α (TNF-α) as well as some other pro-inflammatory cytokines, however, IL-6 seems to be the main role player (5-8).

Labor, regardless of being a term or preterm, is an inflammatory phenomenon and is considered an inflammatory-based process (9-12). Considering the role of inflammation in the labor (9-12) and also in the pathogenesis of severe COVID-19 (especially cytokine storm) (5-8), labor might start/deteriorate systemic inflammation which could lead to an increase in morbidities or even mortality in these patients. Herein, related molecular pathways and clinical steps will be briefly discussed through different aspects.

Labor and Immune System

The nature of labor has been known as an inflammatory phenomenon (9-11). According to the data, in both term (12) and preterm (10) labors, different pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α lead to the inflammation cascade as the key role players. Furthermore, these cytokines are also involved in the production and/or release of chemokines (such as prostaglandins) and matrix metalloproteinases (MMPs) which could cause/start many other steps of labor/parturition (10).

Other than an alteration in the cytokine profile, white blood cells (WBCs) are among the other changes in the immune system following labor. A study on more than 12,000 pregnant women shows a significant increase in WBC count after delivery regardless of the method of delivery and analgesia (13). Specifically, studies show a significant increase in the number of neutrophils in the circulation system following parturition (9, 14). These cells, and during labor, contribute to the secretion of different pro-inflammatory cytokines as well as MMPs (9). Moreover, it has been shown that there is a significant increase in the number of neutrophils following an acute wound/tissue trauma that affects the cytokine network (15). Thus, acute traumatic injury, during the delivery especially cesarean section (CS), could be another etiology for pro-inflammatory cytokines release. It has been revealed that any surgical wound could increase the levels of pro-inflammatory cytokines such as IL-6 (16). Since inflammation is among the primary responses of an acute tissue injury, the release of pro-inflammatory cytokine during this process could affect the general inflammatory state (15). Also, surgical site infection which is a prevalent complication following CS (17) (especially in emergency surgeries) (18) is another situation that could cause a hyper-inflammatory state. Bacterial infection(s) and immune system activation against them could lead to the activation of toll-like receptors (TLRs) which in turn activate the nuclear factor κB (NFκB). NFκB is an important transcriptional factor responsible for the expression of pro-inflammatory cytokine genes such as *IL-1β, IL-6,* and *TNF-α* (10).

COVID-19 and Labor

According to the studies, pregnant women are more vulnerable to respiratory viral infectious diseases such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS)

(19). For COVID-19, it has been suggested that it is safer to consider pregnant women as a more vulnerable population (4, 20). The performed investigations on pregnancy-related morbidities and outcomes in pregnant women have shown issues such as preterm labor, stillbirth, abortion, and other findings (21-24). Considering the already mentioned crucial role of inflammation in labor and especially preterm labor (9-11), and the role of this phenomenon in the pathogenesis of cytokine storm in patients with COVID-19 (25), the increased prevalence of preterm labor in pregnant women with COVID-19 was not far from expectation before these studies (22-24). In Table 1, the importance of some of the common cytokines, chemokines, receptors, and transcription factors involved in both COVID-19 cytokine storm and parturition has been shown. It should be noted that their importance should not be compared with each other and the Table is just a clue for common important pathways in both pathological conditions rather than the importance of the factor in a certain condition.

COVID-19, Labor, and Inflammation

It has been strongly suggested that the COVID-19 infection itself in a pregnant woman is not an indication for delivery unless oxygenation for the mother is needed. In such a condition, the type of delivery should be chosen according to the patient's condition but certain situations such as fetal distress, organ failure, and septic shock are among the situations that need emergent CS delivery (26, 27). The cytokines involved in the cytokine storm not only cause it but also could increase the other cytokines or even themselves. As an example, IL-1β could cause cytokine storm through an autocrine pathway (28) as well as increase levels of IL-6 (29). Moreover, the released IL-6 from those immune cells with both IL-6 receptor and gp130 could start an autocrine loop and cause a cytokine storm (30, 31) through the JAK-STAT3 signaling pathway (29). Thus, it could be hypothesized that labor (especially its preterm type) could affect the inflammatory state in COVID-19 pregnant individuals and lead to the start/deterioration of the cytokine storm (Figure 1).

