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# Role of Natural Killer cells in Recurrent Spontaneous Abortions

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**ABSTRACT**
*Spontaneous abortion is defined as a spontaneous pregnancy loss prior to the 20th gestational week of pregnancy. Retrospectively studied to identify the possible solution from literatures published since 1975 via Medline search with particular focus on Peripheral blood Natural Killer (pNK) cells and Uterine Natural killer (uNK) cells, revealed that uNK cells play a major role in supporting placental growth, providing defense against infection, and defects in them result in improper implantation and placenta formation. However it has not ascertained to concrete NK cells for these miscarriages. In this review we will explore the immunosurveillance and cytotoxicity profiles of pNK and uNK at maternal-fetal interface that leads to normal pregnancies and recurrent spontaneous miscarriages*
*Keyword : pNK cell, uNK cell, pregnancy , $CD56^{bright}$ and $CD56^{dim}$*

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## INTRODUCTION

In mammalian species, pregnancy elicits an evolutionary adaptation of the uterine environment to make sure there is a mutual tolerance present among mother and fetus and, therefore, implantation of blastocyst, hemochorial, decidualization, early embryo and fetal development are carried out successfully till the child birth yet, miscarriages/pregnancy loss have become a common complication and this topic is the subject of wide research to discover the underlying causes.

A spontaneous loss of pregnancy is defined as a miscarriage that occurs shortly after implantation and ends in bleeding. Studies reveal that, 10-25% of all clinically recognized pregnancies end in miscarriage. Chemical pregnancies have been related to this scenario where this type of pregnancies may account for 50-75% of all miscarriages. Recurrent Spontaneous Abortion (RSA) or miscarriages are generally noted when pregnancy ends within the first 20 weeks of gestation and it is the most familiar type of pregnancy loss [1]that has occurred approximately 1 in 300 pregnant women. Recurrent Spontaneous abortions is defined as three or more consecutive spontaneous abortions [2].

There are two types of miscarriages that relates RSA; women who have primary abortions in that they are those who have missed all previous pregnancies whereas women with secondary abortions are those who have had at least one successful pregnancy irrespective of the number of pregnancies. In majority of women who experienced RSA, there were no concrete causes identified. Generally a successful mammalian pregnancy is tackled with a perfect interplay of self antigens (autoimmune) and foreign antigens (alloimmune). In this context, RSA is caused by various arrays of factors. Chromosomal abnormality or alteration is found to be the main course of fetal loss during early phase of gestation [3] Endocrine etiologies (luteal phase defect, thyroid dysfunction, uncontrolled diabetes mellitus), antiphospholipid syndrome, inherited trombophilias, alloimmune causes [4] infections during pregnancy, amniotic abnormalities [5] life style, improper implantation of egg into the uterine, maternal age and also maternal trauma [6], are other factors. Approximately 40-60% clinical manifestation of repetitive abortions remains unknown in many cases [4,5] .

In the past decades, satisfactory effort has been put together to discover cellular constituents underlying immune-based etiology of pregnancy loss. Pregnancy is an exciting dilemma for immunobiology because it has created an interesting field to analyze the potential histocompatibility between developing semi-allogenic fetus and the mother's immune system.. Studies on pregnancy loss are under investigation which mainly relates maternal immune cells or lymphocytes population towards the pregnancy loss.

Although there are many upcoming new findings to overcome this arising problem, there have been no complete satisfactory results. In this point of view, Natural Killer (NK) cells have been extensively studied, mainly because they are noted as the predominant population in the endometrium at the point of implantation and in early pregnancy. This review prominently illustrates and examines the presence of NK in pregnancy and their unexplained role in recurrent spontaneous abortions (RSA).

