

Serial Measurements of C-Reactive Protein and Interleukin-6 in the Immediate Postnatal Period: Reference Intervals and Analysis of Maternal and Perinatal Confounders

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Background: There is a wide range of reported sensitivities and specificities for C-reactive protein (CRP) and interleukin-6 (IL-6) in the detection of early-onset neonatal infection. This prompted us to assess reference intervals for CRP and IL-6 during the 48-h period immediately after birth and to identify maternal and perinatal factors that may affect them.

Methods: CRP and IL-6 values were prospectively obtained for 148 healthy babies (113 term, 35 near-term) at birth and at 24 and 48 h of life, and from their mothers at delivery.

Results: Upper reference limits for CRP at each neonatal age were established. At birth, CRP was significantly lower than at 24 and 48 h of life. Rupture of membranes ≥ 18 h, perinatal distress, and gestational hypertension significantly affected the neonatal CRP dynamics, but at specific ages. There was no correlation between CRP concentrations in mothers and their offspring at birth. The IL-6 values observed in the delivering mothers and in their babies at all three neonatal ages were negatively associated with gestational age. In the immediate postnatal period, IL-6 dynamics for term babies were significantly different from those for near-term babies. Maternal IL-6 concentrations correlated with babies' IL-6 concentrations only for term deliveries. Apgar score had a significant effect on babies' IL-6 values at birth.

Conclusions: The patterns of CRP and IL-6 responses in the healthy neonate should be taken into account to optimize their use in the diagnosis of early-onset neonatal sepsis.

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The difficulties inherent in the diagnosis of early-onset (≤ 48 h of life) neonatal infection have prompted the development of several screening tests, including C-reactive protein (CRP),⁶ a very commonly used marker. A delay of at least several hours is intrinsic to the cascade of events leading to increased serum CRP; therefore, the predictive value of CRP improves with time and is best between 24 and 48 h after infection is suspected (1, 2). Serial measurements are therefore recommended (3–7). However, although serial CRP measurements have an excellent negative predictive value for the presence of infection, the reverse does not hold true, especially for culture-confirmed early-onset infection (1). On the other hand, the use of CRP in the first few days of life is complicated by a nonspecific, 2- to 3-day increase that may greatly reduce the positive predictive value of CRP determinations (3, 8).

In recent years, the search for diagnostic tests for early-onset sepsis in newborns has turned to cytokines, alone or in combination with CRP, based on the premise that their increases in response to infection may precede that of CRP (9). As a cytokine, interleukin-6 (IL-6) is the major inducer of hepatic protein synthesis including CRP. Increased IL-6 is a potentially useful diagnostic marker of early-onset septicemia, but reports in the literature are

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⁶ Nonstandard abbreviations: CRP, C-reactive protein; IL-6, interleukin-6; GBS, group B streptococcus; CI, confidence interval; and NICU, neonatal intensive care unit.

conflicting, quoting sensitivities of 69–100% and specificities of 36–93% (9). Such wide ranges are the result of using different cutoff points for abnormal values (25–150 ng/L), when and how many samples are collected, how patients and controls are selected, and how reference values are defined and identified.

As a prerequisite for analyzing the CRP and IL-6 responses associated with infectious and noninfectious conditions during the immediate postnatal period, there is a need to establish the “normal” dynamics of both variables in the healthy neonate, counterbalanced by a greater awareness of the maternal and perinatal factors that may affect them. To this end, we report prospective, simultaneous measurements of both CRP and IL-6 in healthy babies at birth and at 24 and 48 h of life, and in their mothers at delivery. We also sought to identify maternal and perinatal factors that could confound the interpretation of these measurements.

