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

Sars-CoV-2 in pregnancy: Why is it better than expected?

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ABSTRACT

Since the outbreak of Coronavirus disease in December 2019, information specific to pregnancy remains limited and controversial. Based on data from previous reports, it has been noticed that contrary to prior pandemics such as SARS, MERS and H1N1 and although pregnancy is usually considered as a condition of high susceptibility to viral infections, new SARS-CoV2 infection seems to have a more benign clinical course when affecting pregnant women. We speculate that during pregnancy the physiological "silencing" of the Th1 pro-inflammatory response may blunt the cytokines storm which is thought to play a key-role in the pathogenesis of the severe complications of Covid-19.

Contents

In December 2019, a novel coronavirus (Sars-CoV-2) was first reported in Wuhan, in the Hubei province of China and was declared pandemic by the World Health Organization (WHO) on March 11, 2020. While data regarding COVID-19 continues to come out improving our understanding of this disease, data specific to pregnancy remains limited and the clinical characteristics of SARS-CoV-2 infection in pregnant women are still scarce.

In prior pandemics such as SARS, MERS and H1N1, pregnant women were more susceptible to serious illness and had greater mortality rates than that reported in the general population. More specifically, reported mortality rates among pregnant women were about 18 % for SARS-CoV, 25 % for MERS and 5% for H1N1 while severe disease requiring mechanical ventilation occurred in 25 %, 41 % and 19 % of cases, respectively [1,2].

Similarly, in case of common seasonal influenza all pregnant women (regardless of the presence of comorbidities) have an 18-fold higher risk of being hospitalized compared to nonpregnant women with comparable age and health status [3].

At the light of these observations WHO has identified pregnant women to be at increased risk for severe outcomes from influenza virus infections and recommends that they should be prioritized for influenza vaccination when available.

Despite a similarity in RNA sequence of about 79 % with SARS-CoV and 59 % with MERS-CoV, the new SARS-CoV-2 infection seems to have a more benign clinical course when affecting pregnant women [1].

Although the beliefs regarding the susceptibility of pregnant women to Sars-CoV-2 compared to general population are discordant [4–6], few studies including small series of pregnant patients have demonstrated that women presented a mild disease in 80 % of cases, severe disease in 15 % of cases and critical disease in 5% of cases [7] ; based on a recent meta-analysis of 108 cases, the rate of ICU admission in pregnant women was about 3% and the incidence of severe disease requiring mechanical ventilation of about 2%[8]. Sporadic cases of maternal mortality due to SARS-CoV-2 infection have been reported to date [9].

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These percentages are not different from those reported on the general population with similar demographic characteristics. A large study including 72,314 cases from the Chinese Center for Disease Control and Prevention, reported an overall mortality rate of 2.3 % and a similar distribution of cases among mild (81 %), severe (14 %) and critical (5%) disease [7]. In addition, 2–4 % people aged 20–44 were admitted to ICU with about two third of them (2%) requiring mechanical ventilation within the first 24 -hs from the admission [10].

Due to physiological cardiorespiratory and immune system changes, pregnancy is usually considered as a condition of high susceptibility to viral infections, especially to those affecting the respiratory system such as SARS-CoV-2. The diaphragmatic displacement by the gravid uterus and the gestational weight gain are responsible for altered pulmonary volumes leading to a reduced total lung capacity and to an inability to clear effectively the pulmonary secretions [11].

From an immunological point of view, pregnancy is characterized by a strong first line response against viral pathogens mediated by an effective activation of Natural Killer (NK) cells and monocytes [12]. But when the first barrier is overcome, the second line defense is defective due to the attenuation of cell mediated Th1 immunity and the physiological shift to a Th2 dominant environment which contributes to an overall increased infectious morbidity from intracellular pathogens [13]. In addition, the enhanced function of T regulatory lymphocytes (Treg), that are usually implicated in the maintenance of maternal immunological tolerance and in pregnancy implantation, further contributes to this Th1/Th2 shift by suppressing Th1 and Th-17 immunity [14].

All these factors should concur to an increased morbidity and mortality in pregnant women infected by SARS-CoV-2 but as said above this allegedly higher risk has not been confirmed in the preliminary observational studies [1,7,8].

This apparent conundrum may be explained by the fact that the inflammatory cascade of the host has a primary role in the pathogenesis of the severe and fatal complications of SARS-CoV-2 infection and this cascade might be more dysregulated in nonpregnant vs pregnant subjects.

