

Procalcitonin levels during pregnancy, delivery and postpartum*

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Abstract

Aims: To determine the normal value ranges of procalcitonin (PCT) in women with uncomplicated pregnancies.

Methods: This prospective cohort study was conducted between May 2009 and February 2010 among 60 women without signs of clinical infection (31 vaginal deliveries, 29 cesarean sections) attending the maternity unit of the University of Geneva Hospitals. Sequential follow-up of PCT levels was performed at 24–28 weeks ($n=7$), 36–40 weeks ($n=60$), at delivery ($n=59$), and at days 2–3 ($n=58$) and 10 ($n=53$) postpartum using a sensitive PCT assay with a functional sensitivity of 0.06 $\mu\text{g/L}$.

Results: Median levels of PCT were: 24–28 weeks: 0.043 $\mu\text{g/L}$ (range 0.010–0.080); 36–40 weeks: 0.061 $\mu\text{g/L}$ (range 0.010–0.110); at delivery: 0.068 $\mu\text{g/L}$ (range 0.010–0.170); days 2–3: 0.200 $\mu\text{g/L}$ (range 0.030–5.00); and day 10: 0.060 $\mu\text{g/L}$ (range 0.020–0.120). At days 2–3 postpartum, three women had a PCT level between 0.25 $\mu\text{g/L}$ and 0.5 $\mu\text{g/L}$ and two women had a level higher than 0.5 $\mu\text{g/L}$.

Conclusions: This study provides reference values for PCT during the third trimester, at delivery and at the immediate

postpartum period. A cut-off PCT level of 0.25 $\mu\text{g/L}$ can be used during the third trimester, at delivery, and at the immediate postpartum period to rule out infection.

Keywords: Delivery; normal values range; postpartum; pregnancy; procalcitonin.

Introduction

Early detection of infection is of the utmost importance in obstetrics and failure to diagnose it can lead to severe complications for the mother, the fetus, and the newborn [16]. However, infection during pregnancy is not reliably predicted by commonly used laboratory tests, such as white cell counts (WBC), neutrophil count or vaginal bacterial culture [19]. Indeed, a physiologic increase in WBC exists during uncomplicated pregnancy and the threshold to diagnose an infection has to be modified during pregnancy [5]. In addition, clinical signs, such as fever and fetomaternal tachycardia usually appear late [8]. C-reactive protein (CRP) is a biological blood marker frequently used as a predictor of intraamniotic infections (IAI), [19, 8] but a recent meta-analysis has shown that there is no evidence to support its use for the early diagnosis of IAI [23]. Therefore, an accurate and rapid marker for the diagnosis of early infection in the context of pregnancy complications, such as preterm labor or the premature rupture of membranes, is urgently needed.

Procalcitonin (PCT), a prohormone consisting of 116 amino acids, is a normal precursor of the active hormone calcitonin and was first described in 1990 as a sepsis-induced protein [1]. PCT levels are elevated in severe bacterial infections, but remain low in viral infections and non-specific inflammatory disease [1, 10]. In healthy individuals, the normal PCT level is lower than 0.2 ng/mL [9]. Values increase rapidly in pathologic conditions, leading to systemic inflammatory response syndrome (SIRS), [15] and a cut-off level of 0.25 $\mu\text{g/L}$ has been recently suggested for considering the use of antibiotic treatment [15].

Contradictory results have been reported in the few studies that have measured PCT levels during pregnancy [2, 20–22]. Therefore, there is a need to better define normal PCT values in pregnant women before using PCT levels as a tool in the management of infectious complications during the perinatal period.

The objective of this study was to determine the normal value ranges of PCT during the third trimester, at delivery, and during postpartum in pregnant women without clinical infection.

***Condensation:** This study gives reference values of procalcitonin during the third trimester, at delivery and the immediate postpartum period in pregnant women without clinical infection.

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Material and methods

Patient population

The study was conducted at the Department of Gynecology and Obstetrics of the University Hospitals of Geneva, Geneva, Switzerland, a tertiary care hospital with approximately 4000 deliveries per year. The study protocol was approved by the institutional Ethics Committee and written informed consent was obtained from each participant. We included women with singleton pregnancies, older than 18 years, gestational age ≥ 24 weeks, and able to consent during the prenatal consultation. Exclusion criteria were fever ($\geq 38^\circ\text{C}$), preterm labor, symptomatic urinary infection, preterm rupture of membranes, preeclampsia and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Blood samples were taken at five time-points: 24–28 weeks, 36–40 weeks, delivery (after placental delivery), and at days 2–3 (D2–3) and day 10 postpartum (D10). We collected data on age, gestational age, parity, smoking status, previous medical history, labor/delivery, postpartum complications and neonatal outcome.

