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**Research Paper**

# The Role of Body's Immunology System Against Covid-19 Infection in Pregnancy: A Review Study

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***ABSTRACT:****The pregnancy period is a condition in which a woman not only lives independently, but other individuals in her belly grow and develop. Various changes during this period will impact the body of the pregnant woman. Less physical resistance may lead to the risk of exposure to various infections more easily. Coronavirus disease 2019 (COVID-19) due to coronavirus 2 (SARS-CoV-2) is a serious acute respiratory syndrome. Pregnant women need strong immunity to prevent COVID-19 infection and to minimize the complications this infection can cause for both the mother and the fetus it contains. This literature review aims to describe and deepen studies related to the role of the body's immune system by increasing the body's resistance to infection with the Covid-19 virus, especially in pregnant women. The methodology used in this study is to gather and analyze data on the role of the body's immune system in coronavirus infection in pregnant women. Articles are sourced from the Google Scholar database, PubMed and Pediatric Research. The keywords used are the body's immune system, Covid-19, pregnancy, innate antiviral immunity, and vaccination.*

***KEYWORDS:*** *Pregnancy, COVID-19, Innate Antiviral Immunity, Body's Immune System*

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## I. INTRODUCTION

Immunity is very important to sustain pregnancy and fetus growth. The primary role of the immune system is to protect the body from invasion of foreign organisms and toxic products. This requires the ability to differentiate between auto-allergen and non-allergenic antigens so that the immune system can damage invasive organisms and not normal tissues. In pregnancy, the fetus, a foreign antigen grows within the mother for nine months. Immunological adaptations during pregnancy allow the maternal tolerance of the fetus for the survival of the fetus while maintaining the mother's capacity to fight infection. When protection is insufficient, especially in case of infection, the body condition of pregnant women becomes weaker[1]. Infection during pregnancy can interfere with fetal viability, which causes pregnant women to be at greater risk for infection compared to the general population and non-pregnant women. Infection at the mother-fetal interface and the interaction of the placenta with the immune system of pregnant women are thought to occur due to immunological changes[1].

Alterations in the immune system during pregnancy can make pregnant women vulnerable to infections, including influenza viruses, hepatitis E and the novel coronavirus. They will be more at risk of experiencing severe and fatal disease symptoms. Pregnant women with COVID-19 who are infected in the first, second and third trimesters can spread the virus to the fetus. While there is no evidence that pregnant women can transmit COVID-19, COVID-19 infection among pregnant women can affect organogenesis and fetal development. The earlier the infection occurs, the greater the risk of miscarriage or premature childbirth[2].

Pregnancy involves complicated adaptations of a woman's immune system to defend the fetus against invasive pathogens. The early theory of maternal-fetal tolerance has proposed that a transient state of maternal immunosuppression is essential for successful implantation and development of pregnancy[3].

Coronavirus disease 2019 (COVID-19) caused by coronavirus 2 (SARS-CoV-2) is an acute respiratory syndrome. The main clinical symptoms are fever (temperature higher than 38ºC), cough and shortness of breath. Then there are severe cramps, fatigue, myalgias and gastrointestinal symptoms. The condition can deteriorate

quickly in severe cases, including septic shock, ARDS, persistent metabolic acidosis and bleeding/clotting system dysfunction within a few days [4].

Information on COVID-19 in pregnant women is still limited to this point. To prevent the spread of COVID-19, the body's defense system is necessary to increase the body's resistance to infectious disease attacks in pregnant women.The study aims to describe and deepen studies related to the role of the body's immune system by increasing the body's resistance to infection with the Covid-19 virus, especially in pregnancy.

## II. METHOD

The method used in this study is to collect and analyse data on the role of the body's immune system in coronavirus infection in pregnant women. The articles reviewed were sourced from the Google Scholar database, PubMed and Pediatric Research. Keywords include immune system, COVID-19, pregnancy, innate viral immunity and vaccination.

## III. DISCUSSION

The pregnancy period is a condition where a woman not only lives independently, but other people in her womb grow and develop. Various changes in this time will affect the body of the pregnant woman. Less physical resistance may lead to the risk of exposure to various infections more easily. The most effective way to prevent infection is to avoid exposure to pathogenic viruses on a daily basis[1].

