

Changes in immune activation markers during pregnancy and postpartum

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Abstract

Changes in CD4+ cell levels and other immune parameters have been reported to occur during pregnancy but the timing of these alterations and their relationship to changes in immune function have not been well characterized. In addition, the influence of sociodemographic, obstetric, and other covariates on these relationships is largely unknown. We measured three immune activation markers, soluble interleukin-2 receptor (sIL-2R_α), soluble CD8 antigen (sCD8), and neopterin during pregnancy and postpartum in 170 HIV-1-seronegative women enrolled in the Mothers and Infants Cohort Study. Ante-partum and postpartum changes in these markers were examined using multivariable longitudinal random effects models. Neopterin levels began to rise well before delivery and were in decline by 2 months postpartum. sIL-2R_α and sCD8 levels increased at or near delivery and peaked by 2 months postpartum. After adjustment for other variables, the peak in sIL-2R_α was greater among women with pre-term than full-term deliveries ($P = 0.05$). All three markers were higher in whites than non-whites and in 'hard' drug users than non-users ($P \leq 0.001$ for

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each). After adjustment for these and other variables, hepatitis C virus (HCV) seropositivity was associated with higher levels of sCD8 and neopterin ($P \leq 0.001$ for each) but not sIL-2R_α ($P = 0.27$). These longitudinal data indicate that a state of broad immune activation develops at or near delivery. A number of maternal variables appear to influence the magnitude of these changes. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

A number of observations, including survival of the fetal allograft and an increase in the frequency and severity of certain infectious diseases, have long been interpreted as evidence that at least some immune responses are depressed during pregnancy (Greenberg et al., 1958; Pickard, 1968; Weinberg, 1984; Pope, 1990; Wegmann et al., 1993; Rich et al., 1995; Mast et al., 1996; Chaouat and Menu, 1997; Raghupathy, 1997). Many investigators have sought to identify the mechanisms involved but their results have been inconclusive and, at times, conflicting. For example, peripheral blood CD4+ and CD8+ cell levels have been reported to decline, remain unchanged, and increase during pregnancy (Sridma et al., 1982; Vanderbeeken et al., 1982; Barnett et al., 1983; Glassman et al., 1985; Castilla et al., 1989; Miotti et al., 1992; Johnstone et al., 1994; Brettle et al., 1995; Burns et al., 1996).

More important, perhaps, than changes in immune cell numbers and proportions are alterations in immune function. One indication of immune activation is the release of soluble factors such as interleukin-2 (IL-2) receptor, CD8 antigen, and neopterin. Soluble IL-2 receptor (sIL-2R_α) has been shown to be a sensitive and quantitative marker of T cell activation and proliferation (Rubin et al., 1985; Rubin and Nelson, 1990). Activation of T cells is associated with increased cell-surface expression of IL-2R_α (CD25). IL-2R_α has been shown to associate with IL-2R_β and IL-2R_γ to form a high affinity receptor that binds IL-2, inducing T cell proliferation and release of soluble IL-2R_α (Rubin and Nelson, 1990; Treiber-held et al., 1996). sIL-2R_α is elevated in autoimmune and other inflammatory disorders, allograft rejection, certain malignancies, and infectious diseases (Rubin and Nelson, 1990).

The interaction of CD8+ T cells with HLA class I antigen-bearing target cells results in CD8+ cell activation and release of soluble CD8 antigen (sCD8) (Fujimoto et al., 1983, 1984; Tomkinson et al., 1989). Whereas release of sIL-2R_α is generally taken to reflect T cell proliferation, a rise in sCD8 appears to mark the effector phase of the immune response (Treiber-held et al., 1996; Tomkinson et al., 1989; Hofmann et al., 1992). During

measles infection, for example, sIL-2R_α levels begin to rise during the prodromal period, whereas sCD8 levels increase with the onset of rash (Griffin et al., 1989).

