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## Review article

## COVID-19 and immunomodulation treatment for women with reproductive failures



Joanne Kwak-Kim<sup>a,\*</sup>, Kuniaki Ota<sup>b</sup>, Nayoung Sung<sup>a</sup>, Changsheng Huang<sup>a,c</sup>, Lujain Alsubki<sup>a,d</sup>, Sungki Lee<sup>e</sup>, Jae Won Han<sup>e</sup>, Aera Han<sup>f</sup>, Xiuhua Yang<sup>g</sup>, Wael Saab<sup>h</sup>, Youssef Derbala<sup>i</sup>, Wen-Juan Wang<sup>j</sup>, Qiaohua He<sup>k</sup>, Aihua Liao<sup>l</sup>, Toshifumi Takahashi<sup>b</sup>, Marcelo Borges Cavalcante<sup>m,n</sup>, Ricardo Barini<sup>o</sup>, Shihua Bao<sup>p</sup>, Atsushi Fukui<sup>q</sup>, Nathalie Lédée<sup>r,s</sup>, Carolyn Coulam<sup>t</sup>

<sup>a</sup> Reproductive Medicine and Immunology, Obstetrics and Gynecology, Clinical Sciences Department, Center for Cancer Cell Biology, Immunology and Infection, Chicago Medical School, Rosalind Franklin University of Medicine and Science, 830 West End Court, Vernon Hills, IL, 60061, USA

<sup>b</sup> Fukushima Medical Center for Children and Women, Fukushima Medical University, 1 Hikarigaoka, Fukushima City, Fukushima 960-1295, Japan

<sup>c</sup> Traditional Chinese Medicine Department of Rheumatism, Huazhong University of Science and Technology Union Shenzhen Hospital, China

<sup>d</sup> Department of Obstetrics and Gynecology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

<sup>e</sup> Department of Obstetrics and Gynecology, Myounggok Medical Research Center, Konyang University College of Medicine, Daejeon, South Korea

<sup>f</sup> Department of Obstetrics and Gynecology, MizMedi Hospital, Seoul, South Korea

<sup>g</sup> Department of Obstetrics, The First Hospital of China Medical University, Shenyang, China

<sup>h</sup> The Centre for Reproductive & Genetic Health, 230-232 Great Portland St, Fitzrovia, London W1W 5QS, UK

<sup>i</sup> Obstetrics and Gynecology, Beaumont Hospital, Dearborn, Grosse Pointe, MI, USA

<sup>j</sup> Reproduction Medical Center, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, 264000, China

<sup>k</sup> Department of Reproductive Medicine Center, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, Henan Provincial People's Hospital of Henan University, Zhengzhou, Henan, 450003, China

<sup>l</sup> Institute of Reproductive Health, Center for Reproductive Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

<sup>m</sup> Department of Obstetrics and Gynecology, Fortaleza University (UNIFOR), Fortaleza, CE, Brazil

<sup>n</sup> CONCEPTUS – Reproductive Medicine, Fortaleza, CE, Brazil

<sup>o</sup> Department of Obstetrics and Gynecology, Campinas University (UNICAMP), Campinas, SP, Brazil

<sup>p</sup> Department of Reproductive Immunology, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Shanghai, 201204, China

<sup>q</sup> Department of Obstetrics and Gynecology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan

<sup>r</sup> MatriceLAB Innove, Pépinière Paris Santé Cochin, Hôpital Cochin, 29 rue du faubourg St Jacques, 75014 Paris, France

<sup>s</sup> Centre d'assistance médicale à la procréation, Hôpital des Bluets, 4 rue Lasson, 75012, Paris, France

<sup>t</sup> Clinical Immunology Laboratory, Rosalind Franklin University of Medicine and Science, North Chicago, 60064, IL, USA

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## ABSTRACT

COVID-19 pandemic is affecting various areas of health care, including human reproduction. Many women with reproductive failures, during the peri-implantation period and pregnancy, are on the immunotherapy using immune modulators and immunosuppressant due to underlying autoimmune diseases, cellular immune dysfunction, and rheumatic conditions. Many questions have been raised for women with immunotherapy during the COVID-19 pandemic, including infection susceptibility, how to manage women with an increased risk of and active COVID-19 infection. SARS-CoV-2 is a novel virus, and not enough information exists. Yet, we aim to review the data from previous coronavirus outbreaks and current COVID-19 and provide interim guidelines for immunotherapy in women with reproductive failures.

