REVIEW ARTICLE

# Emerging Role of Uterine Natural Killer Cells in Establishing Pregnancy

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## Abstract

Normal pregnancy has been considered as a controlled state of inflammation at an early stage of blastocyst implantation that subsequently develops systemically. Till recent past most popular hypotheses regarding status of immune system in pregnancy were dominated by the $Th_1$ and $Th_2$ hypothesis, in which the fetus avoids maternal rejection through a bias towards T-helper ($Th_2$) cytokine production. Recent findings have shown that predominant immune interactions in the human deciduas are between the placental trophoblast and maternal uterine natural killer (uNK) cells rather than the T cells. Thus NK cells are emerging as important players in the uterine immune response to invasive forms of placenta, as in cases of hemochorial placenta. In humans there is a lack of evidence for T-cell responses to trophoblast cells; therefore it was thought that uterine NK cells are the key factors by which the maternal immune system recognizes trophoblast cells. In this review we are trying to summarize the role of uNK cells in the maintenance of normal pregnancy in humans.

**Keywords: NK cells, Pregnancy, Trophoblasts, Decidua, Implantation**

## INTRODUCTION

Immunologically, human fetus has always been considered as an allograft to the pregnant mother and thus traditionally the study of the immunology of the pregnancy follows the classical transplantation model for pregnant women. Physiologically, pregnancy is a condition characterized by the persistent local tolerance of the maternal immune system to the paternal HLA antigens expressed by the fetus (1). This induction of maternal local tolerance to the fetus during pregnancy has provoked the reproductive immunologists to find out the causes of persistent local tolerance of the maternal immune system to the fetus.

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In 1993, it was initially proposed by the late Tom Wegmann that fetal survival during pregnancy depends on a bias of maternal immune response towards T-helper (Th2) immunity and inhibition of the cytotoxic Th1 T-cell responses (2). This bias has been demonstrated in mouse models of pregnancy and was just applied to human pregnancy and was not proven (3). On the basis of data available till recent times, the T-cell mediated rejection of the pregnancy has been demonstrated only in mice and not in humans (4).
These studies in recent years compelled reproductive immunologists to pay more attention to the role of innate immune cells, the natural killer (NK) cells in the understanding of the normal pregnancies, recurrent miscarriages, intrauterine fetal growth retardation, and pre-eclampsia (5) (Figure 1). In contrast to non-pregnant uterus which is almost devoid of NK cells before ovulation, researchers have observed a striking abundance of these cells in the pregnant womb (6).

