SPECIAL ISSUE ARTICLE

COVID-19 and Treg/Th17 imbalance: Potential relationship to pregnancy outcomes

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Abstract

Caused by a novel type of virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19) constitutes a global public health emergency. Pregnant women are considered to have a higher risk of severe morbidity and even mortality due to their susceptibility to respiratory pathogens and their particular immunologic state. Several studies assessing SARS-CoV-2 infection during pregnancy reported adverse pregnancy outcomes in patients with severe conditions, including spontaneous abortion, preterm labor, fetal distress, cesarean section, preterm birth, neonatal asphyxia, neonatal pneumonia, stillbirth, and neonatal death. However, whether these complications are causally related to SARS-CoV-2 infection is not clear. Here, we reviewed the scientific evidence supporting the contributing role of Treg/Th17 cell imbalance in the uncontrolled systemic inflammation characterizing severe cases of COVID-19. Based on the recognized harmful effects of these CD4$^+$ T-cell subset imbalances in pregnancy, we speculated that SARS-CoV-2 infection might lead to adverse pregnancy outcomes through the deregulation of otherwise tightly regulated Treg/Th17 ratios, and to subsequent uncontrolled systemic inflammation. Moreover, we discuss the possibility of vertical transmission of COVID-19 from infected mothers to their infants, which could also explain adverse perinatal outcomes. Rigorous monitoring of pregnancies and appropriate measures should be taken to prevent and treat early eventual maternal and perinatal complications.

KEYWORDS
COVID-19, pregnancy outcomes, SARS-CoV-2, systemic inflammation, Th17 cells, Treg cells

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pneumonia pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] First identified in December 2019 in an outbreak of pneumonia in Wuhan City (Hubei Province, China), COVID-19 currently affects over 210 countries and territories worldwide.[2] The World Health Organization (WHO) declared COVID-19 to be a Public Health Emergency of International Concern,[3] then a pandemic, on March 11, 2020.[4] By June 30, 2020, there had been over 10 million confirmed cases, including over 500.000 patient deaths.[2]

The majority of COVID-19 patients manifest mild to moderate symptoms; approximately 15% progress to the severe form of the

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disease (pneumonia); and approximately 5% eventually develop acute respiratory distress syndrome (ARDS), or multiple organ failure.[5] Elderly patients and those with comorbidities (hypertension, diabetes, cardiovascular disease, and cerebrovascular disease) are at risk of developing the severe form of COVID-19 and have a high mortality rate.[6,7] Due to their singular immune characteristics and susceptibility to respiratory pathogens, pregnant women infected with SARS-CoV-2 should be considered to present a higher risk for severe morbidity and even mortality.[8]

Numerous studies have reviewed COVID-19 in pregnant women and reported adverse pregnancy outcomes among these patients.[9-12] Using four databases (Medline, Web of Science, Scopus, and CINAHL) to search for relevant studies published as at March 25, 2020, Khan et al[9] selected nine studies (involving 101 infected pregnant women) that were summarized employing a narrative synthesis approach. Yan et al[10] evaluated the clinical characteristics and outcomes of pregnancy in 116 pregnant women with COVID-19 from 25 hospitals in China within and outside of Hubei province between January 20, 2020, and March 24, 2020 In Wuhan, as at March 20, 2020, Chen et al[11] identified 118 infected pregnant women (92% with mild and 8% with severe disease) in 50 COVID-19-designated hospitals. Gajbhiye et al[12] reviewed 23 studies (involving 172 pregnant women and 162 neonates), including 20 from China and one each from the USA, Republic of Korea, and Honduras.

The maternal adverse pregnancy outcomes reported in these studies included spontaneous abortion,[10,11] premature rupture of membranes,[10,12] preterm labor,[9-12] fetal distress,[12] and cesarean section.[9-12] Among the neonates of COVID-19 mothers, preterm birth,[9-12] neonatal asphyxia,[10,12] pneumonia,[9,12] low birth weight,[9,12] stillbirth, and neonatal death[12] have been reported. These adverse pregnancy outcomes can be attributed to the progression of the disease toward the severe stage (ARDS, septic shock, and multiple organ failure) or are linked to the challenge of treating pregnant women considering the effects of certain therapeutic protocols on the fetus. However, whether these outcomes are causally related to the effects of SARS-CoV-2 infection during pregnancy requires further clarification.