Table 1. Role of cytokines, chemokines, and transcription factors in labor and COVID-19 cytokine storm

Transcription factor/Enzyme/Cytokine/ Receptor	Labor (Term and/or preterm)	COVID-19 cytokine storm
Nuclear factor κB (NF-κB)	Essential and important	Essential and important
Hypoxia inducible factor 1α (HIF-1α)	Not very crucial	Important
Toll-like receptors (TLRs)	Not very crucial (except infection –induced labor)	Essential and important
Interleukin 1 β (IL-1β)	Essential and important	Essential and important
IL-6	Essential and important	Essential and important
IL-8	Essential and important	Essential and important
IL-17	Essential and important	Essential and important
Matrix metalloproteinase 2 (MMP-2)	Essential and important	Important
MMP-3	Essential and important	Important
MMP-9	Essential and important	Important
Tumor Necrosis factor α (TNF-α)	Essential and important	Essential and important
Vascular endothelial growth factor (VEGF)	Not very crucial	Important
Granulocyte colony-stimulating factor (G-CSF)	Not very crucial	Essential and important
Granulocyte-macrophage colony-stimulating factor (G-CSF)	Not very crucial	Essential and important
Cyclooxygenase-2 (COX-2)	Essential and important	Essential and important
Prostaglandin E2 (PGE2)	Essential and important	Important
PGF2α	Essential and important	Important

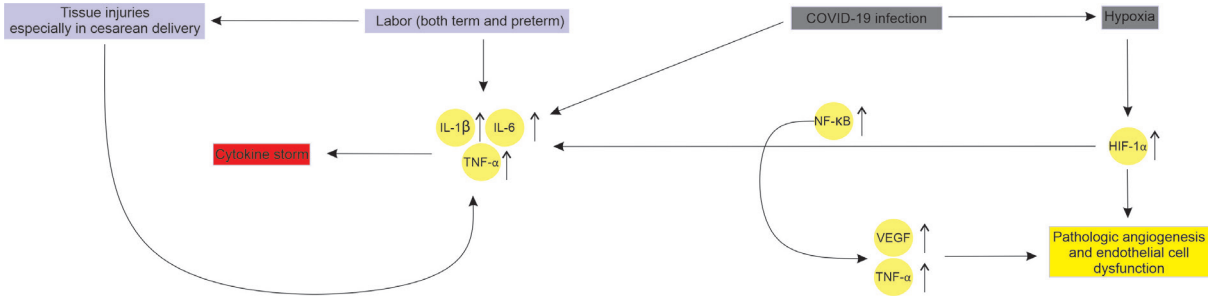

Figure 1. Preterm/term parturition could increase the levels of pro-inflammatory cytokines directly and indirectly and cause/deteriorate cytokine storm in patients with coronavirus disease 19 (COVID-19). Also, in case of postpartum hemorrhage in COVID-19 pneumonia, the risk of hypoxia would increase which might lead to pathologic angiogenesis and endothelial dysfunction through the mentioned pathway.

A systematic review and meta-analysis of pregnant women diagnosed with COVID-19 have shown notable ratios of cesarean and vaginal deliveries that occurred in hospitalized patients (48% and 26% respectively). Also, postpartum hemorrhage (PPH) has been reported to increase in COVID-19 patients (24). Considering PPH and blood loss during labor (24), as well as respiratory system involvement in COVID-19, in pregnant women with at least moderate severity (<93% SpO_2according to the NIH guideline) (32), hypoxemia is very probable. Hypoxemia-induced hypoxia activates hypoxia-inducible factor 1 α (HIF-1α) which in turn activates a cross-talk between hypoxia and inflammation which could lead to pro-inflammatory cytokines response and the release of IL-1β, IL-6, TNF-α (33). Interestingly, HIF-1α has a cross-talk with nuclear factor κB (NFκB) (34) which is responsible for the expression of different pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α in COVID-19 and has been suggested as a potential target for the treatment of critically ill COVID-19 patients (35). Interestingly, other than the mentioned cytokines, NFκB is involved in the angiogenesis process through the vascular endothelial growth factor (VEGF) expression. VEGF, in turn, activates angiogenesis pathways through the expression and/or release of different pro-angiogenic factors. It should be noted that IL-1β (36), IL-6 (37), and TNF-α (38) are among the pro-inflammatory factors which have crucial roles in angiogenesis. It has been shown that angiogenesis and endothelial dysfunction caused by COVID-19 infection (especially in the lungs) are important in the pathogenesis of the disease (39-42). Thus, it seems that blood loss during delivery could be an important issue not only in cytokine storms but also in pathologic angiogenesis.

