Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

What immunological and hormonal protective factors lower the risk of COVID-19 related deaths in pregnant women?

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ABSTRACT

Despite anticipated increased risk of COVID-19 and increased expression of the SARS CoV-2 receptor (ACE2), the relatively low mortality of pregnant women with COVID-19 has been an area of wonder. The immunological changes predominantly inclining to anti-inflammatory state, which is augmented by placental hormones' immune modulating action, looks against with COVID-19 inflammatory reaction leading to cytokine storm and multiple organ failure. Unlike many other viral infections, the bilateral immune activation of COVID-19 may preferentially make pregnant women at low risk. Taking the physiological advantage of pregnant women, potential clinical trials are proposed. Quite a large number of epidemiological and obstetrics related studies have addressed the cases of women with COVID-19. However, to the best of the author's knowledge, little is done to explore the physiological internal milieu of pregnant women in relation to COVID-19. This review provides an insight into how the hormonal and immunological changes in pregnancy potentially reduce SARS-CoV-2-mediated inflammatory response.

1. Introduction

Coronavirus disease (COVID-19) was first recognized in late 2019 in Wuhan/China as caused by severe acute respiratory syndrome corona virus (SARS CoV-2) and has become pandemic (World Health Organization, 2020). In due course, among several unprecedented events, the relatively low mortality of COVID-19 in pregnant women has been an area of wonder. What is known before is that the immunological change during pregnancy inclining to the anti-inflammatory state is for the benefit of the fetus, but an increased risk for the mother to have many of the viral infections (predominantly in the respiratory system) and severity of malaria (Silasi et al., 2015; Robinson and Klein, 2012). Interestingly, pregnant women can have as remission of symptoms of many of the autoimmune diseases as noted below (Shah et al., 2019; Piccinni et al., 2016). It looks that autoimmune diseases and COVID-19 have something in common during pregnancy.

Previous studies have shown that pregnant women are at increased risk of morbidity and mortality due to many of the fatal viral infections, including hepatitis E virus, influenza A virus, SARS CoV, and MERS CoV (Rasmussen et al., 2020; Schwartz, 2020). Table 1 summarizes the comparative maternal mortality risks in different infection outbreaks over the past two decades (Guthmann et al., 2006; Rayis et al., 2013; Louie et al., 2010; Wong et al., 2004a; Alfaraj et al., 2019; Knight et al., 2020; Zaigham and Andersson, 2020; Yan et al., 2020; Breslin et al., 2020; World Health Organization, 2019; Ellington et al., 2020).

The systematic review of 108 pregnant women from different countries has shown that severe infections were relatively uncommon and there was no maternal death as compared to the aforementioned viral infections (Zaigham and Andersson, 2020). Report of the WHO-China Joint Mission has also concluded that severe disease due to SARS CoV-2 infection was uncommon among pregnant women (World Health Organization, 2019). As an unpublished data shows, the infection rate of COVID-19 to pregnant women, however, is not different from the general population. So, multiple cases series reviews have demonstrated that pregnancy did not add risk to deterioration due to SARS CoV-2 infection (Zaigham and Andersson, 2020; Mullins et al., 2020; Ferrazzi et al., 2020).

The second largest cohort study has shown that 427 pregnant women (0.5 % of estimated maternity across the UK) with confirmed SARS-CoV-2 infection were hospitalized in about one and half months, dominantly black and minor ethnicity with preexisting co-morbidities, overweight/obesity, and older maternal age (Knight et al., 2020). In the same study, 40.9 %) required critical care (the majority in the third trimester); 4(0.9 %) required cardiopulmonary life support; 5(1.2 %) died; and was concluded that most women do not have severe illness. The USA cohort study has shown an increased risk of hospitalization and intensive care unit admission (ICU), but not death; out of 8207 pregnant women with COVID-19, the proportion of death was 0.2 %

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Table 1
Selected viral infection outbreaks and maternal mortality since 2000.

