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Maternal serum interleukin-1β, -6 and -8 levels and potential determinants in pregnancy and peripartum

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Abstract

Aims: To measure maternal serum interleukins (IL) in pregnancy, delivery and early puerperium, and to identify their potential determinants.
Methods: Prospective longitudinal measures of serum IL-1β, IL-6 and IL-8 in 38 healthy pregnant women at antenatal visits, through labor and delivery, with clinical correlates (infection, vaginal hemorrhage and anemia) recorded by questionnaire.
Results: Pregnancy IL levels remained consistently low. IL-1β increased shortly before delivery, then returned to pregnant levels, except where blood loss exceeded 500 ml. IL-6 and IL-8 rose at labor onset and exceeded pregnancy levels through postpartum day three. Postpartum IL-6 was higher after non-elective cesarean section than after spontaneous delivery ($P < 0.0001$), and where blood loss exceeded 500 ml. IL-6 and IL-8 were higher with systemic infection during delivery ($P < 0.0001$) and on postpartum day one ($P < 0.05$); IL-8 was higher in anemia (delivery: $P < 0.005$; postpartum day 1: $P < 0.05$). Differences due to delivery mode and systemic infection remained significant after correction for other conditions.
Conclusions: Labor-dependent inflammation increases all IL levels at delivery. Further studies with larger sample sizes are required to establish reference values differentiating physiology from pathology as an aid to peripartum management.

Keywords: Infection; interleukins; labor; pregnancy; puerperium.

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Introduction

The inflammatory cytokines, interleukins-1β (IL-1β), IL-6 and IL-8, help to maintain the trophoblast in early pregnancy. They also play a major role in intrauterine infection, especially after premature rupture of membranes, and in preterm and term labor irrespective of infection [23, 25]. IL-1β has been proposed as the master cytokine of the inflammatory response [7], capable of inducing IL-6 and IL-8, among other cytokines. IL-8 is a chemotactic cytokine involved in rupture of the membranes and cervical ripening [14]; together with IL-6, it plays an important role in preterm cervical remodeling [6, 25].

Although cytokines generally have paracrine and autocrine effects, they can also act remotely. Thus their presence in peripheral venous blood may reflect remote disease (e.g. candidiasis [21], and acute sepsis [11]). Previous studies in pregnancy have looked at amniotic fluid and/or tissues directly involved in parturition (cervix, amnion, chorion, placenta, lower uterine segment, and vagina) [9, 22]. Serum IL-1β, IL-6 and IL-8 appear to play a major role during pregnancy [5, 10, 15, 27], towards term and at delivery [3, 16, 28], notably with increased levels in labor [10, 13, 14].

In suspected amniotic fluid infection syndrome, the benefit of measuring inflammatory IL levels using an invasive procedure (amniocentesis) — with the risk of inducing premature contractions and/or premature rupture of the membranes — has to be weighed against treating the patient solely on the basis of clinical findings and non-invasive investigations. As yet, while there is a reference profile for maternal serum IL-6 throughout pregnancy, there is none for IL-1β or IL-8 [28]. There are no longitudinal cytokine profiles encompassing labor and the early puerperium; current values are at best trimestrial. Such studies have found no causal relationship between cytokine levels and events during pregnancy and delivery.

The aims of this study were therefore to establish longitudinal reference cytokine profiles through pregnancy and peripartum and to identify their potential determinants.

Patients and methods

A longitudinal prospective study of inpatients and outpatients of the Department of Obstetrics, Zurich University Hospital, was

conducted following institutional review board approval. Healthy women (no chronic or acute infection, degenerative disease and tumors, or medication other than routine oral iron and vitamin supplementation during pregnancy) were recruited consecutively in the first trimester ($>8.0 \leq 12.0$ weeks). Gestational age was calculated from the first day of the last menstrual period and first trimester ultrasound; dates were corrected to the ultrasound data where appropriate. Women giving their written informed consent were included if the clinical examination was normal. At the booking visit, history and general status were obtained using a standardized questionnaire. At subsequent visits, relevant signs, symptoms, results, diagnoses and treatments were added to each patient's file.