In this review, we show that the uncontrolled systemic inflammatory state characterizing COVID-19 involves an increased number of Th17 cells, and a decrease in Treg cell levels, which could contribute to the occurrence of adverse pregnancy outcomes observed in infected pregnant women.

2 | IMMUNE PATHOGENESIS OF SARS-COV-2 INFECTION

SARS-CoV-2 is a positive-sense single-stranded RNA virus (betacoronavirus genus) in the same subgenus as the severe acute respiratory syndrome (SARS) virus, but in a different clade.[13] This novel virus likely originated in chrysanthemum bats; the pangolin is reported to be an intermediate host between bats and humans; and person-to-person viral transmission is thought to occur mainly via respiratory droplets.[14] The incubation time varies from 2 to 14 days after infection. Clinically, SARS-CoV-2 infection can be asymptomatic or can result in mild to severe symptomatic disease.[15] Both innate and adaptive immune cells synergistically participate in antiviral responses during SARS-CoV-2 infection.[16]

The virus uses a spike glycoprotein (S) protein to bind its receptor (angiotensin-converting enzyme 2 (ACE2) receptor) on target cells.[17] The virion then enters the host cells (endocytosis) and releases its RNA genome, which constitutes a pathogen-associated molecular pattern (PAMP). Inside host cells (immune or non-immune cells), the viral RNA (PAMP) is recognized by pathogen recognition receptors (PRRs), which collect the specific signal adapter protein and activate IRF3 and IRF7 before being translocated to the nucleus to promote the synthesis of type I interferons (IFNs).[17] In infected innate immune cells (macrophages and dendritic cells (DCs)), type I IFNs lead to an increase in antigen presentation activity and production of immune response mediators, such as cytokines and chemokines (Figure 1A).[18] Antigen presentation to T cells induces T-cell activation and differentiation, including the production of cytokines associated with different T-cell subsets (such as Th17), followed by a massive release of cytokines for immune response amplification (Figure 1B).[19] In adaptive immunity, type I IFNs may also act by increasing antibody production by B cells (IgM and IgG) and amplify the effector function of T cells.[18] Type I IFNs produced by infected non-immune cells (fibroblasts and epithelial cells) induce an intracellular antimicrobial program that limits the spread of infectious agents in infected and neighboring cells.[18]

Pulmonary and systemic inflammatory responses associated with COVID-19 are often triggered by the innate immune system when it recognizes the viruses.[20] Depending on the general health and genetic background (HLA) of patients,[21] this immune response promotes virus clearance, inhibits viral replication, induces tissue repair, and triggers a prolonged adaptive immune response against the infectious agent.[20]

2.1 | Uncontrolled systemic inflammation (cytokine storm)

