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Peripheral Blood Natural Killer Cells and Th1 Cytokines in Unexplained Female Infertility

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ABSTRACT

Objectives: To compare the percentage and absolute numbers of peripheral blood (PB) natural killer (NK) cells and its subsets and levels of T helper cells 1 (TH1) cytokines [interferon-gamma (IFNγ) and tumor necrosis factor-alpha (TNFα)] in women with unexplained infertility with that of healthy fertile women.

Materials and Methods: This was a three-year study which included 31 women with history of UI and 33 fertile controls. Flow cytometry was done on ethylene di-amine tetra-acetic acid samples to determine the percentage and absolute count of total PB NK cells and its subsets. Enzyme linked immunosorbent assay was done on serum samples for IFNγ and TNFα.

Results: The ratio of mean percentages of CD56dim and CD56bright NK cells [31.36 in patients vs 18.06 in controls (p = 0.034)], mean percentage of CD56+CD16+ NK cells [7.04 in patients vs 4.96 in controls (p = 0.034)] and CD56dim CD16+NK cells [81.02 in patients vs 60.49 in controls (p = 0.004)] was significantly increased in infertile women compared to fertile women. The percentage and absolute count of CD56+CD16- NK cells [p = 0.017 and p = 0.022, respectively] and CD56dimCD16- NK cells [p = 0.002 and p = 0.02, respectively] was significantly raised in fertile controls compared to infertile patients. Mean percentage of total PB NK cells, mean percentage and absolute count of CD56bright, CD56dim, CD56brightCD16+, CD56brightCD16-NK cells and mean serum levels of TNF-α and IFN-γ in infertile groups were higher but not significant compared to fertile group.

Conclusion: CD56+CD16+ NK cells which constitute the major population of PB NK cells and its major subset, CD56dim CD16+ NK cells was significantly raised in unexplained infertile women.

Keywords: Natural killer cells, TNF-α and IFN-γ, unexplained infertility.

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Introduction

Infertility is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse"[1]. The combined pooled global prevalence of infertility according to a study is around 10%[2]. There are various causes of female infertility out of which unexplained infertility, which is a diagnosis of exclusion, accounts for around 25% of patients investigated for reproductive failure after tests of semen analysis, concentrations of progesterone in mid-luteal phase, tubal patency and uterine cavity are normal[3]. Natural Killer (NK) cells are the first line cellular defense mechanism and are in close contact with conceptus and placenta. NK cells are part of innate immune system and express the cell surface antigens CD16 and CD56. On the basis of intensity of CD56 expression, NK cells are divided into two subsets: CD56dim and CD56bright. NK cells that are cytotoxic in vitro are CD56dim. However, little cytotoxic activity is caused by CD56bright NK cells, but they produce immunoregulatory cytokines like interferon-γ (IFNγ) and tumor necrosis factor-α (TNFα)[4].

Increased number of uterine NK (uNK) cells are present in mid-secretory phase of the menstrual cycle although the underlying mechanism is not known. There are two theories given for this: peripheral blood natural killer (PB NK) cells are recruited which differentiate into uNK cells in uterine microenvironment by various organized processes or they are derived from proliferation and differentiation of stem cells in utero or the endogenous NK cell population present in endometrium[5, 6]. Fetal non-polymorphic human leucocyte antigen (HLA-G) and HLA-E are recognized by uterine NK cells which results in the secretion of T- helper type 2 (Th2) cytokines leading to a successful pregnancy outcome[7-10].

PB NK cells are mainly (90%) CD56dim CD16+ and a minor population (10%) of PB NK cells are CD56bright CD16-[11]. Evidence suggests that increased proportion and activity of PB NK cells determined by immunophenotyping are related to recurrent spontaneous abortion (RSA), so functional assays for NK cells cytotoxicity are being used to monitor treatment and pregnancy outcomes[12, 13]. IV immunoglobulins (IVIg) or allogenic lymphocyte treatment results in successful pregnancy in RSA by decreasing the percentage and activity of NK cells[14, 15]. These treatments also result in production of Th2 cytokines (IL-4, IL-10) which subsequently decrease Th1/Th2 ratio and thus favour a successful pregnancy outcome[16]. Th1 cells produce TNFα, IFNγ and IL-2. Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13[17, 18]. It has been proposed that successful pregnancy results in an immune bias towards T helper type 2 (Th2) immunity[19]. As both unexplained infertility and RSA are immune related conditions, so in this study, we have tried to determine and compare the levels of peripheral blood NK cells, its subsets and serum levels of Th1 cytokines (TNFα and IFNγ) in women with unexplained infertility and in healthy fertile women.

