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Review article

Changes in physiology and immune system during pregnancy and coronavirus infection: A review

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the 3rd epidemic coronavirus after severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Since December 2019, the outbreak of the Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2 has aroused great attention around the world. Pregnant women and their fetuses have been concerned as a high-risk population. We explained why pregnant women are susceptible to coronavirus in terms of their adaptive changes in physiology and immune system during pregnancy, and described the associations between maternal clinical symptoms, perinatal outcomes and coronavirus infections.

Contents

Background

Corona Virus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been labeled as a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO) on January 30, 2020 [1,2]. SARS-CoV-2, a new type of enveloped RNA coronavirus, can be transmitted by human-to-human via droplet and contact [3]. As of May 27, 2020, more than 5.6 million confirmed cases had been documented globally, with more than 350 thousand deaths. Fever, cough, and myalgia/fatigue are the main clinical manifestations of illness caused by coronavirus. In a few cases, life-threatening pneumonia infection can also be caused by coronaviruses [4,5]. Pneumonia is the third leading cause of pregnancy deaths globally [6], and compared to bacterial infections, viral

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infections has a higher mortality rate [7–11]. With the spread of the coronavirus, pregnant women and their fetuses have been concerned as a high-risk population [8]. The interaction between coronavirus infections and pregnancy is worthy of our further study. Here we described the association between pregnancy and coronavirus infection.

Structural changes of the ribcage and abdominal compartments

With the formation and development of fetus, placenta and amniotic fluid, the uterine body is gradually enlarged and softened. The enlarged uterus increases the abdominal pressure and lifts the diaphragm. In response to hormonal changes, the subcostal angle of the rib-cage is increased and the ribs are expanded outward during pregnancy, at the same time, the chest wall compliance is decreased (35–40 %) [9]. These factors can explain the common phenomenon that many pregnant women feel “physiologic dyspnea”. Increased resting minute ventilation aggravates the maternal subjective feeling of breathlessness during pregnancy [10], and the common "physiologic dyspnea" can complicate the diagnosis of pulmonary disease [11]. Due to the decrease in chest wall compliance, the functional residual capacity (FRC) is reduced. Compared with nonpregnant women, the decrease in FRC will lead to the compensatory respiratory alkalemia [12]. This change can shift the oxygen dissociation curve to the right, which is beneficial to oxygen transfer across the placenta, making oxygen more available to the fetus [13]. However, this altered respiratory state can decrease the ability to further augment respiratory function and can decompensate rapidly for pregnant women with pulmonary complications [14].

Anemia during pregnancy

To adapt to the increased blood flow of the uterus, placenta, various tissues and organs during pregnancy, circulating blood volume are increased. With the volume of plasma increasing more than that of red blood cells, decreased hemoglobin concentration occurred. It's estimated that anemia prevalence in pregnant women is 38 % [15]. Hemoglobin, as a molecular carrier, is responsible for the transport of atmospheric oxygen from the lungs to the tissues. Anaemia can reduce blood oxygen content, which gives priority to vital organs, such as the heart and brain by increasing cardiac output [16]. While immune organs which are relative to other less vital organs will experience different degrees of hypoxia, resulting in a decline in immune function [17]. On the other hand, many pregnant women suffer from iron deficiency due to decreased iron intake but increased iron demands [18]. Iron plays a vital role in the binding and transport of oxygen, and iron deficiency will lead to further aggravation of anemia for pregnant women. Besides, iron has pivotal importance for immunosurveillance due to its effects in immune cells proliferation, cell-mediated immune effector pathways and cytokine activities [19]. Therefore, gaining control over iron homeostas represents a vital first-line defense against infection or a malignant disease [20]. People with Iron-deficiency anemia may susceptible to infection, and is correlated with increased risk of maternal mortality [21].

Immune system and sex hormones

It should be acknowledged that a successful pregnancy is consisted of three specific stages, which are confronted with different immunological challenges respectively [22]. The pro-inflammatory stage (implantation and placentation in the first trimester), anti-inflammatory stage (fetal growth in the second trimester) and second pro-inflammatory stage (initiation of parturition respectively) are the three specific stages [23]. When changes in the maternal immune system can’t adapt to each specific developmental stage, adverse obstetrical events will occur. For example, any ongoing pro-inflammatory signal at the second trimester can lead to miscarriage, and any ensuing pro-inflammatory insult at the third trimester such as infection, can lead to preterm birth [24]. Although the innate immune cells (e.g.NK cells and monocytes) during pregnancy are well prepared to defend foreign pathogens invasion by the maternal immune system, some adaptive immune responses are down-regulated (such as the decreased numbers of T cells and B cells) [25].

