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Implications of physiological changes in pregnancy in COVID-19

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ABSTRACT

Pregnant women generally constitute a group at high risk of infectious diseases due to gestational immunological and physiological changes in their system. That is why the objective of this work is to explain the implications of the physiological changes of pregnancy in SARS-CoV-2 disease. Physiological changes in pregnant women not only increase their susceptibility to the virus, but also increase the severity of the disease. Changes in the respiratory and immune systems, the role of the placenta in coagulation, and the function of endothelial cells are the physiological changes that most influence the disease. The decrease in lung capacity and the variations that occur in the immune system represent new treatment challenges for pregnant women with COVID-19 disease and therefore new areas of research limited so far.

Keywords: COVID-19; Pregnancy; SARS-CoV-2.

Pregnant women are generally in a high-risk group for infectious diseases due to gestational immunological and physiological changes in their system. Viral pneumonia is a factor that especially contributes to increased morbidity and mortality among pregnant women. The death rate for pregnant women during the influenza pandemic in 1918-1919 was 27-50 % if the exposure occurred in the third trimester, while in the Asian influenza epidemic of 1957-1958 it was twice as high for pregnant women as for non-pregnant women[1]. Additionally, statistics show that of the 484 people in the US who died from H1N1 influenza in 2009, 28 (5,8 %) were pregnant women, representing only 1 % of the American population. However, in previous epidemics of coronavirus, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) reported maternal mortality were 18 % and 25 %, respectively, and were associated with preterm delivery, fetal growth restriction, and perinatal death. Thanks to these experiences, it is stated that pregnant women are more likely to develop severe pneumonia in case of infection by respiratory pathogens than non-pregnant patients, and chronic or pregnancy-related comorbidities may increase the risk[1,2,3,4].

Although the evidence is accumulating rapidly, there are still several outstanding issues that need to be resolved soon regarding the effect of COVID-19 on perinatal outcomes to guide prenatal counseling and treatment of women with COVID-19 during pregnancy. In a large multinational cohort study, COVID-19 in pregnant women was recently shown to be associated with a low maternal mortality rate, but an intensive care unit (ICU) admission rate of 11,1 %, although other studies report frequencies between 4,6 % and 9,2 %. However, precise risk stratification of women with COVID-19 is needed to determine the association between different maternal characteristics or clinical findings and adverse perinatal outcomes [5,6].

Undoubtedly, the physiological changes in the respiratory, circulatory, and immune systems during pregnancy play a decisive role in the development of the disease, and, in addition to the organic implications that a virus infection brings, pregnant women position themselves as a high-risk population group. That is why the objective of this work was to explain the implications of the physiological changes of pregnancy in COVID-19.

DEVELOPMENT

The virus uses a spike glycoprotein (S) to bind to its receptor [angiotensin-converting enzyme 2 (ACE2) receptor], which is abundantly present in the pulmonary alveolar epithelial cells and the enterocytes of the small

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intestine, as well as the arterial and venous endothelial cells and in the cells of the arterial smooth muscle in almost every organ[7,8].

A high expression of ACE2 in pregnant women also increases their susceptibility to SARS-CoV-2 infection. A higher level of ACE2 in the kidneys of pregnant women its reported and an increase in (Angiotensin-1) ANG 1 immunocytochemical staining-7 and ACE2 in the kidney of pregnant rats, indicating that this increase was gradual in both the cortex and the medulla during pregnancy. Furthermore, was found that the amount of ACE2 mRNA in the kidney, placenta, and uterus increased significantly during pregnancy, resulting in a two-fold increase in total, compared to non-pregnant women. So there is plausibility to think that the elevated level of ACE2 to regulate blood pressure during pregnancy may be a favorable condition for SARS-CoV-2 infection. Furthermore, ACE2 is not only a receptor but is also involved in post-infection regulation, including immune response, cytokine secretion, and viral genome replication[2].

The virion then enters the host cells (endocytosis) and releases its RNA genome, which constitutes a pathogen-associated molecular pattern (PAMP). Within host cells (immune or non-immune), viral RNA (PAMP) is recognized by pathogen recognition receptors (PRRs), which harvest the specific signal adapter protein and activate IRF3 and IRF7 before being translated into the nucleus to promote the synthesis of type I interferons (IFNs)[7].