In nonpregnant patients with severe SARS-CoV-2 interstitial pneumonia the elevated serum level of pro-inflammatory cytokines including IL-2, IL-6, IL-1 and TNF which are described in the advanced phase of the infection seems to be the primary trigger of the Acute Respiratory Distress Syndrome (ARDS). It has been hypothesized that this “cytokine storm” may be responsible of a macrophage activation (MAS)-like syndrome complicating SARS-CoV-2 pneumonia. The hyperactivation of immune response appears to be initially confined to lung parenchyma and lymphoid tissue of bronchial alveolar and progressively extends to the closely pulmonary vasculature. Furthermore, this MAS-like inflammation may determine a local vascular dysfunction leading to a pulmonary intravascular coagulopathy characterized by the presence of micro-thrombosis and hemorrhage. The levels of the pro-inflammatory cytokines (e.g. IL-6) produced as consequence of macrophages activation induced by the Th1 response are considered predictors of severe morbidity/mortality [15].

On the contrary, in pregnant women with SARS-CoV-2 pneumonia the progression of the inflammatory lung process towards the extensive tissue damage and the ARDS has been more rarely observed.

We herein speculate that in pregnant women with COVID 19 the physiological “silencing” of the Th1 pro-inflammatory response together with the relative dominance of Th2 over Th1 immunity may account for a more restrained inflammatory cascade compared with non-pregnant subjects.

While the Th1 lymphocytes cytokines including gamma interferon (IFN-γ), interleukin (IL)-1α, IL-1β, IL12, IL6 are microbicidal and proinflammatory, the cytokines produced by Th2 cells mainly represented by IL-4, IL-10, IL-13 and transforming growth factor beta (TGF-ß) have an anti-inflammatory effect [1,15]

Due to this, during the SARS-CoV-2 infection the pregnancy is dominated by an anti-inflammatory milieu which makes less dysregulated the immune response and can ultimately blunt the fatal cytokines storm set by the Th1 cells (Fig. 1).

How critical is the inhibition of the unrestrained inflammatory response of the host in the clinical course of the COVID 19 has been suggested by a series of observations. On this ground it may be explained, why hydroxychloroquine (HCQ), colchicine, monoclonal antibody anti-IL6R and anti-IL1R (Tocilizumab and Anakinra) seem to provide a clinical benefit on the advanced course of the disease by mitigating against the hyper-inflammation. The ability to reduce IFN-γ and IL-1 secretion are among the potential effects of HCQ and colchicine while the inhibition of IL-6 receptor is the main mechanism of action of Tolicizumab [15].

The beneficial effect of heparin that has been consistently described in Covid-19 patients may be also attributed to its anti-inflammatory action which may itself decrease the risk of arterial and venous thrombosis [15].

In summary, in pregnant women with SARS-CoV-2 infection the predominance of the Th2 response may hamper the severity of the

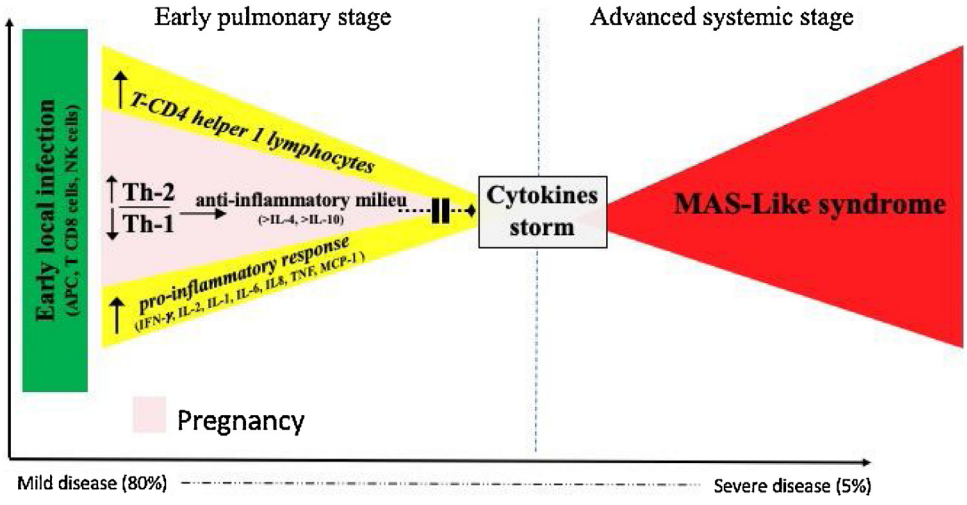

Fig. 1. The protective effect of pregnancy on the natural history of Covid-19 infection.

disease and may account for the lower incidence of maternal deaths in comparison with other respiratory viral infections.

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Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

None to declare

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