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Review article

Is pregnancy a risk factor of COVID-19?

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ABSTRACT

This review evaluates whether pregnancy is a risk factor for COVID-19 by looking at the expression of immune markers such as immune cells and cytokines in order to have a better understanding on the pathophysiology of the disease, thus reducing maternal deaths. Pregnant women are more at risk of contracting COVID-19 due to their weakened immune system. Studies demonstrate that COVID-19 is an immune condition which is marked by reduced lymphocytes and elevated selected proinflammatory cytokines. Similar immune expression has been demonstrated in pregnancy by several studies. In addition, the placenta has been shown to possess ACE2 receptors on the villous cytotrophoblast and the syncytiotrophoblast and findings suggest that the coronavirus enters the host cells via these ACE2 receptors. The immune response in pregnancy increases the risk of contracting COVID-19. Both normal pregnancy and COVID-19 are marked by decreased lymphocytes, NKG2A inhibitory receptors, and increased ACE2, IL-8, IL-10, and IP-10 it therefore safer to conclude that pregnancy is a risk factor for COVID-19 development. Furthermore, the presence of the ACE2 receptors in the placenta may increase the risk of mother to baby transmission of the virus. Therefore, more studies investigating the link between pregnancy and COVID-19 are needed.

Contents

Introduction

Coronavirus-2019 (COVID-19) is a global pandemic respiratory disease caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. COVID-19 individuals are usually affected by viral pneumonia, most commonly fever, cough, sore throat, myalgia, and fatigue [2–5]. Classification of COVID-19 can be divided into severe (defined as tachypnoea [≥30 breaths per min], oxygen saturation ≤93 % at rest, or PaO_2/FiO_2 ratio <300 mm Hg) and critical (respiratory failure requiring mechanical ventilation, septic shock, or other organ dysfunction or failure that requires intensive care) [6]. The epicentre of COVID-19 is reported to be China, in the city of Wuhan, Hubei [7]. Worldwide, there are currently 3 004 887 people infected with the virus. Since the

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outbreak of this disease, several American and European countries have been affected more especially the USA (2 241 178), Spain (246 272), Italy (238 499), and France (154 567), and geographic expansion of this pandemic has reached Africa with South Africa (97 302) as a leading country with the highest rates of infection from this virus [1,8]. Individuals who are susceptible to the virus have been reported to be the elderly (>65 years), individuals with a compromised immune system, meaning those with other underlying or chronic infections, and perhaps pregnant women [4,5,9]. Reports have indicated that women are more vulnerable to respiratory infections during pregnancy [9].The main objective of this review is to investigate whether pregnancy is a risk factor for COVID-19.

Signs and symptoms of COVID-19

This virus has been reported to possess three stages: Stage 1 is the incubation period where in some cases it may be asymptomatic and survive in the host undetected, stage II is where the virus is now detectable with minor or mild symptoms such as a fever, and lastly, stage 3, where severe symptoms arise including respiratory distress and subsequently death [10].The incubation period from the day of infection is about 5 days [11]. Thereafter, infected individuals with symptoms show signs of extremely high fever accompanied by coughing, headaches, difficulty breathing, pneumonia, diarrhoea, haemoptysis and excessive sputum [5,12–14]. (Fig. 1). Some individuals with infection are asymptomatic and are labelled as highly infectious since they are unaware of their health status [10]. Fatal cases involved conditions such as respiratory distress, cardiac injury, RNAanemia and grand-glass opacities [5].

Pathogenesis of COVID-19

The COVID-19 structure is described as a positive single stranded RNA genome characterised by four genes; a spike protein, an envelope, a membrane and a nucleocapsid [15]. The main target of the virus is the pulmonary area. The virus binds to the host receptor, which has been described as the angiotensin converting enzyme 2 (ACE2) via receptor binding domains [16]. After the successful binding to the receptor of the host cell, the spike protein undergoes a conformational modification for the viral envelope to bind to the cell membrane for RNA release into the host cell. This process occurs through the endosomal pathway. Once RNA enters the host cell, it becomes translated into viral replicases, which are split into smaller particles by enzymes called proteinases. The particles are then translated into viral proteins by mRNAs and congregated into virions on the endoplasmic reticulum and the Golgi apparatus where they are released out of the cell via vesicles [17]. Following their release, they enter the alveoli cells, endothelial cells and blood cells. This causes exaggerated activation of immune cells and cytokines.

