Immunology changes in pregnancy

Immunology of Pregnancy (In human context)

ABSTRACT:

Nowadays there are cases of infertility, preeclampsia and recurrent abortions. For treating these problems it is important to gain knowledge of complex mechanism underlying pregnancy. These mechanisms are studied in the field of reproductive immunology. Immunology of pregnancy is not fully understood due to its complexity, yet a very interesting topic to study. Foetus acts like a semi-allograft, which in spite of being 50% genetically non identical to mother grows successfully for nine months in the uterus. Placenta, which is a feato-maternal organ, acts like a first line of defense in protecting foetus from maternal immune system. Many factors are involved in creating a receptive state of uterus. Factors present in seminal fluid helps in creating pro-inflammatory environment in uterus, which is ideal for implantation. This pro-inflammatory environment is resolved soon after implantation. Decidualization of endometrial stromal cells is also an important factor for implantation. Soon after implantation an anti-inflammatory environment is created, which helps the foetus in evading maternal immune responses. Anti-inflammatory environment is created at foeto-maternal interface due to secretion of anti- inflammatory cytokines. Cases of preeclampsia and recurrent abortions occur if maternal immune system fails to create anti-inflammatory environment at foeto-maternal interface. Pregnancy is thought be an immunosuppressed state due to presence natural immunosuppressant progesterone, cytokine shift that occurs during pregnancy as well as involvement of regulatory T cells in inducing tolerance against foetal antigens. In addition dendritic cells and NK

cells are also involved in inducing tolerance to the semi-allogenic graft. During parturition, anti-inflammatory environment is converted into pro-inflammatory environment due to shift of cytokine subset and drop in progesterone level. Pro-inflammatory environment is suitable for delivery of the foetus.

Pregnant women are more susceptible to some types of infections like Malaria, influenza and toxoplasmosis. Treating these infections in pregnant women is a challenge. Antibiotics selected for treating pregnant women should not cause any abnormalities in foetus. Most-probably antibiotics used are of Type B, as they are not known to cause any abnormalities in developing foetus.

INTRODUCTION

Maternal and foetal immune interaction is a complex and still very interesting topic to study. In case of a pregnant woman foetus represents a ‘ semiallogenic conceptus’ which manages to evade rejection. [1] The study of Immunology of pregnancy is done in the field Reproductive Immunology. [2] The cases of recurrent abortions, haemolytic disease of newborn and preeclampsia (abnormal immune response towards placenta) still puzzle us with the question ‘ why did this rejection happen?’ There are many cases of successful pregnancies, so in this case ‘ why didn’t the rejection happen? ’[3] In this review we will try to understand the complex immune mechanisms involved in pregnancy which helps the foetus to evade the maternal immune system.

We can divide the nine months gestational period into three trimesters in order to understand the immunology of pregnancy. In the first trimester when implantation and placentation occurs female body is trying to adapt to the foetus. [4] When implantation occurs embryo invades endometrial lining. [5] Pregnant women experiences morning sickness during hormonal changes and other changes taking place in female body in order to adapt to the foetus. [3, 4] The second trimester of pregnancy is anti-inflammatory stage. In this stage female does not suffer through morning sickness. [3] In this stage foetus develops rapidly. Now in the last stage of pregnancy, foetus is fully developed female needs to deliver it. [3, 4] Parturation helps in influx of immune cells in the myometrium to promote rejection of placenta. We can say that pregnancy comprises of anti-inflammatory as well as pro-inflammatory stage depending on the stage. [4]

The overall maternal immune system is modulated during pregnancy in order to protect the foetus from maternal immune system as well as preventing developing foetus from all types of infections. [5] The organ that helps in creating an immunologically previllaged site is Placenta. [6] Placenta is a foeto-maternal organ. It has two components maternal component (Decidua Basalis) develops from maternal endometrial cells which are decidualized (after fertilization endometrial lining gets transformed for facilitating implantation of an embryo) and foetal component (Chorion Frondosum) which develops from the blastocyst. [7] Other than placenta there are certain other factors which help in protection of foetus from maternal immune system those factors involve 1. Suppression of maternal

immune system during pregnancy due to production of immunosuppressive molecules such as complement inhibitors, progesterone and matrix metalloproteinases by placenta 2. Cytokine Shift 3. Suppressed expression of MHC-I molecules on placental trophoblast cells 3. Expression of atypical HLA-E and HLA-G molecules on placental trophoblast cells. 4. Th1/ Th2 balance 5. [7]

ARE PREGNANT WOMEN MORE SUSEPTIBLE TO INFECTIONS?