Neopterin is produced primarily by activated monocytes and macrophages when stimulated by interferon (IFN)- γ released by activated T cells and natural killer (NK) cells (Huber et al., 1984; Wachter et al., 1989). IFN- γ also induces monocytes to express HLA-DR, stimulates their production of the pro-inflammatory, T helper type 1 (Th1) cytokine tumor necrosis factor-alpha (TNF- α), and downregulates the anti-inflammatory, T helper type 2 (Th2) cytokine IL-10 (Donnelly et al., 1995; Docke et al., 1997). Like sIL-2R_α, neopterin is typically elevated during allograft rejection and with the development of certain malignancies, infectious diseases, and autoimmune disorders (Wachter et al., 1989).

The current study was undertaken to examine changes in sIL-2R_α, sCD8, and neopterin during pregnancy and postpartum and to assess the influence of selected covariates such as age, race, pre-term delivery, drug use, and chronic viral infection.

2. Materials and methods

2.1. Study participants

The Mothers and Infants Cohort Study enrolled pregnant women at five study sites in Brooklyn and the Bronx, New York between January 1986 and January 1991. Both HIV-1-seropositive and seronegative pregnant women were enrolled at each study site, as previously described (Burns et al., 1994). Informed, witnessed, signed consent was obtained from each woman. The study was approved by the Institutional Review Board of each institution. HIV-1-seronegative women that delivered live-born infants and who had one or more serum and/or plasma repository specimens of sufficient pre-determined volume were included in the current study.

2.2. Data collection

Standardized interviews and physical examinations were performed, and blood was drawn at enrollment, during the sixth and eighth months of pregnancy, at 2 and 6 months postpartum, and at 6 month intervals thereafter up to 4 years post delivery. For the current analysis, plasma or serum specimens from the following study periods were examined: 14–23, 24–31, 32–36, and ≥ 37 weeks gestation ante-partum and 2, 6, and 12 months (6–14, 20–32, and 46–58 weeks, respectively) post-delivery. To

reduce the likelihood that parturition influenced assay results, specimens collected < 48 h prior to delivery were not included. Information regarding substance use was obtained by confidential interview at enrollment and during the eighth month of pregnancy. ‘Hard’ drug use was defined as any injection drug use or cocaine use by any route. Gestational age was determined by pediatric examination at delivery. If this was unavailable, ante-natal ultrasound or ante-natal obstetric evaluation (in that order) was used.

2.3. Laboratory methods

Plasma was obtained from heparinized blood shipped overnight at room temperature to a central repository. Serum was frozen at -70°C until shipped overnight to the central repository on dry ice. All serum and plasma aliquots were stored at the central repository at -70°C until shipped overnight on dry ice to a research laboratory. All three immune activation marker assays were performed at the same laboratory (Center for Interdisciplinary Research in Immunology and Disease, UCLA Center for the Health Sciences, Los Angeles, CA). sIL-2R $_{\alpha}$ and sCD8 were measured using enzyme immunoassay test kits supplied by T Cell Diagnostics, Cambridge, MA. Neopterin was measured using a radioimmunoassay double antibody technique (Henning Berlin GMBH, Berlin, Germany).

Stored sera were screened for hepatitis C virus (HCV) antibodies with a second or third-generation EIA (Ortho Diagnostic Systems, Raritan, NJ, USA) and confirmed by a second-generation radioimmunoblot assay (RIBA2, Chiron Corporation, Emeryville, CA, USA). All of the women in this analysis cohort were seronegative for HIV-1 by one or more commercially available enzyme-linked immunosorbent assays (ELISA).

2.4. Statistical analysis

Overall associations between each immune activation marker and specific covariates were first assessed adjusting only for the study period during which the individual measurements were made. To examine changes over time, a multivariable longitudinal analysis was also performed for each activation marker (Laird and Ware, 1982). Correlations between markers were examined with Spearman’s rank correlation. SAS procedures were utilized (SAS Institute, Cary, NC).

Age, race, number of prior pregnancies, pre-term delivery (prior to 37 weeks gestation), hard drug use during pregnancy (cocaine and heroin injection drug use, other hard drug use, or neither), cigarette use during pregnancy, HCV serostatus, and maternal peripartum fever, peripartum

infection, and clinical chorioamnionitis were examined for inclusion as covariates in the multivariable analyses. Covariates associated with longitudinal changes in the marker under study were included in the final models.