## IMMUNOLOGICAL RELATIONSHIP BETWEEN MOTHER AND FETUS

The developing fetus has both paternal and maternal genetic information, and therefore it grows in a condition of semi-allograft to the maternal immune system. The immunological relationship between the mother and the fetus is a paradoxical communication determined by fetal antigen presentation. The recognition and reaction to these antigens are balanced by the maternal immune system. Immunological analysis during pregnancy is mounting for successful gestation of fetus and at the same time to avoid high chances of abnormalities in the maternal-fetal immunological relationship in the placental bed. The concept of immune tolerance was introduced in 1953 by Medawar as 'the paradox of pregnancy" [6]. In his theory, the semi-allogenic fetus was able to survive as because of the balance of immunologic communication among the mother and fetus regulated and reserved with a co-operation of fetal antigen expression or a functional suppression of maternal lymphocytes. In addition, there were also signs of lack of antigen stimulation attempted by maternal lymphocytes toward fetal development [7-9]. However, the accurate mechanism for the immunologic tolerance was not completely understood.

The successful fetus development involves synchronized interactions that are considered as a semiallogenic graft acceptance, between embryonic and uterine cells. Here the fetus escapes immune attack of the maternal lymphocytes, and thereafter, alteration of human leukocyte antigen expression [10, 11] trophoblast cells and immunologic balance [12] , peripheral NK cells, uterus NK cells [13-15] macrophages [12] and chemokines [16,17] play their role to form a successful pregnancy outcome. Knowing their specific role during pregnancy, there has been brave attempts by many research teams globally to understand the concept of a successful pregnancy and a failure pregnancy.

## NATURAL KILLER CELLS ROLE IN HUMAN REPRODUCTION

### Peripheral Natural Killer cells (pNK cells)

pNK cells are generally found in the range of 10-15% of total population (Robertson et al., 1990) of the lymphocytes with CD16 and CD56 surface driven from bone marrow. Phenotypic differentiation and functional activities of NK cells are regulated by interferon-γ and negatively modulated by glucocorticoids [18]. In humans, based on the expression of CD56 surface antigen, pNK cells are divided in to two populations such as $CD56^{bright}$ and $CD56^{dim}$. A majority of approximately 90% NK cells that are characterized from peripheral blood are $CD56^{dim}$ cells which express a high level of CD16 and are cytotoxic; whereas the remaining 10% are $CD56^{bright}$ cells which express low level of CD16 and the main source of NK cells-deriven immunoregulatory [19].

Studies reveal that there is no concrete change in pNK cells level between follicular and the luteal phases of the normal menstrual cycle and pregnancy in woman [20] ; either no changes in NK cells activity [21] nor entirely unrelated to influence the progesterone level [22] However, as contrast to this, there are studies, in normal human pregnancies which show that pNK cells reduce in quantity, since there is a decrease in the $CD16^{+}$ subset in the progressing pregnancies [23.24]. Also evidence shows that pNK cells from normal pregnant woman exhibit low lytic activity compared to non-pregnant woman [25] Ponte M (1999) suggested that there is an increased expression of inhibitory receptors between peripheral T cells and NK cells during the first week. However, within third month of gestation, a subsequent decrease can be observed and the level comes down to basal levels by the end of pregnancy [26]

It was further explained that progesterone possibly will inspire NK cell apoptosis, stimulate cytokines secretion (by monocytes or trophoblasts ),induce pregnancy protein TJ6 and other significant factors present in pregnant serum . Indeed, NK cells are key regulators of allograft rejection and whispered to be involved in the dearth of maternal rejection of the semi-allogeneic fetus. Interactions between pNKs and various cell types [T helper-1 (Th1), T helper 2 (Th2), T helper 3 (Th3) Tr1, CD4+ CD25+ (T regulatory)] allows the fetus to be immunologically tolerated for a successful pregnancy (Saito et al., 2008).

### Uterine NK cells (uNK cells)

The maternal part of the placenta is deciduas, in which there is a close contact between maternal and fetal cells. Therefore, the decidua plays an central role in acceptance of the fetus and the control of trophoblast invasion. The decidua restrain a diverse population of cells, such as lymphocytes, monocytes, decidualized stroma cells, uNK cells and epithelial cells. uNK cells are unique subset of NK cells found in uterine endometrium. However they are different in their phenotype and function compared to peripheral natural killer cells [28]. Endometrium hosts a significant number of leukocytes, which will