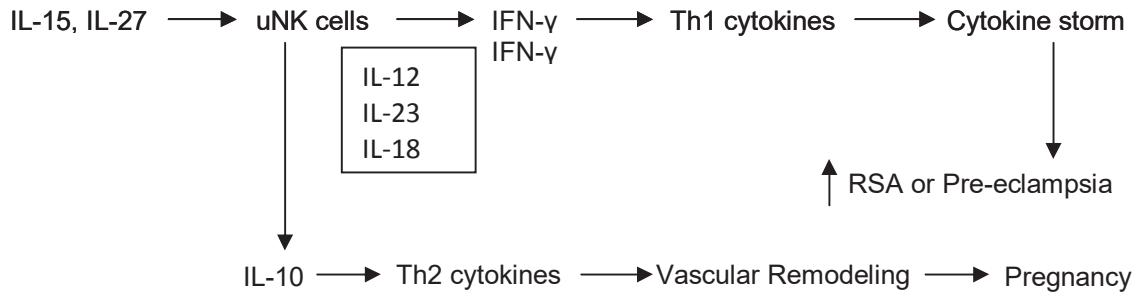


**Fig 1.** Role of uNK cells in human pregnancy

## MATERNAL–FETAL IMMUNE (NK CELLS) RELATIONSHIP

Human pregnancy takes place in a highly specialized organ, the uterus, where the implant is protected by the mucosal lining of the uterus or deciduas, thus human pregnancy is considered a unique immune challenge. Besides this uterine environment, the pregnancy outcome also depends on hormonal status of the gravid female and also the various cytokine levels which directly or indirectly regulate the maternal uterine immune system in the presence or absence of pregnancy. The placental as well as the fetal cells penetrate into the maternal blood. Thus a direct contact between maternal uterine tissues and the placenta forms the background for understanding the immunological basis of human pregnancy. Immunological interaction of mother and the fetus occurs directly through the decidua and the blood (7).
A peculiar feature of the decidua at the level of immune mediated reactions is influx of the distinctive type of the maternal NK cells called uterine NK cells (uNK) (8, 9). The increased innate immune cells infiltrating the decidua at the time of blastocyst implantation are mostly NK cells and $CD56^{+}$ $CD16^{-}$ NK cells. They comprise the majority of the NK cells (>40%) that reside in the decidua during implantation (10-13). In peripheral blood this subset of NK cells comprises only 5-10% of the total NK cells and the peripheral NK cells (pNK) have usually lower cytotoxic activity but greater ability to secrete cytokines (14,15).
NK cells as a whole comprise about 10-15% of the peripheral lymphocytes present in the circulation (16). The two subsets of peripheral blood NK cells, $CD16^{high}CD56^{dim}$ and $CD16^{dim}CD56^{high}$ have been described in healthy individuals (17). CD16 is a low

affinity receptor for IgG complexes (FcRIII) expressed on the majority of NK cells and on other immune cells i.e. neutrophils, a small T-cell population, and some activated macrophages (17). CD16 acts as a receptor for NK-cell mediated antibody dependent cellular cytotoxicity, where CD56 is an isoform of the neural cell adhesion molecule (NCAM) which is expressed essentially on all kinds of NK cells, on cytotoxic T cells and some neural derived tissues (18).

About 90% of pNK cells are $CD16^{high}CD56^{dim}$ which express high levels of CD16 and are highly cytolytic type whereas other 10% of the peripheral blood NK cells are $CD56^{high}CD16^{dim}$ type and produce high levels of immunoregulatory cytokines (14).

NK cells are almost absent during the pre-ovulatory phase of the endometrium of the non-pregnant women, and become highly proliferative following ovulation. They constitute about 70% of the lymphocytes in the decidua or the transformed pregnant endometrium (19,20). Decidualization takes place in the endometrium of pregnant women under the influence of hormonal control, providing an environment receptive to embryo implantation (21).

**Hormonal Regulation of Peripheral and Uterine NK Cells (uNK cells).** Many studies have shown that there is no significant change in the number of peripheral blood NK cells between the follicular and the luteal phase of the menstrual cycle in the women (22,23). Various studies investigating the changes in the activity of pNK cells during menstruation indicate similar evidence and show that there is no change in pNK cell activity or a decrease in NK cell lytic activity especially in the luteal phase of the menstrual cycle (23). However, these studies on NK cells were unrelated to plasma progesterone levels of normal and pregnant women (24).

As the $CD16^{+}$ NK cells decrease during normal human pregnancy, pNK cells also diminish (25,26). Besides their role in pregnancy, the pNK cells from the pregnant women also develop decreased lytic activity compared to NK cells from the normal non-pregnant women (27). Borzychowski et al have shown that the type 2 shift occurs as a means of establishing pregnancy and this shift is mainly dominated by NK cells ($CD56^{high}$and $CD16^{dim}$) and NKT cell population ($CD56^{+}$-$CD3^{+}$) instead of helper T cells or cytotoxic T cell population (28). This shift towards type 1 immune response in terms of NK-cell and NK-T cell population has been observed in recurrent pregnancy loss and also in such conditions as pre-eclampsia (29).

This is further supported by Borzychowski's data which showed the marked increase in circulating $CD56^{high}$ NK cells of type two shift as early as 12 weeks of gestation, whereas changes in T cells do not occur upto the 3rd trimester of pregnancy. Thus NK cells are a kind of immune cells that play important roles during early periods of pregnancy in humans.