\* Corresponding author at: Reproductive Medicine and Immunology Obstetrics and Gynecology, Clinical Sciences Department Center for Cancer Cell Biology, Immunology and Infection, Chicago Medical School, Rosalind Franklin University of Medicine and Science, 830 West End Court, Suite 400, Vernin Hills, IL, 60061 USA.

E-mail address: [Joanne.KwakKim@rosalindfranklin.edu](mailto:Joanne.KwakKim@rosalindfranklin.edu) (J. Kwak-Kim).

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## 1. Introduction

With the Coronavirus Disease 2019 (COVID-19) pandemic, patient care has been significantly challenged not only for the COVID-19 cases but for the others, including pregnant women with a history of reproductive failures (RF), such as recurrent pregnancy losses (RPL), and repeated implantation failures (RIF), with immune etiologies including autoimmune diseases, cellular immune dysfunction, and rheumatic conditions. These RF women with immune etiology (RFI) may have been on various immunosuppressants, immunomodulators, or anticoagulants. Whether these treatment modalities increase the risk for COVID-19 infection and aggravate COVID-19, have been a major concern for already vulnerable pregnant women with RFI.

SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus), which caused the SARS outbreak in 2003, infects macrophages and T cells (Perlman and Dandekar, 2005) and induces various cytokines, such as type I IFN, TNF- $\alpha$ , IL-1, etc., and B cell-related antibodies (Prompetchara et al., 2020). However, it is unclear if SARS-CoV-2 infects the same kinds of immune effectors. SARS-CoV-2 has been speculated to induce the influx of neutrophils and monocytes/macrophages at the infection site, which results in hyperproduction of proinflammatory cytokines. Specific T helper (Th) 1 and Th17 cells may be activated and contribute to exacerbating inflammatory responses. B cells and plasma cells produce SARS-CoV-2 specific antibodies that may neutralize viral particles (Prompetchara et al., 2020). B cell reduction was reported in the early phase of the COVID-19, which in turn, affects antibody production (Lin et al., 2020), and severe lymphopenia was often manifested in severe COVID-19 cases (Zhu et al., 2020b). In hospitalized severe COVID-19 patients, high plasma levels of various cytokines, including IL-2, IL-7, IL-10, G-CSF, inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1A (MIP-1A), and TNF- $\alpha$ , were observed (Huang et al., 2020). The primary cause of mortality in severe cases was cytokine storm, and these findings were in line with SARS and middle east respiratory syndrome (MERS) (Price et al., 2020).

The novel SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) for the cellular entry like SARS-CoV and mainly spreads through the respiratory tract (Guo et al., 2020). The ACE2 mRNA is abundantly expressed in endometrial epithelial cells in the secretory phase (Vaz-Silva et al., 2009), ovaries, and testes (Honorato-Sampaio et al., 2012). Renin-angiotensin system is involved in female reproductive processes, including follicular development (Barreta et al., 2015), steroid hormone production, oocyte maturation, and ovulation (Reis et al., 2011). Considering the reported relationship between ACE2 and viral pneumonia (Xu et al., 2020), COVID-19 may attack the follicular membrane and granulosa cells of the ovary, affecting folliculogenesis and the quality of oocytes, and causing female infertility and pregnancy losses. Additionally, it may damage endometrial epithelial cells and affect early embryo implantation, although no studies suggested that COVID-19 has any specific effect on the female reproductive system.

The specific effect on pregnancy has not been reported in COVID-19 cases, although studies are limited. However, previous studies have confirmed that the viral pandemic, such as the 2003 SARS pandemic, 2009 H1N1 influenza, or 2013 MERS, was associated with an increased incidence of maternal and perinatal complications, such as spontaneous abortion, premature delivery, and intrauterine growth restriction (Assiri et al., 2016). SARS-CoV and MERS-CoV, however, did not show any vertical transmission (Assiri et al., 2016). A recent analysis of 38 pregnant women with COVID-19 showed no intrauterine or transplacental transmission of SARS-CoV-2 from mother to fetus (Schwartz, 2020), although there is a concern for vertical transmission.

