Lehigh Valley Health Network
LVHN Scholarly Works

Department of Obstetrics & Gynecology

Intrapartum Fever at Term: Serum and Histologic Markers of Inflammation

John C. Smulian MD, MPH
Lehigh Valley Health Network, john.smulian@lvhn.org

Vineet Bhandari MD

Anthony M. Vintzileos MD

Susan Shen-Schwarz MD

Carlene Quashie MD

See next page for additional authors

Follow this and additional works at: https://scholarlyworks.lvhn.org/obstetrics-gynecology

 Part of the Congenital, Hereditary, and Neonatal Diseases and Abnormalities Commons, Medical Pathology Commons, Obstetrics and Gynecology Commons, and the Tissues Commons

Published In/Presented At

Smulian, J., Bhandari, V., Vintzileos, A., Shen-Schwarz, S., Quashie, C., Lai-Lin, Y., & Ananth, C. (2003). Intrapartum fever at term: serum and histologic markers of inflammation. *American Journal Of Obstetrics And Gynecology*, *188*(1), 269-274.

This Article is brought to you for free and open access by LVHN Scholarly Works. It has been accepted for inclusion in LVHN Scholarly Works by an authorized administrator. For more information, please contact LibraryServices@lvhn.org.

Authors

John C. Smulian MD, MPH; Vineet Bhandari MD; Anthony M. Vintzileos MD; Susan Shen-Schwarz MD; Carlene Quashie MD; Yu-Ling Lai-Lin RNC, MSN; and Cande V. Ananth PhD, MPH

This article is available at LVHN Scholarly Works: https://scholarlyworks.lvhn.org/obstetrics-gynecology/145

Intrapartum fever at term: Serum and histologic markers of inflammation

John C. Smulian, MD, MPH,[a] Vineet Bhandari, MD, DM,[e] Anthony M. Vintzileos, MD,[a] Susan Shen-Schwarz, MD,[b] Carlene Quashie, MD,[d] Yu-Ling Lai-Lin, RNC, MSN,[a] and Cande V. Ananth, PhD, MPH[c]

New Brunswick, NJ, New Haven, Conn, and Philadelphia, Pa

OBJECTIVE: This study was undertaken to determine whether intrapartum fevers at term are associated with markers of acute inflammation in maternal, fetal, and placental compartments.
STUDY DESIGN: Term cases with intrapartum fever (temperature ≥100.4°F) were recruited with gestational age–matched controls. Maternal serum and umbilical vein blood were collected and assayed for interleukin-6 (IL-6) levels. Placentas were examined for histologic chorioamnionitis. Demographic and clinical data were collected and compared between cases and controls.
RESULTS: Forty-seven case-control pairs were analyzed. Maternal IL-6 levels were higher in cases than in controls (median of 145 pg/mL vs 42 pg/mL, $P < .0001$). Umbilical vein IL-6 levels also were higher in cases than controls (median 9 pg/mL vs 3.5 pg/mL, $P = .01$), but more than half of levels in cases were below 11 pg/mL. Only 31.1% of febrile cases had moderate or severe histologic chorioamnionitis. Multivariable logistic regression identified maternal serum IL-6 levels, nulliparity, and number of vaginal examinations as the major predictors of intrapartum fever at term.
CONCLUSION: The maternal inflammatory response as measured by maternal serum IL-6 levels is a strong marker for term intrapartum fever. The much weaker association of fetal and placental inflammatory responses suggest a smaller than expected contribution of intra-amniotic inflammation to term intrapartum fevers. (Am J Obstet Gynecol 2003;188:269-74.)

Key words: Inflammation, fever, chorioamnionitis, interleukin-6, pregnancy, placenta

Intrapartum fever is common in the United States. It has a reported incidence of 1.6% in singleton live births, of which more than 90% are term gestations.[1] Intrapartum fever is considered a risk factor for a variety of adverse outcomes, including maternal and infant infectious complications, neonatal encephalopathy, seizures, meconium aspiration syndrome, hyaline membrane disease, need for assisted ventilation, and perinatal mortality.[1-5] Fever is one of the hallmark features of the clinical diagnosis of chorioamnionitis and is commonly considered a sign of infection.[6] However, epidemiologic studies have suggested that the majority of intrapartum fevers may be related to other noninfectious causes.[7]

Because of the limited ability to directly link the clinical symptom of fever with actual infection, it is necessary to explore the use of adjunct markers to improve our understanding of inflammation, infection, and fever during labor. The majority of studies examining cytokines as predictors of intra-amniotic infection and histologic examination of the placenta to confirm acute inflammation have focused on pregnancies delivered preterm. There is a limited amount of information regarding these markers of acute inflammation in the term pregnancy complicated by intrapartum fever. We therefore designed this study to evaluate the role of inflammation in the maternal, fetal, and placental compartments as an etiologic factor for intrapartum fever at term by use of maternal and umbilical vein (UV) interleukin-6 (IL-6) levels, as well as placental histologic features.