Materials and Methods

This was a three-year study which included 31 women with unexplained infertility with regular, ovulatory cycles, at least one patent fallopian tube and < or = 40 years of age. Exclusion criteria included women with known uterine fibroids, structural abnormalities of uterus, history of pelvic inflammatory disease (PID), anovulatory cycles polycystic ovarian syndrome (PCOS), immunologic abnormalities, history of diabetes mellitus (DM), thyroid disease or any chronic disease, infectious and inflammatory diseases or partner with male factor infertility. Thirty-three healthy fertile women volunteers matched for age, body mass index (BMI), ethnicity to cases who were < or = 40 years of age, non-pregnant, having > or = 1 healthy child with no history of pregnancy loss or infertility, immunologic abnormalities like systemic lupus erythematosus (SLE), anti-phospholipid antibody (APLA) etc, history of DM, thyroid disease or any chronic disease, infectious and inflammatory diseases, no history of PID were included in the study.

Informed consent was taken. Blood samples

were taken in two vials, one ethylene di-amine tetra-acetic acid (EDTA) and one plain vial during the follicular phase (day 10-14) of the menstrual cycle from all infertiles and fertiles during their routine sampling for other investigations.

Flow cytometric immunophenotyping of blood samples was performed using five colour flow cytometer (Beckman Coulter FC500 Flow Cytometer). Samples were processed using stain-lyse-wash technique. A four colour analysis was performed using antibody bound to following flurochromes, fluorescein isothiocynate (FITC), Phycoerythrin (R Phycoerythrin), Phycoerythrin-Cyanine 5 (R Phycoerythrin-Cyanin 5.1), R Phycoerythrin-Texas Red-X. Antibodies included were provided by Beckman Coulter and included a cocktail of CD16FITC, CD56PE, CD3ECD and CD45PC5. Flow cytometric data was acquired using CoaXPress acquisition software. Each tube was run on instrument as per panel and events were acquired in the form of dot plots. Maximum number of possible events (upto 1 lakh) was acquired. Gating was done using forward scatter (FSC) vs side scatter (SSC), CD45 vs SSC, CD56 vs CD3, CD56 vs. CD16. The data was stored in list mode files and was analysed using CXP analysis software for total percentage and absolute numbers of total NK cells and its various subsets.

The enzyme-linked immunosorbent assay (ELISA) was also done on the serum samples of the same patients for TNF alpha and IFN gamma using Diaclone kit made in France with a sensitivity of 8 pg/ml.

Ethical clearance was obtained from Ethics Committee for Human Research, Lady Hardinge Medical College, New Delhi.

Results

The various demographic and clinical parameters are listed in Table 1. According to the percentage of total NK cells (CD56+CD3-), the infertiles and fertiles were divided into 3 groups comprising of < 5 % NK cells, 5-12% NK cells and > 12% NK cells as shown in Table 2. These results showed that most of the infertiles and fertiles had NK cells in the range of 5-12% and only 6 infertile women and 6 fertile controls showed NK cells > 12%. The mean value of total PB NK cells and their various subsets is given in Table 3. These results showed that the percentage of CD56+CD16+, CD56dim CD16+ PB NK cells was significantly raised in infertile women compared to fertile controls whereas the percentage and absolute count of CD56+CD16- and CD56dimCD16- was significantly raised in fertile controls compared to infertile patients. The rest of the subsets did not show any significant difference between the two groups. The mean serum levels of TNF-α and IFN-γ in infertile group were higher but did not show any significant difference compared to the controls as shown in Table 4. Fig. 1 shows flow cytometric findings of an infertile patient. Fig. 2 shows flow cytometric findings of fertile control.

