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Changes of natural killer cell activity in normal pregnant and postpartum women: Increases in the first trimester and postpartum period and decrease in late pregnancy

Y. Hidaka^a, N. Amino^a, Y. Iwatani^a, T. Kaneda^a, N. Mitsuda^b, Y. Morimoto^c, O. Tanizawa^b and K. Miyai^a

Departments of ^aLaboratory Medicine and ^bObstetrics and Gynecology, Osaka University Medical School; and ^cAizenbashi Hospital, Osaka (Japan)

Correspondence: Dr. Nobuyuki Amino

Department of Laboratory Medicine,
Osaka University Medical School,

1-1-50 Fukushima, Fukushima-ku, Osaka 553, Japan

Summary

Changes in the activity and number of natural killer (NK) cells in peripheral blood in normal pregnant and postpartum women were examined. NK activity was measured in a 4-hr ^{51}Cr -release assay and evaluated by conventional relative lytic units and absolute lytic units which represent the total NK activity within a fixed volume of circulating blood. The number of NK cells was analyzed with FITC-conjugated monoclonal antibodies and by use of an automated flow cytometer. Unexpectedly the relative NK activity increased in the first trimester ($n=34$; 27.4 ± 14.4 relative lytic units (RLU), $P < 0.01$) and also for one month postpartum ($n=36$; 25.2 ± 15.5 RLU, $P < 0.05$) compared to the activity in normal non-pregnant controls ($n=58$; 19.6 ± 11.8 RLU). On the other hand, absolute NK activity decreased in the third trimester ($n=36$; 26.1 ± 16.0 absolute lytic units (ALU), $P < 0.05$) compared to the activity in normal non-pregnant controls (36.5 ± 23.0 ALU). The percentage of $\text{CD}57^+$ cells decreased in the second trimester, but the percentage of $\text{CD}16^+$ cells did not change during pregnancy or the postpartum period. The absolute counts of $\text{CD}57^+$ cells and $\text{CD}16^+$ cells decreased in the second and third trimesters and increased transiently in the postpartum period. These findings indicate that the increased NK activity in the first trimester and at one month postpartum is induced by increased cytotoxic activity of individual NK cells, and that the decreased NK activity in late

pregnancy is induced by a decreased numbers of NK cells. These physiological changes may play an important role in implantation in early pregnancy, protection of allograft in late pregnancy and in the natural defense against infection during the pureperal period.

Key words: natural killer cells; NK activity; pregnancy;
puerperium.

Introduction

Natural killer (NK) cells are usually defined as a small subpopulation of lymphocytes which have the capacity to kill malignant and virus-infected cells without prior sensitization (Herberman et al., 1975; Trinchieri and Santoli, 1978). Furthermore, NK cells function as suppressor cells on immunoglobulin synthesis (Arai et al., 1983) and may relate to allograft rejection (Nemlander et al., 1983).

Pregnancy is one example of successful allograft for 10 months. However, the exact mechanisms involved in the maternal prevention of fetal-allograft rejection is not fully understood. In human pregnancy, a variety of studies resulted in conflicting results, with a suggested tendency toward a decrease of NK activity (Baines et al., 1978; Okamura et al., 1984; Tartof et al., 1984; Toder et al., 1984a; Gregory et al., 1985a,b; Baley and Schacter, 1985; Hill et al., 1986; Lee et al., 1987), although most of the information available relates to the second and third trimesters. Moreover, there are few reports on NK activity in the postpartum period (Gregory et al., 1985b; Hayslip et al., 1988). Recently, we reported that peripheral large granular lymphocytes, which possess a variety of cytotoxic activities related to NK, K and cytotoxic T lymphocytes, increased in the first trimester and decreased in the third trimester (Iwatani et al., 1989).

In this study, therefore, we have analysed changes in NK cell activity and cell number in normal pregnant and postpartum women. In particular, NK cell activity was evaluated by conventional relative lytic units and also by absolute lytic units, which represent the total NK activity within a fixed volume of circulating blood.