Subjects and Methods

SUBJECTS

This study was performed at the Obstetric Unit and the well-baby nursery of the Saint Camillo Hospital, Rome. As part of an ongoing prospective investigation of serum CRP and IL-6 values in complicated and uncomplicated pregnancies, mothers were eligible for enrollment if (a) they agreed to participate in the study and signed consent forms approved by the Institutional Review Board of the Saint Camillo Hospital, and (b) they delivered at ≥ 35 weeks of gestation singleton newborns with birth weights appropriate for gestational age and with normal results on physical examination at birth that implied no need of empiric management. The mother-infant pair was included in the study if all of the following criteria were met: (a) a blood sample was collected at the time of delivery from the mother; (b) a blood sample was obtained at birth and at 24 and at 48 h after birth from each infant for measurement of CRP and IL-6; (c) the neonate had a continuous uncomplicated hospital stay and was discharged as healthy from the well-baby nursery on day 3 (vaginal births) or 4 (cesarean births); and (d) the neonate had normal assessments at the 1-week follow-up visit (for newborns who were born at 35–36 weeks gestational age only) and the 2- and 4-week follow-up visits. We excluded parturients with multiple preexistent or pregnancy-related noninfectious complications, or with clinically evident intraamniotic infection (10).

All antepartum and intrapartum data were collected prospectively and included maternal age, preexistent or pregnancy-related diseases, mode of delivery, use of anesthesia, duration of active labor (11), interval between rupture of membranes and delivery, maternal group B streptococcus (GBS) colonization, intrapartum antimicrobial administration, and abnormalities in intrapartum fetal heart monitoring. The institutional policy was to give intrapartum penicillin or broad-spectrum antibiotics to all women identified as GBS carriers at 35–37 weeks of

gestation. If the results of GBS cultures were not known at the onset of labor or rupture of membranes, intrapartum antimicrobial prophylaxis was administered if either or both of the following risk factors were present: preterm labor at < 37 weeks of gestation, and rupture of membranes ≥ 18 h before delivery (12). Neonatal data included gestational age, birth weight, gender, and Apgar scores at 1 and 5 min. Gestational age was established on the basis of best obstetric estimate, including last menstrual period and first or second trimester ultrasonography.

BLOOD COLLECTION AND CRP AND IL-6 MEASUREMENTS

Maternal serum was sampled at the time of delivery, and fetal serum was obtained from the umbilical vein at birth. Maternal, umbilical cord, and postnatal blood (100 μ L, to allow a double determination) samples for IL-6 measurements were stored in small aliquots at -70°C until analysis. IL-6 concentrations were measured in duplicate by an enzyme-linked immunoassay (Endogen) sensitive to < 1 ng/L. For the IL-6 assay, both the inter- and intraassay CVs are $< 10\%$ according to the manufacturer. Measurements of serum CRP concentrations were available in all study subjects within a few hours after blood collection. CRP was measured by rate nephelometry using a Beckman Array System protein analyzer (C-reactive protein reagent set 449760; Beckman Instruments). According to the manufacturer, this CRP assay has a detection limit of 4 mg/L and has inter- and intraassay CVs $< 4\%$ at both low and high concentrations.

STATISTICAL ANALYSIS

The observed CRP and IL-6 values were distributed with a long tail to the right (positive skew), but their logarithms were approximately normally distributed. Thus, all comparisons of CRP and IL-6 values and all regression analyses were done after the observed values were log-transformed. Consequently, all quoted mean values are geometric means with 95% confidence intervals (CIs), and regression coefficients are exponentiated to obtain ratios of geometric means.