The criteria for retrospective exclusion from the final analysis were non-compliance/withdrawal of consent; multiple pregnancy; and during pregnancy: acute systemic infection (malaria, toxoplasmosis), recent vaginal hemorrhage, oligohydramnios, premature contractions or rupture of the membranes; elective cesarean section or instrumental vaginal delivery. There were no other exclusion criteria for delivery or the puerperium.

Blood samples were taken a) during pregnancy either monthly at the routine outpatient visits or once at the last pregnancy visit near term (>36.0 weeks), b) during labor, c) at delivery (max. 30 min thereafter) and d) at 1, 2 and 3 days postpartum during hospitalization.

At each visit a vaginal wet preparation was taken for microscopy and the urine was analyzed using Uristix (Bayer Diagnostics MfG, Bridgend, UK). Local vaginal infection was diagnosed by unusual discharge (typical quality, quantity, color, odor, associated symptoms), which was pH-tested, examined for clue cells, and treated with KOH using Amsel's criteria for bacterial vaginosis. The wet preparation was examined for hyphae and/or spores, and microbiological confirmation sought for typical mycosis symptoms, mainly Candida. Carriership alone did not qualify as infection. A urine culture was done routinely at the booking visit and at least once per trimester, but more often if indicated. Urinary tract infection was diagnosed by positive urine nitrite and microbiological culture, with or without clinical symptoms. Further diagnostic tests were only performed in cases of overt clinical infection.

Other information collected included details of contractions (frequency, amplitude), respiratory and gastrointestinal symptoms, and current medication. Delivery blood loss was estimated using our standard department procedures and the hemoglobin was checked on postpartum day three. Postpartum hemorrhage was diagnosed as blood loss ≥ 500 ml, and puerperal anemia as a postpartum Hb ≤ 9.5 mg/dl. Standardized placental histology was performed in all cases as detailed in a previous study [10].

Cytokines

Samples (10-ml) of venous blood were taken into untreated sterile glass tubes and immediately centrifuged on site at 3500 rpm for 10 min at 4°C; 0.5-ml aliquots of the supernatant were immediately frozen in polypropylene tubes at -70°C and stored until assay. There were no freeze-thaw cycles. Commercial enzyme-linked immunoassays were used according to the manufacturer's recommendations to measure IL-1β, IL-6, IL-8 (Quantikine TM, R&D Systems, Minneapolis, MN, USA). All reagents and samples were brought to room temperature before use. The lower limits of detection were 1, 0.7 and 10 pg/ml, corresponding to log values 0, -0.155 and 1 pg/ml, respectively.

Table 1 Population demographics (mean ± se; n = 38).

Age (years)	28.4 ± 0.87
Parity	1.9 ± 0.14
Gravidity	2.4 ± 0.19
Race (patients, n)	
Caucasian	22
Asian	12
African	4
Marital status (n)	
Married	37
Unmarried	1
Cigarettes > 5/day (n)	5

Statistical analysis

Data were sampled prospectively after each outpatient visit and analyzed in Statview 5.4 (Abacus Concepts, Berkeley, California) for Windows 6.0. The Kolmogorov-Smirnov test was used to test for normal distribution of cytokine concentrations, and log transformation was performed if necessary. The paired *t*-test (log values) was used to test the mean differences in the same group, and the unpaired *t*-test (log values) for mean differences between the two groups. Analysis of variance (ANOVA) was used to test the dependence of cytokine levels on several parameters. A P value <0.5 was considered significant. Values are given as mean ± se.

Results

Subjects

The initial recruitment of 70 women was reduced to 38 in the final analysis due to spontaneous abortion (n = 5); non-compliance/withdrawal of consent (n = 6); toxoplasmosis seroconversion during pregnancy (n = 3); delivery at <36 weeks (n = 2); twin pregnancy, fetal malformation, severe intrauterine growth retardation, severe vaginal bleeding, malaria, preeclampsia, instrumental vaginal delivery (n = 1 each) and elective cesarean section (n = 9). Table 1 shows the demographics of the 38 women. Mean gestational age at delivery was 39.5 ± 1.4 (range: 36.4–41.6) weeks. No woman had premature contractions; one ruptured her membranes >24 hours before term delivery. Details of potential obstetric determinants of cytokine levels are given in Table 2.