Table 1. Demographic and clinical parameters of patients and controls.

Parameters	Patients	Controls
Number	31	33
Age (mean in yrs.)	27.03	29.64
Type of infertility	20-primary	-
	11-secondary	
Number of live births (range)	0-1	1-4
Any history of abortion	10/31	1/33
History of tubal ectopic pregnancy	3/31	0

Table 2. Distribution of total natural killer cells in patients and controls.

		Group		Total	Chi-square	p value
		Patients	Control			
Total NK cells % (CD56+CD3-)	0-5%	6	9	15		
	5-12%	19	18	37		
	> 12%	6	6	12		
Total		31	33	64	0.565	0.754

NK: natural killer

Table 3. Mean value of total peripheral blood natural killer cells and its various subsets in patients and controls.

Parameter	Patients (mean) (percentage / absolute value)	Controls (mean) (percentage / absolute value)	p value (percentage / absolute value)
Total NK cells (CD56+CD3-)	8.12 / 139.71	7.70 / 153.85	0.684 / 0.587
CD56 bright CD3- NK cells	0.58/11.71	0.44/8.42	0.512/0.557
CD56 dim CD3- NK cells	7.54/128.03	7.26/146.64	0.779/0.455
Ratio of CD56dim NK cells/ CD56bright NK cells	31.36	18.06	0.034
CD56+CD16+	7.04 / 120	4.96 / 96.15	0.034 / 0.288
CD56dimCD16+ (out of total NK cells)	81.02 / 111.97	60.49 / 92.33	0.004 / 0.369
CD56brightCD16+ (out of total NK cells)	4.47 / 8.10	2.82 / 3.76	0.242 / 0.35
CD56+CD16-	1.08 / 19.65	2.74 / 58.91	0.017 / 0.022
CD56dim CD16-(out of total NK cells)	11.31 / 15.91	31.86 / 54.24	0.002 / 0.02
CD56brightCD16- (out of total NK cells)	2.69 / 3.74	4.60 / 4.67	0.089 / 0.466

PB: peripheral blood, NK: natural killer, CD: cluster of differentiation.

Table 4. Comparison of serum IFN-γ AND TNF-α levels (pg/ml) between patients and controls.

	TNF-α		IFN-γ	
	Patients	Controls	Patients	Controls
N	31	33	31	33
Mean	40.49	19.72	5.89	3.39
Median	16.5	10.3	1.37	2.06
Std. Deviation	62.56	37.29	11.53	5.96
p-value	0.109		0.275	