3. Results

3.1. Characteristics of study subjects

A total of 194 HIV-1-seronegative mother-infants sets were enrolled, including 12 maternal re-enrollments during subsequent pregnancies. One or more repository specimens of sufficient pre-determined volume were available for 170 (93.4%) of the 182 unique women enrolled. To avoid inclusion of non-independent data, only specimens from a woman's first enrollment resulting in a live birth were tested. A total of 563 repository specimens were available for the 170 women (mean, 3.3 per woman). Specimens were collected during the periods 14–23 weeks gestation ($n = 78$), 24–31 weeks gestation ($n = 102$), 32–36 weeks gestation ($n = 78$), and ≥ 37 weeks gestation ($n = 49$) ante-partum and at two ($n = 109$), six ($n = 63$), and 12 ($n = 84$) months post-delivery from 66, 87, 75, 47, 109, 63, and 83 women, respectively.

Table 1 provides selected characteristics for the 170 women. As shown, roughly half of the women were above and below 30 years of age. Most were African-American or Hispanic, a majority were multiparous, and most had full-term deliveries. A substantial minority used cocaine and heroin or other hard drugs during the current pregnancy. A somewhat smaller number were hepatitis C virus (HCV) seropositive. Only 18.5% of women who were HCV seropositive were aware that they had ever had hepatitis; statistically, this was not significantly greater than the 9.8% of HCV seronegative women who reported ever being told by a physician that they had 'hepatitis of any kind' ($P = 0.19$).

3.2. Influence of covariates on overall levels of activation markers

As shown in Table 2, levels of each immune activation marker tended to be highest among non-Hispanic whites, lowest among African-Americans, and intermediate among Hispanics. Similarly, all three markers were highest in women who used both heroin and cocaine by injection, lower in women who used other hard drugs, and lowest in those who denied any hard drug use during the current pregnancy. Mean levels of all three markers were also higher among women who were HCV seropositive.

Table 2 also shows that sIL-2R_α and sCD8 levels were higher among cigarette smokers than non-smokers, sCD8 levels were higher among women < 30 than those ≥ 30 years of age, and sIL-2R_α levels tended to be higher among women who delivered preterm than among those who delivered full-term infants (< 37 weeks versus ≥ 37 weeks gestation). There was also a suggestion that sCD8 levels were reduced among women with one but not two or more prior pregnancies.

Table 1
Selected characteristics of the study population (*n* = 170)

	<i>n</i>	%
Age (years)		
< 20	2	(1.2)
≥ 20–29	86	(50.6)
≥ 30	82	(48.2)
Race/ethnicity		
African-American	90	(52.9)
Hispanic	62	(36.5)
White, non-Hispanic	15	(8.8)
Other	3	(1.8)
No. of prior pregnancies		
0	21	(12.4)
1	20	(11.8)
≥ 2	120	(70.6)
Unknown	9	(5.3)
Pre-term delivery ^a		
Yes	26	(15.3)
No	144	(84.7)
Substance use during pregnancy ^b		
Cigarettes	87	(51.2)
Cocaine and heroin ^c	13	(7.6)
Other hard drug use ^d	37	(21.8)
HCV serostatus ^e		
Positive	27	(15.9)
Negative	143	(84.1)

^a Less than 37 weeks gestation.

^b Refers to use after the first trimester of the current pregnancy. Cigarette and drug use were unknown for 10 and 7 women, respectively.

^c Use of both cocaine and heroin by injection.

^d Use of any drug by injection or cocaine by any route.

^e Proportion that were hepatitis C virus seropositive and seronegative.