These changes in pNK cell number, phenotype and activity during pregnancy suggest that NK cells are hormonally regulated by estrogen, progesterone and prolactin (Figure 2).

Like pNK cells, several changes also occur in uNK cells during the normal menstrual cycle and human pregnancy (Figure 2) (17). There is a significant increase in the number of uNK cells throughout the secretory phase of the menstruation and their number reaches a peak in early pregnancy when uNK cells comprise about 75% of the uterine leukocytes (30) and also uNK cell phenotype changes during the normal menstrual cycle and early pregnancy. That is why uNK cells appear differently from pNK cells (31). Also during the proliferative phase of the menstrual cycle, the activation antigen CD69, HLA-DR and leukocyte function associated antigen 1 molecules i.e. CD11a and CD18 are highly expressed on the uNK cells but decrease immediately during menstrual bleeding (31). Expression of activation antigens CD69 and HLA-DR as well as CD11a and CD18

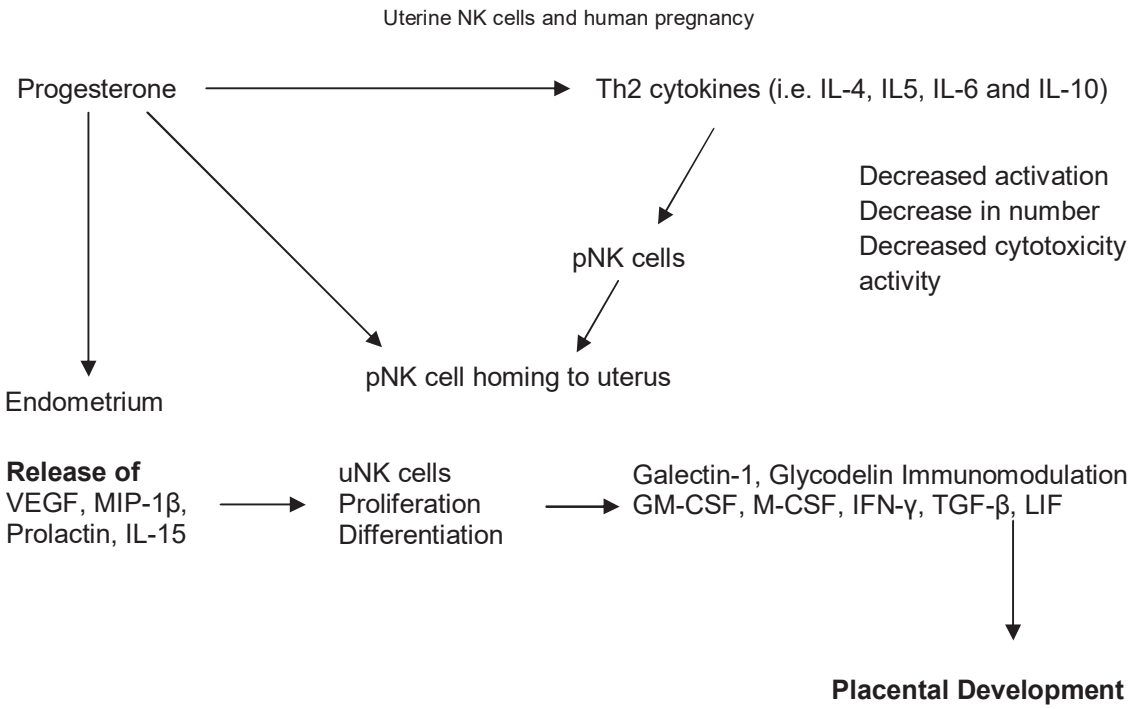


**Fig 2.** Hormonal regulation of NK cells during human pregnancy

maximizes in the proliferative phase and decreases gradually during the menstrual cycle (31). This indicates that the increased NK cell activity is involved in the preparation of uterus for the adaptation of the embryo. Similarly in pregnancy there is a decrease in the expression of many markers of activation like CD69, HLA-DR as well as LFA-1 and CD45RA by uNK cells. These are used as markers of active NK cells (27). Besides these changes, almost all uNK cells have been found to express one or more inhibitory receptors of KIR family in early pregnancy (32).