Women with a history of RFI already have an increased risk of obstetrical complications. Therefore, the continuation of immunotherapy is critical for these women. In this review, we aim to deliver the interim guidelines for current immunotherapy for women with RFI, concerning the COVID-19 pandemic. This article was developed by the

international collaboration of experts who have been working in the field of reproductive immunology.

## 2. Immunotherapy

### 2.1. Prednisone

Prednisone is a synthetic corticosteroid that mainly acts as an immunosuppressant. For its potent and broad-spectrum anti-inflammatory and immune-suppressive properties, prednisone has been utilized to treat autoimmune and chronic inflammatory diseases, and often the first line immunotherapeutic agent prescribed in the painful context of repeated implantation failure (RIF) or RPL of immune etiologies (Rhen and Cidlowski, 2005). Prednisone also plays an important role in mediating proper folliculogenesis, increasing production of growth factors, suppressing androgenic hormones, and suppressing NK cell activity and Th1/Th2 cell ratios (Keay et al., 2001). In early reports (Quenby et al., 2003), corticosteroid therapy has been reported to be beneficial in women with consecutive miscarriages since it reduces endometrial NK cells in women with RPL (Quenby et al., 2005). However, in routine in-vitro fertilization (IVF) cycles, the Cochrane review did not demonstrate the benefit of peri-implantation corticosteroid administration (Boomsma et al., 2012). On the other hand, prednisolone, which has a relatively mild effect, was reported to improve the embryo implantation rate after IVF and protect against miscarriage when administered from embryo implantation through the early placentation phase (Robertson et al., 2016). It is reported that less than half of RIF patients with immune deregulation may be prednisone responders and would benefit from its administration (Lédée et al., 2018a).

Low-dose prednisolone treatment was suggested to have a beneficial effect on COVID-19 and have been widely used to treat COVID-19 induced lung injury or septic shock (Russell et al., 2020). However, current interim guidance from WHO advises against the routine use of corticosteroids for the management of suspected and confirmed COVID-19 cases (Clinical management of severe acute respiratory infection SARI when COVID-19 disease is suspected, interim guidance). Currently, no data is available for women in early gestation with COVID-19 infection, although previously, 57.1 % of miscarriage rate was reported in women infected with SARS-CoV in the early pregnancy (Wong et al., 2004). Therefore, pregnant women with RFI and infected with COVID-19 may have an increased risk of early pregnancy loss. Overall, no specific evidence exists to demonstrate whether women infected with COVID-19 in the early pregnancy might get benefit from corticosteroids to prevent miscarriage. Therefore, prednisone is not recommended for women with early pregnancy and COVID-19 infection unless otherwise indicated.

In pregnant women with RFI, low dose prednisone treatment can be continued if the COVID-19 infection chance is low. If the patient has an increased risk of COVID-19 infection or on high dose prednisone treatment, tapering off or decreasing the dose is recommended to reduce the susceptibility to viral infection. If women have COVID-19 infection, tapering off the prednisone treatment is recommended to avoid worsening the disease, and switching into another treatment modality should be considered for the maintenance of pregnancy.

### 2.2. Heparin treatment

Women with RFI are often accompanied by thrombophilia, such as antiphospholipid syndrome and inherited thrombophilia. Anticoagulants are commonly used to treat the thrombotic features of RFI during pregnancy or assisted reproductive technology (ART). With the pandemic spread of SARS-CoV-2, many reports and guidelines concerning pregnancy are being updated, but there are only a few reports about heparin use in RFI patients. So, it is necessary to address some recommendations regarding anticoagulation treatment in RFI

women with COVID-19.

Heparin is primarily used for anticoagulation in women with RFI, and low molecular weight heparin (LMWH) is the drug of choice due to its numerous advantages over unfractionated heparin (uFH). These drugs are safe in pregnancy, and in addition to its antithrombotic effect, heparin provides a favorable environment for implantation and placental development (Nelson and Greer, 2008). By adhering to selectin, heparin initiates the implantation process and downregulates E-cadherin expression in the decidua, which promotes trophoblast invasion. Additionally, heparin enhances the heparin-binding epidermal growth factor, which is important in preventing the apoptosis of trophoblast (Nelson and Greer, 2008). LMWH has been reported to have various immunological effects, including inhibition of TNF- $\alpha$  and IL-6 in placental villi (Mousavi et al., 2015; Zenerino et al., 2017).