Immune expression in COVID-19 versus normal pregnancy

Coronavirus adaptive immune response

Following investigation in 99 Wuhan patients revealed, increased total neutrophils (38 %), reduced total lymphocytes (35 %), increased serum IL-6 (52 %) and increased c-reactive protein (84 %) [18]. Another Wuhan study reported that in 41 patients, there was increased total neutrophils, and decreased total lymphocytes in patients of ICU vs. non-ICU care. They

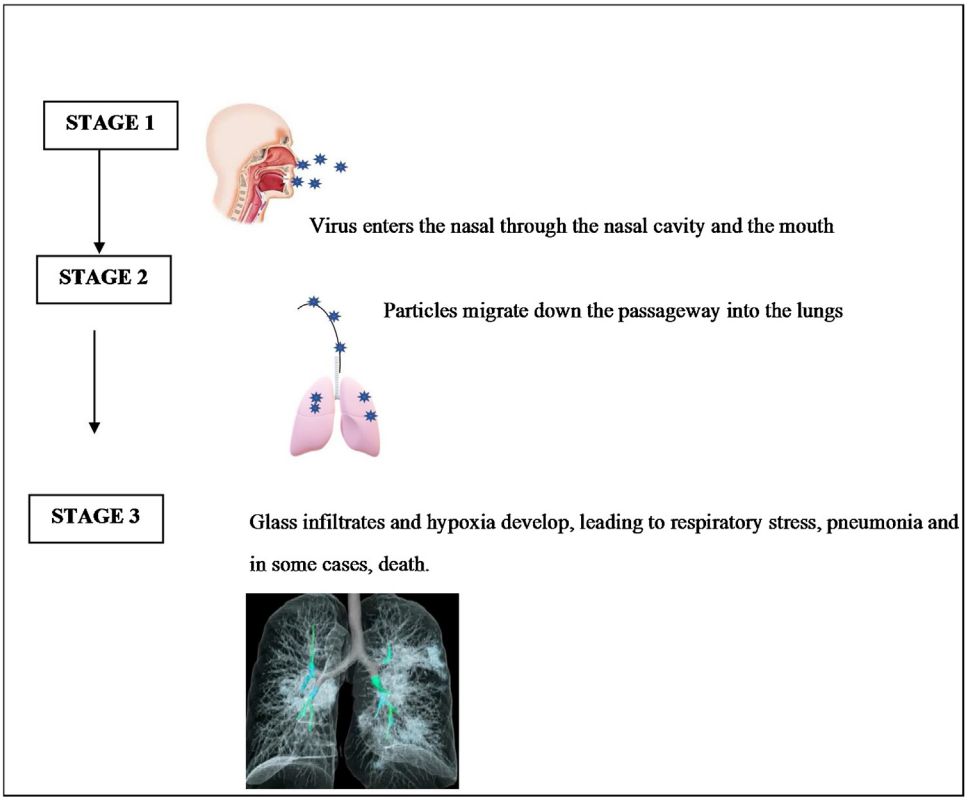

Fig. 1. Schematic diagram representing the stages involved in the pathogenesis of GOVID-19. Adapted from Huang et al. [5]. The virus enters the respiratory system through the nasal cavity and the mouth. The innate immune system is triggered to activate inflammation, which results in blockage of the alveoli. This results in hypoxia and grand-glass opacities and subsequent death.