When patients are not in good general health, or when they are susceptible to infections (unfavorable genetic background), protective immune responses can be impaired.[21] The virus will propagate, and massive destruction of the affected tissues will occur, especially in organs that have high ACE2 expression, such as the lungs, intestines, and kidneys. Lung inflammation is the leading cause of life-threatening respiratory disorders when at a severe stage of disease.[22] Indeed, prior reports show that at the critical stage of COVID-19, ARDS is the main cause of death.[23] ARDS is mostly provoked by cytokine storms (CSs), which occur in viral infections when a large number of cytokines are produced. A deadly uncontrolled systemic inflammatory response results from the release by immune effector cells of large amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-17, IL-18, IL-33, TNF-α, TGFβ, etc) and chemokines
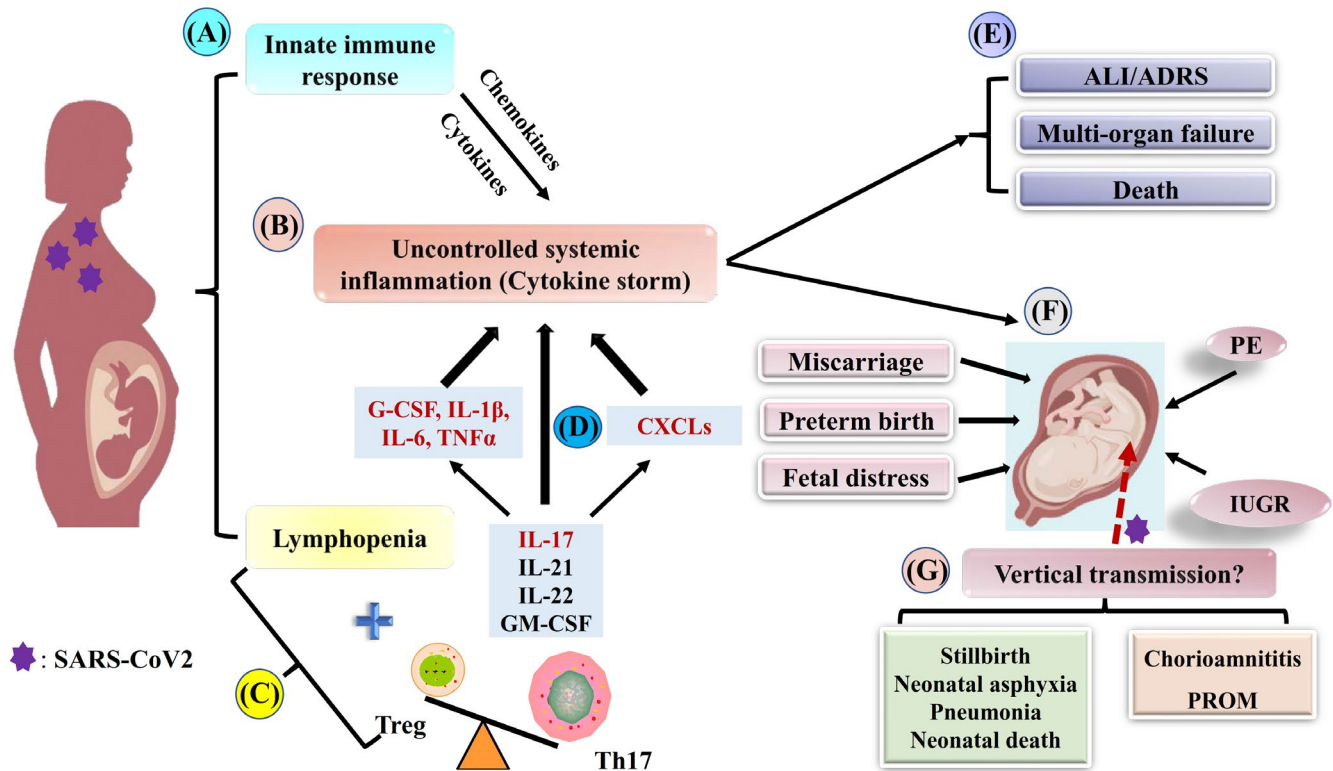
FIGURE 1 Treg/Th17 cell imbalance and related outcomes in severe COVID-19 pregnant women A, Infected innate immune cells (macrophages and dendritic cells) produce type I interferons (IFNs). Type I IFNs lead to an increase in antigen presentation activity and the production of cytokines and chemokines to ensure pathogen clearance and help to mobilize adaptive immune responses. B, In the case of prolonged inflammation, continual activation and recruitment of effector cells might establish a feedback loop that perpetuates inflammation and results in the release of large amounts of pro-inflammatory cytokines and chemokines by immune effector cells (cytokine storm). C, In this severe condition, adaptive immune cells, particularly T cells, are impaired. B cells, T cells, and NK cell numbers are significantly decreased (lymphopenia). Although the lymphopenia also involves CD4$^+$ T cells, the proportion of Treg cells and Th17 cells is affected by SARS-CoV-2 in a different way. Indeed, the increased circulating IL-6 levels induce the differentiation of naïve CD4$^+$ T cells toward Th17 cells, while inhibiting Treg cells, leading to Treg/Th17 ratio imbalance. D, IL-17 released by Th17 cells activates other downstream cascades involving cytokines (G-CSF, IL-1β, IL-6, TNF-α) and chemokines (CXCLs), followed by the recruitment of more effector cells and massive release of inflammatory cytokines that amplify the uncontrolled systemic inflammation (cytokine storm). E, Uncontrolled systemic inflammation might provoke acute respiratory distress syndrome (ARDS), multiorgan failure, and death. F, Uncontrolled systemic inflammation might also cause adverse pregnancy outcomes (miscarriage, preterm birth, fetal distress, preeclampsia, and intrauterine growth restriction). G, In the case of vertical transmission of SARS-CoV-2, anticipated complications might involve infection of the placenta (chorioamnitis, premature membrane rupture), and adverse neonatal outcomes, such as stillbirth, neonatal asphyxia, pneumonia, and neonatal death

(CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc) (Figure 1B).[23] CSs can worsen the condition of patients and cause multiorgan failure, which is frequently fatal (Figure 1E).

2.2 | Impaired adaptive immune responses in COVID-19 patients

During SARS-CoV-2 infection, dysregulation of the immune system and involving T cells has been reported.[24] Differences in blood cell counts are observed between severe and non-severe groups. Compared with non-severe patients, most severe cases of COVID-19 have lower percentages of monocytes, eosinophils, and basophils.[24,25] Moreover, they exhibit lower lymphocyte counts (lymphopenia) (Figure 1C), higher leukocyte and neutrophil numbers,

and, consequently, higher neutrophil-to-lymphocyte ratio (NLR).[24,25] Lymphopenia in COVID-19 patients has been reported in several other studies.[22,26-30] B cells, T cells, and NK cell numbers are significantly decreased in patients with COVID-19, and this is more evident in severe cases.[22,24,31,32] However, T-cell numbers are more affected than other cell types.[24] Analyzing different T-cell subsets, Qin et al[24] found that both suppressor T cells (CD3$^+$CD8$^+$) and helper T cells (CD3$^+$ CD4$^+$) were below normal levels. In addition, the percentage of naïve helper T cells (CD3$^+$CD4$^+$CD45RA$^+$) increased, while memory helper T cells (CD3$^+$CD4$^+$CD45RO$^+$) decreased in severe cases, indicating the severity of immune system impairment. Although the number of T cells decreased, their functions remained within the normal range[24] or were even hyperactivated, as evidenced by the high proportion of HLA-DR (CD4) and CD38 (CD8) double-positive fractions.[22] The impaired adaptive immune response observed in severe

COVID-19 patients might be caused by the pulmonary recruitment of immune cells from peripheral blood and the infiltration of lymphocytes into the airways as suggested by several authors.[33-36] The release of pro-inflammatory cytokines (such as IFN-γ and IL-6) and chemokines (such as CCL2 and CXCL10) attracts immune cells, notably monocytes and T lymphocytes, but not neutrophils, from the blood to the infected site.[22,37] This will result in lymphopenia, eosinopenia, and increased neutrophil-lymphocyte ratio in peripheral blood,[38,39] as well as ARDS in COVID-19 patients.[35]

In summary, these data show that, in its severe stage, the pathogenesis of COVID-19 involves impaired adaptive immune responses and uncontrolled release of pro-inflammatory cytokines, which cause systemic inflammation, ADRS, multiple organ failure, and finally lead to death.

3 | ROLE OF TREG/TH17 CELL RATIO IN COVID-19 PATHOGENESIS

Although helper T-cell (CD3$^+$ CD4$^+$) levels were below normal, the proportion of Treg cells and Th17 cells was affected by SARS-CoV-2 in different ways. Indeed, severe COVID-19 patients had a significant decrease in Treg cell levels (CD3$^+$CD4$^+$CD25$^+$CD127low$^+$),[24,40] increased levels of Th17 cells (CCR6$^+$ Th17),[22,41] with a consequent decrease in the Treg/Th17 cell ratio (Figure 1C).

