OBSTETRICS

Maternal inflammatory markers and term labor performance

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OBJECTIVE: We sought to examine the relationship between maternal markers of inflammation and labor performance.

STUDY DESIGN: A nested cohort study was performed utilizing an established cohort of term nulliparous patients. Maternal blood was collected at the onset of regular, painful contractions in patients undergoing labor induction or at admission in patients with spontaneous labor. Levels of cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor-α were determined using standard multiplex methodology. Maternal demographic data were collected prospectively. Detailed retrospective chart review was performed to extract data on cervical dilation, effacement, and station during labor. Subjects were excluded if they failed to achieve complete dilation. Mixed effects modeling was used to examine the association between serum cytokine quartiles and labor progress in the latent and active phases.

RESULTS: In all, 334 women were included in our analysis. The lowest quartile of IL-6 was associated with slower latent labor ($P = .001$). In contrast, the highest quartiles of IL-1 and tumor necrosis factor-α were associated with slower active labor ($P = .03$ and $.0002$, respectively).

CONCLUSION: Proinflammatory activation is important in labor initiation. However, once active labor is established, excess inflammation can be detrimental to efficient labor progress. These data may explain, in part, the known associations among clinical chorioamnionitis, cesarean delivery, and postpartum hemorrhage.

Key words: cytokines, failure to progress, inflammation, interleukins, labor

The mechanism of parturition is a complex interplay of inflammatory, mechanical, and endocrine factors.[1] Proinflammatory cytokines stimulate or enhance early labor through multiple mechanisms[2,3] including: stimulation of prostaglandins prostaglandin $F_{2\alpha}$ and its receptor through prostaglandin H synthase-2[4,5] and enhancing the process of cervical ripening.[6] Our group has reported that higher levels of maternal serum interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α are found in asymptomatic term patients who subsequently experience the onset of spontaneous labor within 48 hours.[7] These data suggest a significant role for maternal inflammatory activation in process of labor initiation.

In contrast, a separate body of research has focused on the detrimental effects of inflammation on labor progress. Chorioamnionitis increases the risk of prolonged labor, cesarean delivery, and postpartum hemorrhage.[8-10] Maternal fever in labor is associated with an increased risk of both cesarean and assisted vaginal delivery.[11] This suggests that pathologic levels of maternal inflammation and or hyperthermia adversely affect myometrial contractility and labor progress. Taken together, the data suggest a biphasic role for inflammation, with physiologic levels contributing to normal labor initiation but excessive levels degrading labor performance. The objective of this study was to explore the relationship between serum cytokine concentrations at the beginning of active labor and labor performance at term.

MATERIALS AND METHODS

A nested cohort study was performed. The initial cohort consisted of 607 nulliparous women who were candidates for a trial of labor from Feb. 5, 2006, through March 12, 2009. Subjects were enrolled prospectively prior to labor onset at $\geq$37 0/7 weeks' gestation. Women with active infections, autoimmune conditions, or those taking antiinflammatory agents were excluded. Labor progress is modeled in reverse time with the time of full dilation anchoring at time 0; only parturients who reached full dilation were considered. Subjects were excluded if

TABLE 1
Cohort demographic, labor, and neonatal characteristics (n = 334)

Demographic	Value
Age, y	23 (15−42)
BMI, kg/m^2	30.0 (17.2−54.2)
Racial/ethnic group	
White	40.1%
Black	18.9%
Hispanic	38.3%
Other	2.7%
GA at delivery, wks	40.0 (37.1−42.1)
Cervical dilation at admission, cm	
Overall	1.7 (0−9)
IOL	1.0 (0−5)
Spontaneous labor or PROM	3.0 (0−9)
WBC on admission, 9/L^{10}	11.4 (5.9−24.9)
Induction	29.0%
Oxytocin use	82.3%
Maximum oxytocin dose, mU/min	14 (1−42)
AROM	64.5%
Regional anesthesia	91.2%
Time from admission to 10-cm dilation, h	
Overall	11.4 (0.1−47.2)
IOL	17.5 (3.0−47.2)
Spontaneous labor or PROM	9.43 (0.1−42.7)
Mode of delivery	
Spontaneous vaginal	77.5%
Cesarean	7.8%
Operative vaginal	14.7%
Birthweight, g	3376 ± 446

AROM, artificial rupture of membranes; *BMI*, body mass index; *GA*, gestational age; *IOL*, induction of labor; *PROM*, prelabor rupture of membranes; *WBC*, white blood cell count.

Continuous variables reported as medians (range) or mean ± SD.

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they failed to achieve complete dilation, yielding a total of 334 subjects. Maternal blood was collected on our labor and delivery unit at the onset of regular, painful contractions in patients undergoing labor induction or at admission in patients with spontaneous labor. Maternal serum samples were stored at −80° C until batch multiplex analysis. Levels of cytokines IL-1, IL-6, and TNF-α were quantified using custom kits (BioRad, Hercules, CA) and standard protocols on the Luminex 200 platform (Luminex Corp, Austin, TX). Maternal data on gestational age at enrollment, height, weight, race, ethnicity, and other demographic variables were collected prospectively. Intrapartum data including hourly maternal temperature and duration of epidural analgesia were collected prospectively on specific study forms. Detailed chart review was performed to abstract data on every cervical examination over the course of labor. For each cervical examination, the associated self-reported maternal pain score, oxytocin dose, and membrane status was recorded. Cervical examinations were performed at the discretion of the physician, and were not proscribed at a set interval.

Statistical analysis on demographic variables was performed with SAS software (version 9.2; SAS Institute, Cary, NC) and SPSS software (version 12.0, IBM Corp, Armonk, NY). Maternal and neonatal characteristics were compared by the Mann-Whitney U test for continuous variables and χ^2 or Fisher exact test for categorical variables. Patients were categorized by cytokine quartiles for each cytokine for further analysis as the distribution was not normally distributed. Where there was a positive association with both first and fourth quartile, the strongest association was considered for inclusion in the final model.

Labor progress model
Labor progress was analyzed using the biexponential model for labor progress previously derived and validated by Debiec et al.[13] This model requires estimation of 3 variables: a rate constant for latent labor, a rate constant for active labor, and the number of centimeters of cervical dilation associated with the active phases. The relationship is described by the equation:

$$CD = Ce^{-\lambda_1 \times time} + (10 - C)e^{-\lambda_2 \times time}$$

where CD is the cervical dilation, λ_2 is the rate constant for the slow change in cervical dilation during latent labor, and λ_1 is the rate constant for the rapid change in cervical dilation during active labor. C is the number of centimeters associated with active labor, and $(10 - C)$ is the number of centimeters associated with latent labor. Time is the number of hours prior to 10 cm of cervical dilation. When time = 0, the cervix is fully dilated, and the equation at time = 0 reduces to CD = 10.

The biexponential model above is similar to the structural model proposed