Furthermore, it has been shown that thromboembolic events are among the most common important pathologies in patients with COVID-19, especially non-survivors (43). It has been suggested that conditions such as cytokine storm and endothelial dysfunction (due to inflammation and oxidative stress) are associated with thromboembolic events (44). As mentioned above, there is a notable ratio of CS among pregnant women with COVID-19 (24). Since CS itself is a major risk factor for venous thromboembolic events (45), it seems high prevalence of CS (due to the increased preterm birth) in COVID-19 patients (24) , which seems to be caused by cytokine storm, could increase thromboembolic events in pregnant women who have undergone CS.

In a study on 93 women with COVID-19, an elevation in the TNF-α as well as a modest increase in IL-1β, IL-6, and C-X-C motif chemokine ligand 10 (CXCL10) were observed. The authors have noted that patients with even worse clinical conditions (higher inflammation) had a higher rate of preterm birth (46). As mentioned earlier, labor is an inflammatory process that causes an increase in different pro-inflammatory cytokines levels (10, 25). Also, increased IL-1β, IL-6, and TNF-α are independent risk factors for the

preterm rupture of membranes which cause preterm labor (47). In a study on 90 cases by Tanacan et al., it was shown that the serum levels of IL-6 were significantly higher in pregnant women compared with non-pregnant COVID-19 women. On the other hand, the control group had lower IL-10 levels than the pregnant women (48). Also, a systematic review and meta-analysis have shown that the serum levels of IL-6 increased in pregnant women with COVID-19. Also, increased IL-6 levels were among the predictors of poor maternal outcomes (49). Moreover, as Sherer et al. have stated, pregnant women with laboratory-confirmative COVID-19 had increased IL-1β levels (50).

CONCLUSION

The immune system seems to be the key to COVID-19 infection pathogenesis. One of the most important pathways activated in severe to critically ill COVID-19 is the cytokine storm. Considering the role of inflammation in both COVID-19 pathogenesis and parturition (a term or preterm) it seems that both of these conditions affect each other through several pathways. Unfortunately, there is not enough data or evidence regarding a solid clinical decision for any possible change in the inflammatory state of a woman with COVID-19 following labor. However, considering the issues mentioned above, it seems that clinicians should closely observe their similar patients for any alteration in their inflammatory state. Also, we recommend further investigations regarding the upper pathways which might be common among all of the mentioned steps for further research on this topic.

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REFERENCES

1. Norooznezhad AH, Najafi F, Riahi P, Moradinazar M, Shakiba E, Mostafaei S. Primary Symptoms, Comorbidities, and Outcomes of 431 Hospitalized Patients with Confirmative RT-PCR Results for COVID-19. Am J Trop Med Hyg. 2020;103(2):834-7.
2. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. N Engl J Med. 2020;382(22):2163-4.
3. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, Seferovic MD, Aski SK, Arian SE, et al. Maternal Death Due to COVID-19 Disease. Am J Obstet Gynecol. 2020;223(1):109.E1-.E16.
4. Center for Disease Control and Prevention CDC. Pregnant People At increased risk for severe illness from COVID-19. https://wwwcdcgov/coronavirus/2019-ncov/need-extra-precautions/pregnant-peoplehtml#:~:text=At%20increased%20risk%20for%20severe%20illness%20from%20COVID%2D19&text=Although%20the%20overall%20risk%20of,compared%20to%20non%2Dpregnant%20people.
5. Mulchandani R, Lyngdoh T, Kakkar AK. Deciphering the COVID-19 cytokine storm: Systematic review and meta-analysis. Eur J Clin Invest. 2021;51(1):e13429.
6. Alberca RW, Pereira NZ, Oliveira L, Gozzi-Silva SC, Sato MN. Pregnancy, Viral Infection, and COVID-19. Front Immunol. 2020;11:1672.
7. Mojtabavi H, Saghazadeh A, Rezaei N. Interleukin-6 and severe COVID-19: a systematic review and meta-analysis. Eur Cytokine Netw. 2020;31(2):44-9.
8. Conti P, Caraffa A, Gallenga CE, Ross R, Kritas SK, Frydas I, et al. Coronavirus-19 (SARS-CoV-2) induces acute severe lung inflammation via IL-1 causing cytokine storm in COVID-19: a promising inhibitory strategy. J Biol Regul Homeost Agents. 2020;34(6):1971-5.
9. Gomez-Lopez N, StLouis D, Lehr MA, Sanchez-Rodriguez EN, Arenas-Hernandez M. Immune cells in term and preterm labor. Cell Mol Immunol. 2014;11(6):571-81.
10. Hantoushzadeh S, Aliabad RA, Norooznezhad AH. Antibiotics, Inflammation, and Preterm Labor: A Missed Conclusion. J Inflamm Res. 2020;13:245-54.
11. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science. 2014;345(6198):760-5.
12. Romero R, Espinoza J, Gonçalves LF, Kusanovic JP, Friel LA, Nien JK. Inflammation in preterm and term labour and delivery. Semin Fetal