IFN-γ: interferon-gamma, TNF-α: tumor necrosis factor-alpha

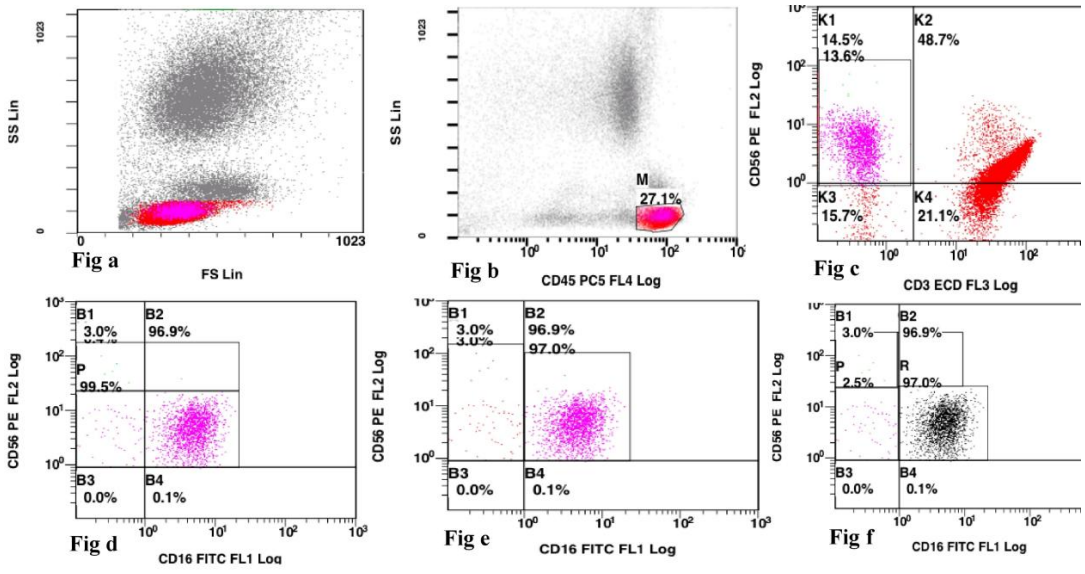

Fig. 1. Flow cytometric findings of an infertile woman a) Side scatter vs CD45 showing the percentage of gated lymphocytes out of total leucocytes = 27.1%. b): CD56 vs CD3 showing total NK cells which are CD56+CD3-:13.6%(pink). c): CD56 vs CD16 show that out of total NK cells, 99.9% are CD56+CD16+ NK cells and 0.1% are CD56+CD16- NK cells. d-e): CD56 vs CD16 showing percentages of various subtypes of NK cells out of total NK cells: CD56brightCD16+ NK cells: 97% and CD56dimCD16+ NK cells: 3%, CD56brightCD16- NK cells: 2.5%, CD56dimCD16- NK cells: 0%.

CD: cluster of differentiation, NK: natural killer.

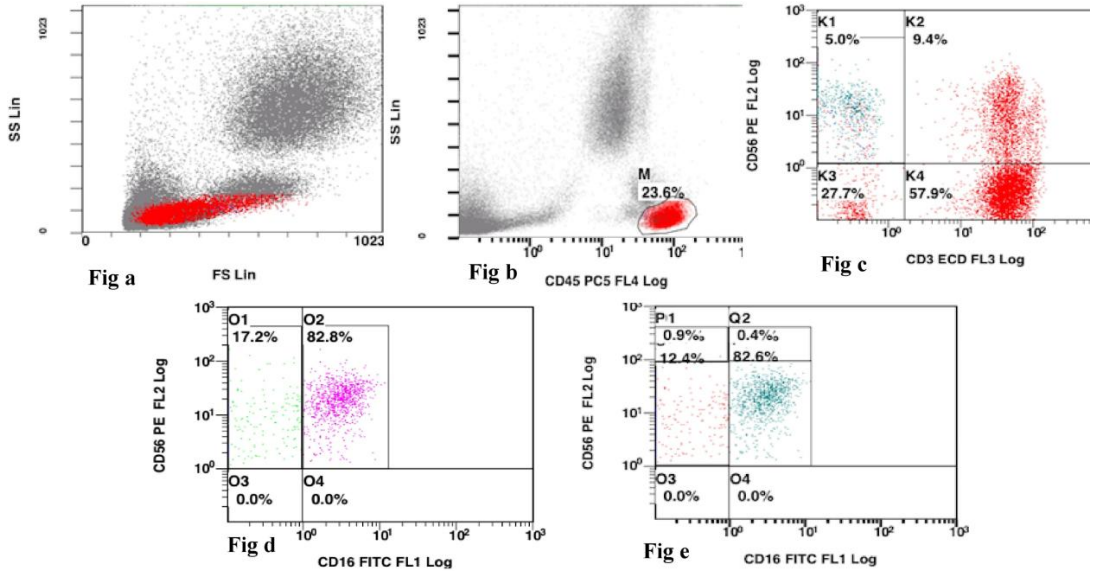

Fig. 2. Flow cytometric findings of a fertile control a): SSC vs CD45: Showing gated lymphocytes =23.6%. b):CD56 vs CD3 showing total CD56+CD3- NK cells (pink) out of total lymphocytes:5%. C-d): CD56 vs CD16 showing percentage of all the subtypes of NK cells out of total NK cells; CD56+CD16- NK cells:82.8%, CD56+CD16+ NK cells: 17.2%, CD56brightCD16+NK cells: 0.4%, CD56dimCD16+ NK cells: 82.6%CD56brightCD16- NK cells: 0.9%, CD56dimCD16- NK cells: 12.4%.