Table 2

Mean soluble IL-2 receptor (sIL-2R_α), soluble CD8 (sCD8), and serum neopterin levels adjusted for time of measurement by selected variables^a

Variable	sIL-2R _α		sCD8		Neopterin	
	Mean (U/ml)	<i>P</i>	Mean (U/ml)	<i>P</i>	Mean (nmol/l)	<i>P</i>
Age (years)						
<30	546.8	0.06	451.5	0.02	7.4	0.72
≥30	478.7		404.8		7.3	
Race/ethnicity						
African-American	449.8	<0.001	366.2	<0.001	6.8	0.001
Hispanic	571.9		503.6		7.8	
White, non-Hispanic	690.1		550.1		9.3	
Other	668.2		498.2		7.4	
No. of prior pregnancies						
None	545.4	0.42	446.7	0.02	6.8	0.15
1	451.9		351.3		6.6	
≥2	512.0		437.9		7.6	
Unknown	600.2		447.8		7.6	
Pre-term delivery ^b						
Yes	608.4	0.04	464.6	0.15	7.9	0.21
No	496.9		421.9		7.3	
Cigarette use ^c						
Yes	559.2	0.02	492.4	<0.001	7.6	0.30
No	458.6		368.9		7.0	
Unknown	544.9		392.7		7.6	
Hard drug use ^c						
Cocaine and heroin ^d	816.6	0.001	592.0	<0.001	10.7	<0.001
Other hard drug use ^c	519.5		492.4		7.3	
None	480.9		397.1		7.0	
Unknown	574.9		385.8		7.5	

Table 2 (Continued)

Variable	sIL-2R _α		sCD8		Neopterin	
	Mean (U/ml)	<i>P</i>	Mean (U/ml)	<i>P</i>	Mean (nmol/l)	<i>P</i>
HCV						
serostatus						
Positive	634.0	0.01	561.7	<0.001	9.5	<0.001
Negative	492.8		407.2		7.0	

^a The means and normal ranges (mean \pm 2 S.D.) for healthy adult males and females were 407 (235, 579) U/ml, 311 (207, 415) U/ml, and 6.1 (2.5, 9.7) nmol/l for sIL-2R_α, sCD8, and neopterin, respectively.

^b Less than 37 weeks gestation.

^c Refers to use after the first trimester of the current pregnancy.

^d Use of both heroin and cocaine by injection.

^e Use of any drug by injection or cocaine by any route.

Most of these associations could be attributed to the correlation of these variables with race or drug use. When adjusted for each of the other variables in Table 2 in a multivariable longitudinal analysis, sIL-2R_α levels remained significantly associated with race (i.e. white versus non-white; $P < 0.001$) and drug use (cocaine and heroin injection drug, other hard drug use, or neither; $P = 0.03$). After adjusting for race, drug use, and pre-term delivery, sIL-2R_α levels were not associated with HCV serostatus ($P = 0.27$) or any of the other variables examined (all Table 2 variables plus maternal peripartum fever, peripartum infection, and clinical chorioamnionitis).

In a similar multivariable analysis, sCD8 was significantly associated with race ($P < 0.001$), drug use ($P = 0.002$) and HCV serostatus ($P < 0.001$) but not with the other variables examined. After adjustment for other variables, neopterin levels were significantly associated with drug use ($P = 0.01$) and HCV serostatus ($P < 0.001$).

3.3. Changes in activation markers during pregnancy and postpartum

Changes in the three activation markers during pregnancy and postpartum are shown in Fig. 1. After declining during the latter half of pregnancy, sIL-2R_α levels increased at or near delivery and peaked by 2 months postpartum (Fig. 1A). Levels at 14–23 weeks gestation and at 2 months postpartum were approximately 10% higher than at other time periods ($P = 0.003$). The increase observed between 32–36 weeks gestation and 2 months postpartum appears to begin prior to delivery but since relatively a