change accordingly during menstrual cycle. A high level of CD56 population is derived from the $CD56^{bright}$ of peripheral blood. Leukocytes consists of 10% stromal cells in proliferative stage, 20% in secretor phase, and 30% in endometrial stromal phase and almost 70% leukocyte population with large granular are NK cells. These compositions are generally identified during first trimester deciduas [29] uNK cells resemble mainly CD56 that lacks CD16 or CD57 (Saito et al., 2000) CD69, an early activation marker and early T cell markers such as CD2 and CDC7, integrins such as CD11a and CD18 and IL2Rβ marker [30]. At early pregnancy, uNK cells constitute about 75% of uterine leukocytes [29]. They undergo phenotypic changes, expression of the activation antigens CD69 and HLA-DR; CD11a and CD18 showing highest number during proliferative phase.

Even though the uNK cells populations are present in large numbers, yet they do not act against the semi-allogeneic non-villous cytotrophoblast. This is in fact because uNK cells express inhibitory receptors, which will bind to the MHC I a and b (HLA-C, HLA-E and HLA-G) on trophoblast, by directly inhibiting the lytic activity of this cells. The inhibitory uNK cell receptors are namely lg-like killer cell inhibitory receptor (KIR)(e.g. KIR2D, KIR2DL4) and lectin-like KIRs (CD94/NKG2A) [31-33]. It is also claimed that uNK cells play a main role in promoting placental growth, protection against infection, improper implantation and placentation [33,34] Moreover it also supports terminal decidual cell differentiation, sensitization of spiral arteries that allow their pregnancy-associated dilation and elongation, and formation of a transient lymphoid aggregate at the portal for vessels and nerves servicing implant sites [35]

During the pregnancy period, a small portion of $CD56^{bright}$ population home into uterine endometrial and subsequently several hormones (Estrogen, Progesterone and Prolactin) alter the uNK cell phenotype and function. The differences of pNK and uNK cells phenotypes markers have mentioned in Fig-1. In uNK cell, maternal KIR2D receptor is highly expressed during the pregnancy period for the recognizing of fetal HLA-C antigen which plays a vital role in placenta regulation.

**THE EFFECT OF pNK and uNK CELLS IN COMPLICATED PREGNANCIES / THE EVIDENCE OF pNK AND uNK MISCARRIAGES**

During pregnancy, maternal and semi allograft coordinate immune mechanisms through T and B lymphocytes, NK cells and an array of soluble immunoregulatory factors such as cytokines, and antibodies. Many theories via wide range of study protocols explain the decreased cell-mediated immunity in pregnancy (decrease in CD4 cells; increase in CD8 cells; and defective cytotoxic activity of NK cells). RSA may occur in a situation when trophoblastic HLA class I molecules are recognized by decidual NK cells lacking the appropriate inhibitory KIRs. NK cells apparently have a key role in immunosurveillance of the invading trophoblast. However, if NK cells activated by tumor necrosis factor alpha (TNF-α), these cells may encourage apoptosis in the trophoblast which then leads to miscarriages [36].

A study conducted by Aoki and coworkers reported the NK cells activity specifically in 68 women who had histories of two consecutive first trimester-abortion and the study showed that women with high preconceptional levels of NK cells activity had a 3.5-fold of risk of pregnancy loss compared to normal level. Furthermore, in another study by Aoki and coworkers (1995), elevations of peripheral blood $CD56^{+}$ concentration predicted the loss of a karyotypically normal conceptus [37] In unexplained abortions, the changes of the NK cell number and its activity are not consistent and no live infants were born when the NK cells proportion appears to be >18% of maternal peripheral blood [23] . The role of pNK cell and uNK cells has related to RSA that has been mentioned in details on Table 1.

In a recent report, embryo cytotoxic activity related to Th1-type cytokines, a type of activated lymphocyte supernatant which is “bad for pregnancy” in trophoblast detected in RSA woman, whereas Th2-type a “good for pregnancy” cytokine IL-10 was detected in normal pregnancy [38] In a similar study, decreased $CD8^{+}$ value and increased CD4:CD8 ratios were also clearly noted in RSA cases compared to normal conditions [39]. In another study done among 244 woman with RSA by Hill and collogues (1995), 125 women were shown to have immune cells that respond to trophoblast antigens by producing high levels of INF-γ [38]. In women with history of recurrent pregnancy loss, uNK in pre-implantation was increased compared to woman without such background [40,41]. However decreased number found in women with a genetically abnormal fetus [42,43].