Treg and Th17 cells are part of the complex machinery that constitutes the immune system. The differentiation of Th17 and Treg cells from naïve CD4$^+$T cells is mediated by TGF-β. However, in the presence of IL-6 or IL-21 (together with TGF-β), naïve CD4$^+$ T cells differentiate into Th17 cells.[42] These two CD4$^+$ T-cell subsets have different actions.[43] Th17 cells are mainly characterized by their production of inflammatory cytokines such as IL-17A,[42] which activates target cells and induces chemokine (C–X–C motif) ligands (CXCLs).[44] CXCLs then attract myeloid cells such as neutrophils to infected or injured tissues.[44] In contrast, Treg cells express anti-inflammatory cytokines (IL-4, IL-10, and TGF-β) and control excessive immune responses.[45,46] The Treg/Th17 balance plays an important role in the severity of lung injury[47] and in uncontrolled systemic inflammation characterizing acute lung injury (ALI)/ ARDS (Figure 1C).[48]

In patients with severe COVID-19, the increase in Th17 cells is accountable, at least in part, to severe immune injury in such patients.[22] Indeed, among the pro-inflammatory cytokines identified during deadly CSs, several cytokines are involved in Th17-type responses.[41] Th17 cells produce IL-17, GM-CSF, IL-21, and IL-22 (Figure 1C).[42] IL-17 recruits monocytes and neutrophils to the site of infection, and activates other downstream cytokine cascades (G-CSF, IL-1β, IL-6, TNF-α) and chemokines (CXCL1, CXCL-2, CXCL10, CXCL10, and CCL20) (Figure 1D), and matrix metalloproteinases.[19,41,49,50]

Treg cells play a crucial role in weakening or dampening overactive innate immune responses for the maintenance of self-tolerance and immune homeostasis during viral.[51,52] In severe COVID-19

cases, decreased Treg numbers indicate insufficient regulation of pro-inflammatory immune responses that may further aggravate hyperinflammation and tissue injury.[53]

In addition, several studies have reported a significant increase in IL-6 levels among other elevated inflammatory cytokines in COVID-19 patients, with significantly higher levels in severe rather than in mild cases.[16,24,30,54,55] IL-6 is a pleiotropic cytokine with mainly a pro-inflammatory function affecting several processes including immunity, tissue repair, and metabolism.[56] Indeed, in response to tissue damage and infections,[57] IL-6 is promptly and transiently produced by a range of cells including fibroblasts, keratinocytes, mesangial cells, vascular endothelial cells, mast cells, macrophages, dendritic cells, and T and B cells.[58] IL-6 trans-signaling promotes the recruitment of monocytes to the inflammation site.[59] Moreover, IL-6 promotes specific differentiation of naïve CD4$^+$ T cells, thus performing an important function in the linking of innate to acquired immune response infections.[57] Indeed, in combination with the transforming growth factor-beta 1(TGF-β1), IL-6 induces the generation of Th17 cells from naïve T cells and inhibits TGF-β1-induced Treg (iTreg) differentiation.[60,61] Thus, by promoting Th17 cell lineages and inhibiting the induction of Treg cells,[55] elevated circulating IL-6 levels contribute to deregulation of the Treg/Th17 cell ratio toward an increase in Th17 cells.

These data suggest that the increase in Th17 cells associated with a decrease in Treg cells may contribute to the uncontrolled release of pro-inflammatory cytokines and chemokines in COVID-19 patients, which might result in aggravated inflammatory responses, production of CSs, worsening the damage to tissues, and leading to multiorgan failure and death.

4 | TREG/TH17 CELL IMBALANCE AND ADVERSE PREGNANCY OUTCOMES

In a healthy pregnancy, the immune system not only recognizes and fights infections (defense), but also regulates undesired immune responses against tissue self-antigens or harmless non-self-organisms (tolerance). Treg and Th17 cells are active players in the establishment of this singular immunologic state. Treg cells and their related cytokines allow the growth and development of the allogeneic fetus,[62] while Th17 cells and their related cytokines are involved in defense against various pathogens.