Moreover, heparin binds to certain proteins that exhibit an antiviral effect. Many different viruses, including herpes simplex virus (HSV)-1 and -2, attach to heparan sulfate on the host cell surface at the beginning of infection (Trybala et al., 2000). Because of the similarity in structure between heparan sulfate and heparin, heparin interacts with viral proteins in HSV, human immunodeficiency virus (HIV), and dengue virus, and inhibits viral entry into the cells (Nelson and Greer, 2008). The antiviral effects of heparin were found in some other viral infection including human cytomegalovirus, human papillomavirus, poxvirus, vaccinia virus, enterovirus 71, hepatitis C virus, orf virus, and respiratory syncytial virus in vitro (Krusat and Streckert, 1997; Scagliarini et al., 2004; Basu et al., 2007; Pourianfar et al., 2014; Khanna et al., 2017; Gonzalez et al., 2018; Liu et al., 2018). Furthermore, replication of SARS-CoV Nsp 15 protein was also inhibited by heparin in vitro (Bhardwaj et al., 2004).

From the Chinese experience of COVID-19, heparin was recommended to rescue severe cases with coagulopathy induced by SARS-CoV-2 infection. A research group suggested the use of 40–60 mg enoxaparin/day or uFH, 10,000–15,000 IU/day, which decreased the mortality of severe COVID-19 patients with sepsis-induced coagulopathy (Tang et al., 2020). Similarly, a review study proposed to inject LMWH 100 IU/Kg, every 12 h for 3–4 days, if the level of D-dimer becomes four times higher than the upper normal limit, unless contraindicated (Lin et al., 2020). From the above, even though data are not enough, heparin, including uFH and LMWH, may play a role in limiting COVID-19 infection via both improvement of tissue circulation and antiviral effect. Thus, it is likely that at least there is no harm to use heparin for anticoagulation, even in pregnant RFI women with thrombophilia. Taken together, when COVID-19 is suspicious or confirmed, there is no need to stop heparin administration in pregnant women with RFI whose heparin is indicated. In the earliest stages of the COVID-19 pandemic, numerous reproductive societies, including ASRM (American Society for Reproductive Medicine), ESHRE (European Society of Human Reproduction and Embryology), HFEA (Human Fertilization and Embryology Authority), etc., recommended postponing the assisted reproductive treatment and pregnancy during COVID-19 pandemic (American Society for Reproductive Medicine ASRM patient management and clinical recommendations during the coronavirus COVID-19 pandemic). Recently, with the additional data and successful mitigation strategies, ASRM and ESHRE sanctioned gradual and judicious resumption of delivery of full reproductive care (COVID-19 and Human Reproduction Joint Statement: ASRM/ESHRE/IFFS). In brief, for non-pregnant and pregnant RFI women with thrombophilia, heparin treatment can be continued even with COVID-19 infection.

### 2.3. Intravenous immunoglobulin G and COVID-19

Intravenous Immunoglobulin G (IVIg) is a blood product, which comprises pooled IgG from the serum of thousands of donors. IVIg is primarily used as a replacement treatment for immunodeficiencies but also indicated for autoimmune and inflammatory disorders. Studies have reported potential benefits of IVIg when applied for patients with

RFI (Kwak et al., 1996), such as increased NK cell levels and cytotoxicity, elevated Th1/Th2 cell ratios, and antiphospholipid antibody syndrome (Ruiz et al., 1996; Kwak-Kim et al., 2003).