During pregnancy, immune cells such as natural killer (NK) and monocytes respond more strongly to viral infection, but certain functions of immune cells (T and B cells) are regulated. 1) COVID-19 has become the primary pathogen in new respiratory outbreaks. Pregnant women need a strong immune system or immunity to avoid the Covid-19 virus and to be able to minimize the complications that this infection may cause, both for the mother and the fetus she contains.Antiviral immunity in every pregnant woman has been found in the body, known as innate immunity. Some of the existing immunity include decidual immunity and systemic immunity.

**Decidual Immunity**

Systemic maternal immunity alterations and fetal cell dialogue combine to maintain tolerance to fetal allograft disease while maintaining the ability to respond to infection. After fertilization, increased levels of progesterone trigger decidualization, turning the endometrium into a specialized tissue that promotes the implantation of blastocysts[5]. Intensive studies of the cellular composition of the decode over the past few years have identified a diverse population of immune cells, including natural killer (NK) cells, macrophages, dendritic cells (DCs), and T cells[3]. Interactions between these deciduous immune cells and the invasive fetus extravillal trophoblast affect placentation, fetal growth and pregnancy outcomes.

The unique unconventional class, my human leukocyte antigen (HLA) molecule HLA-G, is expressed exclusively on trophy oblast extravillon (EVT). Invading EVTs come into direct contact with maternal cells as they infiltrate through the decide into the myometrium, remodeling the maternal spiral arteries into dilated low-resistance channels that maximize blood flow to the developing fetoplacental unit. EVT is capable of immune evasion and tolerance induction due to its unique HLA expression profile, consisting only of class I HLA-C, HLA-E, and HLA-G molecules. HLAG trophoblasts have a strong affinity with the type B1 receptor (LILRB1), an inhibitor receptor largely expressed on cells with deciduous antigens. This interaction modulates decidual DC signalling, suppresses the production of pro-inflammatory cytokines and inhibits the proliferation of maternal T cells. Consequently, HLA-G provides a critical tolerable signal at the mother-fetal interface[3].

The role of innate immune cells in defending against infection is an emerging area in rapid development. Current knowledge is summarized in a recent review [6], and relevant aspects of the decidual innate immune response to viral infection will be discussed in detail below. While significant progress has been made, our understanding of the recalibration of the innate-adaptive balance during pregnancy remains incomplete. This is due to the practical and ethical difficulties of obtaining samples from deciduous tissues and the uncertain correlation between the activity of peripheral and deciduous immune cells[7]. Renewed focus on the role of the maternal innate immune system in the trade-off between fetal tolerance and robust defense against intracellular pathogens will provide further insight into how these two priorities interact in pregnancy. For this review, "tolerance" refers to the state of tolerance specific to the pregnancy of the semiallogenic fetus rather than to a specific phenomenon of T lymphocytes.

Trophoblast cells can control viral replication by secreting interferon-beta (IFNß), which induces an antiviral response in the body. However, it is not surprising that one of the molecular pathways called type-1 interferon (type 1 IFN) can be actively inhibited by viruses. Furthermore, Epstein-Barr virus (EBV) can also reduce IFNß expression by inhibiting placental interferon regulatory factor 3 (IRF3) phosphorylation, resulting in decreased antiviral response. In animal models, non-structural influenza A virus protein 1 (NS1) is associated with decreased production of interferon-alpha (IFNa) and IFNß[7].

A reduction in the production of IFNa and IFNß will reduce the reception of immune cells to the mother fetus and reduce their ability to react to and control microorganisms. The presence of viral infection can reduce IFNß signaling and inhibit IFNß regulators, which causes the loss of its immunomodulatory effect and can lead to inflammation. Based on recent literature, COVID-19 infection is associated with cytokine storms, lymphopenia, and inflammation. In their first and third trimesters, pregnant women produce a pro-inflammatory and cytokinin state due to COVID-19 infection, which can cause more severe inflammation and lead to pregnancy complications. [8].