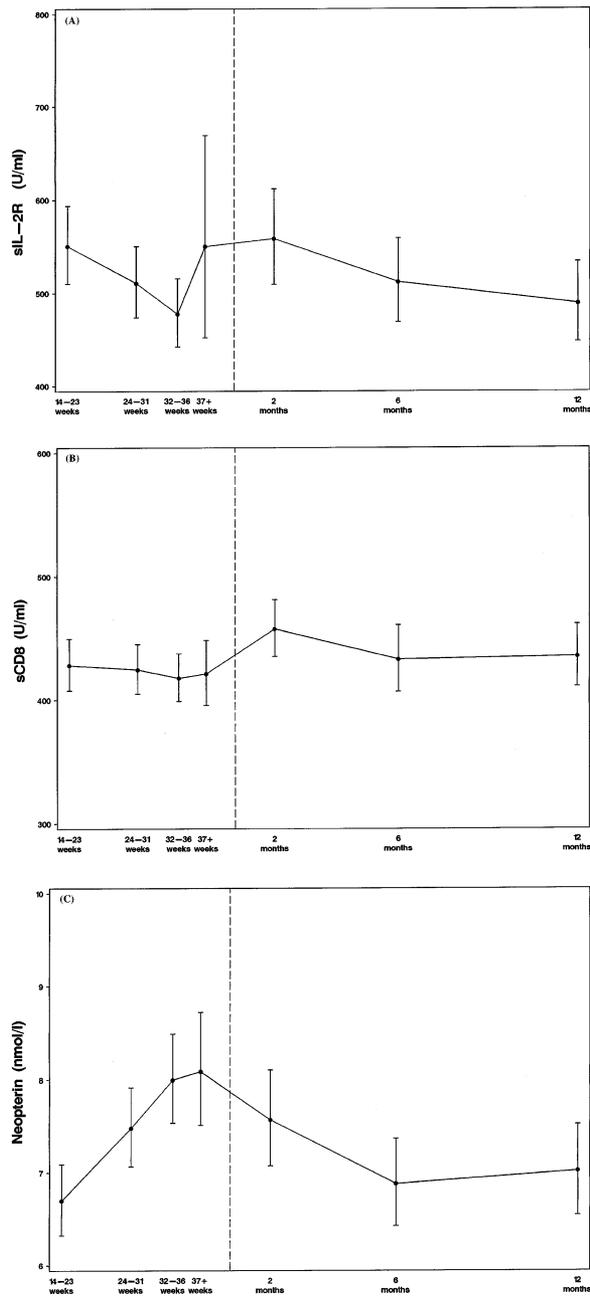


Fig. 1. Mean sIL-2R_z (A), sCD8 (B), and serum neopterin (C) levels and 95% confidence intervals at specified time periods during pregnancy and post-partum. Time to the left of the dashed line is antepartum, to the right, post-partum. Weeks = weeks of gestation; Months = months post-partum.

few women had measurements during this period the standard error was large and the mean was not statistically different from other periods.

This rise in sIL-2R $_{\alpha}$ levels was particularly marked for women with pre-term deliveries. There was a significant interaction between time period (i.e. change over time) and pre-term versus full-term delivery ($P = 0.03$). When examined separately, the pattern of change for women with pre-term and full-term deliveries was similar to that shown in Fig. 1A for all women but the peak at 2 months postpartum was 30% higher than 32–36 weeks gestation and 6 and 12 months post-delivery among women with pre-term deliveries. By comparison, the 2-month postpartum peak for women with full-term deliveries was only 10% higher than these previous and subsequent periods. Given the relatively small number of women with pre-term deliveries, however, this difference in peak sIL-2R $_{\alpha}$ levels was only marginally significant statistically ($P = 0.05$).

There was no detectable change in sCD8 levels during pregnancy but they increased at or near delivery and peaked by 2 months postpartum (Fig. 1B), 7% higher than prior and subsequent levels ($P = 0.001$). Levels at all other time periods were statistically equal ($P = 0.76$). Neopterin levels rose during pregnancy and declined postpartum (Fig. 1C). Levels during 32–36 weeks gestation and ≥ 37 weeks gestation were approximately 20% higher than 14–23 weeks gestation ($P < 0.001$). Like sIL-2R $_{\alpha}$ and sCD8, neopterin levels appeared to stabilize by 6 to 12 months post-delivery.