**Steroid Hormone Receptor Expression on uNK Cells and uNK Cell Recruitment.** uNK cells express not only female steroid hormone receptor, estrogen receptor α (ER α), but also the wild type ER β, its variant form, ER $\beta_{CX}$ / $\beta_2$ and glucocorticoid receptor(GR). ER α expression increases in the proliferative phase of menstrual cycle and decreases in the late secretary phase and in decidual samples when uNK cells are most abundant (33).

In addition to other direct effects of the female sex hormones on immune system, they also affect uNK cells by regulating gene expression of the immunomodulatory proteins by uNK cells (17) such as glycodelin gene expression which is selectively expressed by the human decidual NK cells (dNK cells) and not by the peripheral $CD56^+$ NK cells (29). Glycodelin is known to be a secretory product of endometrial glands (34). Thus increased glycodelin production by uNK cells due to immunomodulatory effects of progesterone in the luteal phase of the cycle and in early pregnancy, provides another way of local immunosuppression at the maternal – fetal interface during pregnancy.

As described above, female sex hormones appear to regulate the number of uNK cells. The mechanism of this increase in the number of uNK cells involves the following: (1) recruitment of pNK cells to the uterus (35), and (2) proliferation of existing uNK cells.

Studies in human females during menstruation and pregnancy provided evidence that macrophage inflammatory protein-1 β (MIP-1β) and VEGF have a potential role in the process of the uterine recruitment of pNK cells (17). MIP-1β has strong chemotactic

properties for peripheral blood NK cells and progesterone upregulates the production of MIP- 1β in human endometrium (36).

The expression of MIP-1β in human endometrium in the secretory phase increases, and besides other features, there is a strong correlation between the level of MIP-1β in the decidua and the number of uNK cells (36). The MIP-1β specific receptor CCR5 is strongly expressed by uNK cells, suggesting a functional role for MIP-1β as a chemoattractant for $CD56^{high}$ NK cells to the uterus (37). Progesterone also has a stimulatory effect on VEGF and VEGF receptor expression by human endometrial cells (38,39). It may stimulate angiogenesis and increase the tissue permeability of the secretory endometrium, facilitating peripheral blood NK cell homing. Due to direct effect of progesterone, endometrial stromal cells can also enhance proliferation and maturation of the existing uNK cell population through production of IL-15 and prolactin (17). Also, human uNK cells express IL-15R, thereby having tendency to proliferate and augment their cytolytic activity against K562 in the presence of IL-15 (40). As IL-2 is normally absent from the decidual environment, it is likely that IL-15 plays the role of IL-2 and acts as the major cytokine helping uNK cell proliferation *in vivo*. It is therefore suggested that IL-15 may play the role of IL-2 in increasing uNK cell number in the luteal phase of the menstruation and in early pregnancy endometrium by stimulating uNK cell proliferation (17).

Prolactin is another female sex hormone and is also produced by endometrial stromal cells during mid-secretory phase of menstruation and during pregnancy. Prolactin synthesis increases significantly and reaches its maximum level at about 20-25 weeks of gestation (41). The exact mechanism of action of prolactin on uNK cells remains to be elucidated, although it may regulate NK cell proliferation or maturation (42).

**Uterine NK cells (uNK cells) and Placental Interaction.** There are two major sites where placental trophoblast cells encounter the maternal immune system in humans: 1) the interaction between villous trophoblast cells and the maternal blood and 2) the interaction between extravillous trophoblast cells and the uterine tissues. In humans, the syncytiotrophoblast forming the area of interaction overlying the chorionic villi is in direct contact with maternal blood coming through maternal arteries into the intervillous space (43), thus syncytiotrophoblast forms a direct contact with mother's systemic circulation but not with the uterine immune response of the pregnant human female. The syncytiotrophoblast does not express MHC antigens on its surface which again justifies the concepts that the placenta is an immunologically neutral tissue (20).