It is well recognized that uNK cells is involved in the production of cytokines [27,44,45]. uNK cells also produce type 1 cytokines, such as TNF-a and IFN-g, which may have negative effects on implantation and trophoblast invasion. Attempts to compare the uNK from woman with history spontaneous abortion with those from normal pregnancies have shown no reasonable results since uNK readily undergo apoptosis as soon as progesterone concentration drops, either premenstrually or if a pregnancy failure occurs. Moreover, inflammation and necrosis also present in tissues obtained from spontaneous

miscarriages[45]. In another approach done in recurrent spontaneous abortions, morphometric analysis shown defective maturation of glandular function which infect causes alteration in leukocytes [30]. Moreover, IVF-ET failure in association with peripheral blood NK cells activity or concentration showed that immunosuppressive effects on NK activity resulted in approximately 6.2 times higher successful pregnancy records[46]. Multiple IVF failures demonstrated significant increase in the level of $CD56^{+}$ NK cells in idiopathic infertile woman compared to normal pregnant woman [22].

Table 1: *Studies on pNK and uNK cell in RSA*

| S. No | Number of patients | Criteria | Interpretation | References |
|---|---|---|---|---|
| 1 | 22 & 45 | Women with history of two or more RSA | pNK cell numbers indirectly reflects the uNK cell changes. In peripheral blood, the $CD56^{+}$ and $CD16^{+}$ cells were increases in RPS while compare to control woman's | [62,63] |
| 2 | 218 | Caucasian RSA patients had three or more consecutive pregnancy losses | Nearly 56% woman's had APS-RSP (Antiphospholipid Syndrome-RSP) that APL (Anti-phospholipid) has causes the damage of pNK cell population and fetal losses with in the first 10 gestation weeks | [64] |
| 3 | 25 | Women with recurrent spontaneous abortion | As compared to healthy women, the percentage of PB $CD56^{bright}$ NK cells, interferon-gamma and TNF-alpha has notably increases in SAB women. | [65] |
| 4 | 16 | Unexplained RSA | KIR2DL2 inhibitory receptors highly increases in RSA compare to healthy control. Significantly imbalance of inhibitory and activating KIRs in uterine NKs might be susceptible to the pregnancy loss | [66] |
| 5 | 65 | Unexplained RSA | In uterine, $CD56^{+}$ cells down regulates the E-cadherin expression at chorionic trophoblasts, subsequently affect the adhesion to the placental bed and thereby interfering with embryo implantation and pregnancy | [67] |

## PAST RELEVANT STUDIES AND FUTURE DIRECTIONS FOR RECURRENT MISCARRIAGE ASSOCIATED WITH IMMUNE ETIOLOGIES

In 1953, Billingham proposed the concept of immune tolerance in fetal allograft within the uterine environment [6]. thereafter many hypotheses have been uploaded to discuss the fact related to miscarriages. Studies on transgenic mice lacking NK cells reveal that uNK cells play an important role in uterine spiral artery modification in the placenta [47]. Numerous investigators have used *murine* knock-out models to clarify the effect of NK cells on pregnancy. However, different knock outs have reported in different results. Using Terhost mutants results, Croy's group have concluded that NK deficient mice have a higher rate of fetal loss[55]. In contrast, the fetal miscarriage rate is not high in IL-15, NK cell-deficient mice, nor amongst IL-2 receptor knockouts, which also lack uNK cells [48,34,49]. These findings were later fine tuned with alloimmunization offers an opportunity to modify the maternal immune response towards preventing additional miscarriages[50-55].