SARS-CoV is capable of showing early and extremely high replication rates, infecting dendritic cells, macrophages, and T cells, using various strategies to avoid the innate immune response of the host, type I IFNs increase antigen-presenting activity and the robust and sustained production of pro-inflammatory cytokines and chemokines. Patients with COVID-19 have higher baseline plasma concentrations of IL1-β (interleukin 1 beta), IL1RA (interleukin 1 receptor antagonist), IL7 (interleukin 7), IL8 (interleukin 8), IL9 (interleukin 9), IL10 (interleukin 10), Basic FGF (basic fibroblast growth factor), GCSF (granulocyte colony-stimulating factor), GMCSF (granulocyte-macrophage colony-stimulating factor), IFN-γ (interferon-gamma), IP10 (interferon-inducible protein 10), MCP1 (monocyte chemotactic protein 1), MIP1-α (macrophage inflammatory protein 1 alpha), MIP1-β (macrophage inflammatory protein 1 beta), PDGF (platelet-derived growth factor), TNF-α (tumor necrosis factor-alpha) and VEGF (vascular endothelial growth factor) than healthy uninfected adults. IL6 (interleukin 6) levels in patients with severe COVID-19 were also significantly higher than in patients with milder infections. [7,8] This produces, in the lungs, diffuse alveolar damage, formation of hyaline membranes, alveolar hemorrhage, desquamation of pneumocytes, extensive infiltration of neutrophils and macrophages in the interstitium and alveoli, and includes edema, protein exudate, focal reactive hyperplasia of pneumocytes with inflammatory cell infiltration in patches and multinucleated giant cells. Which plays an important role in the develop and progression of adult respiratory distress syndrome (ARDS)[8].

Pregnant women are more prone to hypoxia and therefore to develop ARDS, mainly due to physiological changes in the maternal respiratory system during pregnancy. Anatomically, the effects of progesterone and relaxants in the first trimester of pregnancy can cause the rib ligaments to relax. During pregnancy, the diaphragm rises approximately 4 cm due to the gravid uterus. In addition, the subcostal angle and the transverse diameter of the thoracic cavity increase even more in the third trimester. The above anatomical factors, along with decreased chest wall compliance, eventually lead to a 20-30 % reduction in functional residual capacity (FRC), which corresponds to a decrease of approximately 700 ml, which makes the mother prone to hypoxia, later compensated by an increase in tidal volume and hyperventilation[2,3].

Additionally, elevated progesterone can be transmitted through estrogen-dependent progesterone receptors in the hypothalamus, thereby stimulating the respiratory center and increasing tidal volume by 50 % compared to non-pregnant patients. In addition, progesterone-mediated changes in the nasal mucosa during pregnancy can cause the virus to adhere to the upper respiratory tract and make it difficult to eliminate. That makes the woman intolerant to hypoxia. Severe pneumonia is characterized by hypoxemia, which subsequently leads to placental hypoxia. The hypoxic placenta releases antiangiogenic and pro-inflammatory factors that affect the maternal endothelium, inducing endothelial dysfunction, hypertension, and organ damage[2,8].

Furthermore, during the third trimester of pregnancy, the probability of physical dyspnea is high (due to increased maternal oxygen demand, gestational anemia, and fetal oxygen consumption), causing further worsening of breathing difficulties. Women with pneumonia during pregnancy are at significantly increased risk for adverse pregnancy outcomes, such as preterm delivery, pre-eclampsia, low birth weight, and small-for-gestational-age babies. Therefore, severe maternal respiratory distress syndrome can affect fetal oxygen supply and endanger the fetus[8,9].

The immune system, pregnancy, and SARS-CoV-2 infection

A successful pregnancy carries maternal tolerance to the allogeneic fetus because half of the embryo's genome comes from the father, which is then expressed as paternal antigens that can be recognized by the maternal immune system as foreign. Therefore, the mother will undergo a series of complicated processes to ensure acceptance of the fetus and these immune changes can increase the maternal susceptibility to

certain infectious diseases[2].

During pregnancy, there is a shift from Th-1 mediated immunity to Th-2 mediated immunity, while abortion is reversed. Moving away from Th-1-mediated immunity leads to decreased secretion of pro-inflammatory cytokines, including interleukin-2 (IL-2), interferon-α, and tumor necrosis factor. An increase in Th-2-mediated immunity results in an increase in anti-inflammatory cytokines including IL-4, IL-10, and IL-13.17-19. Changes in the maternal environment of a dominant Th-1 to Th-2 population can increase the risk of maternal susceptibility to various pathogens, including viruses, resulting in an altered clearance of infected cells, changes in peripheral response to respiratory virus infection, and autoantigen[2,3,4].