The interplay between immune system and sex hormones is complex and multifactorial. At the first trimester, human chronic gonadotropin (hCG) is secreted by embryonic blastocyst to promote many processes including implantation and fetal tolerance [26]. The serum concentration of hCG continues to rise until the 11th gestational week and then dropped rapidly after lasting for about 10 days. The hCG serum concentration in the remainder of the pregnancy is only 10 % of the peak value. Except preventing degradation of the corpus luteum and stimulating progesterone production [27], hCG can also inhibit the immunity of lymphocytes and protect the trophoblast from maternal immune attack [28]. Progesterone is very important for the establishment and maintenance of the fetus during pregnancy, and its functional withdrawal in reproductive tissue can cause the onset of labor [29]. In the early pregnancy, progesterone is produced by corpus luteum, but after the 8th gestational week, the placenta is the major source. The level of progesterone gradually rises throughout pregnancy [29]. Pregnant women are suspected to aspiration pneumonia because of the decreased sphincter tone in the lower esophagus, which is thought to be associated with high levels of progesterone [30], which can reduce both pro-inflammatory and cytotoxic T cell responses. It was reported that the majority of progesterone engagement increases regulatory T cell (Treg) immune suppressive function by interacting with glucocorticoid receptor in murine models [31]. Same as progesterone, estrogen is indispensable for the establishment and maintenance of pregnancy. However, estrogen is a double-edged sword, which can not only induce peripheral T cells to secrete pro-inflammatory cytokines (e.g. IFN-g and interleukin-2(IL-2)) [32], but also can promote tolerance by inducing IL-10 secretion [33]. Estradiol-17b (E2) can regulate the pro-inflammatory response. E3, which is detectable only in pregnant women, plays an important role in reducing the production of pro-inflammatory cytokines. At the same time, due to the influence of hormones, mucous membrane of upper respiratory tract (nose, pharynx, trachea) become thickening, mild hyperemia, edema, and is prone to upper respiratory tract infection [13].

Absorption and metabolism of drugs

During pregnancy, delayed gastric emptying, decreased intestinal motility and prolonged gastrointestinal transit time can lead to reduced actual intake dose and delayed absorption of the drug. However, the increased contact time with intestinal mucosa may increase drug absorption and comprehensively affect drug absorption. After entering the circulation, the drug first binds to the plasma protein, the unbound drug exists in a free state, and the two states can be converted to each other [34]. Plasma protein decreased from the early stage of pregnancy to 60−65 g/mL in the second trimester and this level continues until delivery, thus affecting the distribution of drugs. The process of drug metabolism during pregnancy can also undergo complex changes that significantly affect the steady-state concentration of the drug. Most of the drug metabolism is carried out in the liver, and the liver clearance rate depends on protein binding effect, metabolic enzyme activity and hepatic blood flow. Many observational

studies suggest that pregnancy has different effects on various metabolic enzymes [35]. The increasing effect of pregnancy on the clearance rate of different drugs is very variable, and the clearance rate of most drugs fluctuate is between 20 % and 60 % [36]. Pregnancy increases the renal excretion capacity and reduces the plasma concentration of drugs excreted in the form of crude drugs [36]. Therefore, the dosage should be adjusted during pregnancy to maintain a reasonable blood concentration level. Actually, the effects of infection on the fetus have not been fully understood, and prophylaxis and treatment effective for the general population may not effective for the maternal [37,38].

Clinical symptoms of pregnant women with coronavirus

From the aspect of pathophysiology, influenza is lung inflammation and response resulted from direct viral infection of respiratory epithelium, along with the effects of lung inflammation caused by immune responses on spreading virus [39]. The data on maternal pneumonia caused by highly contagious coronavirus (SARS, MERS, COVID-19) is limited. It is reported that the clinical symptoms of pneumonia in pregnant woman are similar to those in non-pregnant people, including fever, cough, myalgia/fatigue, dyspnea, etc. [40,41] (Table 1). Fever exposure in the first trimester could be associated with oral clefts, neural tube defects, and congenital heart defects [42], and is thought to be related to increased hyperactivity disorder in the offspring [43]. Cough, myalgia/fatigue, and dyspnea will increase the discomfort of pregnant women. Cough will cause airway mucosa congestion and edema, as well as airway obstruction, and will increase abdominal pressure [44] that can induce contractions leading to premature rupture of membranes, miscarriage, premature birth and other adverse pregnancy outcomes. Dyspnea caused by pneumonia will increase the risk of hypoxemia and lead to the increased severity, and may be interfered for the timely and accurate diagnosis of pneumonia due to the common physiological characteristics of dyspnea in pregnant women.