Author and study year	Country	Outbreak period	Etiology for maternal deaths	Pregnant women infected	Case fatality ratio
Guthmann et al. (2006)	Sudan	Jul-Oct 2004	Hepatitis E virus	61	31.1 %
Rayis et al. (2013)	Sudan	Nov 2010–Mar 2011	Hepatitis E virus	39	28.2 %
Louie et al. (2010)	USA	Apr-Aug 2009	H1N1 influenza A	102	7.8 %
Wong et al. (2004a)	Hong Kong[a]	2002 – 2003	SARS CoV	12	25 %
Alfaraj et al. (2019)	Middle East	2012 – 2013	MERS CoV	11	27 %
Knight et al. (2020)	United Kingdom	2020	COVID-19	427	1.2 %
Zaigham and Andersson (2020)	Multicountry[b]	2020	COVID-19	108	0
Yan et al. (2020)	USA	2020	COVID-19	43	0
Breslin et al. (2020)	China	2020	COVID-19	116	0
World Health Organization (2019)	China	2020	COVID-19	147	0
Ellington et al. (2020)	USA	2020	COVID-19	8207	0.2 %

[a] Mainly Honk Kong.
[b] Review of 18 articles. USA = United States of America. 8% had severe disease and 1% had critical illness, which was lower than the non-pregnant population (14 % with severe disease and 6% with critical illness) (World Health Organization, 2019).

(Ellington et al., 2020). The big limitation of these two studies was that pregnancy related problems for hospitalization and ICU care were not included in the reports.

This is despite anticipated increased risk of COVID-19 (taking their high vulnerability to viral infections) (Silasi et al., 2015), and increased expression of the SARS CoV-2 receptor (angiotensin converting enzyme/ACE2) (Zhao et al., 2020). A recent review by Liu and colleagues have also predicted as COVID-19 may be altering the maternal immune responses, and affect the well-being of mothers and their babies (Liu et al., 2020). Hereunder, in depth review of the multisystem physiological changes in pregnancy as protective factor, which may show the window of acumen to search for a possible remedy for those who developed the disease of SARS CoV-2.

Therefore, the purpose of this review is primarily to give an insight on the physiological and immunological changes of pregnancy and shed light on the unfavorable nature of the internal milieu of the pregnant women to the COVID-19 related inflammatory tissue damage and microthrombotic events and propose potential clinical trials.

2. A brief update on the pathophysiology of COVID-19

The spectrum of COVID-19 is broad and not yet clearly defined. Since SARS CoV-2 can infect a large array of respiratory and extra-respiratory tract cells, the severity and mortality risks were reported as being predominantly related to pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS) and sepsis (Baraniuk, 2020; Zhou et al., 2020).

In recently emerging reports, however, viral pneumonia is highly questioned; rather, thrombotic microangiopathy or atypical disseminated intravascular coagulation (DIC) with increased risk of pulmonary vascular coagulation and thromboembolism are emphasized as major pathological disorders associated with COVID-19 (Belen-Apak and Sarıalioğlu, 2020; Cao and Li, 2020; Kollias et al., 2020).

Unlike other causes of ARDS, the typical features of ARDS with COVID-19 leading to respiratory failure (relatively preserved lung compliance, high alveolar-arterial oxygen gradient, and diffuse pulmonary microthrombi) are also attributed to occlusion of the pulmonary microvasculature (Wang et al., 2020). The previously thought interstitial pneumonia from lungs X-ray is reinterpreted as disseminated interstitial coagulation, primed by inflammation.

Postmortem examinations have also indicated the diffused microthrombi, which are more of fibrin deposits and mainly in the pulmonary microvascular system. Further, unlike other causes of DIC, modest thrombocytopenia, little change in fibrinogen level, prothrombin time and activated partial thromboplastin time are observed, but the D-dimer is exceptionally high in severely ill COVID-19 patients (Baraniuk, 2020; Zhou et al., 2020; Levi et al., 2020). One more, the absence of hemolysis indicators (like schistocytes) and low hemorrhagic disease, even in severe cases, are additional findings for the distinct nature of DIC and for non-red blood cells source of the high lactate dehydrogenase (LDH) in COVID-19 patients (Zhou et al., 2020; Kollias et al., 2020; Tang et al., 2020a).

The pathological changes in the lungs in a state of ARDS, for instance, include diffused alveolar damage, hyaline membrane formation, extensive microvascular thrombosis and interstitial edema, which may progress to fibrosis among survivors of the acute insult (Kollias et al., 2020; Xu et al., 2020). As a result, most of the deaths were reported to be due to diffused thrombotic microangiopathy and respiratory failure (Belen-Apak and Sarıalioğlu, 2020; Chen et al., 2020).