The immunomodulatory effects of IVIg are mediated through two functional domains: F(ab')<sub>2</sub>, antigen-binding fragment, and Fc, crystallizable fragment. The F(ab')<sub>2</sub> fragment plays a role in neutralizing cytokine and autoantibody, scavenging of complements, killing of target cells by antibody-dependent cytotoxicity, and blocking cell-cell interactions mediated by cell-surface receptors. The Fc fragment modulates by activating and inhibiting Fc $\gamma$  receptor (FcR) expression on immune cells (Schwab and Nimmerjahn, 2013). IVIg has shown efficacy in the treatment of patients with influenza (Liu et al., 2016a) and SARS (Ho et al., 2004), including SARS cases with leukopenia and thrombocytopenia (Wang et al., 2004). It is speculated that massive IVIg treatment (300–500 mg/kg/day, 5 days) may become an effective treatment to interrupt cytokine storm for severe COVID-19 cases and prevent lung injury by blocking FcR in COVID-19 with pneumonia (Fu et al., 2020; Lin et al., 2020). IVIg clinical trial (The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia) is on-going now for the treatment of severe COVID-19. Recently, three COVID-19 cases were reported to be treated with high-dose IVIg (25 g per day for five days) at the early stage of clinical deterioration (Cao et al., 2020). IVIg, either conventional or created from recovered patients after COVID-19 were suggested as a treatment option combined with antiviral drugs to neutralized COVID-19 (Jawhara, 2020).

IVIg is a plasma protein therapy, which might be of concern for the risk of virus contamination. During the manufacturing process, viral particles are inactivated and removed by solvent–detergent, low pH incubation, nanofiltration, or others process (Dichtelmüller et al., 2009, 2011; Caballero et al., 2014). The Plasma Protein Therapeutics Associations (PPTA) has issued that the SARS-CoV-2 is not a concern for the safety of plasma protein therapies, including immunoglobulin, manufactured by PPTA member companies (New coronavirus SARS-CoV-2 and the safety margins of plasma protein therapies). With the currently available data, it is unlikely that the use of IVIg in patients with RFI will impact the chances of contracting the disease or negatively affect the clinical course in women with COVID-19 infection during pregnancy. Hence, IVIg treatment can be continued for these women with RFI during the COVID-19 pandemic.

### 2.4. Lymphocyte immunotherapy (LIT) during COVID-19 pandemic

LIT has been proposed for the treatment of couples with a history of RPL of unknown etiology since 1981 (Taylor and Faulk, 1981). However, in 2002, its effectiveness in treating pregnancy losses and safety got challenged, and the Food and Drug Administration (FDA), USA limited its use to a research protocol (Wong et al., 2014). Due to the controversies in its effectiveness and the outbreak of Zika virus infection, the Federal Council of Medicine in Brazil limited the use of LIT to a research project in 2014 (Cavalcante et al., 2018). Currently, LIT is utilized in China and other countries, and an updated meta-analysis with a larger number of participants have demonstrated a beneficial effect of LIT over placebo, which reinitiated the debate in its usage (Liu et al., 2016b; Cavalcante et al., 2017).

Briefly, LIT is a lymphocyte concentrate prepared from the fresh peripheral whole blood of the partner or third party. Most protocols inject the lymphocyte concentrates intradermally before and during the first trimester of pregnancy (Cavalcante et al., 2017). Therefore, there is a potential risk of infectious disease transmission with LIT. Early studies investigated infectious complications of LIT demonstrated that women submitted to LIT had a lower infection rate compared to controls (Anon, 1994; Kling et al., 2006). However, recently, HIV transmission was reported in five Chinese women who received LIT, due to multiple failures in the laboratory process, such as delay in the diagnosis of HIV in blood donors and the reuse of blood tubes during vaccine processing



(Pan et al., 2018).

The dynamics of SARS-CoV-2 during the active phase of the disease is still poorly understood. It is known that the main form of contagion of COVID-19 is through respiratory droplets, but other forms of transmission are possible. Studies evaluating biodistribution of SARS-CoV-2 revealed the highest viral detection rate in bronchoalveolar lavage fluid (14/15; 93 %), followed by sputum (72/104; 72 %), nasal swabs (5/8; 63 %), fiber bronchoscope brush biopsy (6/13; 46 %), pharyngeal swabs (126/398; 32 %), feces (44/153; 29 %), and blood (3/307; 1%) (Wang et al., 2020b), while another study detected SARS-CoV-2 in 40 % (6/15) of blood specimen (Zhu et al., 2020b). Due to possible transmission of SARS-CoV-2 via lymphocyte donors' blood and a lack of knowledge about the impact of LIT on the immune response in COVID-19 cases, we suggest the suspension of LIT for women with RFI during COVID-19 pandemic period.