SSC: side scatter, CD: cluster of differentiation, NK: natural killer.

Discussion

Infertility is an increasing medical and social issue. Immune system plays a definite role in implantation process of the embryo. Since many years, unexplained infertility has been suspected to have an immunological basis[20]. A study by Park et al[21] reported that the levels of peripheral NK (pNK) cells mirror those of decidual NK (dNK) cells, suggesting that pNK cell measurement may serve as a clinically valuable marker for predicting pregnancy outcomes. Although some other studies have refuted this claim[22, 23].

Many studies have tried to find out the relationship between altered PB NK cell parameters and RPL[12, 13]. It is speculated that an elevation of natural killer (NK) cells may have an effect on reproductive performance, and PB NK cell levels are currently being used as a diagnostic test to guide the initiation of therapies in patients with infertility. However, not much research has been done regarding the various NK cell parameters in women with UI. So, in this study we have tried to evaluate the percentage and absolute count of NK cells and its subsets along with levels of Th1 cytokines to determine their diagnostic utility and as a therapeutic target in women with unexplained infertility and compared them with that of healthy fertile women.

It has earlier been reported that the normal percentage of total NK (CD56+CD3-) cells in peripheral blood is around 5-12% and >12% was taken as elevated NK cell percentage [24], so the infertiles and fertiles were divided into 3 groups: - < 5 % NK cells, 5-12% NK cells and >12% NK cells. Most of the infertiles and fertiles had normal range (5-12%) of NK cells and only 6 infertile women and 6 controls show NK cells >12%. So, no single cut off value could be established as normal NK cell count.

A few previous studies[25] have reported the percentage of total PB NK cells (CD56+) to be significantly higher in infertile subjects with multiple IVF failures compared to fertile controls. However, in the present study, the percentage and the absolute count of total PB NK cells did not show a significant difference between the two groups.

Two clearly different subgroups of human NK cells are identified by cell surface expression of CD56 (D56bright or CD56dim). Although both PB NKcells and uterine NK (uNK) cells show the surface CD56, however PB NK cells differ from uNK cells in both phenotypically and functionally with the fact that almost 10% of pNK cells are similar to uNK cells[26]. There are two main subsets of PB NK cells: the majority (more than 90%) which lyses target cells express CD56 at low density and CD16, and referred to as CD56dim CD16+ cells; while approximately 10% of PB NK cells have high surface expression of CD56, but do not express CD16, and are referred to as CD56bright CD16– cells. These PB NK cells have little or no cytotoxic activity but produce abundant cytokines. The relationship between these two main subsets of PB NK cells is not very clear; and they may play completely different roles in the human immune response[27].

Our study showed a significant increase in the mean ratio of the percentage of CD56dim and CD56 bright cells in infertiles than in fertiles. Only a few previous studies have calculated this ratio, which was higher but not significant[25]. Our study did not show any significant difference in the percentage of CD56dim cells similar to the findings reported by McGrath et al[28].

The mean percentage of CD56+ CD16+ NK cells was significantly raised in women with UI compared to fertile controls. The mean absolute count was also raised in women with unexplained infertility compared to fertile controls, however it did not reach statistically significant levels. This is in concordance with the finding of Fukui et al[29] who reported that on the day of embryo transfer in IVF patients, the percentage of these cells was significantly higher ($p < 0.05$) in the failed group than in the implanted group.

Mardanian et al[30] reported that women with failed IVF had significantly higher levels ($p < 0.0001$) of CD56dim CD16+ NK cells compared to fertile women. The mean percentage of peripheral blood

CD56dim CD16+ NK cells out of total NK cells was significantly raised in infertile group compared to the fertile group between the two groups. The mean percentage and absolute count of CD56bright CD16+ NK cells which constitutes a minor subset of CD56+CD16+ NK cells did not show any significant difference.