The second area of contact which forms during human pregnancy develops between extravillous trophoblast cells of the placenta and the immune cells present in the decidua. As previously mentioned, syncytiotrophoblasts are devoid of MHC antigens, while extravillous trophoblast cells express a rare combination of MHC antigens, comprising HLA-C, HLA-G and HLA- E antigens. HLA-G is highly expressed in trophoblast cells infiltrating and accumulating in the pregnant uterus, whereas polymorphic MHC antigens i.e. HLA- A & HLA-B molecules, which are essential for initiation of allograft rejection, are not expressed by trophoblasts (43). The observation that invasive trophoblasts express class I MHC antigens and uNK cells are predominant in the pregnant uterus, led to the development of a hypothesis that trophoblasts resist NK cell mediated lysis by expressing class I MHC molecules and the recognition of trophoblasts by NK cells promotes the secretion of cytokines that both enhance placental growth and modulate local allogenic responses (Th2 deviation) (44).

Human uterine NK cells express various kinds of receptors, some of which could bind to HLA class I molecules expressed by extravillous trophoblast cells (20). Also uNK cells express high levels of CD94-NKG2A receptors which upon binding with HLA-E molecules result in the inhibition of NK cell mediated cytotoxicity. KIR2DL4, a KIR family member expressed on uNK cells binds to the HLA-G molecules leading to its endocytosis and causing up-regulation of the expression of pro-inflammatory and pro-angiogenic cytokines, thus demonstrating the role of uNK cells in providing the increased blood supply to placenta (45,46).

Also any soluble HLA-G molecules present in the maternal blood circulation can bind to the KIR2DL4 on blood NK cells and cause vascular and inflammatory changes that are characteristic of all pregnancies (47). Thus signaling via trophoblast cell's MHC to decidual innate immune system through both KIR2DL4 on the NK cells and LILRB1 (or LILRB2) on myelomonocytic cells indicates that HLA-G acts as a "placental" signal that induces pregnancy specific function in the uterus.

Trophoplast cells also express polymorphic HLA-C molecules which act as dominant ligands for KIR family of receptors on NK cells and these receptors have two Ig – like domains (KIR2D), which may be of activating (KIR2DS) or inhibitory (KIR2DL) type.

Further KIR haplotypes are composed of 2 groups of A and B where A is an inhibitory group and B is an activating group. Thus in any pregnancy the maternal genotype could be of AA (no activating KIR) or AB/ BB (activating KIR) type. Also HLA-C ligands for KIR are also further divided into two groups of HLA-C1 and HLA-C2 and these two polymorphic interactions (maternal KIR and fetal HLA-C) can vary in each pregnancy i.e. some KIR / HLA-C interactions would be more favorable to trophoblast cell invasion and could cause increased blood supply to placenta than other KIR/ HLA-C combinations.

This hypothesis was further supported by the study carried out by Hiby et al (48) who showed that pre-eclampsia occurs with increased frequency in those pregnant women who express AA genotype of KIRs only when these KIRs get bound to fetal HLA-C2 allotype. Binding of HLA-C2 to KIR2DL1 delivers stronger inhibitory signals compared to HLA-C1 – KIR2DL2 or HLA-C1 – KIR2DL3 interactions (49).

Thus in pregnancies where fetal trophopblast cells express HLA-C2 MHC molecules, the mother should express activating (AB/BB) KIRs to overcome the inhibitory effect of HLA-C2, otherwise there should be less or inadequate blood supply at feto -placental level. However, if trophoblast cells are homozygous for HLA-C1, the NK cell inhibition will be less and will not require the presence of activating KIRs that are needed to compensate for HLA-C1. Thus the expression and polymorphism of KIRs on uNK cells and their counter ligands HLA-C on fetal tropholbast cells play important roles in human pregnancy and are detrimental to human reproduction (Table 1).