Laboratory test

PCT was measured using a rapid sensitive assay (Kryptor PCT, BRAHMS, Hennigsdorf, Germany) based on a sandwich-typed immunometric test with a lower detection level of $0.02 \mu\text{g/L}$ (functional sensitivity, $0.06 \mu\text{g/L}$). Inter-assay and intra-assay variations are as follows: for $0.1 \mu\text{g/L}$, 15% for both; for $0.2 \mu\text{g/L}$, 6% and 10%, respectively, and for levels above $0.3 \mu\text{g/L}$, <6% and 5%, respectively (data from our laboratory and BRAHMS).

Statistical analysis

Data are expressed as medians, interquartile ranges, extreme values and box-plots for each time-period considered. PCT levels between sampling periods and according to mode of delivery (vaginal vs. cesarean section) were compared using the paired Wilcoxon and Mann-Whitney *U*-tests, respectively. Calculations were performed with EpiInfo (Centers for Disease Prevention and Control, Atlanta, GA, USA) and SPSS version 17 (SPSS Inc., Chicago, IL, USA); graphs were drawn using R 2.10.1 (R project). We calculated the specificity of the threshold of $0.25 \mu\text{g/L}$ to rule out infection as this PCT value is commonly used in clinical practice to manage infectious complications.

Results

From May 2009 to February 2010, 60 pregnant women were included and followed prospectively. In group 1 (vaginal delivery group), we included 31 women (28 spontaneous vaginal deliveries and three instrumental deliveries). In group 2 (cesarean section [C-section]), we included 29 women (26 elective and three emergency). In order to have two homogeneous groups regarding the mode of delivery, we included 21 women at 35–36 weeks gestation when the indication for delivery by C-section was established. The main characteristics of study participants according to the mode of delivery are presented in Table 1. Only maternal age at delivery was different between the C-section group and the vaginal delivery group ($P=0.001$). Four women (two in each group) had a history of urinary infection prior to pregnancy, and two

Table 1 Clinical characteristics of women stratified by mode of delivery.

	Vaginal delivery			Cesarean section			P-value
	Spontaneous n = 28	Instrumental n = 3	Total n = 31	Elective n = 26	Emergency n = 3	Total n = 29	
Maternal age (years), mean (SD)	29.86 (6.15)	26.00 (1.00)	29.48 (5.96)	34.58 (4.38)	32.00 (3.61)	34.31 (4.33)	<0.01
Gestational age at delivery (weeks), mean (SD)	39.07 (1.27)	39.00 (1.73)	39.06 (1.29)	38.27 (0.83)	39.67 (1.16)	38.41 (0.95)	0.03
Birthweight (g), mean (SD)	3243.21 (396.35)	3130.00 (680.00)	3232.26 (416.37)	3337.69 (458.73)	3326.67 (642.68)	3336.55 (466.26)	0.36
Apgar at 5 min, mean (SD)	9.82 (0.39)	9.67 (0.58)	9.81 (0.40)	9.77 (0.86)	9.33 (1.16)	9.72 (0.88)	0.64
Arterial pH, mean (SD)	7.23 (0.07)	7.26 (0.02)	7.24 (0.07)	7.28 (0.05)	7.20 (0.13)	7.27 (0.06)	0.07

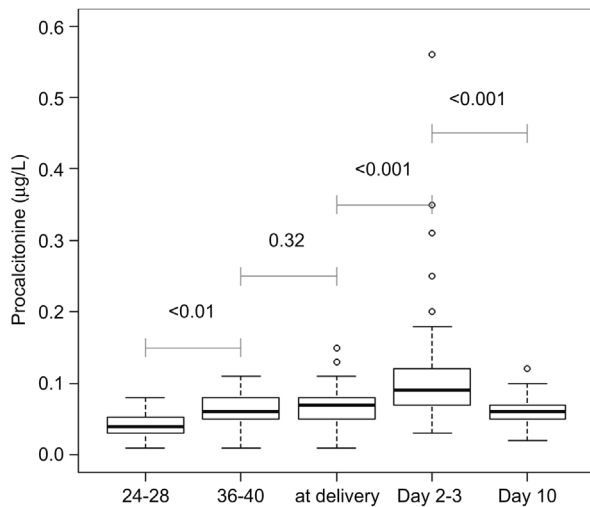


Figure 1 Evolution of procalcitonin levels at the end of pregnancy (24–28 weeks, 36–40 weeks), immediately after delivery and in the postpartum period (days 2–3 and day 10). The boxes represent 50% of the values, the horizontal bar inside the median, and the lower and upper bars the 10th and 90th percentiles, respectively.