The unregulated overproduction of proinflammatory chemokines and cytokines (interleukin-6/IL-6 and tumor necrosis factor-alpha/TNF-α, in particular) are attributed to many of the severe and fatal complications of COVID-19 (what is commonly described as “cytokine storm” with ARDS) (Li et al., 2020; Nile et al., 2020). On top of mediating inflammation, the increased IL-6 level in COVID-19 patients is also attributed to initiating coagulation activation and thrombin generation by inducing tissue factor expression on mononuclear cells (Kollias et al., 2020).

As discussed hereunder, accumulating evidence from other infections and autoimmune diseases shows that immune modulating hormones, cytokines and other anti-inflammatory endogenous ligands are determinant factors in reducing the severity of several diseases during pregnancy; which could also be the most plausible explanation for the less severity and mortality of Covid-19 in pregnant women.

3. Pregnancy induced immunological changes favoring anti-inflammatory response and lesser mortality of COVID-19

Pregnancy has a triphasic shift of immunological response: a proinflammatory in early stages of pregnancy, anti-inflammatory throughout the rest of pregnancy and proinflammatory in the peripartum and postpartum period (Brännn et al., 2019). The proinflammatory state is characterized by T-helper/Th-1 and Th-17 immunity dominance (hereafter Th-1), resulting in overproduction of proinflammatory cytokines, including IL-1β, IL-6, Il-8, IL-12, TNF-α, chemotactic cytokines (interferon gamma/IFNγ, eotaxin) and growth factors.

The anti-inflammatory state is Th-2 and T-regulatory (Tg) cells (hereafter Th-2) dominated with overproduction of anti-inflammatory cytokines, including IL-4, IL-5, IL-10, IL-13, and TGF-β. The anti-inflammatory response is further augmented by other cells and hormonal factors, which are again part of the physiological adaptation of pregnancy. Some of the predominant pregnancy related factors that amplify the Th-2 anti-inflammatory response, and inhibit the Th-1 cytokine secretion are placental hormones (estriol, estradiol, progesterone, human chorionic gonadotropin/hCG, prostaglandins, corticosteroid),

decidual Vitamin D, type 2 macrophages (M2), and leukemic inhibitory factor (Bränn et al., 2019; Schumacher et al., 2009; Mantovani et al., 2013).

The switch from Th-1 dominated to Th-2 dominated immune response is partly mediated by IL-10 and macrophage colony-stimulating factor (M-CSF). At cellular and chemotactic level, the switch is from proinflammatory cells (M1-macrophages) and Th-1 secreted cytokines dominance to anti-inflammatory cells (M-2 macrophages) and Th-2 secreted cytokines dominance. The M-2 macrophages and Tg cells produce quite large amount of IL-10 and TGF-β that further enhance the anti-inflammatory immune response and damaged tissue healing process (Bränn et al., 2019; Mantovani et al., 2013).

One of the key differences between SARS CoV-2 and SARS CoV infections is the immunological response, which is probably one of the factors contributing to the less morbid and less fatal nature of COVID-19 as compared with SARS CoV infections in pregnant women. The immune response to SARS CoV-2 infection is activation of both proinflammatory (Th-1) and anti-inflammatory (Th-2) mediators (Huang et al., 2020; Dashraath et al., 2020). As a result, mixed type of cytokines and chemokines (IL-1ra, IL-2, IL-2R, IL-6, IL-8, IL-17, IL-10, TNF-α, IFNγ, M-CSF, granulocyte colony-stimulating factor/G-CSF) were found markedly elevated among severely ill COVID-19 patients. Whereas, SARS CoV and MERS CoV typically triggers activation of the Th1 immunity, thereby resulting in overproduction of inflammatory cytokines (IFNγ, IL-1β, IL-6, and IL-12), which were attributed to the extensive lungs damage and high mortality (Wong et al., 2004b; Mahallawi et al., 2018).

It is not clearly known why the Th-2 immunity/anti-inflammatory cytokines were equally prominent in all investigated COVID-19 cases. Although the overall condition is a sort of cytokine release syndrome (CRS), the concentration of proinflammatory cytokines such as IL-6, TNF-α, IL-1 and IP-10 was much higher among severe COVID-19 patients (Dashraath et al., 2020; Rahmati and Moosavi, 2020). IL-6 is thought to be responsible for increased capillary leakage, activation of complement and the coagulation cascade, partly leading to the development of the atypical DIC (Hunter and Jones, 2015; Tanaka et al., 2016).