**Uterine NK Cells (uNK cells) and Cytokines Released During Pregnancy.** As compared to peripheral cells which at the resting stage produce very few cytokines, the uNK cells express different kinds of cytokines, thus they are both in terms of receptor expression and also functionally different from pNK cells. For example mRNAs for various cytokines including GCSF, GMCSF, MCSF,TNF $\alpha$ , IFN $\gamma$, TGF $\beta$ and LIF have been found in the uNK cells (50,51) whereas only mRNA for TNF $\alpha$ and TGF $\beta$ have been found to be expressed in pNK cells during their resting stage (50).

Receptors for GM-CSF, CSF, IFN-$\gamma$ and TNF-$\alpha$ have been demonstrated on human trophoblast cells and thus these uNK cell-derived cytokines may play important roles in

**Table 1. Interaction between uterine natural killer cells and HLA molecules expressed on human trophoblasts during pregnancy**

| Sl | Tropoblast HLA | u NK cell receptors | Function |
|---|---|---|---|
| 1 | HLA C2 | KIR 2DL1 | NK cell inhibition |
| 2 | HLA C2 | KIR 2 DS1 | NK cell activation |
| 3 | HLA C1 | KIR 2 DL2/3 | NK cell inhibition |
| 4 | HLA C1 | KIR 2 DS2 | NK cell activation |
| 5 | HLA G | IL T2, KIR2DL4 | 1.Prevention of fetus by NK cell mediated lysis<br>2.Inhibits trans endothelial migrations of NK cells<br>3.Programme uNK cells into the pathway of tolerance |
| 6 | Soluble HLA G | | 1. Influence cytokine production by blood mononeuclear cells<br>2. Effect cytotoxic T cells and induce T cells apoptosis under some circumstances<br>3. Programme helper T cells to tolerance |
| 7 | HLA-G5 and HLA-G6 | | 1. Induce TGF-β1 production by mononuclear phagocytes.<br>2. Tolerize DCs |
| 8. | HLA-E | CD94/NKG2A | Inhibits NK cell function |
| 9. | HLA-E | CD94/NKG2C | Activates NK cell function |

trophoblast growth and differentiation (52-55). Besides these cytokines, uNK cells produce various isoforms of vascular endothelial growth factor (VEGF), placental growth factor (PLGF) and NKG5, an alternative splicing product of the granulysin gene that stimulates mitogenicity of endothelial cells (47). Genes encoding several chemokines including IL-8, IFN-inducible protein (IP)-10 and CCL5 (or RANTES) are also expressed by these decidual NK cells (dNK cells) (47). In order to respond to chemokines secreted by dNK cells, invasive trophoblasts need to express the matching chemokine receptors. It has been found that invasive trophoblasts which are HLA-$G^+$ express CXCR1, CXCR3, CXCR4 and CCR3 (56). The analysis by Hanna et al (47) showed that dNK cells are potent secretors of IL-8, the ligands for CXCR1 and IP-10, one of the ligands of CXCR3 receptor. The chemokine RANTES is expressed in dNK cells but its receptor CCR5 has not been detected on trophoblast cells. Therefore, the cross talk between uNK cells and invasive trophoblasts would probably be mediated through the stimulation of CXCR1 and CXCR3 pathways.

In addition, CSF-1 increases the production of hCG and human placental lactogen by the human trophoblast (57). LIF also plays an important role in the implantation of blastocysts (58). IFN-γ secreted by uNK cells causes human trophoblast cells to become partially protected from lysis by IL-2 stimulated decidual NK cells (59). Along with these cytokines or chemokines, uNK cells also secrete galectin-1 and glycodelin A (29). Galectin-1 inhibits T–cell proliferation and survival and affects the cytokine environment by decreasing TNF-α, IL-2 and IFN-γ production from activated T cells (60)(Table 2).