There are many types of treatment mode viable for miscarriges such as aspirin, heparin, progesterone hCG, prednisone, leukocyte Immunization and intravenous immunoglobulin (IVIG) [56, 4]. Two types of immunotherapy applications involving injections of paternal leukocytes and the use of intravenous immunoglobulin (IVIG) have been reported in recurrent spontaneous abortion (habitual abortion or miscarriage) patients. There were numerous studies done in recurrent abortion cases with known causes that have been treated with allogenic lymphocyte application since last decade[57,58]. Moreover, there are notable beneficial effects of immunization with allogenic lymphocytes which have resulted in implantation and fetal growth[50,51,59]. However, A meta-analysis of randomized controlled trials concluded that IVIG and paternal leukocyte injections provided less or no reasonable positive effects over placebo in preventing future abortions[60]. NK cells are an interesting component of immune system and the particular class of NK cells (CD3-, CD16-, CD56+) in the placenta promotes cell growth, secretes growth molecules for the placenta and down regulates the mother's immune response locally at the maternal/placenta interface. This type is opposing to another group of NK cells (CD3-, CD16+, CD56+),

which when activated by the cytokine IL-2, they will act as an cytotoxic to placental trophoblast and at the same time secrete tumor necrosis factor (TNF) that is responsible to destroy the placenta. Women with CD16+, CD56+ NK cells in excess of 20% are at risk for miscarriage despite optimal immune treatment (paternal leukocyte immunization, prednisone, aspirin and heparin).

Development of newer diagnostic modalities are needed to analyze the peripheral blood NK cells percentage in pregnant woman with RSA as reports seem to suggest that an elevated NK cell activity in the peripheral blood might be a reflection of the status or development of pregnancy. The lymphocytes profiling in different abnormalities offered predictive analysis of RSA with normal fetal karyotyping and alloimmune causes[61]. The diagnostic work-up adopted to determine the treatment of patients with single or recurrent spontaneous abortion is crucial and must include primary and secondary investigations. Therapeutic approaches must depend on the exact aetiopathogenesis of miscarriage and may involve a combination of both surgical and various types of treatment approaches.

## CONCLUSION

In this review an analysis of the various populations of Peripheral Blood NK cells (pNK cells) and Uterine NK (uNK) cells has thrown light on various facts surrounding RSA. Based on earlier studies, however a population of phenotypically distinct (CD56bright, CD16dim) NK cells in the uterus has been shown to be associated with favorable pregnancy outcomes. Strategies by increasing the uNK cells help in successful implantation of the embryo. Extensive research and clinical studies are needed in this regard.

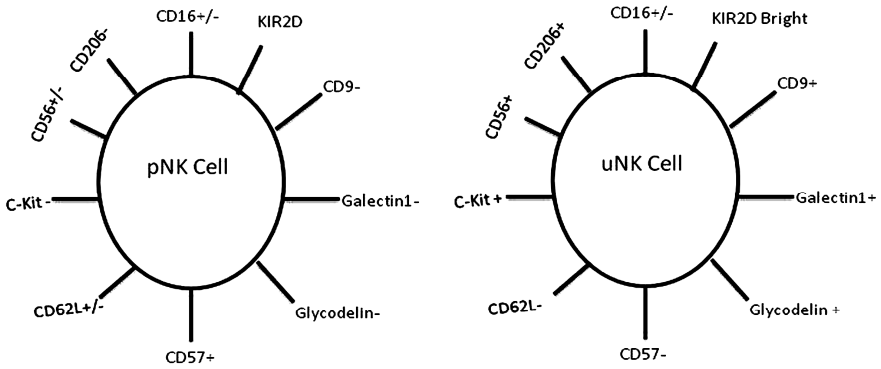


Figure 1: Significant surface markers differences between pNK and uNK cells. pNK cells have both two population CD56bright and CD56dim, whereas uNK cell have single subset which is $CD56^{bright}$ alone. uNK and pNK cells have different surface receptors. CD9, Galectin-1, c-kit and Glycodelin markers are expressed in uNK cells, whereas, pNK cells do not express these markers. In contrast, CD16 and CD57 markers are not expressed in uNK cells however they are expressed in pNK cells. Furthermore, CD62L receptor is missing in uNK cells but it is either expressed or not expressed in pNK cells.

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