Therefore, the parallel activation of the Th-1 and Th-2 immunity in COVID-19 may not lead to a profound proinflammatory cytokine storm in pregnant women who already have dominant Th-2 immunity. That is to mean, as noted below, the dominated anti-inflammatory state during pregnancy (the IL-10 and placental hormones, in particular) may reduce the risk of COVID-19 mediated cytokine storm and thrombotic microangiopathy.

3.1. Interleukin-10, a potent Th-1 immunity suppressant and antifibrotic cytokine

The markedly elevated IL-10 level, starting from early pregnancy and throughout pregnancy, is a unique characteristic of normal pregnancy. The multitude sources of IL-10, particularly at the placental-decidual interface (trophoblasts, uterine natural killer cells, monocytes, and Tg cells), make it to be available in abundant amount (Thaxton and Sharma, 2010), which is a benefit for the dominance of the anti-inflammatory state of pregnancy. The implication is that the anti-inflammatory and antifibrotic actions of IL-10 in the lungs and other tissues by suppressing the Th-1 immunity (Steen et al., 2020) is probably protective from COVID-19. Interestingly, while inhibiting the Th-1 cells, IL-10 enhances B cells survival and antibody production, which is beneficiary to balance the immune suppression and induction (Matilainen et al., 2010).

Generally, there is a large body of evidence which showed that IL-10 is a key cytokine with multifaceted actions during healthy pregnancy. The significantly lower level of IL-10 in the placenta and decidua of women with missed abortion, recurrent spontaneous abortion, preterm birth, preeclampsia, and fetal growth restriction (Steen et al., 2020) may also suggest how potent it is in protecting the normal progress of pregnancy unless the other way round is considered (some other pathology compromising its secretion). Several studies have also indicated the lower risk of the aforementioned obstetric complications in women with adequate IL-10 (Plevyak et al., 2002; de Groot et al., 2004; Kalkunte et al., 2009).

Whatever the mechanism is; the elevated level of IL-10 in COVID-19, in particular, is probably an additional benefit for pregnant women to further boost the anti-inflammatory and antifibrotic actions of the already in high level IL-10. The disproportionately elevated level of IL-10 is also probably an advantage to minimize the profibrotic effect of IL-4.

Therefore, until proved otherwise, the author surmises that the increased risk of COVID-19 severity and mortality in non-pregnant adult and geriatric population is partly associated with relatively low level of IL-10. Among the potential treatment options, IL-10 amplification or selective blocking of inflammatory cytokine production in the early stage of COVID-19 is an attractive area of research, probably better than monoclonal antibodies which are under trial for blocking IL-6, TNF-α and IL-1 (Tang et al., 2020b).

3.2. Lower risk of protease activated receptor (PAR-1) mediated inflammation during pregnancy

The deterioration of COVID-19 patients is mainly due to overproduction of proinflammatory cytokines and activation of the coagulation pathway partly via protease activated receptors (principally PAR-1) and IL-6 (Tang et al., 2020b; Jose et al., 2014). This will lead to exaggerated inflammatory response and procoagulant-anticoagulant imbalance, which in turn results in a cascade of catastrophic events (extensive tissue damage, release of excess tissue thromboplastin, diffused microthrombosis, DIC, and multiorgan failure).

In pregnant women, however, this is not the case probably partly because of the physiological changes in the hematological system. Among multiple actions of thrombin, there is a large body of data that has shown its involvement in the induction of systemic intravascular inflammation mediated through PAR-1 (by increasing the release of IL-1β, IL-6 and IL-8, activation of endothelial and mast cells, and recruitment of monocytes), which is also ascribed for the pathogenesis of preeclampsia (Asokananthan et al., 2002; Dugina et al., 2003, 2002).

In non-pregnant COVID-19 patients, the diffused inflammatory reaction already induced by the proinflammatory cytokines is a triggering factor in the over activation of PAR-1-thrombin induced inflammation and defective anticoagulant system (ineffective antithrombin III, tissue factor pathway inhibitor, and the protein C system) as already noted in other fibroproliferative inflammatory lung disease (Tang et al., 2020b).