Variations in the cytokine profile may explain differences in severity of COVID-19 disease. Studies in non-pregnant patients have found that activation of Th-1 and Th-2 increases interferon-γ, IL-1β, IL-4, and IL-10´s levels. Patients requiring ICU admission were found to have more IL-2, IL-7, IL-10, granulocyte-stimulating colony factor, and TNFα than those that did not require ICU care. The severity of the disease associated with COVID-19 may be related to an impaired adaptive immune response and increased release of pro-inflammatory cytokines, leading to systemic inflammation, severe organ damage, and ultimately death[3].

Treg and Th17 cells are active players in establishing this unique immune state. Treg cells produce mainly anti-inflammatory cytokines, such as IL-4 and transforming growth factor-beta (TGF-β) that allow the growth and development of the allogeneic fetus, while Th17 cells, which produce predominantly inflammatory cytokines such as IL-17A, are involved in defense against various pathogens. A proper balance between Treg / Th17 cells, mainly in favor of Treg, is essential for support the immune tolerance of the fetus, for a consequent healthy fetal implantation and pregnancy development[3,7].

In contrast, uncontrolled proliferation of Th17 cells is unfavorable because it is associated with the rejection of the fetal allograft in the fetal-maternal region. Dysregulation of this tight balance between Treg and Th17 cells is involved in the pathogenesis of adverse pregnancy outcomes. Decreased Treg cell numbers and increased Th17 cell percentages are associated with pregnancy complications such as miscarriage, pre-eclampsia, and preterm labor. The pathogenesis of severe COVID-19 involves dysregulation of the Treg / Th17 cell ratio towards an increase in Th17 cells, resulting in uncontrolled systemic inflammation[7].

Furthermore, in patients with severe COVID-19 disease, the ratio of Treg / Th-17 cells appears to change in favor of Th-17 cells. The changes in hormonal balance during pregnancy and the physiological shift towards the predominant Th-2 environment may result in a less severe form of COVID-19 in pregnant compared to non-pregnant women. Increased Treg cells in pregnancy may also prevent the excessive inflammatory response that has been seen in COVID-19 patients with severe disease. Also, the total number of CD3 + T cells in the blood decreases[3].

Other modulations of the maternal immune system during pregnancy can affect the response to infections, and specifically to viruses. The altered inflammatory response to viruses during pregnancy is believed to be mediated, at least in part, by:

i. Decrease in circulating natural killer (NK) cells during pregnancy. NK cells play an important role in viral clearance from the innate immune system, and a decrease in these cell populations can impair the ability to clear viruses. However, it is not clear whether this decrease in circulating NK cells has clinical effects for COVID-19[4].

ii. Decreased circulating plasmacytoid dendritic cells (pDC). These cells are key to the production of type 1 interferon against viruses. Furthermore, the pDCs of pregnant women have also been shown to have an attenuated inflammatory response to the H1N1 / 09 virus. This is believed to be one of the reasons why pregnant women were most affected by the H1N1 pandemic in 2009[4].

iii. An increase in circulating progesterone levels. Progesterone is a steroid hormone that has immunomodulatory properties, with the ability to enhance lung repair of influenza virus-induced damage, making high levels during pregnancy potentially beneficial for recovery after viral lung infections. Nevertheless leads to reversible degeneration of the thymus, which may explain the decrease in CD4 + and CD8 + T cells, as demonstrated in a mouse model of influenza A infection, treatment with progesterone or the progestin, levonorgestrel, also resulted in a decrease in virus-specific antibody levels, as well as a decrease in specific CD8 + T cell virus in mice. When these mice were re-exposed to influenza A, it resulted in a more serious illness[2,4].

iv. Alterations in the innate immune system, including pattern recognition receptors, toll-like receptors (TLRs) during pregnancy. COVID-19 infection causes host cell pyroptosis and release of DAMP, which can be TLR ligands and further increase inflammation[4].