## NK CELLS AND HIGH RISK PREGNANCY

Recurrent pregnancy loss (RPL) or recurrent miscarriage is defined as 3 or more consecutive spontaneous abortions (17). It commonly affects about 1% of the female population of the child bearing age (61). Besides numerous proposed causes of RPL in the past decade, considerable effort has been made to identify cellular constituents and processes underlying immune-based RPL. Several studies have tried to establish enhanced pNK cell activity or elevated NK cell number as causes of recurrent miscarriages.

**Table 2. Uterine natural killer cell cytokines and their roles in human pregnancy**

| Sl No. | u-NK cell cytokines | Function in human pregnancy |
|---|---|---|
| 1 | CSF | Increases production of hCG and human placental lactogen by human trophoblast (mostly by CSF) |
| 2 | M-CSF | |
| 3 | GM-CSF | Trophoblast growth and differentiation |
| 4 | TNF-α | |
| 5 | TNF-β | |
| 6 | IFN-γ | 1. Protects human trophoblast cells from lysis by IL-2 stimulated uNK cells. 2. Maintains decidual integrity, 3. Vascular remodeling, 4. Normal uNK cell development |
| 7 | TGF- β | Inhibits human trophoblast invasion |
| 8 | MIF | Inhibits cytolytic activity of uNK cells |
| 9 | LIF | 1. Implantation of blastocyst 2. Stimulation of hCG and oncofetal fibronectin production by human trophoblasts |
| 10 | VEGF | Favors vascular growth in decidua |
| 11 | PLGF | Favors vascular growth in decidua |
| 12 | NKG5 | Stimulates mitogenicity of endothelial cells |
| 13 | IL-8 | Regulates trophoblast invasion by binding to CXCR1 and CXCR3 on trophoblast cells |
| 14 | IP-10 | Regulates trophoblast invasion by binding to CXCR1 and CXCR3 on trophoblast cells |
| 15 | CCL5 (RANTES) | ? |
| 16 | Galectin | Inhibits T- cell survival and proliferation |
| 17 | Glycodelin ( Placental protein -14, Progesterone associated endometrial protein) | Local immunosuppression, down regulation of T-cell activation |

CSF, colony stimulating Factor; M-CSF, macrophage colony stimulating factor; GM-CSF, Granulocyte- Monocyte colony stimulating factor; TNF- α, Tumor Necrosis Factor alpha; TNF- β, Tumor Necrosis Factor beta; IFN- -γ, Interferon gamma; TGF- β, Transforming growth factor beta; LIF, Leukemia inhibiting factor; VEGF, Vascular Endothelial Growth Factor; PLGF, Placental Growth Factor; IL-8, Interleukin-8; IP-10, Interferon inducible protein 10; CCL5, Chemokine Ligand 5; and MIF, Macrophage migration inhibitory factor.

As NK cells play an important role in the establishment of pregnancy and its outcome, so any abnormal change of their activity can lead to complications during pregnancy and the loss of the fetus. It has been shown in the women with the history of RPL that increased NK cell activity contributes to a relative risk of 3.5 for pregnancy loss in the next pregnancy, compared to women with normal NK cell activity throughout the gestation period (62). In early pregnancy, increased NK cell mediated cytotoxicity peaking at 8 weeks and also increased number of $CD56^+$ $CD16^-$ NK cells were found in women with RPL (63).

Ntrivalas et al examined the phenotype of peripheral blood NK cells in women with a history of RPL or infertility of uncertain etiology and found an increased expression of CD69, an early activation marker, on pNK cells in women with RPL compared to controls (64). Also, CD94/NKG2 inhibitory receptor expression was significantly lower in women with RPL as compared to control healthy women. Thus this imbalance of CD69 and CD94 expression on peripheral blood NK cells in women with RPL may be one of the contributing factors in this disease.

