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Immunology of Normal Pregnancy: Cellular Immune Response during Infections in Pregnancy

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Abstract

Cellular and molecular processes and pathways responsible for successful pregnancy development and maintenance are still mysterious and unknowable clearly. Poor development can cause defects in placentation and fetal outcome, so understanding molecular and cellular mechanisms leading to successful pregnancies can help in the development of a newer intervention to prevent pregnancy complications like preeclampsia, intrauterine growth restriction, pregnancy loss, and premature delivery. All through the pregnancy, the mother's immune system should actively adapt to the fetal antigens. The frequency of various immune cells in the maternal-fetal interface changes during pregnancy to maintain and support good pregnancy outcomes. How body responds to infections in pregnancy, immunological reasons of the severity of infections in pregnancy and fetal response to infections is discussed in this review along with the involvement and interactions of various immune cells in pregnancy like Nk cells, macrophages, dendritic cells, T cells, Th17 cells, T regulatory cells and B cells.

Keywords: Fetal antigens; Immune system; T cells; Semi-allogenic blastocyst; Decidualization; Macrophages

Introduction

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Pregnancy imparts a big immunological challenge to the maternal body. All through the pregnancy, the mother's immune system should actively adapt to the fetal antigens. So different innate immune cells adapt accordingly, for example, T regulatory cells increase in pregnancy, and effector T cells which are anti-fetal decrease [1]. There are three stages in pregnancy in general, early pregnancy stage,mid-pregnancy stage, and late pregnancy stage. Adhesion and implantation of the blastocyst into the endometrium occur in the early stages of pregnancy, which are essential stages of human pregnancy.

This period brings the most important change in the frequency of endometrial immune cells [2]. During the peri-implantation period, changes in the endometrium occur that further lead to decasualization. These changes are brought out by maternal hormones like progesterone and estrogen which regulate the expression of various cytokines, chemokines, and other endometrial immune cells [3]. This is the period when the mother's immune cells start recognizing fetal antigens so it has to develop immunologic tolerance for the establishment and maintenance of pregnancy. The maternal immune response plays a very important role in tolerating the semi-allogenic blastocyst.

Maternal immunity tolerates the fetus (semi-allogenic) for a long duration of 280 days i.e the gestation period. The innate and adaptive immune response system of the mother plays an incredible role to save the pregnancy throughout the gestation period.

Cellular and molecular processes and pathways responsible for successful decidualization, trophoblast invasion, placentation, and fetal growth are still mysterious and unknowable clearly. Poor decidualization can cause defects in placentation and fetal outcome, so understanding molecular and cellular mechanisms leading to successful pregnancies can help in the development of a newer intervention to prevent pregnancy complications like preeclampsia, intrauterine growth restriction, pregnancy loss, and premature delivery [1].

Literature Review

Important immune Cells playing a role in the establishment and maintenance of pregnancy

The frequency of various immune cells in the maternal-fetal interface changes during pregnancy to maintain and support good pregnancy outcomes. It makes the fetus development in the mother's body even though it gets recognized by the immune cells of the mother. The uterine endometrial stromal cells get transformed into larger decidual cells leading to decidualization. Secretory glandules develop in glandular cells [4] and they start producing many secretory products and cytokines [5]. Ovariansteroid hormones control the expression of various chemokines, growth factors, cytokines in the endometrium [3].

Natural killer cells

Natural killer cells, antigen-presenting cells such as macrophages and dendritic cells, effector CD4+ T cells, Foxp3+ regulatory T cells, CD8+ T cells, and CD4+ HLA- G+T cells are all essential immune cells that function in pregnancy to develop immunotolerance in the mother's body against the semi-allogenic fetus [6]. Many recent studies have discussed the function of uterine NK cells in the acquisition of immunotolerance in mothers during pregnancy [7-11].