### 2.5. Intralipid treatment

Intralipid® is a fat emulsion containing soy bean oil, glycerin and egg phospholipids. The classical use of Intralipid® infusion is parenteral nutrition in patients unable to tolerate an oral diet. Influence of soy-beanoil emulsion on the immune system has been reported (Furukawa et al., 2002). Intralipid has been reported to be an effective treatment for women experiencing RFI who display elevated uterine NK cells (Coulam and Acacio, 2012). However, the level of evidence is Level III or IV because of significant heterogeneity across the studies using various methods to quantify NK cells. Measurement of the number of NK cells does not address the more significant issue of the biological activity of these cells (Roussev et al., 2007). Tests defining the function of uterine NK cells are needed. Despite these limitations, the results of published studies suggest that Intralipid® can be used successfully as a therapeutic option for the treatment of women experiencing RFI (Coulam and Acacio, 2012).

In a RIF or RPL context, Intralipid® infusion are administrated at low dose (slow perfusion of 100 ml diluted Intralipid®) when compared with the classical dose used in parental nutrition (500 ml) and once a month and not daily as it is used in parental nutrition. Immune effects of Intralipid® appear to be highly dependent on the dose (Kagawa et al., 2013). In healthy volunteers receiving soybean oil emulsion as a single dose of 500 ml, it promoted lymphocyte and neutrophil death that might enhance the susceptibility to infections (Cury-Boaventura, 2006). However, Kagawa et al., reported that Intralipid® infusion (0.5g/kg/day) did not affect plasma cytokines (IL-6, MCP) and ex vivo T cell proliferation of severely stressed patients who need hyperalimentation (Kagawa, 2013). Patients with the essential fatty acid deficiency have a susceptibility to infection (Fell et al., 2015), and intralipid® infusion is indicated for these patients. In women with RFI, Intralipid® infusion (low dose and monthly administration) has been reported to suppress immune properties of circulating NK cells and decrease the hyper-activation of uterine NK cells through the regulation of NK cell recruitment and the downregulation of endometrial IL-18 and IL-15 (Lédée et al., 2018b). There is no evidence that Intralipid® infusion increases infection susceptibility. However, in patients with Intralipid® infusion, contamination of the intravenous catheter may result in sepsis or thrombophlebitis when hypertonic solutions are concurrently infused. Based on these findings, in pregnant women with RFI and on-going Intralipid® infusion treatment, Intralipid infusion® can be continued if patients do not have an increased risk for viral exposure or infection. In pregnant women with RFI and COVID-19, Intralipid® infusion should be curtailed due to a possible immunosuppressive function of intralipid infusion (Roussev et al., 2007) unless otherwise indicated. In severe COVID-19 cases, intralipid infusion has been utilized for parenteral nutritional supplementation (Caccialanza et al., 2020).

### 2.6. Hydroxychloroquine

Hydroxychloroquine, a multi-purpose drug, was initially used as an antimalarial agent in 1955 (Wallace, 1996). Subsequently, anti-inflammatory and immunomodulatory properties of hydroxychloroquine have been reported (Sciascia et al., 2016). Hydroxychloroquine has been utilized for autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid antibody syndrome, and RFI (Sciascia et al., 2016; Ghasemnejad-Berenji et al., 2018). It exerts its role in the immune system via multiple mechanisms. One of the mechanisms is inhibiting the Toll-like receptors (TLR-3, 7, and 9). It binds to nucleic acid in the maternal circulation, released from trophoblast as a response of placental hypoxemia, thus inhibiting an inflammatory immune response (Scharfe-Nugent et al., 2012). Another mechanism is inhibiting the release of Th1 cytokines, such as TNF- $\alpha$  and IFN- $\gamma$  (Weber and Levitz, 2000), leading to a switch toward a Th2 predominance which promotes maternal-fetal tolerance (Wegmann et al., 1993).

Over the past few decades, hydroxychloroquine has been proposed to be utilized for certain viral infections since it inhibits cytokine production by T cells, including IL-1, IL-2, IL-6, IL-18, TNF- $\alpha$ , IFN- $\gamma$ , and Th17 related cytokines, reduces chemokines, such as CCL2 (MCP-1) and CXCL10 (IP-10), inhibits micro-RNA expression, and decreases the synthesis of DNA, RNA, and proteins in thymocytes (Al-Bari, 2015). Since its function is mainly immune-modulatory, infection risk has been reported not to be increased in pregnant patients with hydroxychloroquine treatment, even though pregnancy and autoimmunity are associated with increased susceptibility and severity of infections (Maddur et al., 2010; Sappenfield et al., 2013), unless patients have autoimmune flare-ups or on the other types of immunosuppressant, like prednisone or cyclophosphamide (Danza and Ruiz-Irastorza, 2013).