There are two common ways of estimating percentiles from observed frequency distributions. The first is to arrange the data in ascending order and to identify the value of the variable that cuts off the desired percentage. The second method requires that the distribution has some known or supposed mathematical form, e.g., that the logarithms are distributed normally. In this case, the mean and SD of the distribution can be estimated from the observed data, and the percentiles can be obtained using tables of the standard normal distribution. Both methods have advantages and disadvantages. The first method has the advantages that no assumption is necessary about the distributional form of the data and that it is nonparametric, but it has a disadvantage in that estimates of the 95th and 97.5th percentiles may have large sampling errors if the total sample size is not large. The second method has the advantage of being more precise but only

if the distributional form is correctly known. In the present study, an additional difficulty in applying the second method was that many of the observed values of CRP and IL-6 were less than the minimum concentrations detectable by the instruments used to analyze the blood samples; thus, with these values missing, it was impossible to see the shape of the whole distribution. If it can be assumed that the distributions are log-normal, the observed values can be used to reconstruct the whole distribution using normal scores (not *z*-scores). Clearly, the method will fail if the true distribution is not the one that is assumed. Both methods were applied to the observed data, and fortunately the results were very similar. Only the nonparametric direct estimates are reported.

Multiple linear regression analyses were performed to explore the association between CRP and IL-6 responses in the mother-infant pairs and the following variables: gestational age, pregnancy-induced hypertension, gestational diabetes, intrapartum fetal distress, maternal GBS colonization, type of delivery (spontaneous vaginal, elective cesarean section, emergency cesarean section, and induced delivery), duration of active labor, interval (hours) between rupture of the membranes and delivery, intrapartum antimicrobial administration, and use of epidural or general anesthesia. The relationships between the CRP and IL-6 concentrations in the mother and the concentrations in the baby at birth and at 24 and 48 h of life were investigated by Spearman rank correlations. All statistical tests were considered significant if *P* was <0.05.

Results

One hundred ninety-nine neonates born on 55 randomly selected study days were enrolled at birth. Fifty-one neonates were subsequently excluded from the study for the following reasons: 19 infants were transferred to the intermediate nursery or the neonatal intensive care unit (NICU) within the first 72 h after birth because of clinical manifestations (tachypnea, dyspnea, temperature instability, hypoglycemia, or apneic episodes); for 24 infants, CRP or IL-6 was not measured according to the protocol design; and 8 infants were inadequately followed up after discharge from hospital. Thus, data from a total of 148 mother-newborn pairs, of whom 113 term (≥ 37 weeks of gestation) and 35 near-term (35–36 weeks of gestation) were available for simultaneous analysis of CRP and IL-6.

The characteristics of mothers and their healthy infants are summarized in Table 1. The reference intervals that were established for both CRP and IL-6 at the three fixed neonatal ages included 148 neonates who were not necessarily free of history of maternal and intrapartum complications but whose postnatal clinical course from birth to the 4-week follow-up visit was unremarkable, implying therefore, no need of management (including antimicrobial treatment) throughout this study period. The distribution of crude CRP values among the delivering mothers and their healthy offspring at the three

Table 1. Maternal and neonatal characteristics.

Maternal	
Mean (SD) age, years	30.9 (4.5)
Complications during pregnancy, n (%)	
Gestational diabetes	6 (4.1%)
Pregnancy-induced hypertension	12 (8.1%)
Mode of delivery, n (%)	
Spontaneous vaginal	51 (34.5%)
Induced vaginal	36 (24.3%)
Emergency cesarean section	28 (18.9%)
Elective cesarean section	33 (22.3%)
Use of epidural anesthesia, n (%)	20 (13.5%)
Mean (SD) length of active labor, h	2.5 (2.6)
Mean (SD) time of ruptured membranes, h	11 (37)
Ruptured membranes ≥ 18 h, ^a n (%)	19 (12.8%)
GBS colonization, ^a n (%)	13 (8.8%)
Intrapartum antimicrobial administration, n (%)	30 (20.3%)
Fetal distress, n (%)	33 (22.3%)
Infant	
Mean (SD) birth weight, g	3039 (601)
Mean (SD) gestational age, weeks	38.4 (2)
Male gender, n (%)	82 (55.4%)
Mean (SD) Apgar score	
at 1 min	7.7 (0.6)
at 5 min	9.1 (0.5)

^a Occurring as an isolated event.

neonatal ages is shown in Fig. 1A. Nineteen (12.8%), 54 (36.4%), and 55 (37.1%) of the healthy newborns had detectable concentrations of CRP at birth and 24 and 48 h of life, respectively, which implies that the median values are undetectable. Table 2 lists the 90th, 95th, and 97.5th percentiles of CRP values for each neonatal age.