Inflammation caused by COVID-19 infection can be associated with adverse pregnancy outcomes such as miscarriage, premature birth, and stillbirth; it affects several aspects of fetal brain development and even preeclampsia in pregnancy. In such cases, increased maternal inflammatory response levels and inflammatory cytokines, including interleukins (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)-a, may affect fetal brain development and circulatory system and may increase the risk of fetal mental disorders.

Additionally, coronaviruses including SARS-CoV, MERS-CoV, and SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) are associated with miscarriage, intrauterine growth restriction (IUGR), preterm birth, low birth weight, and perinatal death. However, there was no vertical transmission of SARS-CoV, MERS, and COVID-19 to their fetuses. There has always been a complicated relationship between COVID-19 infection and the absorption of micronutrients. COVID-19 infection can affect the absorption of micronutrients, causing certain complications such as diarrhea and fever. Malabsorption and loss of nutrients during diarrhea can lead to weakened immune systems, micronutrient deficiencies, and exacerbation of infections. In addition, fever substantially increases micronutrient requirements in virus-infected individuals [8].

**Systemic Immunity**

Systemically, there is a global regulation of innate immune cells and effector mechanisms in normal pregnancy. Complement activity is increased relative to the non gestational state, and there is a substantial increase in circulating phagocytes and plasmacytoid CD which produce interferon type I (IFN) with advanced gestation. Longitudinal studies of serial blood samples from pregnant women show specific increases in innate pathways that mediate antiviral immunity: for example, IFN-a-induced STAT1 signaling, a critical response to the viral challenge, is increased during pregnancy in NK cells, monocytes, and myeloid DCs[3]. This situation must be well calibrated: overactivation can be associated with tissue damage in response to acute viral infection and adverse obstetric outcomes [such as complement overactivity in antiphospholipid syndrome, while an attenuated immune response can predispose to over-infection. Whether the maternal susceptibility to infection with RNA viruses is due to overactive or under activity of the innate immune system is unclear; some effector mechanisms are likely regulated while others are suppressed.

**The effect of vaccines on the risk of Covid-19 infection in pregnancy**

Vaccinations are the most effective and cost-effective way to prevent infectious diseases. Require the development of SARS-CoV-2 vaccines. So far, over 40 pharmaceutical companies and academic institutions around the world have launched SARS Cov-2 vaccine development programs[4]. It is well tolerated in all populations without significant safety concerns. Minor side effects are tiredness and headaches after the second dose of vaccine. It is strongly recommended that pregnant and lactating women be vaccinated[9]. Studies have assessed the levels of SARS-CoV-2 virus in the blood of the umbilical cord and placenta. Real-time RT-PCR was used to evaluate amniotic fluid, neonatal blood, urine, nasopharynx, faeces and rectal swabs. Positive samples and respiratory distress in neonates are rare. Overall, the risk of mother-to-fetal transmission of SARS-CoV-2 virus is approximately 3.2% [10].

In the uterus, fetal IgG and IgM antibodies begin within 20 weeks of pregnancy. As a result, most newborn IgG are of maternal origin. Positive IgG cannot support or deny vertical transmission. IgM antibodies do not pass through the placenta, therefore IgM in the fetus or newborn is thought to represent the fetal or neonatal production in response to infection. However, in a case report describing the identification of COVID-19 IgM antibodies in a neonate, the infant was asymptomatic and tested negative for SARS-CoV-2 viral RNA at birth. Although the presence of IgM antibodies is a trade-off between maternal and fetal circulation, the presence of IgM antibodies in these infants can provide evidence of intrauterine transmission. Several case reports show evidence of transplacental transmission; overall production of IgM and IgG during COVID-19 infection is necessary for the development of long-term immunity, significantly contributing to the risk of mother-to-fetal transmission.