Hydroxychloroquine is a chloroquine analog. Both drugs have been recommended by the Centers for Disease Control and FDA to treat hospitalized COVID-19 patients (Centers for Disease Control and Prevention, 2020; Colson et al., 2020; Food and Drug Administration, 2020), and recently, recommended against the use of both drugs for the treatment of COVID-19 except in a clinical trial. In vitro study has shown that both drugs inhibit SARS-CoV, SARS-CoV-2, and other coronaviruses, while the efficacy of hydroxychloroquine is relatively higher than chloroquine (Wang et al., 2020a; Yao et al., 2020). There are on-going studies regarding the role of hydroxychloroquine in the treatment and prevention of COVID-19.

In light of the available data, urgent cessation or tapering off hydroxychloroquine and chloroquine are not necessary for pregnant women with RFI, autoimmune diseases, or rheumatic conditions due to the COVID-19 pandemic. In COVID-19 cases, the continuation of hydroxychloroquine and chloroquine treatment should be further discussed with primary care physicians since the contradictory data have been reported in regards to COVID-19.

### 2.7. Anti-TNF drug

TNF- $\alpha$  is one of the most important mediators for acute and chronic systemic inflammatory responses. It promotes the production of other cytokines and chemokines and plays an important role in severe inflammatory conditions such as septic shock (Chu, 2013). In patients with SARS, plasma TNF- $\alpha$  levels are moderately upregulated (Yoshikawa et al., 2009), although an in vitro study has suggested that TNF- $\alpha$  induction may be mediated by the shedding of ACE2, thus allowing cellular entry to coronavirus (Haga et al., 2008). In patients with COVID-19, the levels of certain cytokines, including TNF- $\alpha$ , IL-6, and IL-10, correlate with disease severity (Huang et al., 2020). TNF- $\alpha$  hyperproduction in the serum of patients with COVID-19 was a phenomenon that was not observed in patients with SARS. Therefore, it is possible that anti-TNF- $\alpha$  drugs, which are widely used in the clinical practice of rheumatology, may be effective in patients with COVID-19

(Fu et al., 2020). A randomized controlled trial of adalimumab (Humira®), a human monoclonal TNF- $\alpha$  antibody, on COVID-19 is currently underway in China (ChiCTR2000030089, <http://www.chictr.org.cn/showprojen.aspx?proj=49889>).

RPL has been reported to be associated with dysregulation of Th1 and Th 2 immunity to trophoblasts and excessive local TNF- $\alpha$  production, which prevents implantation of the embryo and triggers immunological pregnancy losses (Reid et al., 2001). Furthermore, TNF- $\alpha$  inhibitors such as Humira® counteract the increased production of Th1 cytokines and consequently improve the IVF and embryo transfer success rate by modulating high TNF- $\alpha$  levels (Winger et al., 2009). Pregnant women in the very early stages of pregnancy may benefit from the fertility-promoting effects of TNF- $\alpha$  inhibitor treatment. However, there are not enough clinical data to support anti-TNF treatment for RPL and RIF.

Currently, no clear evidence is present if TNF- $\alpha$  blocker is harmful to patients with COVID-19 (Russell et al., 2020). TNF- $\alpha$  inhibitors, as immunomodulators, it is reported that TNF- $\alpha$  inhibitors can be continued if viral symptoms by COVID-19 are mild; however, if viral symptoms worsen or high fever develops, TNF- $\alpha$  inhibitors should be stopped (Price et al., 2020). Therefore, TNF- $\alpha$  inhibitors may be continued in pregnant women with autoimmune and rheumatic conditions. In pregnant women with COVID-19, TNF- $\alpha$  inhibitors may be continued unless viral symptoms worsen and febrile.

