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The evaluation of COVID-19 effect on pregnancy loss; a molecular and diagnostic approach

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus originates from Wuhan, China; it has spread around the world. According to studies, the results of the SARS-CoV-2 test have been reported positive for some pregnant women. However, not much is known about the effect of this virus on pregnancy and the outcome of baby. The aim of this review study was to evaluate the molecular and diagnostic approach in evaluating the effect of coronavirus disease 2019 (COVID-19) on pregnancy loss. The entry of COVID-19 virus into the pregnant mother's body through various channels, such as the angiotensin-converting enzyme receptor (ACE2) affects immune and coagulation systems and hormone levels. These changes include D-Dimer, platelets and antithrombin III (AT-III) raises and protein C (PC) decrement and also elevated levels of pro-inflammatory cytokines, including IL-6, followed by disruption of various signaling pathways such as JAK / STAT and PI3K. Additionally, decreased expression of cyclooxygenase 1 (COX1) and prostaglandin E2 (PGE2) and hormones such as progesterone were observed. These changes ultimately lead to serious pregnancy risks, including miscarriage. Therefore, identifying pathways by which COVID-19 impairs immune and coagulation systems of pregnant women can be a way to design abortion preventive strategies.

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Introduction

Coronavirus disease 2019 (COVID-19) belongs to the coronavirus family, whose study of clinical effects has become one of the main topics of research in the scientific communities. The pandemic of the virus began in late 2019 in Wuhan, China (1). Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is the name now given to this new virus. It is named by the international committee of virus taxonomy (2). COVID-19 can infect all age groups, while it is easily transmitted through the respiratory tract. Clinical signs of the virus include shortness of breath, fever, cough, headache, gastrointestinal and heart problems, blood clotting disorders and other complications (3).

Several studies have focused on the effects of COVID-19 on the general population, but not enough research has been conducted to investigate its effects on people with certain conditions, including pregnancy, while pregnant women are considered as vulnerable group (4,5). In one case, placental infection was observed with COVID-19, which may cause preeclampsia and premature termination of pregnancy or abortion while it may also worsen mother's physiological condition (6). A recent study of 116 pregnant women with COVID-19, found clinical findings of preterm delivery and miscarriage; however, no significant association was found between viral infection and reported cases.

In another case, the traces of COVID-19 in placenta and miscarriage for no reason in the second trimester in a 28-year-old mother can bring us closer to understand the relationship between viral placental infection and miscarriage (7). Due to the clinical effects of this virus on various organs

Key point

The COVID-19 can affect coagulation factors in pregnant women which lead to abortion. In COVID-19 infected pregnant women, imbalance between hormones, cytokines and factors cause endometrial decidualization, which may lead to abortion.

and to improve the control and management of the pandemic and increase the knowledge about the disease pathogenesis, it is necessary to conduct studies about virus effects on different populations in different conditions such as pregnancy (8). Therefore, in the present review study we evaluated the clinical effects of virus on pregnant women and their specific physiological conditions, as well as the relationship between maternal viral infection and abortion.

COVID-19 and coagulation disorder

Coagulation disorders are one of the clinical symptoms in COVID-19 infected individuals, which cause an imbalance in homeostasis. Among the related factors to the coagulation system, elevated D-dimer has been frequently observed in pregnant women with COVID-19 (9). D-dimer is a protein, which increases in the plasma as a result of blood clotting; high levels of D-dimer can be explained by local increase in fibrin formation. Coagulation disorders and increased risk of disseminated intravascular coagulation are the results of D-dimer and inflammatory cytokines increment. They can lead to clot formation and deposition of fibrin in the placenta bloodstream and prevent proper blood supply to placenta, which may lead to abortion.

Antithrombin III (AT-III) has a binding site for thrombin and heparin, which is an important inhibitor of coagulation cascade. AT-III can inhibit serine-activated proteases such as FXa, FIXa, FXIa, and FXIIa (10). It also potentially prevents activation of nuclear factor-κB (NF-κB), which is involved in inflammation. When the COVID-19 enters the body, ACE-2 glycosylation facilitates virus entry into the body. In the virus infected pregnant women, who have recurrent miscarriages, increased AT-III levels have been observed (11).