further concluded that increased neutrophils and decreased lymphocytes also correlate with disease severity and death [19]. Similar findings were reported by Chuan et al., (2019) who observed that patients with severe cases of COVID-19 tend to have lower lymphocyte counts, higher leukocyte counts and neutrophil-lymphocyte ratio (NLR), as well as lower percentages of monocytes, eosinophils, and basophils [4]. More interestingly another study reported that most COVID-19 cases showed that lymphocytes were reduced to lower than 5% within 2 weeks after disease onset in COVID-19 patients. This clearly indicates that lymphocytes play a detrimental role in the progression of the diseases [20]. A study conducted by Evangelos et al. investigating immune responses of 54 COVID-19 patients, 28 of whom had severe respiratory failure (SRF) indicated that; all patients with SRF displayed either macrophage activation syndrome (MAS) or very low human leukocyte antigen D related (HLA-DR) expression accompanied by profound depletion of CD4 lymphocytes, CD19 lymphocytes, and natural killer (NK) cells [21]. Lymphocytes are a subtype of white blood cells that play a fundamental role in in protecting the immune system against infectious microorganisms and other foreign substances. These cells include natural killer cells (NK) cells, T cells (for cell mediated-cytotoxic adaptive) and B cells (for humoral, antibody driven adaptive immunity). Both NK and T cells are important for control of infection [22]. In COVID-19 cases, depletion of these cells has been associated with the severity of the disease. Zheng et al. showed that the total number of NK and $CD8^+$ T cells was decreased markedly in patients with COVID-19 and patients with SARS-CoV-2 infection. They also noticed an increase in the expression of NKG2A [23]. NKG2A is an inhibitory receptor for NK cells [24]. Increased NKG2A inhibits NK cells from performing their normal function.

Coronavirus innate immune response

Pro-inflammatory cytokines such as IL-1β, IL-6, IFNγ, MCP1 and IP-10 have been reported to be elevated into the blood of patients infected by SARS-CoV and MERS-CoV [5,25] which are both related to COVID-19 (Table 1). It was observed that patients with severe COVID-19, requiring intensive care in hospitals, exhibited higher blood plasma levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, VEGFA, IL2, IL7, IL10, GCSF, IP10, MCP1, cIP-10, MCP-1, MIP-1A, macrophage inflammatory protein 1α (MIP1α) and tumour necrosis factor (TNF) [5,9]. IL-6 levels in these patients continue to increase over time and are relatively more elevated in non-survivors than survivors [26]. Also, patients with severe disease show a significantly higher percentage of $CD14^+CD16^+$ inflammatory monocytes in peripheral blood than patients with mild disease [27]. These cells secrete inflammatory cytokines that contribute to the cytokine storm, including MCP1, IP-10 and MIP1α. cytokine storm also has ripple effects across the body. Elevated levels of cytokines such as TNF can cause septic shock and multi-organ failure which may result in myocardial damage and circulatory failure observed in some patients [28].

Table 1
The immune response in Normal Pregnancy vs COVID-19.

PREGNANCY	COVID-19
↓ Natural Killer cells	↓ Natural Killer cells
↑ NKG2A receptors	↑ NKG2A receptors
↓ Lymphocytes	↓ Lymphocytes
↑ Pro-inflammatory Factors	↑ Pro-inflammatory factors
↑ ACE2 receptors	↑ ACE2 receptors

Normal pregnancy immune response

The role of NK cells is to protect the body from diseases by secreting cytokines such as IFNγ and TNFα, which act on other immune cells like Macrophage to fight the infection. Natural Killer cells have also been shown to be involved in pregnancy [29]. In a normal healthy pregnancy, the percentages of NK cells in the peripheral blood tend to increase during the first trimester, decrease in the second trimester, and decrease again in the third trimester. In addition, uterine NK cells during the first trimester become progressively less granular and decrease in number, leaving very few uNK cells at term [30]. In both humans and mice, uNK cells participate in spiral artery remodeling with trophoblast cells [31]. A study by Hanna et al., (2006) demonstrated that uNK cells have a limited ability to kill trophoblast cells, and instead they regulate trophoblast invasion by producing the chemokines interleukin (IL)-8 and IFN-inducible protein (IP)-10. In addition, uNK cells induce vascular growth by secreting angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) [32]. Both VEGF and PIGF are known to play an important role in maintaining normal pregnancy development. However, exaggerated activation of uNK cells has been associated with pregnancy complications such as spontaneous abortion and pre-eclampsia (PE) [29]. During normal pregnancy NK cells are controlled by NK cells inhibitory receptors such as NKG2A (Table 1). Activation of NK2GA receptors prevent NK cells from destroying trophoblast cells. Several studies have associated increased NKG2A expression with normal pregnancy development [24,29,33].