## 2.8. Tacrolimus

Tacrolimus is a macrolide immunosuppressant, which is widely used in solid organ transplantation, especially the liver, kidney, and heart transplantation. It is a calcineurin inhibitor that suppresses the production of IL-2 and thus, inhibits the development and proliferation of T cells (Kay et al., 1989). It has been reported that tacrolimus regulates T cell subsets in patients with RIF and shifted Th1/Th2 cell ratios. Consequently, it promotes the development of a pregnancy and improving the pregnancy outcome of these patients (Nakagawa et al.). Recently, the effectiveness of immunosuppressants, such as tacrolimus in women with RFI, has been reported (Nakagawa et al., 2015; Nakagawa et al., 2017).

Recent studies have found that IL-2, IL-6, IL-7, IP-10, G-CSF, TNF- $\alpha$ , and IL-10 were all elevated in most severe COVID-19 patients (Huang et al., 2020), suggesting that cytokine storm may be associated with disease severity. Furthermore, regulatory T (Treg) cells were decreased in patients with severe COVID-19 (Chen et al., 2020). Regulating immune balance and reducing non-specific inflammatory responses by immunosuppressants may be beneficial for COVID-19 patients with severe inflammation (Mehta et al., 2020). Tacrolimus has inhibitory effects on Th1 immunity, which may play a critical role in patients with severe COVID-19. However, currently, there is a lack of relevant reports on the use of tacrolimus in COVID-19, but in severe patients, the use of related cytokine inhibitors and corticosteroid hormones has achieved some results (Russell et al., 2020).

Theoretically, immunosuppressants used in the post-transplant population may lead to lower immune function, and infection with the virus may cause more severe symptoms. However, an Italian study showed no increased risk of severe complications in immunosuppressed patients compared to the general population (children and adults) (D'antiga, 2020). It is speculated that due to the preexisting hyper-activated immune responses, the application of immunosuppressive agents may not worsen the outcomes. For patients with severe COVID-19 pneumonia, tacrolimus may be an attempted method (Russell et al., 2020). However, for mild patients, the use of immunosuppressive agents is not conducive to fight against viral infection. Renal transplant recipients diagnosed with non-critical COVID-19 pneumonia were successfully cured by reducing the use of immunosuppressants, including tacrolimus, mycophenolate, and prednisone and a low-dose methylprednisolone-based treatment regimen (Zhu et al., 2020a).

In pregnant women with RIF, tacrolimus can be continued with caution to avoid a viral exposure, but stopping the medication should be considered when viral symptoms present, especially with known or potential exposure for COVID-19 (Price et al., 2020).

## 2.9. Vitamin D

Vitamin D suppresses viral replication while it has immune regulatory effects on various immune effectors (Wu et al., 2019; Jakovac, 2020). It reduces the incidence of influenza infections and acute respiratory tract infections (Cannell et al., 2006; Martineau et al., 2017). Women with RPL have an increased prevalence of vitamin D deficiency, and vitamin D plays a major role in auto- and cellular immune responses (Ota et al., 2013, 2015). Hence, women with RPL and vitamin D deficiency may have increased susceptibility to COVID-19 infection.

Both SARS and the current COVID-19 became epidemic in winter-time when vitamin D levels were decreased since UV-B exposure for vitamin D synthesis in the skin is low (Yin and Wunderink, 2018; Zhu et al., 2020b). The mortality rate of COVID-19 was lower in countries south of latitude 35 degrees of northern hemisphere (Rhodes et al., 2020), suggesting the role of vitamin D in COVID-19. Since no specific treatment is present for COVID-19, vitamin D supplementation as adjuvant therapy for pregnant women with RFI and COVID-19 infection can be considered.

## 3. Conclusion

At different stages of pregnancy, the immune responses and hormonal status vary, which is closely associated with the outcome of the COVID-19 infection (Jiao, 2020). Therefore, when considering immunosuppressive and immunomodulatory treatment for pregnant women with RFI, pharmacokinetics, and pharmacodynamics of intended drugs, gestational age, and their current immune profiles should be considered not only for avoiding infection with SARS-CoV-2 but not to exacerbate COVID-19. So far, low dose prednisone, IVIg, tacrolimus, and heparin may have some beneficial effect on COVID-19. There is no clear evidence for limiting the application of anti-TNF- $\alpha$  agents and Intralipid® in non-infected women with RFI. Most immune therapy, except LIT can still be used with caution on a case-by-case, and the information is evolving rapidly. The majority of the current clinical data are based on the observation, and further validation is needed.

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