Cytokines

For data analysis, blood taken monthly from 26 women and once near term was available from 12 women, resulting in 38 data sets for delivery and the puerperium. Cyto-

Table 2 Potential obstetric determinants of cytokine levels.

	Patients (n)
During pregnancy	
Local vaginal infection	9*
Urinary tract infection	9
During delivery/puerperium	
Local vaginal infection	10†
Urinary tract infection	4
Non-elective cesarean section	7
Systemic infection	8‡
Postpartum hemorrhage (>500 ml)	6
Postpartum anemia (Hb<9.5 g/dl)	9

* bacterial vaginosis (n=1); mycosis (n=8)
† bacterial vaginosis (n=1); mycosis (n=7); beta-hemolytic streptococci group B (n=2)
‡ chorioamnionitis (n=4); endomyometritis (n=1); pneumonia (n=2); urosepsis (n=1)

kine values were log normally distributed, and are thus given as log values.

For pregnancy, antenatal profiles in the 26 women longitudinally analyzed did not differ significantly between the beginning (≤12.0 weeks) and the end of pregnancy (>36.0 weeks) in terms of either IL-1β (0.30±0.12 versus 0.34±0.04 pg/ml) or IL-8 (1.21±0.07 versus 1.15±0.03 pg/ml) (paired *t*-test). Many IL-1β levels were just above the limit of detection. IL-6 levels were slightly higher at the end than at the beginning of pregnancy (0.52±0.03 versus 0.47±0.03 pg/ml; $P<0.05$) (Figure 1). Patients with local vaginal and/or urinary tract infection had no higher values for all three analyzed cytokines than healthy women without any complication during pregnancy.

For peripartum data analysis, the last prelabor values of the 26 women studied longitudinally plus the single values of the 12 additional women were used as a baseline (prelabor). All three cytokines increased significantly after labor onset (Table 3). Only IL-1β levels fell back to the prelabor baseline; IL-6 and IL-8 levels remained significantly raised through postpartum day three. With respect to mode of delivery, prelabor IL-6 levels did not differ, but subsequent peak values were higher in the cesarean section group, significantly so on postpartum days one and two ($P<0.0001$; Figure 2). The changes in IL-8 and IL-1β followed a similar but less significant pattern (IL-8: postpartum day one versus prelabor: $P=0.03$; IL-1β: NS). Tests of the relationship to potential determinants (Table 2) found no evidence of higher levels peripartum in women with versus women without local vaginal or urinary tract infections. However, all three cytokines were elevated during labor in women with systemic infections (n=8); IL-6 levels remained significantly higher at delivery and on postpartum day one, similarly IL-8 until delivery only (Figure 3). In women with blood loss >500 ml (n=6), IL-1β and IL-6 levels were higher during delivery and/or postpartum day one and postpartum day two ($P<0.05$; Figure 4). In anemic women (n=9), IL-6 levels followed a parallel course to that in their non-anemic counterparts, although at a non-significant higher level, while IL-1β levels only differed from prelabor during delivery ($P<0.05$); IL-8 levels (Figure 5) were highest at delivery ($P<0.005$ versus prelabor) and on postpartum day one ($P<0.05$).

Using the ANOVA test, all shown significant cytokine elevations remained independent of other determinants.

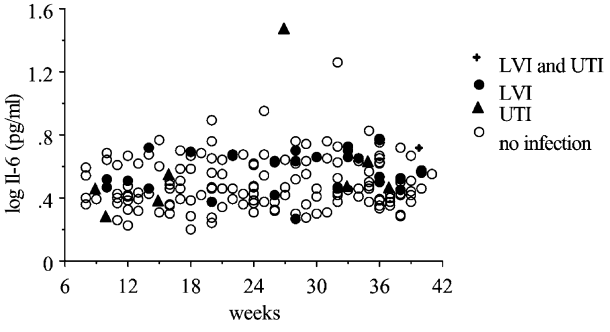

Figure 1 Antenatal longitudinal log IL-6 concentrations (n=26). Levels were not increased in women with local vaginal infection (LVI) and urinary tract infection (UTI) (cross; n=1), local vaginal infection (closed circle; n=9) and urinary tract infection (triangle; n=8) versus normal women without any complication during pregnancy (open circle).