Protein S (PS) and protein C (PC) also have a vitamin K-dependent anticoagulant role and can bind to activated protein C attached to the phospholipid platelet surface and reduce the effect of FXa on FVa in the coagulation cascade. As a result, PS and PC significantly prevent fibrin clotting and formation (12). PS and protein C also impair the expression of thrombomodulin and endothelial PC receptor on the endothelium. Studies have shown that thrombomodulin has anticoagulant function by binding to thrombin and activating protein C. Decreased protein C levels in COVID-19 infected individuals are associated with imbalance in thrombin regulation (13).

COVID19- entrance to the body is associated with an increase in interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which are linked to insulin resistance, endothelial dysfunction and blood clotting. Insulin resistance is associated with increased plasminogen activator inhibitor-1 (PAI-1) (14). Increasing PAI-1 has a significant effect on fibrinolytic process by increasing platelet count and decreasing prothrombin activity time and thromboplastin activation. Therefore, maintaining balance in PAI-1, especially in pregnant women with COVID-19 is essential for a successful pregnancy. Platelet lymphocyte ratio (PLR) and neutrophil lymphocyte ratio (NLR) levels also change in COVID19- infection. Increased PLR and NLR levels are associated with impression on inflammatory factors and reactive oxygen species, which cause lack of coagulation factors and bleeding and miscarriage (15).

It can now be concluded that COVID-19 can affect coagulation factors; it increases D-dimer, platelets and prothrombin time and also decreases protein C and vitamin K levels, especially in pregnant women. It would be a risk for mother and fetus, and finally it may lead to abortion.

COVID-19 and immune system disorder

The immune system plays an important role in the body homeostasis. Its irregularities can trigger systemic immune responses, following rapid spread of virus, which in turn can lead to COVID-19. The spread of viral agents and inflammation can cause tissue damage, which results in cytokines releasing by damaged cells. Due to the activated signaling cascade, these cytokines affect gene expression. High levels of cytokine in association with a variety of infectious conditions are often called cytokine storms, indicating an immune response characterized by release of interferons, ILs, tumor necrosis factors, chemokines and several other mediators (16).

In COVID-19 infected pregnant women, pro-inflammatory cytokines such as IL-6 increase. This factor causes adverse consequences of abortion or abnormal fetal development. Modulation of the mother's immune system during pregnancy may affect the response to infection, particularly viruses. In general, the immune system during pregnancy adapts to the growth of semi-allogeneic fetus, resulting in an altered immune response to infection during pregnancy. In the placental trophoblast cells of women with the abortion history, this response includes increased production of pro-inflammatory cytokines such as interferon-gamma (IFN-γ)/IL-2/IL-6/IL-7/TNF-α/IL-1 and decreased concentration of anti-inflammatory cytokines (17).

In other words, in the inflammatory and stimulated conditions, IL-1, TNF-a and IL-6 also increase, followed by IL-17 increment; this increase in cytokines activates NF-κB, MAPK, PI3K and JAK/STAT pathways (18). By activating these signaling pathways, serum and urinary concentration of progesterone-induced blocking factor decreases; as a result, by increasing NK cells and TNF production, NK cells target trophoblast cells and cause spontaneous abortion (19).

The proliferation, differentiation and function of NK cells are regulated by direct effect of progesterone and estrogen on intracellular nuclear receptors, or by intermediate cells in the uterus in early pregnancy. In normal pregnancy, lymphocytes are able to produce progesterone and

progesterone induced blocking factor; they increase fetal immunity, inhibit NK cell activity and reduce the risk of miscarriage by increased production of anti-inflammatory cytokines. However, when immune system becomes abnormal due to virus spread, this ability is lost. Natural killer cells spread increases spontaneous abortions (20). Meanwhile, IL-10 modulates resistance to inflammatory stimuli by reducing the expression regulation of pro-inflammatory cytokines, such as IL-1A, IL-12, IL-6 and TNFα (21). In general, inflammatory cytokines increment, especially IL-6 is associated with activation of STAT 3 and STAT 1 in the JAK/stat pathway and imbalance between Treg/Th17 and cellular immunodeficiency. On the other hand, increasing IL-6 disrupts the expression of genes in this pathway (22).