Adverse obstetrical outcome of pregnant women with coronavirus

The associations have been observed between coronavirus infection and obstetric adverse events, including miscarriage/stillbirth, preterm birth, mechanical ventilation, sepsis, etc.. Compared to non-pregnant patients with SARS, adverse outcomes were more common among pregnant patients [48]. And it seems that pregnant women with SARS were more likely to die [38]. At the maternal– fetal interface, trophoblast cells as one of the majority immune regular, can sense and respond to pathogen-associated molecular patterns (PAMPs) from pathogenic microorganisms, and this process is essential for successful pregnancy [49,50]. Toll-like receptors (TLRs) can be expressed by trophoblast cells [51], and type I interferons (IFNs) can be produced by the interaction between TLR4 and lipopolysaccharide (LPS) [22]. Type I IFNs, particularly IFNβ, not only can induce an antimicrobial state, but also can response to the viral. By TLR signalling pathways, IFNβ can strongly modulate inflammatory responses [52]. The baseline of IFNβ expression in the placenta is associated with microbiota presented at the maternal–fetal interface [53]. Viral infection can affect the expression of IFNβ through modifying TLR4-induced responses to commensal bacteria causing the change in specific stage of inflammatory (from being anti-inflammatory to being pro-inflammatory) in nature [53]. These changes can lead to pregnancy complications such as miscarriage, preterm birth and so on [23,24]. It was reported that COVID-19 infection, especially in severe cases, is associated with a cytokine-storm [40]. As mentioned earlier, pregnant women in their first and third trimester of pregnancy are both at the pro-inflammatory state, and the cytokine storm induced by SARS-CoV-2 in these periods may exacerbate the severity of inflammatory state, following the obstetric adverse outcomes.

On the lung immune cells surface, some key negative regulators are up-regulated to response viral infection, and because of the suppressor activity, increased bacterial growth are allowed [54]. What's more, bacterial infections can promote the inflammation, causing the injury or even death of fetal–placental units' cellular components [23,55]. As we know, bacterial infections can also lead to pregnancy complications, such as preterm birth and chorioamnionitis [56]. In patients with viral pneumonia, progressive respiratory failure, severe sepsis or even the death can be induced by secondary severe bacterial infection [38,57]. MERS was reported with the highest fatality rate in pregnant women compared with the other two coronaviruses, in which respiratory failure and severe sepsis were the leading causes of death [58]. Wong et al. showed that about 50 % of pregnant women with "SARS" were admitted to intensive care units, in which about 33 % of pregnant women with "SARS" needed mechanical ventilation. Moreover, the mortality rate of SARS was as high as 25 % in pregnant women compared to 10 % in the general population [59].

Table 1
Clinical symptoms of patients with coronavirus.

symptom	coronavirus		
	SASA [45]	MERS [46]	COVID-19 [47]
Fever	99.3	98	98.6
Cough	74.3	83	59.4[a]
Myalgia/fatigue	49.3[b]	32[b]	34.8/69.6
Dyspnea	41.7	72	31.2
Headache	35.4	13	6.5
Malaise	31.2	/	/
Chills	27.8	/	/
Diarrhoea	23.6	/	10.1
Vomiting/nausea	19.4[c]	21/21	3.6/10.1
Chest pain	10.4	/	/
Dizziness	4.2	26	9.4
abdominal pain	3.5	17	2.2
Arthralgia	3.5	/	/
Rhinorrhea	2.1	4	/
haemoptysis	/	17	/
anorexia	/	/	39.9
pharyngalgia	/	/	17.4

Note: % with symptom at admission to hospital "/" not report.
[a] Dry cough.
[b] Myalgia.
[c] Including Vomiting and/or nausea.

Conclusion

In a word, this study summarized the changes in pregnancy physiology and immunity system and the effects of coronavirus on pregnancy for better understanding of the correlation between pregnancy and coronavirus. Although there is insufficient evidence supporting maternal-fetal vertical transmission for these three coronaviruses, the potential risks on the fetus deserve our concerns. Further study and long-term follow-up about the effects of coronavirus on the offspring should be conducted.

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Details of ethics approval

Not applicable.

CRediT authorship contribution statement

Miaomiao Chen: Conceptualization, Data curation, Writing - original draft. **Jing Zeng:** Writing - original draft. **Xiyao Liu:** Conceptualization, Data curation, Funding acquisition. **Guoqiang Sun:** Writing - review & editing. **Ying Gao:** Writing - review & editing. **Jiujiang Liao:** Writing - review & editing. **Jiaxiao Yu:** Writing - review & editing. **Xin Luo:** Conceptualization, Data curation, Funding acquisition. **Hongbo Qi:** Conceptualization, Data curation, Funding acquisition.

Declaration of Competing Interest

The authors report no declarations of interest.

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