Tim-3+dNK cells (about 60% decidual NK cells) expressing T-cell immunoglobulin domain and mucin domain-containing molecule-3 serve as an immune-tolerant subset. If Tim-3 expression in dNK cells falls, it would lead to human pregnancy failures so Tim-3+ dNK cells play a significant role in the maintenance of normal pregnancies [7]. Nk cells are also involved in decidual spiral artery remodelling, i.e. a key step in raising blood flow to the placenta and growing fetus. Nk cells modify the decidual vasculature through various interactions with other cells and by secreting various factors [8-10,12]. Changed number of Nk cells have been associated with reduced angiogenesis, decreased trophoblast invasion and defective vascular growth in pregnancy pathogenesis [11].

Macrophages

Macrophages have an important role in maintaining pregnancy. 20%-30% of all white blood cells of decidua in human pregnancy are macrophages [13]. The decidual macrophages take part in many important processes that occur at the maternal-fetal interface like immunomodulation of decidual lymphocytes, immunotolerance, vesicular remodeling and in commencing the parturition [14-16]. During different stages of pregnancy, macrophages keep polarizing either toward M1(classically activated macrophages) or M2 (alternatively activated macrophages) phenotype [17,18].

Microenvironment signals lead macrophages to express different functions, it is described as macrophage polarization [19]. M1 macrophages secrete Th1 type cytokines to express inflammatory responses [20] and M2 macrophages show immunosuppressive nature by promoting Th2 type response [21]. M1 macrophages are more in action during the peri-implantation period, but after implantation and during the invasion of a fetus in the uterine stroma and vascular remodeling in the first trimester, as well as the beginning of the second trimester, a mixed macrophage profile acts i.e both M1 and M2 [22,23].

To avoid the rejection of the fetus after placentation till parturition, M2 macrophages come into action. Tim-3 expressing M2 macrophages take part in maintaining immunotolerance also at maternal-fetal interface [24]. Human chorionic villi contain a special type of mature macrophages known as Hofbauer cells. These cells also maintain immunoregulation in pregnancy [25,26]. They are involved in angiogenesis in the placenta, inflammatory response, and extracellular remodeling [27-29] For the adjustment of growing new fetus in the uterus, decidual macrophages play role in the damaged cells apoptosis also [30]. They eliminate the apoptotic cells and phagocytose pathogens to save the adjacent cells from an inflammatory immune response [23,27]. So they are a major line of defense to save the growing fetus from pathogens [30].

Dendritic cells

Dendritic cells are important participants in adaptive immune responses. They are involved in recognizing and processing the antigen and presenting antigens to T cells. Dendritic cell precursors, in the beginning, grow into immature dendritic cells. They show very low MHC I and MHC II expression and therefore are unable to activate T cells.

Immature dendritic cells uptake antigen in lymph nodes and undergo maturation. The MHC-peptide complex is transported to the cell surface by mature dendritic cells. These mature dendritic cells also express co-stimulatory molecules like CD40, CD80, which lead to specific T cell activation [31]. Dendritic cells play the main role in primary immune response and immunological tolerance. Depletion of CD11c+ decidual dendritic cells in mice delayed decidualization, which increased fetal resorption [32,33].

During the third trimester of pregnancy, peripheral myeloid dendritic cells become partially inactive and very tolerogenic [34]. These cells are involved in maintaining fetal tolerance in the mother's body. Some dendritic cells, such as dendritic cell-specific ICAM-grabbing nonintegrin cells, have also been shown to stimulate regulatory T cells during pregnancy, implying that they aid in maintaining maternal tolerance to fetal antigens [35].