Interestingly, in normal pregnancy, however, PAR-1 is undetectable after 12 weeks of gestation (Even-Ram et al., 2003). Taken together, the suppression of PAR-1 expression and the domination of Th-2 anti-inflammatory state during pregnancy may contribute to the relatively benign course of COVID-19 in normal pregnancy. Further, being the risk of DIC in women with COVID-19 is lower while pregnancy is a hypercoagulable state (Brenner, 2004), which is another evidence to deduce that the anti-inflammatory cytokines and placental hormones are strong in normal pregnancy.

3.3. The anti-inflammatory and Th-2 immune boosting actions of progesterone during pregnancy

As noted earlier, progesterone is one of the anti-inflammatory hormones. It promotes the production of Th-2 cytokines to protect the pregnancy (Piccinni et al., 2000, 1995; Szekeres-Bartho et al., 1996). The increased level of progesterone (mainly from the placenta) stimulates the synthesis of progesterone-induced binding factor (PIBF) in lymphocytes (Schwartz, 2020). The increased concentration of PIBF in pregnancy promotes the differentiation of Th-1 cells into Th-2 cells,

which results in augmented production of the aforementioned anti-inflammatory cytokines and progressive decline in Th-1 secreted proinflammatory cytokines (Schwartz, 2020).

Abnormally elevated IFN-γ and TNF-α (Th-1 cytokines) can cause damage to the placenta and fetal tissue by activating the inflammatory reaction, macrophage, cytotoxic cell, and natural killer cell. Progesterone also inhibits macrophage and natural killer cell activity, toll-like receptor (TLR-4) induced cytokine production and TNF-α, thereby exposing to bacterial infection and complications (Jones et al., 2008), as the Th-2 dominated immunity increases the risk of viral infection.

In animal model with autoimmune encephalomyelitis, progesterone treatment has shown a significant reduction in disease severity and increases the level of IL-10 (Yates et al., 2010), which is another important indicator of its multiplied effect. Therefore, the increased level of progesterone during pregnancy may complement to the physiological defense to COVID-19.

3.4. The anti-inflammatory and Th-2 immune boosting actions of estriol and estradiol during pregnancy

The immune modulating and anti-inflammatory actions of estradiol (E2) and estriol (E3) is also well noted during pregnancy. E3 (90 % of all estrogens secreted during pregnancy) increases 1000 times during pregnancy from the only detectable level in non-pregnant women (Voskuhl, 2010). Emphatic

E3 increases the production of anti-inflammatory cytokines (IL-10 and IL-5) and reduces the production of proinflammatory cytokines (like TNF-α) (Oldan et al., 2003). The relatively increased E2 level (100 times) (Voskuhl, 2010) and the extremely elevated E3 level during pregnancy promote Th-2 responses and humoral immunity. Whereas a reduction in E2 level results in augmented Th-1 responses/proinflammatory cell-mediated immunity and bad pregnancy outcome (Straub, 2007; Bouman et al., 2005).

As a result, the anti-inflammatory action of estriol, in particular, is opening a new horizon of research to use it as an important therapeutic option for viral, autoimmune and neurodegenerative diseases outside pregnancy, including men and postmenopausal women (Tiwari-Woodruff et al., 2007; Palaszynski et al., 2004a; Kim et al., 1999). In animal models, E3 had significantly reduced proinflammatory transcriptional activity, pulmonary immune cell recruitment, and pulmonary inflammation during influenza A virus infection (Vermillion et al., 2018).

A pilot trial of exogenous estriol administration to non-pregnant women with multiple sclerosis has resulted in 80 % reduction in gadolinium-enhancing lesions from the pretreatment state within 3 months, which was correlated with the favorable shift in cytokine profiles (Oldan et al., 2003; Sicotte et al., 2002). Therefore, the Th-2 immunity activation and anti-inflammatory actions of E2 and E3 are likely to contribute to reduce the proinflammatory cytokine storm and subsequent complications of COVID-19, which need to be further explored with clinical trial.