Neonatal Med. 2006;11(5):317-26.
13. Arbib N, Aviram A, Gabbay Ben-Ziv R, Sneh O, Yogev Y, Hadar E. The effect of labor and delivery on white blood cell count. J Matern Fetal Neonatal Med. 2016;29(18):2904-8.
14. Yuan M, Jordan F, McInnes IB, Harnett MM, Norman JE. Leukocytes are primed in peripheral blood for activation during term and preterm labour. Mol Hum Reprod. 2009;15(11):713-24.
15. Wang PH, Huang BS, Horng HC, Yeh CC, Chen YJ. Wound healing. J Chin Med Assoc. 2018;81(2):94-101.
16. Grimstad Ø, Sandanger Ø, Ryan L, Otterdal K, Damaas JK, Pukstad B, et al. Cellular sources and inducers of cytokines present in acute wound fluid. Wound Repair Regen. 2011;19(3):337-47.
17. Rezazadeh D, Aliabad RA, Norooznezhad AH. Autologous amniotic membrane: An accelerator of wound healing for prevention of surgical site infections following Cesarean delivery. Med Hypotheses. 2020;137:109532.
18. Yang XJ, Sun SS. Comparison of maternal and fetal complications in elective and emergency cesarean section: a systematic review and meta-analysis. Arch Gynecol Obstet. 2017;296(3):503-12.
19. Rajewska A, Mikołajek-Bedner W, Lebdowicz-Knul J, Sokołowska M, Kwiatkowski S, Torbé A. COVID-19 and pregnancy - where are we now? A review. J Perinat Med. 2020;48(5):428-34.
20. Phoswa WN, Khaliq OP. Is pregnancy a risk factor of COVID-19? Eur J Obstet Gynecol Reprod Biol. 2020;252:605-9.
21. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020;2(2):100107.
22. Capobianco G, Saderi L, Aliberti S, Mondoni M, Piana A, Dessole F, et al. COVID-19 in pregnant women: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2020;252:543-58.
23. Yee J, Kim W, Han JM, Yoon HY, Lee N, Lee KE, et al. Clinical manifestations and perinatal outcomes of pregnant women with COVID-19: a systematic review and meta-analysis. Sci Rep. 2020;10(1):18126.
24. Jafari M, Pormohammad A, Sheikh Neshin SA, Ghorbani S, Bose D, Alimohammadi S, et al. Clinical characteristics and outcomes of pregnant women with COVID-19 and comparison with control patients: A systematic review and meta-analysis. Rev Med Virol. 2021;31(5):1-16.
25. Hantoushzadeh S, Norooznezhad AH. Inappropriate Antibiotic Consumption as a Possible Cause of Inflammatory Storm and Septic Shock in Patients Diagnosed with Coronavirus-19 Disease (COVID-19). Arch Med Res. 2020;51(4):347-8.
26. Poon LC, Yang H, Lee JCS, Copel JA, Leung TY, Zhang Y, et al. ISUOG Interim Guidance on 2019 novel coronavirus infection during pregnancy and puerperium: information for healthcare professionals. Ultrasound Obstet Gynecol. 2020;55(5):700-8.
27. Favre G, Pomar L, Qi X, Nielsen-Saines K, Musso D, Baud D. Guidelines for pregnant women with suspected SARS-CoV-2 infection. Lancet Infect Dis. 2020;20(6):652-3.
28. Karakike E, Giamarellos-Bourboulis EJ. Macrophage Activation-Like Syndrome: A Distinct Entity Leading to Early Death in Sepsis. Front Immun. 2019;10:55.
29. Turnquist C, Ryan BM, Horikawa I, Harris BT, Harris CC. Cytokine Storms in Cancer and COVID-19. Cancer Cell. 2020;38(5):598-601.
30. Lamertz L, Rummel F, Polz R, Baran P, Hansen S, Waetzig GH, et al. Soluble gp130 prevents interleukin-6 and interleukin-11 cluster signaling but not intracellular autocrine responses. Sci Signal. 2018;11(550):eaar7388.
31. Narazaki M, Kishimoto T. The Two-Faced Cytokine IL-6 in Host Defense and Diseases. Int J Mol Sci. 2018;19(11):3528.
32. National Institute of Health NIH. Management of Persons with COVID-19. https://wwwcovid19treatmentguidelinesnihgov/overview/management-of-covid-19. 2020.
33. D'Ignazio L, Bandarra D, Rocha S. NF-κB and HIF crosstalk in immune responses. FEBS J. 2016;283(3):413-24.
34. D'Ignazio L, Batie M, Rocha S. Hypoxia and Inflammation in Cancer, Focus on HIF and NF-κB. Biomedicines. 2017;5(2):21.
35. Kircheis R, Haasbach E, Lueftenegger D, Heyken WT, Ocker M, Planz O. NF-κB Pathway as a Potential Target for Treatment of Critical Stage COVID-19 Patients. Front Immunol. 2020;11:598444.
36. Fahey E, Doyle SL. IL-1 Family Cytokine Regulation of Vascular Permeability and Angiogenesis. Front Immunol. 2019;10:1426.
37. Catar R, Witowski J, Zhu N, Lücht C, Derrac Soria A, Uceda Fernandez J, et al. IL-6 Trans-Signaling Links Inflammation with Angiogenesis in the Peritoneal Membrane. J Am Soc Nephrol. 2017;28(4):1188-99.
38. Sainson RC, Johnston DA, Chu HC, Holderfield MT, Nakatsu MN, Crampton SP, et al. TNF primes endothelial cells for angiogenic sprouting by inducing a tip cell phenotype. Blood. 2008;111(10):4997-5007.
39. Ackermann M, Verleden SE, Kuehnel M, Haverich