Materials and methods

Subjects

The subjects studied were 111 healthy pregnant women: 34 in the first trimester (7-13 weeks; mean age: 30.1 ± 4.3 years old), 41 in the second trimester (14-27 weeks; 29.5 ± 5.0 years old), 36 in the third trimester (28-40 weeks; 28.9 ± 4.5 years old); 126 healthy postpartum women (36 at 1 month postpartum, 29.8 ± 3.6 years old; 40 at 4 months postpartum, 28.3 ± 4.3 years old; 30 at 7 months postpartum, 28.5 ± 4.0 years old; and 20 at 10 months postpartum, 30.1 ± 4.7 years old); and 58 healthy non-pregnant women as controls (29.4 ± 6.0 years old). The mean age of each group was not significantly different. Samples of peripheral venous blood from individual subjects were taken from 2:00-3:00 p.m. None of the subjects were receiving any medication. Subjects with subclinical autoimmune diseases, which were judged by measuring serological tests including anti-nuclear antibody, anti-DNA antibody, rheumatoid factor, anti-thyroglobulin antibody, anti-thyroid microsomal antibody, and anti-mitochondrial antibody, were excluded from this study.

Differential Leukocyte Counts

Leukocyte, lymphocyte and monocyte counts were obtained using an automated leukocyte differential system, Total Hematology Management System H-6000 (Technicon Co., Tarrytown, NY),

based on principles of cytochemistry, electrooptical measurement, and signal logic processing (Mansberg et al., 1974).

Monoclonal Antibodies

Fluorescein-isothiocyanate (FITC) conjugated monoclonal antibodies, anti-CD20 (B1) (Coulter Immunology, Hialeah, FL), anti-CD57 (Leu 7), anti-CD16 (Leu 11), and anti-CD19 (Leu 12) (Becton Dickinson, Mountain View, CA) were used.

Lymphocyte Subpopulations

Lymphocyte subpopulations were analyzed with the FITC-conjugated monoclonal antibodies described above in an Ortho Spectrum III automated flow cytometer (Ortho Diagnostic Systems, Westwood, MA) using whole blood as a sample (Stephan et al., 1982). Briefly, samples of 100 μ l of EDTA-treated whole blood were incubated for 30 min at 4 °C with 10 μ l of FITC-conjugated monoclonal antibodies, and shaken at 10-min intervals. The samples were then hemolyzed with 0.83% ammonium chloride and subjected to flow cytometry. The lymphocyte fraction in the hemolyzed blood was analysed, excluding other fractions such as granulocytes, monocytes and platelets, on the basis of the forward angle and 90° light-scattering properties to determine the percentage of each subset in total lymphocytes. The absolute counts of lymphocyte subpopulations in whole blood were calculated as the products of the absolute lymphocyte count and the

percentages of each lymphocyte subpopulation.

Assay of Natural Killer Cell Activity

Peripheral blood mononuclear cells were isolated from 5ml of heparinized blood samples by Sepracell MN, a colloidal silica separation medium (Sepratech Co., Oklahoma) (Visser et al., 1988). Briefly, heparinized blood samples were mixed with equal volumes of Sepracell-MN and were centrifuged at $1,500 \times g$ at room temperature for 20 minutes. Mononuclear cells (opalescent compact band just below the meniscus) were removed and were washed twice with a phosphate-buffered saline solution. The cells were then suspended in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 μ g/ml streptomycin (complete medium), and then incubated in a nylon wool column (Wako Pure Chemical Industries, Ltd., Osaka, Japan) at 37 °C for 1h to remove monocytes and B-cells. Non-adherent cells were gently eluted with a pre-warmed medium, washed, counted by a Coulter counter model D and resuspended at 2.5×10^6 cells/ml in a complete medium. These nylon wool column-passed mononuclear cells contained fewer than 2% monocytes as judged by peroxidase staining, and fewer than 1.5% B cells as judged by anti-CD19 (B cells) monoclonal antibody, and they were used as effector cells in the cytotoxicity assay.

Cytotoxicity was measured by means of a 4-h ^{51}Cr release assay. The human erythroleukemic cell line K562 was used as the

target cell. Target cells (2×10^6) were radio-labeled with 3.7 MBq $\text{Na}_2^{51}\text{CrO}_4$ (Daiichi, Tokyo, Japan) at 37 °C for 1h with occasional shaking. Labeled target cells (5×10^3) in 100 μl of a complete medium were mixed with varying numbers of effector cells (100 μl) in a 96-well U-bottomed microtiter plate (Coster, Cambridge, MA) to give final E:T ratios of 50:1, 25:1, and 12.5:1. Each assay was performed in triplicate. The plates were centrifuged for 5 min at 1000 rpm, and then incubated for 4h at 37 °C in a humidified atmosphere with 5% CO_2 in air. After incubation and recentrifugation, aliquots (100 μl) of the supernatant were removed from each well, and their radioactivity was determined in a γ -counter.