A recent study of 131 patients found that the COVID-19 mRNA vaccine was highly effective in producing vaccine-induced antibody titers in pregnant (median, 5.74; interquartile range, 5.06–6.22) and lactating women (median, 5.62; interquartile range, 4.77–5.98), which had titers similar to those of non-pregnant women (median, 5.59; Interquartile range, 4. 68–5.89)[11]. All vaccine titers are higher than those produced by

a SARS-CoV-2 infection during pregnancy. Furthermore, vaccine-generated antibodies were found in all cord and breast milk samples. This study provides convincing data that pregnant individuals respond to vaccines similarly to non-pregnant individuals. Another cohort study from Israel compared vaccinated pregnant patients, PCR-confirmed SARS-CoV-2 infected pregnant patients, and unvaccinated pregnant controls looking at the effect of the mRNA vaccine (Pfizer-BioNTech) versus native infection in a maternal and acquired humoral transplacental fetal immune response. They discovered a strong mother-induced humorous response to vaccines that is actually transferred to the fetus, supporting a vaccination role during pregnancy.

Regarding the timing of vaccine and antibody production, Prabhu et al has evaluated 122 pregnant patients who received COVID-19 vaccine mRNA. It found that 44% of cord blood samples were positive for IgG antibodies after one dose, compared to 99% of samples after both vaccine doses. Detectable antibodies were present in all patients and cord blood samples when administered at least four weeks after the first dose of the vaccine. They also found that early detection of antibodies in maternal blood samples took place five days after vaccination and 16 days after vaccination for cord blood samples[12].

Maternal morbidity and mortality related to COVID-19 is lower than in previous coronavirus outbreaks, though higher than in the non-pregnant population. However, vertical transmission is not common. Food and Drug Administration-approved mRNA and adenovirus vaccines can reduce the risk of serious maternal morbidity and mortality and induce immunologic protection for newborns by transferring antibodies. In utero and while lactating. The benefits of this vaccine may outweigh the risks of COVID-19 during pregnancy and post-partum. Ongoing research is needed on the effects of COVID-19 infection during pregnancy, covering all times of pregnancy as well as long-term studies related to the effects of the COVID vaccine in pregnancy.

**Nutrition in pregnancy with Covid-19**

The nutritional contribution in pregnant women is very important and should not be neglected. It helps to support the health and development of the fetus by increasing the resistance of the body, which may protect the body from infection. It consists of innate immunity and adaptive immunity. Innate immunity is thought to be the first line of defense against infection through physical barriers (skin and epithelial lining of the digestive and respiratory tracts), biochemical barriers (secretions, stomach acids, and mucus), phagocytes, leukocytes, and natural killer cells. Assume that innate immunity cannot fight the infection optimally. In that case, a more complex adaptive immunity will work, facilitated by T and B lymphocytes, thus producing specific antibodies to kill and destroy the invading pathogens.

During pregnancy, fetal growth and insufficient micronutrient intake may interfere with fetal development. The newborn's predisposition to chronic conditions later in life, poor maternal health and undesirable neonatal outcomes. Complications of pregnancy, including pre-eclampsia, pregnancy-induced hypertension, intrauterine growth restriction (IUGR), low birth weight (LBW) and premature delivery, impact on newborn morbidity and mortality. Inadequate or insufficient intake of micronutrients can be associated with a compromised immune system. However, micronutrients such as vitamins (A, C, D and E) and minerals (Fe, Se and Zn) can stimulate the immune system and prevent pregnancy-related adverse effects[8].

**Vitamin C**

Vitamin C use is a way to increase immunity during the COVID-19 pandemic [13]. Absorption of iron may be facilitated through vitamin C intake. A lack of vitamin C is associated with an increased immune response and sensitivity to infections. A person who lacks vitamin C is also at increased risk of contracting COVID-19 due to a weakened immune system. The daily requirement for vitamin C depends on age and sex, especially for pregnant women who need around 80 mg (age less than 18 years) and 85 mg (age more than 18 years).