A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383:120-8.
40. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
41. Ackermann M, Mentzer SJ, Kolb M, Jonigk D. Inflammation and intussusceptive angiogenesis in COVID-19: everything in and out of flow. Eur Respir J. 2020;56(5):2003147.
42. Norooznezhad AH, Mansouri K. Endothelial cell dysfunction, coagulation, and angiogenesis in coronavirus disease 2019 (COVID-19). Microvascular Res. 2021;137:104188.
43. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7.
44. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. J Thromb Haemost. 2020;18(9):2103-9.
45. Armstrong EM, Bellone JM, Hornsby LB, Treadway S, Phillippe HM. Pregnancy-Related Venous Thromboembolism. J Pharm Pract. 2014;27(3):243-52.
46. Foo SS, Cambou MC, Mok T, Fajardo VM, Jung KL, Fuller T, et al. The systemic inflammatory landscape of COVID-19 in pregnancy: Extensive serum proteomic profiling of mother-infant dyads with in utero SARS-CoV-2. Cell Rep Med. 2021;2(11):100453.
47. Chen R, Zhang S, Su S, Ye H, Shu H. Interactions Between Specific Immune Status of Pregnant Women and SARS-CoV-2 Infection. Front Cell Infect Microb. 2021;11:721309.
48. Tanacan A, Yazihan N, Erol SA, Anuk AT, Yucel Yetiskin FD, Biriken D, et al. The impact of COVID-19 infection on the cytokine profile of pregnant women: A prospective case-control study. Cytokine. 2021;140:155431.
49. Turan O, Hakim A, Dashraath P, Jeslyn WJL, Wright A, Abdul-Kadir R. Clinical characteristics, prognostic factors, and maternal and neonatal outcomes of SARS-CoV-2 infection among hospitalized pregnant women: A systematic review. Int J Gynecol Obstet. 2020;151(1):7-16.
50. Sherer ML, Lei J, Creisher PS, Jang M, Reddy R, Voegtline K, et al. Pregnancy alters interleukin-1 beta expression and antiviral antibody responses during severe acute respiratory syndrome coronavirus 2 infection. Am J Obstet Gynecol. 2021;225(3):301.e1-.e14.