T cells

T cells are also important players in pregnancy success. Out of all CD4+ T cells of decidua basalis, ~50% shows CD25 dim and about 5% shows CD25 bright FOXP3+Tregulatory cells which have immunosuppressive effects. Out of CD8+ T cells ~40% express CD28− marker [36-39]. Raised levels of CD8+ T cells which were virus-specific were observed in the decidua, which indicate that the placenta has an increase in memory T cells, which may protect the fetus from infections [40]. Out of all CD4+ cells of decidua ~5%-30% were Th1 and ~5% were Th2 [36,39]. Th1 cells are effective against intracellular pathogens. Th1 cells secrete inflammatory cytokines mainly like IFNγ and TNF-α. They promote inflammation. Hence Th1 cells are mainly responsible for pregnancy pathologies and create problems for fetal survival. Th2 cells primarily produce interleukin-4, interleukin-5, and interleukin-10 (IL-4, IL-5 and IL-10). During pregnancy, Th2 cells help to reduce the synthesis of Th1 cells. In pregnancy, a higher proportion of Th1 cells and a lower proportion of Th2 cells can lead to abortions and other pregnancy complications [41,42]. We can not see pregnancy only as TH1/TH2 model, that Th1 type cytokines create complications in pregnancy and Th2 type cytokines makes the pregnancy successful. In fact, IFN γ is very important for spiral artery remodeling. Th 1 type cytokines also have a positive effect on pregnancy depending on their time of expression. These two cytokines have stage-dependent functions [43].

Th17 cells

Th17 cells secrete IL-17 pro-inflammatory cytokines [44]. Raised levels of Th17 cells have also been associated with pre-eclampsia in pregnancy [45]. Th17 cells take part in cell-mediated adaptive immunity. These cells are associated with pathology in inflammatory diseases and also in clearing extracellular infections [46].

T regulatory cells

In mice and humans, Treg cells mediate tolerance to both self-and foreign-antigens [47]. Treg cells increase in pregnancy [45]. The fetal alloantigen leads to the expansion of Treg cells in pregnancy [48]. Helios+T-regulatory cells are natural T-regulatory cells, while Helios- T-regulatory cells are induced T-regulatory cells. Around 90% of the Tregs in the decidua are Helios+ which are much higher than the peripheral blood. This shows that the main population in decidua is of Natural Treg cells [39]. Tregs play a protective role in sustaining fetal tolerance. During pregnancy, there is induction of fetal antigen-specific Treg response which develops tolerance in the maternal body against fetal antigens. T reg cells express the foxp3 transcription factor which has a critical role in controlling the inflammatory process [49].

Infections in pregnancy: How the body responds to them

Pregnant women encounter more severe effects of infections as compared to non-pregnant women. Infections such as hepatitis E, influenza, malaria parasites and herpes simplex virus (HSV) cause more serious infections during pregnancy. Pregnant mothers, for example, are at an increased risk of serious infection from the influenza virus infection. Influenza infection in pregnancy brings changes in the cardiopulmonary system, and it increases the risk of hypoxemia and increases severity.

Even in HEV infection, severity increases in pregnancy with high mortality and can even cause fetal loss. HEV infection in pregnancy leads to fulminant hepatic failure, acute viral hepatitis and deaths also during pregnancy. Primary HSV infection during pregnancy can create a high risk of dissemination and hepatitis. Coccidiomycosis during pregnancy is also a high-risk factor for severe disease. The severity of vericella also increases in pregnancy. Listeria infection generally remains asymptomatic but a rare severe infection can occur during pregnancy, but it does not lead to maternal deaths. It may result in a miscarriage, stillbirths, premature births, or a severe neonatal disease. Each of these infections is the most severe during the third trimester of pregnancy [50].

Immunological reasons of the severity of infections during pregnancy

During pregnancy, immunological changes contribute to changes in infection seriousness and susceptibility [50]. There is a dramatic increase in hormone levels in pregnancy which interacts with the immune system and brings many changes in the immune responses which makes women more susceptible to infections in pregnancy [51]. The levels of both estradiol and progesterone increase in pregnancy. In the progesterone presence, lymphocytes of pregnant women release an immunomodulatory protein called progesterone-induced blocking factor (PIBF). This protein influences the Th1/Th2 balance and brings modifications in cytokine ratios which decrease cell mediated immune response in pregnancy [52].