Placental implications

Placenta and viral interaction

The placenta is often an effective barrier that prevents maternal infection from spreading to the fetus (vertical transmission). It is well known that certain pathogens can overcome this barrier, with sometimes devastating effects on the developing pregnancy. Cytomegalovirus

(CMV), herpes simplex virus (HSV), varicella-zoster virus, Zika virus (ZIKV) can cause congenital syndromes, while AH1N1, dengue, and HIV have been associated with alterations in maternal and fetal hemodynamics and with an abnormal architecture of the placental villi, with variable rates of transmission and severity of effects that depend, in part, on the stage of pregnancy in which the infection occurs[4,8].

Early studies indicated that systemic maternal infection and subsequent inflammation may alter placental vasculogenesis and angiogenesis, and alterations in placental hemodynamics may contribute to adverse pregnancy outcomes such as pre-eclampsia, preterm delivery, small-for-gestational-age infants, newborn low birth weight, and stillbirths. Furthermore, it is believed that placental ischemia/hypoxia may trigger increased production of inflammatory biomarkers, such as IL6 and TNFα, which contribute to endothelial dysfunction in preeclampsia. The healthy function of the placenta depends on adequate vascularization and perfusion of the placenta[8].

Notably, many of these infections may have only minor effects on the mother, and there is little recognized correlation between maternal symptoms and the severity of fetal effects. The experience of viral infections during pregnancy has led to three other key observations regarding congenital infections in general. First, the presence of the virus on the surface of the placenta does not necessarily indicate a placental infection; vertical virus transmission depends on some type of rupture of the placental barrier. Second, a viral infection of placental cells does not necessarily mean transmission to the fetus. Third, even if a fetal infection occurs, the responses are heterogeneous; therefore, the fetal infection does not always mean fetal harm[4].

The human placenta is hemochorial, which means that maternal blood is in direct contact with the placental chorionic villi. The placenta is predominantly made up of specialized cells derived from the fetus called trophoblasts, of which there are three main types. Terminally differentiated multinuclear syncytiotrophoblast cells line the villus tree and are in direct contact with maternal blood. The progenitor villous cytotrophoblast cells underlie the syncytiotrophoblast. Invasive cells of the extravillous trophoblast anchor the chorionic villi to the uterus and modify its vasculature. Several potential mechanisms may be involved in vertical virus transmission, including direct damage to the downy tree with breaks in the protective layer of syncytiotrophoblast; spread of virus-infected maternal endothelium to extravillous trophoblast; trafficking of infected maternal immune cells via syncytiotrophoblast, or paracellular or transcellular transport (eg.: immunoglobulin-mediated transcytosis) into fetal capillaries; and/or ascending infection of the vagina[4].

SARS-CoV-2 and the placenta

The expression of SARS-CoV-2 has been detected in samples taken from placentas in the middle of the trimester, but it is not clear if the presence of the virus was due to a primary infection or if it was facilitated by placental damage from other pathologies. SARS-CoV-2 was found in RT-PCR of swabs and biopsies after spontaneous fetal loss at week 19 of gestation. SARS-CoV-2 was also highly expressed in placental and umbilical cord biopsies after pregnancy termination at week 22 of gestation, due to placental abruption and severe maternal pre-eclampsia with thrombocytopenia and coagulopathy. In this case, electron microscopy revealed virus-like particles in the cytosol of placental cells. However, no viral expression was detected in the fetal tissues analyzed[4].

In a study of the placentas of 20 women who tested positive for SARS-CoV-2 on routine tests at birth (weeks 32-40 of gestation), ten placentas showed signs of possible fetal vascular poor perfusion or thrombosis. However, there was no control group for comparison, making the findings difficult to interpret. The findings were mainly low grades and could be related to other etiologies[4].

In a histopathology study of seven placentas from mothers with SARS, two of the women who recovered from SARS in the first trimester were normal. Three placentas from women who delivered during the acute stage of SARS showed an increase in intervillous and subchorionic fibrin, and these findings may be related to disturbances in maternal placental blood flow due to hypoxia. Two other placentas from women who recovered from SARS in the third trimester of pregnancy had extensive thrombotic vasculopathy on the fetal side and their etiology may be related to the tendency to SARS thrombosis and/or placental hypoxia. These two pregnancies were also accompanied by intrauterine growth restriction, oligohydramnios, and low birth weight[8].

Another study of the placental histopathology of three pregnant women who were infected by SARS-CoV-2 in the third trimester of gestation, with mild disease; Chorioangioma was evidenced in one placenta, and another, multifocal infarcts were observed. All three cases had varying degrees of increased intervillous or subchorionic fibrin associated with increased syncytial nodules[8].