Immune system changes during pregnancy are still not well understood, but immunosuppression is believed to occur. [1, 3, 8] Maximum immunosuppression occurs at foetal-maternal interface, but this need not create an immunodeficient state for a pregnant woman. Although pregnant women are not immunodeficient, studies indicate that they are more susceptible to various infections like Influenza and vicerella. [3, 8] They are more susceptible to *Plasmodium faliciparum* which is one of the four parasitic protozoans known to cause Malaria. They are also known to be more susceptible to toxoplasmosis which is caused by Toxoplasma gonadii and Listeriosis. [3, 9]

For treating infections during pregnancy only some antibiotics can be used. These antibiotics include Penicillin, Amoxycliin , Clindamycin, Erythromycin and Ampicillin. [9] These antibiotics are known to be safe during pregnancy and are not involved in causing birth defects. [9, 10]

DECIDUALIZATION OF ENDOMETRIAL CELLS:

Decidualization is a process in which endometrial stromal cells get differentiated into decidual cells. [1, 11] These decidualized cells are now called decidua ready for implantation. This process plays very important role in uterine receptivity. Differentiation occurs due to increased level of progesterone. [12] Changes in endometrial lining include proliferation of eosinophills around arterioles, increase in glandular epithelial secretion, increase number of Glucose transporters (GLUT1), increase in stromal vascularity. Failure of above changes into endometrial lining leads to infertility. [11, 12]

ROLE OF SEMEN IN PREPARING FEMALE REPRODUCTIVE TRACT FOR IMPLANTATION:

It was not known earlier that cytokines present in semen are also involved in preparing female reproductive tract for implantation. After ejaculation, when seminal plasma cytokines interact with estrogen primed endometrial cells, it is known to trigger synthesis of pro-inflammatory cytokines. [13] These cytokines includes Granulocyte-monocyte colony stimulating factor (GM-CSF), IL-6, Monocyte chemotactic protein (MCP) , Macrophage inflammatory protein -1alpha(MIP-1alpha) and MIP-1beta. {1, 13] These pro-inflammatory cytokines facilitates infiltration of large number of immune cells, which includes macrophages, granulocytes, dendritic cells and regulatory cells. This inflammatory response is transient and it resolves by the time of implantation. [14]

Lymphocytes activated right after insemination in female reproductive tract helps in mediating immune tolerance against paternal antigens. This is due to immunological priming of paternal antigens in presence of immune regulatory cells. [1, 13]

FOETO-MATERNAL INTERFACE:

Placenta acts as an immunological barrier between mother and foetus. Placental trophoblast cells forms syncytium (without any extracellular spaces) which helps in preventing transfer of molecules between mother and foetus. [6] Formation of syncytium is known to occur by the help of a viral fusion protein, which is secreted by ‘ Endosymbiotic endogenous reterovirus’. Placental cells do allow transport of IgG antibodies across placenta. [7] Transpalcental transport of IgG1 and IgG4 was found to be more significant than the transport of IgG3 and IgG4 subclasses. [15] These antibodies do not target foetus, instead helps in preventing foetus from infectious diseases. [1] Some foetal blood cells manage to enter the circulatory system of mother. In this case antibodies produced against these cells are of IgM type, which cannot cross placenta, however sometimes IgG antibodies are produced against foetal blood group antigens. These antibodies can cross placenta and can cause haemolytic disease in newborns. [7, 15]

Placental trophoblast cells don’t express MHC-I isotypes HLA-A and HLA-B. [16] This helps in preventing destruction by maternal cytotoxic T lymphocytes. These cells also show expression of atypical atypical HLA-G

and HLA-E antigens, which helps in preventing destruction of foetal cells by Natural Killer cells. [4] Placenta shows normal expression of HLA-C antigens. There are evidences that some of the uterine cells are capable of supressing maternal lymphocytes. These cells include small lymphocytic suppressor cells. [1, 7]

TOLERANCE TO SEMI-ALLOGENIC CONCEPTUS:

There are many ways in which maternal immune system develops tolerance against semi-allogenic conceptus, which is essential for successful pregnancy. Following are the factors involved in inducing tolerance against foetal antiges.