From the results of systematic analysis studies from international journals that have been obtained, the use of Vitamin C as a treatment for COVID-19 is very important, where the administration of vitamin C can accelerate improvement in COVID-19 cases, which work on plasma and neutrophils, besides that Vitamin C can also counteract free radicals and prevent oxidative stress by the corona virus which binds to heme. In the journal, it has also been shown that with the administration of high doses of vitamin C, there is a rapid improvement in the radiological appearance of the chest radiograph after several days of therapy. It is known that the use of vitamin C as prevention or therapy for COVID-19 is still under research. However, vitamin C's antioxidant and antiviral effects have been recognized in several international literature, and this case of COVID-19 is still under further research. Vitamin C deficiency is associated with increased susceptibility to infection, a less robust immune response, poor wound healing, and an increased risk of pneumonia[14].

From the journal review carried out by Armanto et al., the content of vitamin C in plasma has been discussed in 21 journals, and as many as 13 journals discuss the content of vitamin C in plasma. Vitamin C also

reduces the oxidative stress caused by the coronavirus, which is associated with it. One of the recommended ways to increase immunity during the COVID-19 pandemic is to drink vitamin C. Vitamin C consumption may help increase iron absorption. Low vitamin C intake may affect the hemoglobin levels of pregnant women. Vitamin C helps in the absorption of iron from food so that it can be converted back into red blood cells. Hemoglobin levels in the blood increase, so that the food supply and oxygen in the blood can flow through the tissues of the body, ultimately supporting the survival and growth of the fetus[15]. A lack of vitamin C is associated with increased sensitivity to infection and a less robust immune response. People with vitamin C are believed to have a higher risk of contracting the coronavirus or Covid-19 disease because their immune system is declining.

**Vitamin E**

Vitamin E, a fat-soluble vitamin known as antioxidant, and its immunomodulating effects have been found in various animal and human studies. It regulates macrophages that function as antigen-presenting cells (APCs) and regulates NK cells and T cells by producing cytokines while reducing reactive oxygen species (ROS), reactive nitrogen species (RNS), and prostaglandins. It accelerates the activity of NK cells, regulates the maturation and function of dendritic cells (DC), improves the interleukin-2 (IL-2) production capacity of T cells and improves the humoral response of the immune system. Decreased levels of vitamin E in calves are linked to an increased risk of bovine coronavirus. Its supplementation increases resistance to infectious diseases and decreases flu virus titre. It reduces oxidative stress during pregnancy, which can cause pre-eclampsia, premature labor and low birth weight. Population-based studies found that maternal vitamin E was positively associated with fetal growth. This showed a positive effect on pregnancy outcomes under several conditions. As a result, vitamin E supplements are likely to increase immunity, increase resistance to COVID-19 infection and improve pregnancy outcomes[8].

**Iron (FE)**

Iron (Fe) is an important nutrient in many immunologic functions, such as the production and regulation of cytokines, differentiation and proliferation of T lymphocytes. It is a significant component of certain enzymes for immune cell function. The deficiency affects over 50 percent of all pregnant women in developed and developing countries. It can lead to anemia, RCIU, GAS, perinatal morbidity and mortality, induce maternal-neonatal stress and damage fetal erythrocytes. Furthermore, Fe deficiency can lead to long-term cognitive and behavioral problems in childhood. Iron supplementation in pregnancy resulted in a significantly higher mean birth weight and a lower incidence of LBW. Iron supplementation has the potential to increase immunity, reduce the risk and severity of COVID-19 infection, and prevent maternal and newborn morbidity and mortality.

Iron supplementation in pregnancy resulted in a significantly higher mean birth weight and a lower incidence of LBW. Fe supplementation can strengthen immunity, reduce the risk and severity of COVID-19 infection, and prevent maternal-neonatal morbidity and mortality. Iron supplementation in pregnancy resulted in a significantly higher mean birth weight and a lower incidence of LBW. Fe supplementation can effectively strengthen immunity, reduce the risk and severity of COVID-19 infection, and prevent maternal and neonatal morbidity and mortality[8].

## IV. CONCLUSION

The novel coronavirus disease (COVID-19) infected more than three million people globally. Pregnant women are more susceptible to respiratory viral infections than non-pregnant women due to physiological and immunological changes. COVID-19 infection may inhibit the immune system during pregnancy and place pregnant women at increased risk for complications. COVID-19 infection is associated with inflammation and may lead to undesirable perinatal outcomes.

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