These placental changes could have deleterious effects on both the mother and the fetus. In the mouse model, endothelial and thrombotic changes in the placenta are associated with the impaired vascular flow to the fetus and consequent neural inflammation. Therefore, children born to women infected with SARS-CoV-2 could have similar neurological inflammation before birth[10].

Clotting response

In the general population, COVID-19 is associated with high rates of thromboembolic complications. Adding to this, pregnancy is, by itself, a state of

hypercoagulability with increased thrombin production and increased intravascular inflammation, with higher levels of fibrinolytic factors such as plasmin, which may be involved in the pathogenesis of SARS-CoV-2 infection. Pregnant women are at increased risk of thromboembolic events with associated mortality. This hypothesis is supported by a case report describing mortality in a woman at week 29 of gestation with COVID-19 due to a large pulmonary embolism and basilar artery embolism[4].

Endothelial cell function

Mortality in COVID-19 is mainly due to acute respiratory distress syndrome (ARDS), produced by dysfunction of pulmonary endothelial cells. Physiologically, endothelial cells are surrounded by mural cells (pericytes) and limit inflammation by restricting the entry of immune cells and prevent clotting through the expression of anticoagulant factors. In ARDS, this endothelial barrier is damaged, leading to tissue edema, excessive inflammation, and hypercoagulability. COVID-19 risk factors (older age, obesity, diabetes mellitus, cardiovascular disease) are related to endothelial cell dysfunction[4].

Maternal vascular adaptation to pregnancy is essential for optimal pregnancy outcomes. At the time of implantation, the specialized uterine spiral arterioles reshape to form sinuses that become placental villi. Systemic vascular physiology also undergoes significant adaptations to pregnancy. Maternal blood volume increases, heart rate, and stroke volume increase cardiac output by 30-50 %, and vascular resistance decreases. The impact of this increased vasodilation on lung endothelial cell function (adhesions of immune cells and activation of coagulation) has not yet been determined[4].

Pregnancies affected by preeclampsia are characterized by hypertension and proteinuria. Preeclampsia is associated with significant maternal complications (cerebrovascular accident, cardiac arrest, kidney failure, liver failure) and fetal [intrauterine growth restriction (IUGR), premature delivery, fetal death]. Women with preeclampsia have an insufficient decrease in vascular resistance in mid and late gestation and associated endothelial cell dysfunction. Given the potential importance of endothelial cell function in the development and progression of COVID-19, these women may be at particular risk if infected, and one review found higher rates of pre-eclampsia in pregnant women hospitalized with COVID-19[4].

CONCLUSIONS

Physiological changes in pregnant women not only increase their susceptibility to the virus but also increase the severity of the disease. The decrease in lung capacity, as well as the variations that occur in the immune system, represent new treatment challenges for pregnant women in the context of Covid-19, but they also open multiple windows for research, which are also limited up to the moment.

AUTHORSHIP

Rolando Dario Rosales-Campos: data curation, formal analysis, investigation, display, drafting - original draft.
Héctor José Pérez-Hernández: methodology, validation, drafting - original draft.
Soraida Candida Acosta-Brooks: conceptualization, methodology, supervision, drafting - review and editing.

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Implicaciones de los cambios fisiológicos del embarazo en la COVID-19

RESUMEN

Las gestantes constituyen por lo general un grupo de alto riesgo de enfermedades infecciosas debido a los cambios inmunológicos y fisiológicos gestacionales en su sistema. Es por ello que el objetivo de este trabajo es explicar las implicaciones de los cambios fisiológicos del embarazo en la enfermedad del SARS-CoV-2. Los cambios fisiológicos en las mujeres embarazadas no solo aumentan su susceptibilidad al virus, sino que también aumentan la gravedad de la enfermedad. Las modificaciones en los sistemas respiratorio e inmunológico, el papel de la placenta en la coagulación y la función de las células endoteliales son los cambios fisiólogicos con más influencia sobre la enfermedad. La disminución de la capacidad pulmonar y las variaciones que ocurren en el sistema inmunológico representan nuevos desafíos de tratamiento para las mujeres embarazadas que padecen la enfermedad COVID-19 y por tanto nuevas áreas de investigación limitadas hasta el momento.

Palabras clave: Embarazo; COVID-19; SARS-CoV-2.