Percentage of cytotoxicity was determined by the following formula:

$$\% \text{ cytotoxicity} = \frac{\text{experimental cpm} - \text{spontaneous cpm}}{\text{maximal cpm} - \text{spontaneous cpm}} \times 100$$

Spontaneous release was the radioactivity released in supernatants from target cells incubated in a complete medium only, and maximal release was that from target cells incubated in a complete medium containing 0.5 N HCl. Cytotoxic activity was expressed in two ways. Dose-response curves of NK cytotoxicity were determined by plotting percent cytotoxicity versus the number of effector lymphocytes. The number of lymphocytes necessary to lyse 30% of the target cells during the incubation time was referred to as 1 relative lytic unit (RLU). Determination of the

30% RLU was done graphically. RLU was expressed as $\text{RLU}/10^6$ lymphocytes so that the value increased with increasing lytic activity. In this study, we introduced the absolute lytic unit which represents the total NK activity within a fixed volume of circulating blood. Absolute LU (ALU) was calculated as the products of the CD20 negative lymphocyte count ($10^9/\text{l}$) and the RLU.

Statistical analysis

Statistical analysis of the data was carried out by the Student's t-test, or when variances were unequal, by the Mann-Whitney U-test.

Results

Relative NK activity, which expresses NK function in the non-B lymphocyte fraction, increased significantly in the first trimester and also at one month postpartum (Table 1). Individual values are shown in the Fig. 1. On the other hand, the mean value of absolute NK activity, which expresses the total cytotoxic activity in a fixed volume of circulating blood, was decreased both in the second and third trimesters, and the value in the last trimester reached statistical significance at $P < 0.05$ (Table 1). The percentage of lymphocytes in whole leucocytes decreased significantly throughout pregnancy. Mean values of the percentage of CD57 cells decreased during pregnancy and a statistical significance was reached only in the second trimester (Table 1). No significant change was observed in the percentage of CD16 cells. The absolute count of lymphocytes decreased significantly throughout pregnancy, but increased at 4 and 10 months postpartum. In association with these changes, the absolute count of CD57 cells decreased during pregnancy and increased significantly at 10 months postpartum. Similarly, the absolute count of CD16 cells decreased both in the second and third trimesters and increased at 4 months postpartum.

Within the first trimester, the relative lytic unit and absolute lytic unit increased significantly at 7-8 weeks of pregnancy as shown in Table 2.

In order to clarify the nature of increase in NK activity in the first trimester and at one month postpartum, the relative lytic unit of NK activity was divided by the percentage of CD16 cells, which indicates the cytotoxic activity of individual NK cells. This ratio was significantly increased in the first trimester (2.37 ± 1.47 , $p < 0.01$) and one month postpartum (2.16 ± 1.29 , $p < 0.05$) comparing to that of non-pregnancy (1.65 ± 1.01).

Discussion

In this study we newly found that NK activity increased in the early stage of pregnancy, especially 7-8 weeks of gestation. This result is different from previous results, which showed normal or decreased activity (Baines et al., 1978; Okamura et al., 1984; Tartof et al., 1984; Baley and Schacter, 1985; Lee et al., 1987). There are at least three possibilities to explain these discrepancies. Firstly, the assay method might have influenced the result. In our study monocytes were excluded from the mononuclear fraction. However, in some of the previous studies (Okamura et al., 1984; Tartof et al., 1984) NK activity was measured using mononuclear cells containing monocytes, which have a suppressing effect on NK activity (Yang and Zucker-Franklin, 1984). During pregnancy, peripheral monocytes increase, and thus, a mononuclear cell fraction including monocytes might show reduced NK activity. The second possibility involves the difference of examined gestational weeks. In this study, NK activity markedly increased in weeks 7-8, but a significant change was not found in weeks 9-13. Most of the studies reported did not describe the exact weeks of pregnancy (Baines et al., 1978; Okamura et al., 1984; Tartof et al., 1984). A third possibility is the difference in the number of subjects examined. Physiological changes are usually very small when comparing the difference between normal subjects and patients with an abnormal

disease. Especially in the cross-sectional study, we need plenty of subjects in order to obtain the statistical significance. However, all of the previous reports examined fewer than 12 subjects. By contrast, we examined more than 30 subjects in each group in this study.

Increased NK activity in early pregnancy is compatible with our own previous report that peripheral large granular lymphocytes increased in the first trimester (Iwatani et al., 1989). However NK activity measured in the systemic circulation may not necessarily be indicative of local NK activity within reproductive tissues at the maternal-fetal interface. NK activity has been detected in murine decidual cell suspensions, with peak activity occurring in early pregnancy and declining as pregnancy proceeds (Gambel et al., 1985). In humans, NK activity is also detected in decidua in the first trimester (Ritson and Bulmor, 1989; Manaseki and Searle, 1989). Considering these results, change of systemic NK activity is somewhat related to the local immunity in early pregnancy. We further clarified that increased NK activity in the first trimester was induced by the increased function of individual NK cells. This suggests that some humoral factor(s) may enhance NK cell function in vivo. Enhanced NK activity in early pregnancy may possibly be related to implantation, though it is uncertain whether this has a beneficial role for implantation or is simply a secondary reaction to implantation.