When the data were analyzed after a logarithmic transformation, the geometric mean CRP values were significantly lower in cord blood than in blood samples taken at 24 h ($P < 0.0001$) and at 48 h ($P < 0.0001$), with no significant change from 24 to 48 h ($P = 0.6$; Table 2). Fifty-one (34.4%) of the parturient mothers had detectable CRP. There was no correlation between CRP concentrations in parturient mothers and those found in their offspring at birth ($r = 0.058$; $P = 0.48$).

By regression analysis, CRP response at birth was negatively associated with the Apgar score obtained 5 min ($P = 0.01$) after birth and positively associated with rupture of membranes for 18 h or longer ($P = 0.001$). The babies' mean CRP concentration at birth was increased by a factor of 1.50 (95% CI, 1.32–2.03) if the 5-min Apgar score was ≤ 8 and by a factor of 1.32 (95% CI, 1.07–1.61) if the time from rupture of membranes was ≥ 18 h. In contrast, the mean CRP response at 24 h was positively associated with pregnancy-induced hypertension ($P = 0.0038$). The babies' mean CRP concentration at 24 h was increased by a factor of 1.43 (95% CI, 1.01–2.03) if the mother had gestational hypertension. At 48 h of life, the babies' mean CRP response was not significantly affected by any of the variables identified from maternal and

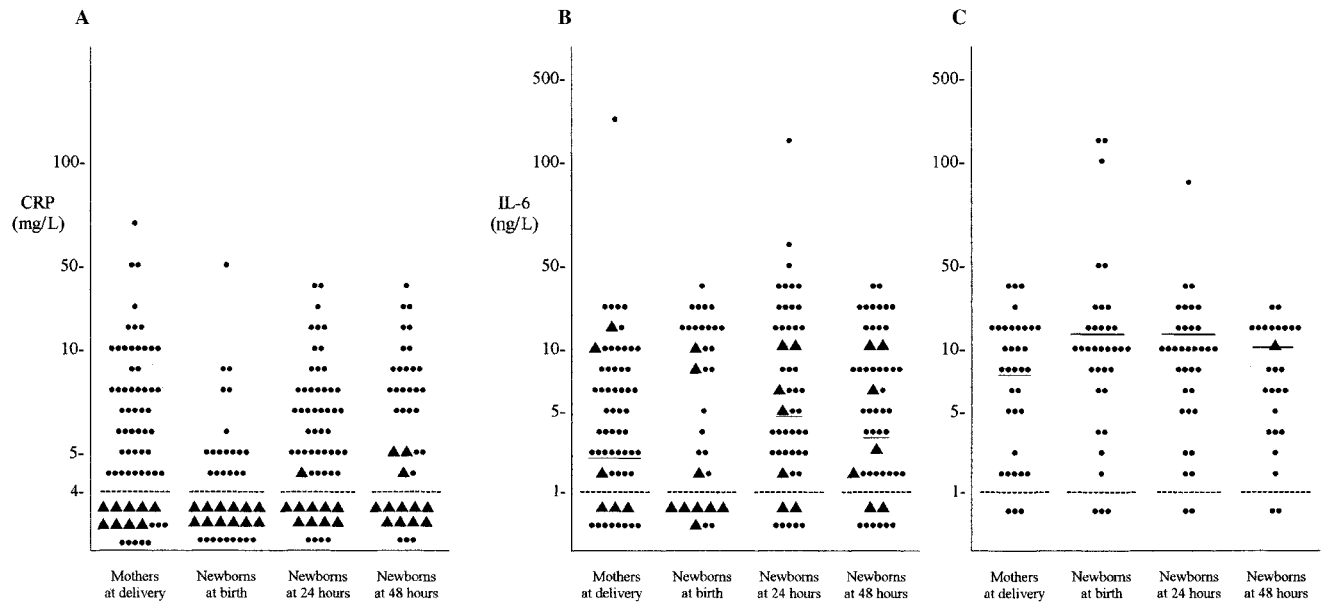


Fig. 1. Distribution of crude CRP (A) and IL-6 (B and C) among 148 delivering mothers and their healthy offspring at the three neonatal ages 0, 24, and 48 h.