Cytokine shift during pregnancy:

We all know that the high level of progesterone is secreted by corpus luteum during pregnancy Increased level of progesterone induce expression of ‘ progesterone induced binding factor’ on lymphocytes. [1, 3] Progesterone induced binding factor present on lymphocytes helps in promoting differentiation of CD4 cells into Th2 subtype. Th2 subtype secretes a group of anti-inflammatory cytokines, which includes IL-10 and IL-4. [1] The concentration of anti-inflammatory cytokines is increased during pregnancy and drops some days before delivery. [6] On the other hand, concentration of IL-2 and INF-gamma is decreased during pregnancy. [1] Increased level of inflammatory cytokines results into preeclampsia. Patients suffering through recurrent abortions are found to express low levels of anti-inflammatory cytokines and high levels of inflammatory cytokines. [1, 3]

Role of regulatory T cells:

T regulatory cells have regulatory or suppressive properties for maintaining antigen specific tolerance. In humans, regulatory T cells are involved in inducing tolerance against self-antigens, which evades negative selection by thymus. [17] T regulatory expresses IL-2 receptor, CD25 and CD95. [16] As they cells expresses IL-2 receptor on its surface, IL-2 promotes its differentiation from naïve CD4 precursor to T regulatory cells. T regulatory cells induce tolerance against foetal antigens. [1, 3, 7] These cells inhibit inflammatory cytokine production and proliferation of both CD4 as well as CD8 cell, which further helps in suppression of B cell proliferation and also inhibits NK cells. [1, 17] They also help in preventing maturation and function of antigen presenting dendritic cells and macrophages. [1, 5]

All these actions of T regulatory cells help in overall suppression of immune response against foetus. [1, 3, 5, 17]

Role of dendritic cells:

Role of dendritic cells in inducing immune tolerance is unclear [1] . Studies suggest that decidua shows presence of dendritic cells. [1, 3] The fate of development of dendritic cells is determined by intradecidual environment and cellular interactions. High levels of IL-10 and TGF-beta are secreted by decidua. [18] This microenvironment promotes development of dendritic cells towards a semi-mature state, which is known to induce tolerace against foetal antigens. IL-10 inhibits maturation of dendritic cells by inhibiting

induction of costimulatory molecules (CD86 and CD83) present on the surface of dendritic cells. [1, 3, 18]

Natural killer cells and pregnancy:

INF-gamma secreted by decidual natural killer subset CD56 CD27 inhibits local inflammatory response, which helps in successful pregnancy. [19] Decidual natural killer cells are also kown to produce chemokines and Interleukin-8, which regulates trophoblast invasion by embryo. Potent arrary of angiogenic factors secreted by NK cells promotes vascularization of decidua. [5, 19]

PARTURATION:

Once the foetus is fully matured and ready to be delivered, the amount of pro-inflammatory cytokines increases. [20] Due to increased level of pro-inflammatory cytokines leukocytes infiltrate the myometrium and cervix. [1] Proteolytic enzymes secreted by lymphocytes helps in matrix remodelling during cervical ripening. Extracellular matrix is rich in proteoglycans and collagen fibres [3] . Proteolytic enzymes help in weakening the matrix. Synthesis of Hyaluronan is increased, which is a space filling glucosaminoglycan. [19] It helps in increasing viscoelasiticity , loss of tissue integrity upon contraction. Monocytes and eosinophills are increased in the cervix, while the number of macrophages remains the same. [21, 22] Number of neutrophils increases after child birth, this suggests their role in repair. At this stage progesterone metabolism fastens and prostaglandins are

increased which helps in parturition. [1] Release of oxytocin helps in contraction of uterine muscles, thereby facilitating child birth. [22

CONCLUSION:

Knowledge of immunological changes taking place during pregnancy is controversial and not-well understood. Pregnancy is supposed to be a immunosuppressive state. Immunosuppression is natural way adopted by women's body for adapting the 50% genetically non–identical foetus and for successful delivery. [1, 3] Placenta acts like a barrier as well as connecting link between the foetus and mother. Placental trophoblast is a site where maximum changes take place. [7] These changes include secretion of anti-inflammatory cytokines (IL-4andIL10), influx of natural killer cells and dendritic cells, which helps in developing tolerance against foetal antigens. [11] T regulatory cells play a key role in developing resistance to foetal antigens. Presence of IL-2 promotes differentiation of CD4 subset to T , regulatory cells. Plancetal trophoblast cells forms syncytium, which helps in preventing transport of antigens from foetus to mother and visa-versa [6] . Placenta allows transport only IgG class of immunoglobulin to pass across. [9] These antibodies help in protecting foetus against various infections. Sometimes IgG antibodies are produced against foetal blood group antiges, which may lead to haemolytic disease in newborns. [7]

If we divide pregnancy in three trimesters, at the beginning of first trimester pro-inflammatory environment is created to facilitate implantation. This proinflammatory environment is followed by an anti-inflammatory

environment soon after implantation. [7] Just before parturition this anti-inflammatory environment is converted into pro-inflammatory due to shift in cytokine subset. Pro-inflammatory environment helps in rejection of placenta hence childbirth. [21]