3.5. The anti-inflammatory and immunomodulatory actions of Vitamin D during pregnancy

Vitamin D is another important hormone, which has both immune modulation and anti-inflammatory actions (Zhang et al., 2012), that can positively influence pregnancy outcome and response to acute and chronic inflammatory diseases during pregnancy. Apart from a wide array of immune cell activation during pregnancy, the stimulating effect to Th-2 cytokine production and the inhibition effect to Th-1/Th-17 cytokine release is a synchronized effect of vitamin D with progesterone and estriol (Monastra et al., 2018; Weisman et al., 1979). A few anecdotal evidences have shown the increased risk of severity and mortality among non-pregnant COVID-19 patients when there is vitamin D deficiency in their serum (1, 25-Dihydroxy vitamin D3 < 10 mg/dl) (Manson, 2020; Alipo, 2020; Laird et al., 2020).

As learnt from animal models and human trials, among many of the Vitamin D innate and adaptive immune modulating actions, its inhibitory action to IL-6 and TNF-α (Sicotte et al., 2002; Hewison, 2011) is implicated in the reduced risk of COVID-19 in Vitamin D sufficient individuals. Vitamin D reduces the inflammatory and T cell stimulatory actions of macrophages through an IL-10-dependent mechanism (Korf et al., 2012). Other investigators also verified its effect in monocytes IL-10 production (first and short lasting repression and long lasting induction action) (Matilainen et al., 2010). Furthermore, Vitamin D is a potent suppressor of IFNγ-mediated macrophage activation (Helming et al., 2005), which all these are likely to be protective of the COVID-19 severity.

Till proved otherwise, the reduction of Covid-19 severity in Vitamin D sufficient individuals is an interesting observation and another milestone to consolidate the significance of anti-inflammatory endogenous mediators in the amelioration of the COVID-19 morbidity and mortality. This observation may have as well programmatic implication as the world is advocating “stay at home/lockdown” preventive measures, while physical distancing at outdoor is probably an appropriate decision.

Vitamin D deficiency is associated with many acute and chronic inflammatory diseases, including increased risk of acute respiratory tract infections, tumorigenesis, pulmonary tuberculosis, atherosclerosis, inflammatory bowel disease, and rheumatoid arthritis (Pham et al., 2019; Liu et al., 2018; Kim et al., 2014; Muscogiuri et al., 2017; Parizadeh et al., 2019; Aslam et al., 2019).

What is special for pregnancy (specific to Vitamin D) is again its additional production by the placenta. According to one study, the placenta and decidua (mainly from macrophages, uterine natural killer cells, B cells, T cells, dendritic cells) is the principal source of Vitamin D outside the renal site (Weisman et al., 1979; Tamblyn et al., 2015; Schröder-Heurich et al., 2020), probably to meet the high demand of it for the fetal physical growth in the state of deficiency. The lower level of IL-10 and TGF-β in vitamin D deficient pregnant women is another evidence on its significance in upregulating effect of the anti-inflammatory cytokines (Schröder-Heurich et al., 2020). Another study has also demonstrated that the placenta, decidua, Therefore, on top of its tolerogenic effect, the immune modulating action is as well towards infection prevention, which is probably an additional advantage for pregnant women to clear SARS CoV-2 before causing serious tissue damage.

4. Common characteristics of autoimmune disease and COVID-19 in pregnancy

Pregnancy is also an advantage to get temporary amelioration from several Th-1 associated autoimmune diseases (including multiple sclerosis, rheumatoid arthritis, Graves’ disease, myasthenia gravis, psoriasis, uveitis) (Rasmussen et al., 2020; Schwartz, 2020). Almost all pregnant women with these kind of autoimmune diseases have exacerbation of symptoms early in pregnancy (while the Th-1 immunity is dominant) and a remarkable remission during the second half of pregnancy. When the placental hormones and the dominant effect of the anti-inflammatory immune response is relieved during the peripartum and postpartum period, there will be a rebound effect of autoantibodies and flare up of the symptoms.

The mechanism for temporary remission of many of the autoimmune disease symptoms is not exactly known; the dominant Th-2 immunity and the collective effect of the anti-inflammatory cytokines and hormones is the most probable explanation. Despite serious concern for patients with autoimmune disease, taking their immune suppression and medications, at least 110 individuals (79 % females) with rheumatoid arthritis and got infected with SARS CoV-2 (from six continents) were not as such at higher risk of mortality, probably as they

were on anti-inflammatory medication; only 6(5%) persons died of COVID-19 (Gianfrancesco et al., 2020). This small data and the remission of autoimmune disease symptoms during pregnancy may still underscore how important the anti-inflammatory state is to reduce the risk of COVID-19.