No significant interactions were found for change in sCD8 levels but change in neopterin differed by race ($P = 0.006$ for interaction between race and time period). Although neopterin levels were consistently higher among white than non-white women, the ante-partum rise was similar for both groups (approximately 20% for each; $P = 0.97$). However, whereas levels rapidly declined and stabilized by 6 months post-delivery among non-white women, they declined only slightly and were still elevated at 12 months post-delivery among white women (overall postpartum decline, 30% versus 2%, respectively; $P = 0.009$).

3.4. Correlations among variables

As shown in Table 3, levels of the three activation markers were significantly correlated during the third trimester (≥ 27 weeks gestation), when data were available for the largest number of women ($P < 0.001$). Similar correlations were found at each of the other time periods examined (data not shown). CD8+ cell levels were significantly correlated with sCD8 levels but not with other activation markers. CD4+ cell levels were inversely correlated with CD8+ cell levels but were not significantly correlated with the three soluble activation markers.

Table 3

Correlation between soluble activation markers and phenotypic antigens expressed on peripheral blood mononuclear cells^a

Marker ^b	sIL-2R _α	sCD8	Neopterin	CD4+ cell level
sIL-2R _α	—	—	—	—
sCD8	0.42*	—	—	—
Neopterin	0.43*	0.40*	—	—
CD4+ cells	0.11	-0.10	-0.04	—
CD8+ cells	0.15	0.39*	0.001	-0.37*

^a Spearman's rank correlation coefficients based on soluble activation marker levels measured on the same 137 third trimester specimens, except for correlations with CD4+ and CD8+ cell levels, which are based on comparisons among 124 women who also had these measurements performed during the same time period.

^b sCD8 = soluble CD8 antigen; sIL-2R_α = soluble interleukin-2 receptor; CD4+ (CD8+) cells = percent CD4+ (CD8+) peripheral blood mononuclear cells.

* $P < 0.001$.

4. Discussion

These longitudinal data indicate that a state of broad immune activation develops in pregnant women at or near delivery. Neopterin levels rose first, followed by sIL-2R_α and sCD8. These changes may reflect one or more events, including termination of hormonal or other immunosuppressive factors active during pregnancy, increasing exposure of the products of conception to genital tract flora, or other perinatal processes.

Overall levels of all three immune activation markers varied by race and injection drug use. Each of the markers was highest among non-Hispanic whites, lowest among African-Americans, and intermediate among Hispanics. Similarly, all three markers were highest in women who used both heroin and cocaine by injection, lower in women who used other hard drugs, and lowest in those who denied any hard drug use during the current pregnancy. With the exception of HCV serostatus, other associations present on univariate analysis disappeared after adjusting for race and drug use.

Many of the findings of this study confirm and extend prior reports but others have not, to our knowledge, been described previously. A population-based study of healthy adults reported that neopterin and sIL-2R levels were higher among whites than blacks (Tollerud et al., 1994; Diamondstone et al., 1994). In addition to confirming these findings, we found higher sCD8 levels among whites. Other immune parameters have also been reported to differ by race, including the number and percentage of activated T cells (CD3 + DR +), specific immunologic factors related to allograft rejection,

and serum immunoglobulin levels (Lucey et al., 1992; Shahabuddin, 1995; Gaston, 1996). These findings may not be surprising given the substantial immunogenetic differences observed between human populations with distinct geographic origins (Riley and Olerup, 1992; Djoulah et al., 1994).

Previous studies have also found an increase in serum neopterin among injection drug users (Strickler et al., 1993; Di Franco et al., 1993). The similar elevations in sIL-2R_α and sCD8 levels in our cohort suggest that there is a broad state of immune activation in injection drug users, apparently involving not only monocyte/macrophage activation but also T cell proliferation and effector responses. The underlying mechanism(s) await full elucidation but repeated 'antigenic stimulation' is a leading hypothesis (Strickler et al., 1993; Di Franco et al., 1993; Barcellini et al., 1995).