For crude IL-6 values, the values are shown separately for the 113 term (B) and the 35 near-term (C) delivering mothers and their corresponding healthy offspring. ▲ indicates 10 subjects; ● indicates 1 subject. Dashed lines, detection limits of assays; solid lines, medians.

perinatal history. The maternal mean CRP concentration was increased by a factor of 1.06 (95% CI, 1.01–1.12; $P = 0.006$) per hour of active labor, by a factor of 1.62 (95% CI, 1.07–2.49, $P = 0.022$) if the mother had GBS colonization, and by a factor of 1.54 (95% CI, 1.06–2.24; $P = 0.021$) if the time from rupture of membranes was ≥ 18 h.

Fig. 1, B and C, shows the distribution of crude IL-6 values in the term and near-term delivering mothers and in their healthy offspring at the three neonatal ages. Table 3 lists the 90th and 95th percentiles of IL-6 values in the term and near-term infants for each neonatal age. The reason for dividing the infants into subgroups in Fig. 1, B and C, and Table 3 was the finding by regression analysis that gestational age was negatively associated with IL-6 values obtained from the mothers as well as the babies at all of the three neonatal ages. Multiple regression analysis of the independent effects of gestational age and birth

weight on IL-6 values revealed that only gestational age had a significant effect. The regression coefficients (SE) for gestational age were -0.192 (0.078; $P = 0.014$) for delivering mothers, -0.281 (0.084; $P = 0.001$) for babies at birth, -0.135 (0.057; $P = 0.020$) for babies 24 h of age, and -0.147 (0.068; $P = 0.032$) for babies 48 h of age. As expected, the geometric mean concentration of IL-6 in the near-term mothers was 2.57 (95% CI, 1.49–4.46; $P = 0.001$) times higher than that of the term mothers. The geometric mean IL-6 concentration in the near-term babies at birth and at 24 and 48 h of life was 6.40 (95% CI, 3.61–11.50; $P < 0.0001$), 2.38 (95% CI, 1.41–3.99; $P = 0.001$), and 2.40

Table 2. Geometric mean CRP values in 148 delivering mothers and their healthy newborns at 0, 24, and 48 h of life, and upper reference limits at the three neonatal ages.

	CRP, mg/L			
	Geometric mean ^a (95% CI)	Percentiles		
		90th	95th	97.5th
Mothers	4.3 (3.9–4.8)			
Newborns				
At birth	3.3 (3.1–3.5)	4.1	5.0	8.4
At 24 h	4.1 (3.7–4.5)	7.8	14.0	24.0
At 48 h	4.0 (3.7–4.4)	8.0	9.7	26.5

^a Undetectable values, <4 mg/L, were arbitrarily given the value 3 mg/L.

Table 3. Geometric mean IL-6 values in 148 delivering mothers and their healthy newborns at 0, 24, and 48 h of life, and upper reference limits at the three neonatal ages.

	IL-6, ng/L		
	Geometric mean ^a (95% CI)	Percentiles	
		90th	95th
Term mothers (n = 113)	2.87 (2.17–3.79)		
Term newborns			
At birth	1.69 (1.28–2.23)	15.7	24.8
At 24 h	4.09 (3.13–5.33)	25.3	40.9
At 48 h	3.45 (2.70–4.43)	20.0	27.0
Near-term mothers (n = 35)	7.0 (4.59–10.7)		
Near-term newborns			
At birth	10.9 (6.53–18.4)	136.8	262.2
At 24 h	9.3 (6.2–14.1)	36.2	55.4
At 48 h	8.4 (5.97–11.9)	21.5	28.0

^a Undetectable values, <1 ng/L, were arbitrarily given the value of 0.5 ng/L.