Consistent with previous reports (Baines et al., 1978; Okamura et al., 1984; Tartof et al., 1984; Gregory et al., 1985 a, b; Baley and Schacter, 1985; Hill et al., 1986; Lee et al., 1987), we found decreased NK activity (absolute lytic unit) in late pregnancy. Mean value of relative lytic unit was lower than that of non-pregnancy but could not reach to statistical significance between the two. Possibly absolute lytic unit is physiologically more important than the relative lytic unit. Pregnancy serum has been reported to inhibit NK cell activity in vitro (Barrett et al., 1982; Toder et al., 1984b), and some experiments showed that pregnant NK cells had a normal binding capacity but a depressed post-binding lytic function (Toder et al., 1984a; Baley and Schacter, 1985). In this study, however, we found that decreased NK activity is induced by the decreased number of NK cells. The exact mechanism for depressed NK activity in late pregnancy should be examined further. In any case, the inhibition of NK activity in the third trimester seems to be a useful adaptation to help ensure fetal survival.

Examination of immunological changes is important not only during pregnancy but also after delivery, since autoimmune diseases frequently develop during the postpartum period (Amino et al., 1982). However, little is known about NK activity in puerperium. We observed a transient increase of NK activity at one month postpartum for the first time. Such a rapid increase of NK activity suggests that activation of lymphocyte-mediated

cytotoxicity may occur in the postpartum period. Indeed, K cells with ADCC activity have been observed to increase in the postpartum period (Asari et al., 1989). The puerperal period is considered to be a vulnerable time for the host defence system because considerable changes in maternal immunity occur after delivery, as shown in the postpartum changes of lymphocytes in this study. Thus, the dynamic postpartum change in NK activity may contribute to a natural defence against puerperal infection. We reported that peripheral large granular lymphocytes increased in postpartum autoimmune thyroiditis (Iwatani et al., 1988). These findings suggest that the physiological increase of NK activity may be one factor that aggravates autoimmune diseases in the postpartum period.

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Figure legends

Fig. 1. Changes of relative lytic units of NK cells in normal pregnant and postpartum women. Each horizontal bar represents the mean.