(one per group) of chronic hypertension. Three women were HIV seropositive (one in the vaginal group and two in the C-section group).

During pregnancy, one woman in each group received preemptive antibiotic treatment after inclusion for recurrent asymptomatic bacteriuria. Their PCT levels were low [0.06 (vaginal) and 0.07 µg/L (C-section) at 24–28 weeks]. One woman had a spontaneous preterm vaginal delivery and developed clinical chorioamnionitis during labor (fever 38°C, WBC 27.5 g/L, and high CRP 13 mg/L). Her PCT values at delivery (0.17 µg/L) and at D3 postpartum (0.51 µg/L) were excluded from the analysis. Eleven women in group 1 received antibiotic treatment during labor (nine for prevention of group B streptococcus neonatal sepsis, one for endocarditis prophylaxis, and the woman with clinical chorioamnionitis). In group 2, all women received antibiotic prophylaxis (1st generation cephalosporin) after umbilical cord clamping.

PCT levels from all 60 women at each sampling period are shown in Figure 1. Median levels for each time period were as follows: 24–28 weeks: 0.043 µg/L (range 0.010–0.080); 36–40 weeks: 0.061 µg/L (range 0.010–0.110); at delivery: 0.068 µg/L (range 0.010–0.170); D2–3: 0.200 µg/L (range 0.030–5.00); and D10: 0.060 µg/L (range 0.020–0.120). PCT levels significantly increased in the third trimester of pregnancy and between delivery and D3 postpartum. At D3, five of 57 women (8.8%) had values ≥ 0.25 µg/L (0.25, 0.31, 0.35, 0.56 and 5.00, respectively (Table 2) without signs of infection during delivery and postpartum. Using this threshold, the specificity of PCT levels at D3 postpartum was 91.1% (exact 95% CI, 80.4; 97.0). The woman with a D3 PCT level of 5.0 µg/L had received antibiotic treatment during delivery (PCT value at delivery, 0.07 µg/L) for endocarditis prophylaxis and the following day received an epidural blood patch for a lumbar puncture. Her

PCT returned to normal at D10 (0.12 µg/L). During the other time periods, the specificity of the threshold of 0.25 µg/L was 100% as no women had a PCT value ≥ 0.25 µg/L.

The evolution of PCT levels according to the mode of delivery are shown in Table 2 and Figure 2. The increase of PCT levels between 24–28 weeks and 36–40 weeks was not statistically significant in the C-section group and was probably due to the low number of women sampled at 24–28 weeks. In contrast, the elevated levels between delivery and D3 was only significant in the group of women delivering by C-section. At D10, PCT levels significantly decreased among both groups, but they were significantly higher in group 2 compared with group 1.

Comment

PCT is a promising biomarker of infection and ubiquitously expressed in response to bacterial endotoxins and cytokines [15]. In the present study, we established normal PCT levels for the third trimester of pregnancy, at delivery, and the immediate postpartum period in women without acute infection delivering vaginally or by C-section.

Our study demonstrates that PCT levels increase significantly at the end of pregnancy and between delivery and D3 postpartum, with a decrease at D10 postpartum. PCT levels are higher at D3 postpartum than at any other time-point and this elevation is also associated with the mode of delivery, being more marked after C-section. Labor and delivery stimulates the inflammatory cascade and this can probably explain the slight elevation of PCT levels at D3 [12]. Previous studies have shown that PCT concentrations rise after abdominal surgery through the liberation of endotoxins without bacterial translocation [13, 3] and this possibly accounts for the more pronounced elevation among women delivering by C-section.

Regardless of the PCT increase observed in our study, PCT levels at the end of pregnancy, at delivery, and during the postpartum period are within the same levels observed in other non-infected adult populations [9, 15]. Our results are in agreement with those of Assumma et al. who also found very low levels of PCT at delivery (geometric mean, 0.01 µg/L), but using a different PCT assay than the one used in our study [12]. In contrast, Torbé et al. found very high PCT values during the second half of pregnancy (mean, 1.06 µg/L) [21] and at delivery (medium PCT value, 0.71 µg/L), thus precluding the use of PCT in the management of infectious complications during pregnancy [20].