(95% CI, 1.49–3.88; $P < 0.001$) times higher, respectively, than the concentration observed in the term babies.

We therefore examined, within each of the two gestational age groups, whether neonatal IL-6 concentrations changed between the three times and whether IL-6 concentration at birth correlated with maternal IL-6 at delivery. Among the term babies, the geometric mean IL-6 values were significantly lower at birth than at 24 h of life ($P < 0.0001$), with no significant change from 24 to 48 h of life ($P = 0.12$; Table 3). In contrast, within the subgroup of near-term babies, the geometric mean IL-6 concentrations at birth were not significantly different from those found at 24 ($P = 0.52$) and 48 ($P = 0.30$) h of life (Table 3). IL-6 concentrations obtained from term babies at birth correlated with maternal IL-6 concentrations (rank correlation coefficient, 0.52; $P < 0.0001$), whereas those obtained from near-term babies at birth did not correlate with those found in their mothers at delivery (rank correlation coefficient, -0.004 ; $P = 0.98$).

Using multiple regression analysis, we investigated whether the remaining variables had a significant effect on IL-6 response in delivering mothers as well as in their healthy offspring at any of the three set times. After adjusting for the effect of gestational age, we found that the mothers' IL-6 concentrations were increased by a factor of 1.17 (95% CI, 1.03–1.34; $P = 0.022$) per hour of active labor, whereas the babies' IL-6 concentrations were increased at birth by a factor of 5.04 (95% CI, 2.44–21.4; $P = 0.027$) if the 5-min Apgar score was ≤ 8 . In contrast, none of the remaining potential confounding factors had a statistically significant effect on the babies' IL-6 concentrations at 24 and 48 h of life.

Discussion

To establish reference intervals useful for correct identification of the infected and uninfected neonate during the 48-h period after birth (when the majority of diagnostic problems are encountered), we assessed the "normal" upper limits for both CRP and IL-6 by serial determinations at three fixed neonatal ages: 0, 24, and 48 h after birth.

To our knowledge, this is the first longitudinal study of CRP dynamics in a large sample of healthy newborns during the immediate postnatal period. In the majority of published reports (2–4, 6, 7, 13–17), upper limits for CRP during the neonatal period have been established in symptomatic uninfected patients. In that vein, the literature has conflicting reports as to the cutoff points (1.5–20 mg/L) for the upper limits of CRP. Possible sources of heterogeneity were wide-ranging differences in postnatal age or inaccuracies in reporting it, single vs serial determinations, different sample sizes, and different measurement methods (18). However, there are fewer cross-sectional studies of upper limits for CRP in healthy newborns (5, 19, 20). Again, among these studies, there is some degree of heterogeneity, based on different measurement methods and different sampling times. Thus,

the fact that there are no established CRP reference intervals in the neonatal period can explain the wide range of reported CRP sensitivities (47–100%) and specificities (6–97%) for detection of neonatal sepsis (8). The present study demonstrates the physiologic CRP changes that occur over the first 48 h of life. In view of this dynamic behavior, previously reported CRP cutoff points may not be appropriate at certain neonatal ages.

The novel finding observed is that in our cohort of healthy neonates, rupture of membranes ≥ 18 h, perinatal distress, or gestational hypertension significantly affected the CRP concentrations during the immediate postnatal period, but at specific ages. The present findings become important with the very latest clinical applications of CRP. Philip and Mills (21) established a CRP value ≥ 10 mg/L in the presence of one (or more) clinical sign(s) or one (or more) risk factor(s) for infection as the clinical pathway for transferring a neonate from the well-baby nursery to the NICU and starting antimicrobial therapy. Franz et al. (22, 23), on the other hand, considered a CRP value > 10 mg/L in the presence of one (or more) clinical sign(s) as a criterion to make a diagnosis of early- as well as of late-onset clinical septicemia in NICU babies. However, it is clear that the patterns of CRP response in the immediate postnatal period should be taken into account to optimize the use of CRP in both the clinical setting of NICU and the well-baby nursery.