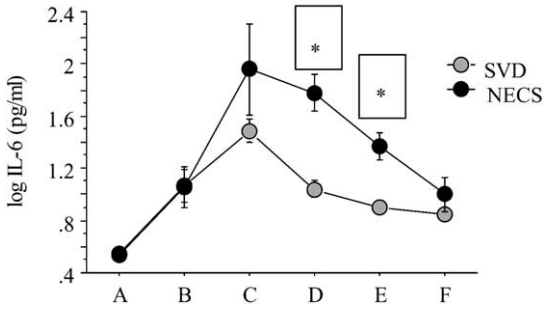

Figure 2 Log IL-6 concentrations (mean±se) before (A) and during labor (B), at delivery (C) and 1, 2 and 3 days postpartum (D–F) in non-elective cesarean section (NECS; n=7) versus spontaneous vaginal delivery (SVD).
*$P<0.0001$ NECS versus SVD at intervals D and E.

Discussion

Our longitudinal study incorporating detailed multifaceted data collection at every time point, notably with regard to infection, has shown that the three inflammatory cytokines, IL-1β, IL-6 and IL-8, are already present in maternal serum in early pregnancy but undergo little subsequent variation until term. At labor onset, IL-1β rises to a sudden short-lasting peak, falling back to pregnant and non-pregnant levels on postpartum day one. IL-6 and IL-8 undergo longer-lasting changes, and are still not back to antenatal levels by postpartum day three.

Table 3 IL-1β, IL-6 and IL-8 levels (mean ± se) prelabor, during labor, at delivery, and on postpartum days one, two & three (n = 38).

	log IL-1β	log IL-6	log IL-8
Prelabor	0.352 ± 0.030	0.539 ± 0.031	1.134 ± 0.027
During labor	0.545 ± 0.079*	1.063 ± 0.109†	1.374 ± 0.096*
Delivery	0.497 ± 0.070	1.558 ± 0.094†	1.435 ± 0.087‡
Postpartum			
Day 1	0.371 ± 0.017	1.190 ± 0.078†	1.235 ± 0.030*
Day 2	0.342 ± 0.013	0.999 ± 0.049†	1.202 ± 0.023
Day 3	0.330 ± 0.010	0.881 ± 0.045†	1.274 ± 0.018§

Versus prelabor: *P < 0.05; † P < 0.0001; ‡ P < 0.005; § P < 0.0005 (paired *t*-test)

The massive increase in IL-6 at delivery and in the early puerperium in non-elective cesarean section is unrelated to either heavy infection, postpartum hemorrhage or postpartum anemia.

Previous studies on antenatal maternal serum levels have been cross-sectional, have performed one measurement per trimester, or were limited to one selected IL [2, 16, 26]. Most have looked at delivery, and at preterm rather than term labor [1, 17]. Our concern was to measure all three cytokines longitudinally from early pregnancy through the early postpartum period.

High cytokine levels in mid and late pregnancy have usually been attributed to (ascending and intrauterine) infection [23, 24]. More recent studies suggest that infection is irrelevant, and that labor resembles an inflammatory process. A study of 28 normal pregnancies and deliveries, which measured IL-6 in each trimester and at delivery, found that the only significant increase occurred at delivery; however, women with a history of recurrent spontaneous abortion had a higher percentage of detectable antenatal IL-6 levels [16]. Similarly, the only previous longitudinal study (to our knowledge) of maternal serum IL-6 levels in pregnancy, by Vassiliadis et al. [28], found no changes in time course.