For example, the sprouty 4 (SPRY4) gene is called IFN-γ, which causes STAT1 phosphorylation via the PI3K/AKT pathway. Increased expression of SPRY4 gene inhibits trophoblast proliferation and increases apoptosis (23). Additionally, the IRF1 gene, which in collaboration with STAT1 reduces miR-103, leads to repeated spontaneous abortions by increasing the M1 macrophage activity (24). Accordingly, STAT3 factor increment in large quantities can suppress GP130 through the suppressor of cytokine signaling 3 (SOCS3), which activates the MAPK/PI3k (25). In these pathways, overexpression of TNF-a and matrix metalloproteinase MMP-3 and MMP-9 factors causes apoptosis of trophoblast cells, by altering B-catenin/wnt pathway activity, inhibiting the integrin-linked kinase (ILK) and also by acting on caspases and activating caspase3 (26).

NF-κB pathway activation and increase affect hypertension. It causes a significant decrease in uterine endometrial immunity and the immunological mechanism of gestational hypertension syndrome. Eventually, these pathways affect estradiol and intracellular hormones and progesterone-induced blocking factor concentration, increasing the risk of miscarriage (27). On the other hand, it has been shown that inflammation in the dental pulp can also affect abortion incidence. It has been shown that inflammation in the dental pulp can stimulate the immune system and produce inflammatory mediators through dysregulation of some miRs (Table 1). Considering that one of the complications of COVID-19 infection is cytokine storm, and since dental pulp is effective in the occurrence of cytokine storm, possibly COVID-19 infection can cause abortion by dental pulp (28).

Besides, stimulatory effect of IL-6 increases miR-223-3p and mir-184. Elevation of mir-184 by targeting WIG1 increases trophoblast cells apoptosis by regulating FAS expression. mir-223-3p increment also has a regulatory effect on FOX1 and APOL1 genes, which are involved in immune cell homeostasis and regulation of inflammation and apoptosis. Finally, they form a complex monitoring network with pro-inflammatory agents and signaling pathways (34).

Due to elevated levels of these inflammatory cytokines in pregnant women undergoing abortion and given that these inflammatory cytokines increase in pregnant women with COVID-19, it can be concluded that these cytokines by activating the signaling pathways and the changes mentioned, cause adverse consequences in pregnancy, such as abortion or abnormal growth and development of fetus.

COVID-19 and endometrial decidualization

Endometrial decidualization, a vital multicellular process for pregnancy progression is one of the first changes that the uterus adapts to. The interactions between pregnancy-related hormones and cytokines produced by embryonic and uterine cells have been identified as an essential event for decidualization (35). In COVID-19 infected pregnant women, due to lack of coordination and balance between cytokines and hormones, a disorder is observed in the decidualization process (36). Endometriosis is one of the most common diseases in pregnant women, which has been partly explained by resistance to progesterone and decreased intracellular progesterone receptor expression in the extra-uterine endometrium. However, overproduction of progesterone can also impair decidualization by inhibiting leukemia inhibitory factor (LIF)/STAT3 (37).

Heart- and neural crest derivatives-expressed transcript 2 is a major factor in the transcription of progestin-induced human endometrial stromal cells. It also plays a key role in activation and survival of uterine natural killer by regulating IL-15. Heart- and neural crest derivatives-expressed transcript 2 balances the production of vascular endothelial growth factor and placental growth factor, resulting in balance in endometrial stromal cells (38). COVID-19 infected pregnant women are at the risk of miscarriage, due to decreased level of progesterone production (39).