HCV infection has been associated with elevations in all three immune activation markers (Leonardi et al., 1991; Quiroga et al., 1994; Hayashi et al., 1995; Gessoni et al., 1998). Among patients treated with interferon- α , a sustained biochemical response to therapy has been associated with elevated pretreatment sCD8 levels (Quiroga et al., 1994). sIL-2R_α levels appear to correlate with the degree of hepatocellular inflammation (Quiroga et al., 1994; Hayashi et al., 1995; Gessoni et al., 1998). One study found that sIL-2R_α levels were normal in asymptomatic HCV seropositive subjects with persistently normal serum alanine aminotransferase (ALT) levels, but elevated among those with persistently elevated ALT levels and histological evidence of chronic active hepatitis (Gessoni et al., 1998). In our cohort of asymptomatic women, most of whom were unaware of ever having hepatitis, we found no statistically significant association between sIL-2R_α levels and HCV serostatus. However, neopterin and sCD8 levels were significantly elevated among women who were HCV seropositive, even after adjustment for race and drug use.

The increase observed in all three activation markers before, at, or shortly after delivery could be partly due to the termination of pregnancy-associated immunosuppressive factors. Numerous investigators have reported that certain immune responses are depressed during pregnancy (Weinberg, 1984; Pope, 1990; Wegmann et al., 1993; Rich et al., 1995; Chaouat and Menu, 1997; Raghupathy, 1997). These changes have been detected using both immunophenotypic and functional assays. For example, lower levels of CD25+ (IL-2R-expressing) lymphocytes and decreased lymphocyte proliferation and IL-2 production have all been reported (Rich et al., 1995; Sabahi et al., 1995; Matthiesen et al., 1996). These immune alterations are thought to involve a complex interaction between pregnancy-related hormonal changes and the immune system (Weinberg, 1984; Pope, 1990; Kimura et al., 1995; Krasnow et al., 1996; Chaouat and Menu, 1997; Komorowski et al., 1997; Nahmias and Kourtis, 1997). The placenta

appears to play a key role in this process (Kimura et al., 1995; Suzuki et al., 1995; Krasnow et al., 1996; Nahmias and Kourtis, 1997; Wang et al., 1997; Marzusch et al., 1997).

Our results are consistent with several but not all previous studies of sIL-2R and other soluble immune activation markers during pregnancy (MacLean et al., 1991; Fuith et al., 1991; MacLean et al., 1992; Lencki et al., 1994; Divers et al., 1995; Mantzavinos et al., 1996; Watanabe et al., 1996; Mikyas et al., 1997). Many of these studies were limited to cross-sectional data on small groups of women. Mantzavinos et al. reported that sIL-2R levels decline shortly after successful in vitro fertilization (Mantzavinos et al., 1996). MacLean et al. found no difference in sIL-2R levels at several stages of normal pregnancy (MacLean et al., 1992) but they reported increased levels during spontaneous abortion (MacLean et al., 1991). Lencki et al. found an increase in sIL-2R among women with clinical chorioamnionitis and pre-term delivery but not among those with pre-term delivery without chorioamnionitis (Lencki et al., 1994). In our cohort, the relationship between increased sIL-2R_x and pre-term delivery persisted after controlling for clinical chorioamnionitis, indicating that subclinical chorioamnionitis or other factors may also contribute to this association.

Watanabe et al. were unable to detect a change in sCD8 levels during pregnancy but observed significantly higher levels 1 month postpartum (Watanabe et al., 1996). Divers et al. found slightly (but not significantly) higher sIL-2R and sCD8 levels in term and pre-term women undergoing labor compared to term and pre-term women not in labor (Divers et al., 1995). However, among both groups each marker was significantly elevated at 48 h postpartum (Divers et al., 1995). Whether immune activation plays a role in the complex series of events that triggers parturition is unclear (Chaouat and Menu, 1997; Schwartz, 1997).

Elevated neopterin levels have also been reported during pregnancy. Fuith et al. found increased urinary levels in a small group of women followed prospectively, particularly after 24 weeks gestation (Fuith et al., 1991). Mikyas et al. reported elevated serum neopterin levels during pregnancy compared to healthy, non-pregnant controls (Mikyas et al., 1997). As with our cohort, levels peaked during the third trimester.