This shows that although the total CD56+(dim + bright) CD16+ NK cells and its major subpopulation, CD56dim CD16+ NK cells were significantly increased in infertile women, CD56bright CD16+ which constitutes a minor subset, did not show any difference between the two groups. There are no published studies to have reported the levels of this particular subset (CD56bright CD16+) in peripheral blood comparing infertile and fertile women.

The mean percentage and absolute count of peripheral blood CD56+CD16- NK cells showed a significant increase in fertile control group compared to infertile women. Similar results were seen in the study done by Michou et al[31].

The mean percentage and absolute counts of CD56bright CD16-, constituting the major population of NK cells in endometrium (uterine NK cells) but a minor subset of total NK cells in peripheral blood were increased in fertile controls compared to infertile women, they did not reach statistically significant levels. This finding is important as these cells are known to take part in successful implantation of the embryo and increase in normal pregnancy. So, these cells being more in fertiles in PB also supports this evidence. Mardanian et al [30] reported no significant differences in these cells in women with failed IVF and with successful IVF.

The mean percentage and absolute counts of CD56dim CD16- NK cells, which constitutes a minor subset of CD56+ CD16- NK cells, showed a significant increase in fertile controls compared to infertile women.

To the best of our knowledge, no study till date has reported the levels of this particular subset (CD56dim CD16-) in peripheral blood comparing infertile and fertile women. So, this subset of NK cells could prove to be a useful marker in infertile women, however more studies with larger sample size are required to prove this finding.

Normal pregnancy has been associated with a shift from Th-1 type and a bias towards Th-2 response[32]. The mean serum levels of TNF-α in infertile group were higher than the fertile group but were not statistically significant ($p = 0.109$). Few previous studies[33] have reported a significant increase in infertile women and with failed IVF treatment respectively compared to controls. These studies corroborated with our finding of raised serum levels of TNF-α in infertile group compared to the fertile group but our results did not reach statistically significant levels which may be because of smaller sample size. Studies done by Okpalaji et al[20] reported that mean serum TNF-α levels in infertile women were not significantly different ($p = 0.26$ and $p = 0.902$ respectively) from fertile women.

The mean serum levels of IFN-γ in infertile group was higher than in control group was but was statistically not significant ($p = 0.275$). Previous study by Thum et al[34] reported a similar finding in women after IVF, although the levels were raised but showed no statistically significant difference between non-pregnant and pregnant group and between miscarriage and live birth group which is in concordance with our study. Okpalaji et al[20] reported that infertile women had significantly raised levels of serum TNF-α compared to fertile controls.

Thus, it is shown in our study that CD56+CD16+ NK cells which constitute the major population of PB NK cells and its major subset, CD56dim CD16+ NK cells was significantly raised in unexplained infertile women as shown in many previous studies. CD56+CD16- NK cells which is a minor population of PB NK cells was significantly raised in fertile women compared to women with unexplained infertility. However, its major subset, CD56bright CD16- was also raised in fertile controls but it did not reach statistically significant levels. Although most previous studies[25] report that total PB NK cells was significantly higher in infertile women compared to

fertile controls, in our study the percentage of total peripheral blood NK cells in infertile group was higher but statistically not significant compared to fertile controls. According to a previous study[24], the normal percentage of NK cells in PB is 5-12% and > 12% is taken as elevated NK cell percentage. However, in our study, most of the infertiles and fertiles had NK cells in the range of 5-12% and only 6 infertile women and 9 controls showed NK cells >12%. The mean serum levels of TNF-α and IFN-γ in infertile group were higher but statistically not significant compared to fertile group.

Conclusion

This study can provide an insight into the pathophysiology of unexplained infertility which shows significantly altered NK cell parameters which can be treated using various therapies like IVIg and steroids. This is the first study that has calculated all the major subsets of PB NK cells using flow cytometry in UI and fertile women. However, the major limitation of this study was the small sample size and overlapping values of total NK cells and its subsets, serum levels of TNF-α in infertiles and fertiles. So, further large-scale studies are required to confirm our findings.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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