COVID-19 has also some common characteristics with systemic sclerosis. In both conditions, the proinflammatory (Th-1) and ant-inflammatory (The-2) cytokines are activated; neither statistically significant deterioration nor improvement was observed during pregnancy (Betelli et al., 2018; Brown and O'Reilly, 2018); the profibrotic effect of IL-4, IL-6 and TGF-β looks counterbalanced by significantly increased IL-10.

5. Conclusion

The author surmises that pregnant women's risk of having severe COVID-19 very early in gestation (before the Th-2 immunity and placental hormones take control) and in the postpartum period may not be different from the non-pregnant population. Given the limited data on this aspect, and the immunological and hormonal destabilization during postpartum period as transiting from pregnancy to non-pregnancy state, the severity of and mortality due to COVID-19 may be higher than the pregnancy period.

As exaggerated chemokine directed immunologic response can be diseases conditions in non-pregnant women (autoimmune disease, chronic inflammatory disease, allergic reaction, atherosclerosis, cancer, and the like), unilateral suppressed Th-1 immunity during pregnancy is an advantage for the fetus's intrauterine survival and symptom free life of the mother from the majority of the autoimmune diseases and less severe disease of COVID-19 in most of pregnant women. Therefore, what looks in common for autoimmune disease and COVID-19 is the less risk of severity during pregnancy, probably due to similar immune modulating action of the pregnancy.

6. Recommended observational studies and clinical trials

First of all, assessing the cytokine profile and determining the Vitamin D level of pregnant women based on COVID-19 illness severity is critically important to verify the postulated mechanisms. Several of ongoing trials aimed to reverse the overactive cytokine response with exogenous immunomodulators. Herein, proposed clinical trial is intended to treat COVID-19 in its early stage with hormonal analogues and anticoagulants. The author postulates that as pregnancy develops a natural way of defense mechanism against COVID-19, the prevention of severe complications of this disease can be sought by boosting the naturally existing protective hormones and cytokines.

Some authors recommended administering anticoagulant for critically ill patients with elevated D-dimer (Tang et al., 2020c). Extending this recommendation to be even earlier for seriously symptomatic patient (with high grade fever and persistent dry cough) may have better outcomes. It is noted that a randomized clinical trial on COVID-19 is planned with Vitamin D (Manson, 2020). On top of administering antibiotic and anti-inflammatory agents for all with high grade fever, the clinical trial arms the author recommending for non-pregnant COVID-19 patients are as follows.

1 Vitamin D + Estriol vs placebo
2 Vitamin D + Heparin vs placebo
3 Estriol + Heparin vs placebo
4 Progesterone + Vitamin D vs placebo

Both Vitamin D and E3 are widely available and widely marketed as an oral preparation for replacement therapy. Therefore, administering E3, Vitamin D, and Heparin as a short course therapy for COVID-19 patients will not be seriously worrying about the adverse effects. The author is happy to collaborate with such trials.

7. Key messages

- Unlike other viral infections, pregnancy may create an unfavorable environment to the proinflammatory and procoagulant condition of COVID-19, thereby avoiding the cascade of inflammatory and microthrombotic events leading to multiorgan failure.
- The pregnancy induced endogenous protective mechanisms against COVID-19 looks interrelated and multifactorial.
- The dissimilarity in immunological response between SARS CoV-2 and SARS CoV/MERS CoV may contribute to the lower risk of COVID-19 in pregnant women.
- As many of women become pregnant under the age of 40 years, age could be an additional important factor for the less mortality of COVID-19 in pregnancy.
- Above all, the immunological and hormonal response in balancing the inhibition of rejecting a semi-allogeneic fetus, and remaining immunocompetent to fight SARS CoV-2 is probably collectively contributing to the lower risk of severe morbidity and mortality associated with COVID-19.
- Time and again, implementing all the necessary preventive measures by all pregnant women so as not to acquire the SARS CoV-2 is the best of all.

Declaration of Competing Interest

The author declares that there is no conflict of interest, and no financial support for this work.

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