Fig 1

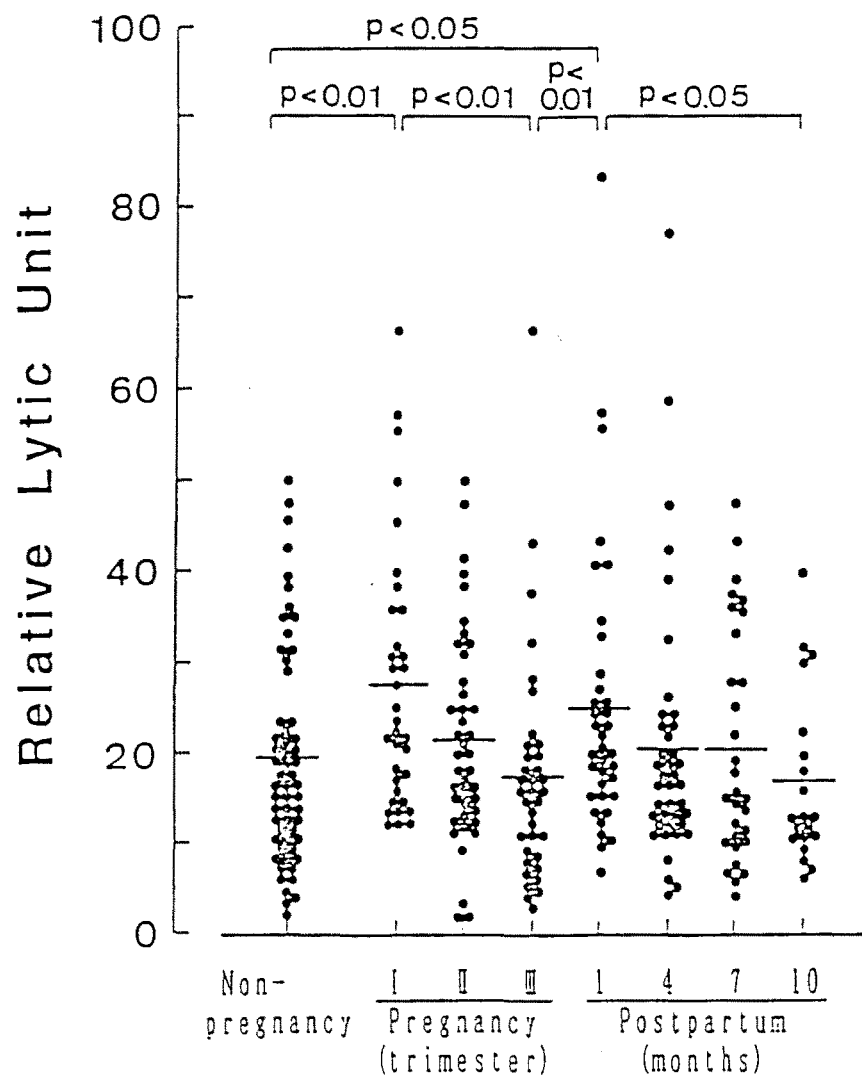


TABLE 1.
Changes in NK activity and NK cell number during pregnancy and in the postpartum period.

	Non- pregnancy	Pregnancy (trimester)			Postpartum (months)				
		First	Second	Third	1	4	7	10	
No. examined	58	34	41	36	36	40	30	20	
NK activity									
Relative lytic unit ^a	19.6 ± 11.8	27.4 ± 14.4**	21.7 ± 11.6	17.6 ± 12.4	25.2 ± 15.5*	20.7 ± 14.5	20.7 ± 12.7	16.8 ± 9.5	
Absolute lytic unit ^b	36.5 ± 23.0	42.8 ± 25.7	31.5 ± 17.5	26.1 ± 16.0*	43.8 ± 26.4	41.2 ± 31.0	38.6 ± 25.3	35.6 ± 26.6	
Cell count									
Percentage									
Lymphocytes	36.5 ± 6.4	23.0 ± 7.4***	21.5 ± 6.0***	22.6 ± 5.5***	35.0 ± 7.9	37.6 ± 5.8	37.5 ± 7.0	38.6 ± 6.2	
CD 57	16.6 ± 3.3	15.8 ± 3.6	15.3 ± 3.1*	16.0 ± 4.1	15.7 ± 2.7	16.3 ± 3.9	15.5 ± 3.2	17.3 ± 2.8	
CD 16	12.6 ± 2.9	12.7 ± 3.3	12.8 ± 3.5	12.4 ± 3.0	11.9 ± 2.0	13.5 ± 3.4	12.2 ± 3.4	12.4 ± 3.3	
Absolute count (10 ⁹ /L)									
Lymphocytes	2.13 ± 0.42	1.88 ± 0.41**	1.76 ± 0.37***	1.86 ± 0.48**	2.11 ± 0.42	2.39 ± 0.59 *	2.27 ± 0.57	2.44 ± 0.51*	
CD 57	0.36 ± 0.10	0.30 ± 0.10*	0.27 ± 0.07***	0.30 ± 0.11**	0.33 ± 0.08	0.39 ± 0.14	0.36 ± 0.13	0.42 ± 0.11*	
CD 16	0.27 ± 0.09	0.24 ± 0.10	0.22 ± 0.07**	0.23 ± 0.09*	0.25 ± 0.06	0.32 ± 0.12 *	0.28 ± 0.11	0.31 ± 0.11	

Data are expressed as mean ± S.D.

a NK activity in non-B lymphocyte fraction

b Product of relative lytic unit and absolute non-B cell count (10⁹/L)

* P<.05 vs. value for non-pregnant controls.

** P<.01 vs. value for non-pregnant controls.

*** P<.001 vs. value for non-pregnant controls.

TABLE 2

NK activity in early normal pregnancy

Pregnancy (Weeks)	No. examined	NK activity	
		Relative lytic unit ^a	Absolute lytic unit ^b
7- 8	12	30.6 \pm 16.3**	53.3 \pm 30.6*
9-10	13	26.4 \pm 16.1	38.8 \pm 27.2
11-13	9	25.4 \pm 10.3	33.9 \pm 11.4
Non-pregnant controls	58	19.6 \pm 11.8	36.5 \pm 23.0

Data are expressed as mean \pm S.D.

a NK activity in non-B lymphocyte fraction.

b Product of relative lytic unit and absolute non-B cell count(10^9 /L).* $P < .05$ vs. value for non-pregnant controls.** $P < .01$ vs. value for non-pregnant controls.