Studies have shown that ACE2, known as a receptor for COVID-19 entry is essential for decidualization

Table 1. Summary of miRs involved in inflammation by dental pulp

miR	Target	Mechanism	Ref.
miR-21	KBTBD7	Cause activation NF-kB and lead to inflammation	(29)
miR-410	MMP-14	Decreased expression of miR-410 causes increased MMP-14 production and inflammation	(30)
miR-146a	bFGF	Cause production of inflammatory mediators	(31)
Let-7c-5p	DMP1	Down regulation of Let-7c-5p lead to NF-kB pathway activation and inflammation	(32)
miR-223-3p	DSPP DMP1	Cause stimulate immune response and inflammation	(33)

Abbreviation: bFGF: Basic fibroblast growth factor; DMP1: Dentin matrix protein-1; MMP-14: Matrix Metalloproteinase; DSPP: Dentin sialophosphoprotein.

of endometrial stromal cells. Angiotensin-converting enzyme 2 is increased during the process of primary human endometrial stromal cell development. Due to increase in ACE2 in various tissues, such as ovaries and uterus, a potential risk to the reproductive system and pregnancy was existed (40). In addition to ACE2, other factors affecting human endometrial stromal cells include prolactin (PRL) and insulin-like growth factor binding protein-1 (IGFBP1). They are produced by decidual cells. Prolactin and insulin-like growth factor binding protein-1 are two known factors for decidual cell maturation and proteoglycan decorin. Decidual cell maturation and proteoglycan decorin inhibit human trophoblast regeneration, migration, invasion and differentiation; while, they are needed to regenerate uterine arteries during normal pregnancy. According to studies, some cytokines increment such as IL-11 is associated with changes in the regulation of expression of IGFBP1 and PRL genes and their incensement. This increase is also achieved through the entry of virus to the pregnant women, followed by activation of other cytokines and changes in the regulation of their expression. As a result, there would be the miscarriage risk during pregnancy (41).

Morphogenetic protein-2 (bmp2) has also been shown to increase the production of pro-inflammatory cytokines. It also reduces the regulation of cyclooxygenase 1 (COX1) expression, followed by a decrease in prostaglandin E2 (PGE2), which is disrupted by the signaling pathway of SMAD1/SMAD5/(Alk3) activin receptor-like kinase 3 in endometrial stromal cells. An increase in the amount of pro-inflammatory cytokines without any controlling effects increases the risk of miscarriage for COVID-19 infected pregnant women (42).

According to the studies, sirtuin 1 (SIRT1) can also be introduced as an effective factor to regulate homeostasis and ESC decidualization (43). Sirtuin 1 through regulating the expression of superoxide dismutase2 (SOD2) and nuclear factor erythroid 2-related factor 2 (NRF2), as well as by deacetylation of Forkhead box O1 (FOXO1) makes adjustment homeostasis of reactive oxygen species (ROS) and NAD^+; since it also enhances cell protection against oxidative stress. Decreased SIRT1 followed by decreased FOXO1 deacetylation and imbalances in ROS and NAD^+ observed in patients with COVID-19 cause recurrent implantation failure (44). FOXO1 is also considered as an endometrial stromal cells decidualization marker, which acts as a transcriptional regulator of PRL and Insulin (45).

Studies have also shown that the effect of norepinephrine on decidualization can be investigated. Norepinephrine prevents endometrial decidualization by activating the protein kinase C signaling pathway via B-adrenergic receptor regulation (46). Given the changes mentioned, and the imbalance between hormones, cytokines and factors involved in pregnancy in COVID-19 infected pregnant women, we can conclude that the process of endometrial decidualization is disrupted and subsequently abortion may happen.

Conclusion

Pregnant women are in a state of suppressed immune system due to physiological changes; they are considered as COVID-19 high-risk group, due to susceptibility to infections and mechanical functions. Immune system suppression disrupts the pregnancy process by affecting the profiles of cytokines and various coagulation systems and hormones. These disorders are associated with the risk of miscarriage. We hope this review be useful for pregnancy and neonatal services, seeking to respond to COVID-19.

Authors' contribution

NA, SKM and MY were the principal investigators of the study. MY and ZJ were included in preparing the concept and design. NH and MR revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any parts of the work.

Conflicts of interest

The authors declare no conflict of interest

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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