IL-8 has been proposed as the final common step in prostaglandin and antiprogestagen action in parturition [12]. However, two studies have failed to find significant changes in peripheral plasma IL-8 levels during pregnancy or at labor onset [3, 15]. We also failed to provide any indication of a controlling role being played by IL-8 in this study.

High levels of IL-1β should parallel high levels of induced cytokines such as IL-8 during vaginal infections [7]. In vaginal fluid from non-pregnant women with bacterial vaginosis (BV), Cauci et al. [4] showed a 20-fold increase in IL-1β levels, with no change in either IL-8 or neutrophils; they concluded that virulence factors are produced in BV that inhibit IL-8 more than they do IL-1β. We could not confirm these results in peripheral serum during pregnancy or peripartum. Yudin et al. [29] found a significant decrease in cervical IL-1β, IL-6 and IL-8 in pregnant women after oral or vaginal treatment of BV. In our study, IL-6 values were not increased in women with BV or Candida infection during the infection or the seven-day treatment period either during pregnancy or peripartum. The increase of IL-6 and IL-8 in preterm [8, 19] and term labor [3] is still controversial [1]. We recently reported an increase of IL-6 and IL-8 during normal term labor [10]. In our present study, all three cytokines were increased at normal term delivery. Non-elective cesarean section was associated with higher IL-6 levels than spontaneous vaginal delivery. Similar maternal cytokine levels

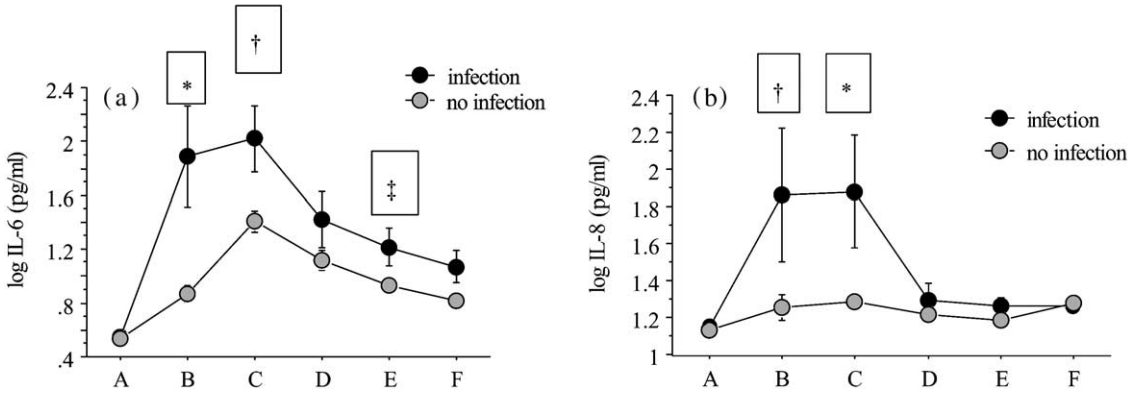

Figure 3 Log IL-6 and IL-8 concentrations (mean ± se) before (A) and during labor (B), at delivery (C) and 1, 2 and 3 days postpartum (D–F) in women with (n = 8) and without systemic infection.
a) IL-6: *P < 0.0001 infection versus no infection at interval B; † P < 0.005 at C; and ‡ P < 0.05 at E.
b) IL-8: *P < 0.005 infection versus no infection at interval C; † P < 0.01 at B.