Our findings are consistent with the hypothesis that pregnancy is associated with a state of partial immunosuppression that reverses at or near delivery. Many factors may contribute to this reversal. In addition to the termination of hormonal or other immunosuppressive factors active during pregnancy, increased exposure of the products of conception to genital tract flora (e.g. due to chronic chorioamnionitis associated with bacterial vaginosis or acute chorioamnionitis associated with prolonged rupture of the fetal membranes) and other perinatal events may also be involved. The net

effect appears to be a supranormal peak (i.e. relative to postpartum plateau levels) in all three activation markers shortly before, at, or shortly after delivery.

This process appears to involve two or more steps, as indicated by the rise in neopterin throughout the third trimester followed by elevations in sIL-2R_α and sCD8 at or near delivery. The rise in neopterin presumably reflects increasing monocyte activation (Huber et al., 1984; Wachter et al., 1989). This and other factors could lead to increased T cell proliferation and effector function. Recent studies indicate that these two immune responses need not be sequential; under certain conditions, CD8 + effector cell activation may occur independent from T-helper cell activation (Ridge et al., 1998). In the present study sIL-2R_α levels appeared to increase prior to sCD8 levels, but this could not be confirmed statistically.

Overall, sIL-2R_α, sCD8, and neopterin levels were significantly correlated. In addition, sCD8 levels were correlated with CD8 + cell levels. Some but not all previous studies have reported similar correlations (Prince et al., 1990; Fahey et al., 1990; Bass et al., 1992; Yagi et al., 1992). The discrepancies may be due to differences in study design, study populations, or other factors. Differences in study populations may be particularly important, especially if they differ in their overall level of immune activation. When Prince et al. examined normal controls they found a moderately significant correlation between sCD8 and neopterin levels but no significant correlation between sIL-2R_α and sCD8 levels or between sIL-2R_α and neopterin (Prince et al., 1990). However, all three markers were highly correlated among HIV-infected persons (Prince et al., 1990). Like our study population, their HIV-infected subgroup had elevations in each of these markers.

Our finding that sCD8 levels were correlated with CD8 + cell levels is consistent with a previous analysis showing that CD8 + cell levels increased at or near delivery and declined postpartum in both HIV-infected and uninfected individuals (Burns et al., 1996). More recent studies have found that sCD8 levels are correlated with CD95 + lymphocyte levels, including CD8 + CD95 + cell levels, among HIV-infected individuals (Jiang et al., 1997). CD95 is the Fas/Apo-1 antigen; ligation of this surface molecule by Fas ligand (FasL) results in rapid cell death (Suda et al., 1993; Nagata, 1994). Limited data suggest that FasL produced by decidual cells at the maternal-fetal interface protects the fetus from an influx of maternal leukocytes (Hunt et al., 1997). It is therefore possible that increased CD95 expression on lymphocytes at or near delivery limits the risk of mother-to-infant transmission of HIV-1 and certain other intracellular infectious agents. A similar mechanism might also contribute to the postpartum decline in CD8 + cell levels, sCD8, and sIL-2R_α.

The immune changes observed in our cohort may have important clinical implications. If our findings are confirmed by other studies, measurement of one or more immune activation markers might be helpful in monitoring selected high-risk pregnancies. For example, a greater-than-expected antepartum rise in sIL-2R α in women at increased risk of pre-term delivery could be useful in deciding whether to initiate appropriate interventions. Further study may also be warranted to examine whether a less-than-expected rise in one or more marker prior to delivery signals an increased risk of vertical transmission of HIV-1 or other infections, maternal peripartum infections, or other complications.

In summary, these longitudinal data indicate that a state of broad immune activation develops in pregnant women at or near delivery. Neopterin levels appear to rise first, followed by sIL-2R α and sCD8 levels. These changes may represent de-repression of immunosuppressive factors active during pregnancy. The elevated levels of all three markers at or near delivery may also reflect a transient peripartum state of heightened immune defenses. Measurement of one or more of these soluble markers may be clinically useful in selected high-risk settings.

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