Pregnancy has been described as an anti-inflammatory state since inflammation would result in maternal, and fetal complications [34,35]. However, this may not entirely be accurate as some studies state otherwise [36]. It has been reported that the first trimester is pro-inflammatory and the second is anti-inflammatory, and the third trimester shifts back into a pro-inflammatory phase [35]. During the first trimester when implantation and placentation take place, an inflammatory response is triggered for the blastocyst to successfully penetrate the uterus for implantation and for trophoblast invasion to occur [37]. At this stage the maternal system weakens, and the mother suffers from morning sickness, fatigue and headaches, indicating a pro-inflammatory phase [38]. Moreover, in the second trimester, an anti-inflammatory state kicks in, and the fetus develops and growths swiftly. Maternal health also improves and morning sickness and other symptoms gradually disappear [39].

In the third trimester, the development of the fetus is complete and the delivery process begins in the maternal system [39]. The immune response is activated again for the delivery of the baby and the placenta [39]. For this to occur, the immune cells invade the myometrium thus creating a pro-inflammatory phase that activates contractions in the uterus [40]. The latter is an indication that the shift in cytokines during pregnancy can trigger susceptibility to infectious diseases. In African countries where malaria is a burden to health, pregnant women are more at risk of contracting the disease in their first trimester, which is a pro-inflammatory phase, while other women in regions where there are cases of Lassa fever developed the disease mostly in their third trimester [41,42].

Coronavirus is a pro-inflammatory disease and therefore may easily invade suitable conditions. For instance, during the first and third trimester of pregnancy women are in a pro-inflammatory phase which is a suitable environment for the virus and are therefore at a higher risk of contracting the disease than the second trimester (Table 1). However, there are currently no reports on mother to baby transmission of the coronavirus, which may be highly unlikely since the placenta creates a protective mechanism against viruses [39]. The placenta has been reported to actively

create protection against foreign pathogens by anti-microbial action as early as the first trimester of pregnancy [39]. The trophoblast cells stimulate the expression of secretory leukocyte protease inhibitor (SLPI) and INF-β, which are known for their inhibitory action against viruses such as HIV [43]. This mechanism protects the fetus against viral infections but not necessarily the mother. Therefore, the sensitisation of the placenta to induce an immune response creates vulnerability to infections in pregnant women [39]. The binding site for the coronavirus is reported as the ACE2 receptor [44].

ACE2 receptor in pregnancy

The potent role of the renin angiotensin system (RAS) in pregnancy has been documented [39,45–48]. The ACE2 receptor is critical for RAS since it is involved in the conversion of angiotensinogen into angiotensin 1, angiotensin 1 into angiotensin II, and angiotensin II into angiotensin (1–7) [49]. The expression of the ACE2 receptor has been reported in the placenta [44]. Other members of the coronavirus family such as MERS-CoV and SARS-CoV have been involved in pregnancy complications [50]. These viruses possess analogous pathogenic traits as the current SARS-CoV2 [50]. This may indicate that SARS-CoV2 is a potential threat to maternal and fetal health.

The expression of ACE2 in the placenta was reported to be higher in the villous cytotrophoblast, syncytiotrophoblast cells and in the decidua during the first trimester of pregnancy [51]. The syncytiotrophoblast cells are involved in maternal and fetal gas exchange as well as nutrient supply [52]. Since ACE2 is highly expressed in this region of the placenta, this not only increases the risk of the mother contracting SARS-Cov2, but is also plausible that transmission from mother to child may occur [44].

Conclusion

Evidence from the literature clearly indicates that healthy pregnant women are more susceptible to developing COVID-19 due to their immune response that predisposes them to develop COVID-19. Both normal pregnancy and COVID-19 are marked by decreased lymphocytes, NKG2A inhibitory receptors, and increased ACE2, IL-8, IL-10, and IP-10 it therefore safer to conclude that pregnancy is a risk factor for COVID-19 development.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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