Estrogens also have immunomodulatory roles. Estrogens, such as estriol and estradiol, glucocorticoids and progesterone, rise during pregnancy, altering the transcriptional signal of the inflammatory immune response at the maternal-fetal interface as well as systemically. It decreases the function of NK cells, Th1 cells, the release of inflammatory cytokines whereas Treg cell activity and anti-inflammatory activity increase. All these affect the pathogenesis of the disease.

The diseases which are caused by inflammatory responses, like auto-immune diseases, arthritis, multiple sclerosis have shown reduced severity during pregnancy. But diseases such as influenza and malaria that are protected by inflammatory response get severe during pregnancy. For such infections, an increased level of inflammatory responses that are required to clear the pathogen becomes harmful for the pregnancy outcome [51]. The correlations between hormones and the immune system help women have a healthy pregnancy, but they also make them more vulnerable to infections. Earlier researchers used to think that pregnancy is a state of general immunosuppression for creating an environment of tolerance against the fetus [53].

Later it was seen that there is a generation of fetus-specific cytotoxic T cell response in pregnancy causing no fetal loss and in many studies, it has been proved that pregnant women generate sufficient immune response to vaccination also and to viral infections also. So the theory of shift from Th1 to Th2 immune response in pregnancy comes into play [50,54]. Th2 cytokines activate B cells which lead to antibody production and decrease cell-mediated immunity.

Therefore, it explains the increased severity of infections by intracellular pathogens such as influenza and malaria which require a cell-mediated immune response. In later stages of pregnancy, adaptive immunity declines, resulting in a rise in the incidence of infections whereas increased innate immunity during pregnancy tends to reduce infection susceptibility [50].

Fetus response to infections during pregnancy: Different or similar to maternal response?

Depending on the pathogen, infections during pregnancy can result in fetal death, organ damage and impaired placental development and function. The most common teratogenic pathogens are known as "TORCH" pathogens (*Toxoplasma gondii*, Others like *Treponema pallidum*, *Rubella virus*, *Cytomegalovirus*, *Herpes simplex virus*). There are many other pathogens like *Varicella zoster virus*, Parvovirus B19 and *Plasmodium falciparum* which influence fetal growth. The fetal infection leads to a systemic inflammatory cascade in the fetus. In the fetal lung and brain, this induces cytokine damage as well as oxidative stress. It may persist postnatal also.

To stop placental and fetal development, some pathogens use oxidative stress and apoptosis. In utero infection of the fetus influences the infant's health later after birth and affects long-term health. Viral infection in pregnancy can affect the fetus as it can raise the chances of diabetes (Type-I) in childhood [55]. Infants born to women with severe chorioamnionitis have raised levels of umbilical serum pro-inflammatory cytokines like TNF-α, IL-8, IL-6 and IL-1β [55,56]. Two models of progression of lung injury and brain injury of a fetus by infections have been given in a study. According to both of these models, inflammatory mediators like IL-6 and IL-8 produced by decidua and other membranes due to bacterial infection lead to both lung injury and brain injury. Infection-related fetal complications such as preterm births and others are caused by pro-inflammatory cytokines and chemokines [57] (Table 1).

Parasite	Viruses	Bacteria
Toxoplosmosis gondii	*Cytomegalovirus*	Gram Positive: Gram B *streptococcus*, *Listeria monocytogenes*
Tryponosomo cruzi	*Parvovirus 819*	
Malaria species	Rubella	Rubella: Gardnerella vagina/is, *Esherichio coli*, *Chlamydia trachomatis*
	Herpes simplex	Fastidious: *Leptotrichia amniomi*
	Voricello zoster	Spirochete: *Treponema pallidum*
	Coxsackie B virus	Mycoplasmataceae: *Ureaplasmo urealyticum*
	Mumps	

Table 1: Pathogens affecting fetal growth [55].

Conclusion

The mechanisms which lead to complications in fetal health should be studied widely and in detail because it can help the researchers to develop therapies to lessen or avoid fetal development changes, preterm birth and promote fetal survival.

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