An appropriate balance between Treg/Th17 cells is critical for healthy fetal implantation and pregnancy development.[63] During healthy pregnancy, the Treg/Th17 ratio shifts in favor of Treg cells. Treg cells also proliferate systemically, as well as at the fetal-maternal interface, to ensure maternal-fetal immune tolerance and successful pregnancy.[64] In contrast, uncontrolled Th17 cell proliferation is unfavorable because it is associated with fetal allograft rejection at the feto-maternal interface.[43] The dysregulation of this tight balance between Treg and Th17 cells has been shown to be involved in the pathogenesis of adverse pregnancy outcomes.[63] Indeed, decreased Treg cell numbers[65-71] and increased Th17

cell percentages[68,72-74] are associated with pregnancy complications such as miscarriage, preeclampsia (PE), and preterm labor (Figure 1F).

The pathogenesis of severe COVID-19 involves deregulation of the Treg/Th17 cell ratio toward an increase in Th17 cells, resulting in uncontrolled systemic inflammation. Thus, in SARS-CoV-2-infected pregnant women, Treg/Th17 cell imbalance might be potentially associated with adverse pregnancy outcomes such as pregnancy loss, preterm birth, and PE. Nevertheless, further investigations are required to validate their causal relationship.

5 | SARS-COV-2 INFECTION AND FETAL/NEONATAL RISK

In COVID-19-infected pregnant women, abortion or preterm delivery can be induced by the severity of the disease, and by the challenge to identify appropriate treatment. However, in the cases of spontaneous abortion or preterm birth, Treg/Th17 cell imbalance and uncontrolled systemic inflammation may be involved in their occurrence.

Another important question raised by the issue of SARS-CoV-2 infection during pregnancy is to determine whether COVID-19 can be transmitted from the mother to the fetus. Currently, the limited data available do not show evidence of intrauterine vertical transmission of SARS-CoV-2 from infected pregnant women to their fetuses.[11,75-77] However, the presence of anti-SARS-CoV-19 immunoglobulins in newborns has been reported in recent studies involving IgG and IgM.[78,79] The lack of amniotic fluid or placental examinations are the main limitations of these studies. Subsequently, in reviewing 23 studies published as at March 31, 2020, Gajbhiye et al[12] estimated a possible vertical transmission rate of 11% based on laboratory methods (RT-qPCR or by the presence of IgM antibodies) used to confirm diagnosis within the first 48 hours of life.

One of the factors determining viral tropism in the decidua and placenta is viral entry receptor expression in these tissues.[80] In their study, Li et al[81] demonstrated the expression of SARS-CoV-2 receptors at the maternal-fetal interface and fetal organs. Moreover, Alzamora et al[82] reported a severe case of COVID-19 in a pregnant woman who delivered a baby which was nasopharyngeal swab-positive for SARS-CoV-2 by RT-qPCR 16 hours after delivery. These recent findings add to the accumulating evidence regarding the possibility of vertical transmission of COVID-19, and further studies are needed.

Thus, the possibility of intrauterine transmission of SARS-CoV-2 exposes the placenta and fetus to viral infection (and inflammation), which could result in severe birth defects or pregnancy loss (Figure 1G).[80]

6 | CONCLUSIONS

Several studies have reported adverse pregnancy outcomes among infected pregnant women, including spontaneous abortion and preterm delivery. However, there is no evidence of direct effects of SARS-CoV-2 infection on pregnancy fate. Here, we showed that severe COVID-19 involves impaired adaptive immune responses, mainly affecting T cells (lymphopenia). Moreover, analysis of CD4+ T-cell subsets showed that, in severe COVID-19 patients, there was a significant increase in Th17 cell numbers, while the proportion of Treg cells decreased. The deregulated Treg/Th17 cell imbalance contributes to the induction of an uncontrolled release of pro-inflammatory cytokines (CSs), which can cause systemic inflammation and multiple organ failure, ultimately leading to death. Treg/Th17 cell imbalance and subsequent systemic inflammation are involved in the pathogenesis of pregnancy complications. Thus, we proposed that, through Treg/Th17 cell imbalance and subsequent uncontrolled systemic inflammation, SARS-CoV-2 infection may lead to pregnancy complications. We also discussed the possibility of intrauterine transmission of COVID-19 to the fetus, which might be associated with adverse perinatal outcomes. Although further supporting studies are needed, the possibility of vertical transmission of COVID-19 should be considered. Based on the above, cautious monitoring of pregnancies and appropriate measures should be taken to prevent and treat early eventual maternal and perinatal complications.

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

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