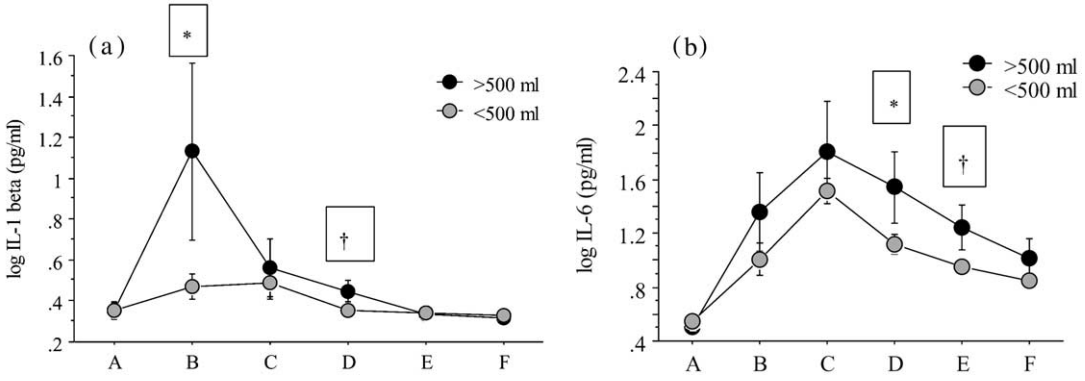

Figure 4 Log IL-1β and IL-6 concentrations (mean ± se) before (A) and during labor (B), at delivery (C) and 1, 2 and 3 days postpartum (D–F) in women with blood loss >500 ml (n = 6) and <500 ml.
a) IL-1β: *P < 0.01 > 500 ml versus <500 ml at interval B; † P < 0.05 at interval D.
b) IL-6: *P < 0.05 > 500 ml versus <500 ml at intervals D and E.

have been found in mothers with fetuses affected by microbial invasion [3]. However, we found higher levels for all three cytokines in mothers with and without systemic infections, including chorioamnionitis.

Our findings support the concept that IL-1β, IL-6 and IL-8 are involved in the maintenance of human pregnancy. They show that increased cytokine levels are a function of labor, and are independent of inflammatory factors such as blood loss, anemia and heavy infection. The role of IL-1β seems to be limited to parturition; it may be the initiating cytokine. IL-8 increases early during labor, possibly as a function of tissue stretching [18] and membrane rupture [10]. Of all the cytokines, IL-6 showed the highest (3-fold) and most prolonged increase. Prolonged exercise is a documented trigger of leukocytosis and monocytosis – both cell types are major sources of IL-6 production [20]; IL-6 increase is also related to strength of contractions and duration of labor [2, 10]. Higher IL-6 levels in non-elective cesarean section compared to spontaneous vaginal delivery may be due to tissue injury and its repair over several days rather than to the onset or maintenance of labor.

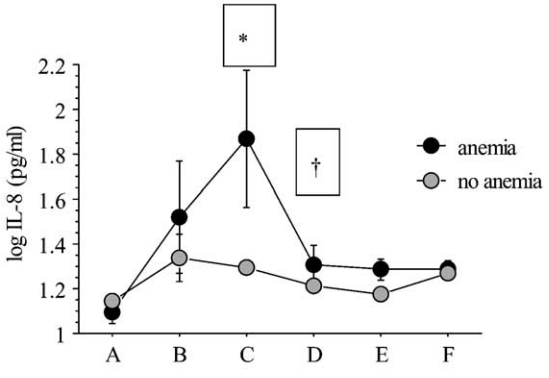

Figure 5 Log IL-8 concentrations (mean ± se) before (A) and during labor (B), at delivery (C) and 1, 2 and 3 days postpartum (D–F) in patients with (n = 9) and without postpartum anemia.
P < 0.005 anemia versus no anemia at interval C; † P < 0.05 at interval D.

A limitation of our study was the 46% decrease in our recruitment population, to a total of 38 in the final analysis. These numbers are too small to show statistical differences between women with and without local vaginal infection and/ or urinary tract infection during pregnancy. The influence of these antenatal factors therefore requires testing in a larger study. As for the puerperium, our results show that cytokine increase around spontaneous onset delivery is independent of systemic infection, postpartum hemorrhage and anemia. We assume that tissue injury accounts for the higher levels found in non-elective cesarean section compared to vaginal delivery. However, we could not correlate labor duration with cytokine concentrations because of external factors (e.g. parity, ethnicity) resulting in subgroups too small for statistical analysis. Further studies of larger numbers using the same sampling schedule could incorporate other potential determinants such as the effect of elective cesarean section, which we believe to be low. At present, our data provide further information on biochemical and cell-mediated changes in labor and peripartum, which could serve as provisional reference values to differentiate normal from abnormal events during delivery and the early puerperium.

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