We have assessed the specificity of the cut-off level of 0.25 µg/L to rule out infection as this value is currently used to diagnose systemic infections and to guide the use of antibiotics in infected adult populations [4, 9, 17]. In our study, this value has a specificity of 91.1% at D3 postpartum and of 100% at the other four time-periods as all women had PCT levels below this threshold. This is in agreement with other studies showing specificities ranging from 78–96% [10, 11, 14, 18]. Causes for “false-positive” PCT values (>0.25 µg/L), such as severe or surgical trauma, have been

Table 2 Evolution of PCT levels (median and ranges) at the end of pregnancy and in the postpartum according to the mode of delivery.

	Vaginal delivery (n=31)				Cesarean section (n=29)				P-value
	n*	Range	Median	Women (n) with values >0.25 µg/L	n*	Range	Median	Women (n) with values >0.25 µg/L	
At 24–28 weeks	29	0.01–0.07	0.04	0	8**	0.03–0.08	0.05	0	0.14
At 36–40 weeks	31	0.01–0.11	0.06	0	29	0.03–0.10	0.07	0	0.05
At delivery	29	0.01–0.15	0.07	0	29	0.02–0.11	0.07	0	0.40
At day 2–3	28	0.03–5.00	0.07	2	29	0.05–0.56	0.10	3	<0.01
At day 10	27	0.02–0.12	0.05	0	26	0.03–0.10	0.07	0	<0.01

*Two samples at 24–28 weeks, one during labor, two at D2–3 and seven at D10 were missed.

**Twenty-one women were included at 35–36 weeks of gestation when the indication for cesarean section was established. No sampling at 24–28 weeks.

identified in other studies [7]. In our study, an example of ‘‘false-positive’’ was the woman who had 5.0 µg/L at D3 postpartum following an epidural blood patch for a lumbar puncture, which is probably explained by an inflammatory non-septic state.

A limitation of this study is that we did not collect data on women with infectious complications and cannot assess the sensitivity of the test. One woman had clinical chorioamnionitis and her PCT values (0.17 µg/L at delivery and 0.51 µg/L at D3) were excluded from the analysis. Nevertheless, those values were high, thus confirming the hypothesis that PCT might be used for the diagnosis of infectious complications during pregnancy. Further studies, including case-control studies, are necessary to validate these data.

Additionally, further analyses should be conducted to evaluate the efficacy of PCT in guiding the duration of antibiotic treatment in pregnant women.

Conclusion

In conclusion, our study provides normal PCT levels for the third trimester of pregnancy, at delivery, and the immediate postpartum period. PCT values are generally low, but with a slight increase at D3 postpartum, especially among women delivering by C-section. The PCT level of 0.25 µg/L can be used to rule out infection during the perinatal period. However, additional studies should be conducted to assess the

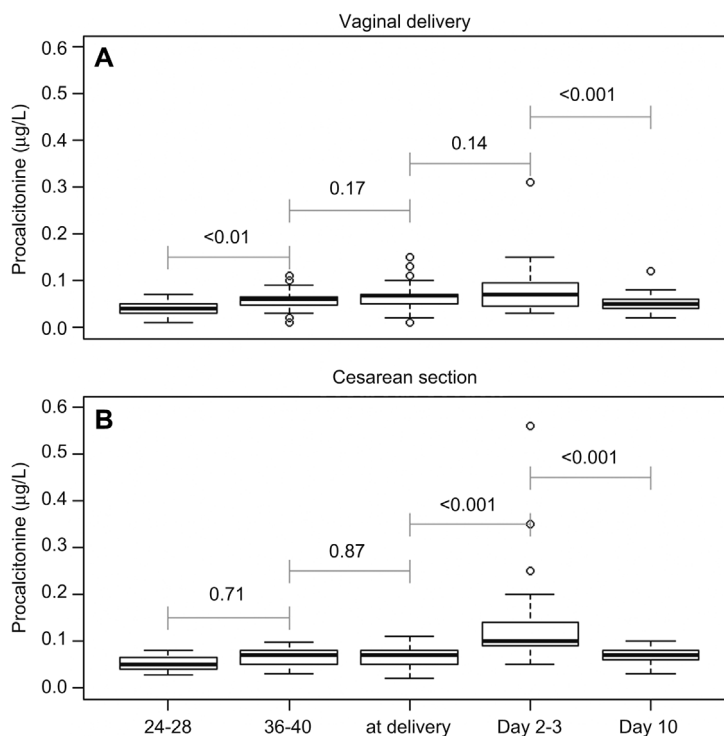


Figure 2 (A, B) Evolution of procalcitonin levels at the end of pregnancy (24–28 weeks, 36–40 weeks), immediately after delivery and in the postpartum period (days 2–3 and day 10) according to mode of delivery.

usefulness of PCT measurements in pregnant women with suspected infection.

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