Several studies have shown increased number of $CD56^+$ NK cells in the peripheral blood of women with recurrent miscarriage (RM) either prior to or during pregnancy compared with healthy fertile non-pregnant or pregnant controls (63,65). Studies have also shown that levels of peripheral blood $CD56^+$ cells both prior to and during pregnancy could predict pregnancy outcome in women with RM (64,66). In normal fertile women, peripheral $CD56^+$ NK cell activity decreases during the first trimester of pregnancy but in women with RM, peripheral $CD56^+$ NK cell activity remains high (65,67).

In contrast to the increased $CD56^+$ cells in peripheral blood, a decreased decidual $CD56^+$ NK cells are reported in the placental tissue from spontaneous miscarriages in women without RM and women requesting termination (68,69). Two separate immunohistochemical studies have shown increased $CD56^+$ cells in the non-pregnant endometrium of women with RM (70,71) and lower numbers were seen in women with RM who subsequently had a live birth compared with those who had a miscarriage(72).

All these results suggest that there are alterations in the $CD56^+$ population of leukocytes with recurrent miscarriages. However, increased or decreased $CD56^+$ leukocytes depends on whether peripheral blood, first trimester decidua or peri-implantation endometrium is analysed. $CD56^+$ cells comprise < 10% of peripheral blood leukocytes, and therefore these changes may not be significant to the total peripheral blood cellular activity. Thus there appears that decreased numbers of $CD56^+$ cells in the decidua and increased numbers in endometrium could be due to $CD56^+$, $CD16^+$cells as suggested previously (73), while the decreased numbers reported in deciduas could be due to $CD56^+$, $CD16^-$ population. The study showing increased numbers of $CD16^+$ cells in early pregnancy deciduas of women with RM would support this hypothesis (74).

**Future Perspectives.** The present available evidence from studies of uNK cells ($CD56^{high}CD16^{dim}$ NK cell) and trophoblast class 1 antigen raises the intriguing possibility that maternal allogenic recognition of the placenta involves a completely different and novel mechanism compared to that seen in classical allograft reaction. In human pregnancy there is much more intimate interaction between mother and fetus and $CD56^+CD16^-$ NK cells are the first immune cells adapted to protect the mother from this novel onslaught. It has been observed that defects in trophoblast invasion result in incomplete spiral artery remodeling, causing reduced blood flow to the feto-placental unit. This leads to preeclampsia, characterized by poor fetal growth as well as hypertension and proteinuria in the mother. Thus uterine NK cells, being the major lymphocytes of the pregnant uterus, play important roles in the development of placenta including vascular growth, fetal trophoblast invasion and also in the remodeling of spiral arteries, thus ensuring normal blood supply to the fetus and placenta throughout the pregnancy in order to prevent the development of preeclampsia in the pregnant mother.

The findings of Hanna et al (47)**,** add to the evidence that maternal uNK cells in the uterus of pregnant healthy women do not use their cytotoxic functions. Instead these cells have regulatory functions, cooperate with trophoblast and stromal cells to assure proper placental development and therefore healthy baby and mother. Also the uNK cells express diverse complement receptors known to recognize MHC class I molecules (45). Some of these receptors are inhibitory and others induce NK cell activation.

uNK cells and peripheral NK (pNK) cells play an important role in human pregnancy. Available evidence suggests that both types of NK cells are regulated by human female sex hormones but predominantly the uNK cell populations regulate endometrial cytokines. Through direct or indirect effects of progesterone, uNK cells may provide appropriate cytokine support and local immunomodulation and pNK cells may down regulate their activity in normal pregnancy.

Thus decidual NK cells are specifically recruited and properly stimulated by physiological endometrial changes to perform previously unknown stroma-like functions by secreting crucial cytokines, chemokines and growth factors.

It is expected that further characterizations of dNK cell functions will provide an insight into the involvement of these cells in several pregnancy related conditions like preeclampsia, excessive breakthrough bleeding, endometriosis and recurrent pregnancy loss.

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