It is known that CRP does not cross the placenta (8). Accordingly, the present study confirms that serum concentrations of CRP and its production in the mother and fetus/newborn are independent of one another; however, the same stimulus may be operating concurrently in each. The major obstetric condition in which determination of maternal serum CRP concentrations might be clinically useful is chorioamnionitis (24). Considerable variation in the sensitivity and specificity of this testing is reported by different authors (25). This may be a result of the use of different cutoff points for abnormal values (12–40 mg/L), different measurement methods, or different gold standards. It is evident from our data that some confounding factors per se should also be taken into account to optimize the use of maternal serum CRP.

To our knowledge, this is the first longitudinal study of IL-6 dynamics in a large sample of healthy newborns during the 48-h period after birth. Recently, De Jongh et al. (26) found that the physiologic concentration of IL-6 in the cord blood may be affected by duration of gestation. In the present study, at any of the three fixed ages, near-term healthy infants had significantly higher IL-6 concentrations than term healthy infants, demonstrating that a gestational age-dependent effect on the normal IL-6 values might be seen over the initial 48 h of life. These higher IL-6 concentrations in near-term healthy neonates may be the result of subclinical perinatal infections, which are frequent with preterm labor, although none of these babies became symptomatic or received antibiotic treatment. There is no reason to believe that near-term infants

would have been more prone to mistaken assignment of healthy status than term infants born in the same clinical conditions. On the other hand, preterm delivery can be more stressful for the unprepared fetus, which can induce an increase in serum IL-6, probably via the stimulation of IL-6 production by adrenal gland cells (27). This may also explain the negative correlation of cord blood IL-6 values with the Apgar score.

We have also shown that the kinetics of IL-6 during the first 48 h of life in healthy infants are different in the near-term infant compared with kinetics in the term neonate, suggesting different physiologic processes. In the term neonate, the surge of IL-6 at 24 h of age probably reflects a physiological stress reaction induced at birth. Similar data regarding IL-6 dynamics in healthy term neonates have also been reported recently (28). In contrast, in the near-term neonate, umbilical cord IL-6 was already increased at the time of birth, suggesting that a physiological stress reaction had begun before birth.

Although placental cells produce IL-6 and other proinflammatory cytokines, the evidence that these cytokines cross the placenta remains unclear (29). In the present study, the positive association between IL-6 values from term mothers and their healthy offspring at birth suggests that IL-6 may cross the placental barrier. However, the finding of higher IL-6 concentrations in cord sera of near-term babies compared with the corresponding maternal samples argues against the dependency of neonatal serum IL-6 concentrations on maternal IL-6 concentrations in the setting of preterm delivery. Taken together, the present data demonstrate the effects of development on serum IL-6 reference intervals and dynamics, as well as on the relationship between maternal and cord blood concentrations during the 48-h period after birth.

Another question addressed in this study was whether the IL-6 concentration in maternal serum was affected by pregnancy-related disorders, mode of delivery, use and type of anesthesia, duration of active labor, and stressful labor. The results confirm that a longer labor is correlated with increased serum IL-6 (and CRP) production in near-term as well as in term delivering mothers (30,31), suggesting that IL-6 and the physical activity of labor are interrelated. Finally, at delivery, near-term mothers had IL-6 values that differed significantly from those for term mothers, demonstrating again the potential confounding effect of gestational age. However, the design of the present study does not allow any conclusion regarding whether IL-6 has an etiologic role as precipitator of human preterm delivery.

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