Material and methods

This prospective incident case-control study was approved by the necessary institutional review boards for human subjects in research. Our primary objective was to determine whether intrapartum fever at term was associated with elevated maternal serum and UV IL-6 levels, or

From the Division of Maternal-Fetal Medicine,[a] the Department of Pathology,[b] and the Section of Epidemiology and Biostatistics,[c] Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School/Saint Peter's University Hospital, the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology at Albert Einstein Medical Center,[d] and the Division of Perinatal Medicine, Department of Pediatrics, Yale University School of Medicine.[e]
Supported by the Samuel A. Pasquale, MD Award, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School.
Presented in part at the Annual Meeting of the Society for Gynecologic Investigation, 2000.
Received for publication February 22, 2002; revised May 2, 2002; accepted September 6, 2002.
Reprints not available from the authors.
© 2003, Mosby, Inc. All rights reserved.
0002-9378/2003 $30.00 + 0
doi:10.1067/mob.2003.11

with histologic acute inflammation. This study was designed to recruit subjects over a 2-year period with planned interim analyses at 12 and 18 months. It was anticipated that 140 subjects could potentially be enrolled over 24 months.

Women with singleton gestations admitted to Saint Peter's University Hospital in New Brunswick, NJ, and Albert Einstein Medical Center in Philadelphia, Pa, in labor at ≥37 weeks' gestation were eligible. Cases were defined as women with an intrapartum temperature of 100.4°F or greater at least once during intrapartum vital sign evaluation. By protocol, women had intrapartum temperature evaluations at least every 4 hours during labor. Temperatures were evaluated more frequently in the presence of risk factors or signs of possible chorioamnionitis.

After a subject was identified with an intrapartum fever, written informed consent was obtained for study participation. Clinical information collected for each enrolled case included demographic information, clinical characteristics of labor, and presence or absence of clinical features for chorioamnionitis. Maternal serum was aspirated from the antecubital vein of the arm without an intravenous catheter by using a sterile technique within 1 hour of delivery, either in the second stage of labor or immediately postpartum. Approximately 5 mL of UV blood was aspirated sterilely from the umbilical cord after delivery of the infant and before delivery of the placenta. Placentas from these deliveries were sent for histologic evaluation of acute inflammation, although several subjects did not have placental specimens sent for histologic examination.

Controls were identified as those without fever in labor (temperature <100.4°F) with a gestational age matched (±7 days) to the respective case. In addition, an attempt was made to match controls to cases by route of delivery. Controls were identified immediately before or at the time of delivery. Maternal and UV blood was obtained in a fashion similar to cases and placentas were sent for histologic examination.

IL-6 assays. Maternal and UV blood specimens were transported to the laboratory after collection where they were centrifuged at 1000*g* for 10 minutes. After separation from the cell pellet, the supernatant was divided into aliquots and stored at –70°C for future determinations of IL-6 levels. Samples were thawed in batches when ready for assay. All assays were performed less than 12 months after specimen collection to ensure optimum IL-6 stability.[8] All assays were performed by a single laboratory technician blinded to case or control status and assays were performed with a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Quantikine Human IL-6 Kit, R&D Systems, Minneapolis, Minn). Briefly, this assay uses a quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for IL-6 was coded onto 96-well microtiter plates. Standards and samples were placed into wells and IL-6 was bound by the immobilized antibody. After washing, an enzyme-linked polyclonal antibody specific for IL-6 was added to the wells to sandwich the immobilized IL-6. After additional washes and the addition of substrate, a colormetric assessment of the optical density of the wells was performed. A standard curve was prepared plotting the optical density versus concentration of IL-6 in the standard well. The concentration of IL-6 in the samples was determined by comparing the optical density of the samples with the standard curve. Each sample was assayed in duplicate. The sensitivity for IL-6 of the assay was 0.7 pg/mL. Intra-assay and interassay variations of this assay are less than 7%.

Placental examinations. Pathologic evaluations were performed blinded to case or control status. Placentas from each subject were examined fresh. At least two sections of the placental disk were taken for microscopic examination, each of which included the center of a placental lobule, chorionic plate, and decidual floor. One of the disk sections was taken close to the umbilical cord insertion site. Another was taken midway between cord insertion and placenta margin. At least one section of umbilical cord 2 cm from the disk insertion site and a rolled strip of extraplacental membranes were examined.

Histologic findings of all placentas were recorded by standardized protocol. For purposes of this study, histologic chorioamnionitis was defined as an inflammatory infiltrate of neutrophils present at more than one site in the chorionic plate and the extraplacental membranes. It was classified into three grades, based on criteria of Naeye et al.[9] Mild chorioamnionitis was identified when there were few (5-10 scattered neutrophils per high-power field) in the subchorionic space and adjacent chorion. Moderate chorioamnionitis was identified when there were many (11-30 neutrophils per high-power field) in the lower half of the chorionic plate from the subchorionic space. Severe chorioamnionitis was identified when there was a dense infiltrate of neutrophils (30 or more per high-power field) throughout the chorionic plate into the amnion. Chorionic vasculitis was identified when neutrophils infiltrated the wall of at least one chorionic vessel. Funisitis was identified when neutrophils infiltrated the wall of at least one umbilical cord vessel.

Statistical analysis. Demographic information, as well as clinical characteristics of labor and clinical features of infection, were compared between cases and controls. Markers of inflammation, including maternal and UV serum IL-6 levels, as well as histologic chorioamnionitis and funisitis, were also compared. Contingency tables based on χ^2 test or Fisher exact test were used to evaluate categorical variables. Normally distributed continuous variables were compared by using a two-tailed *t* test. Nonnormally distributed continuous data were compared by using nonparametric tests, such as the Mann-Whitney *U*

Table I. Demographic features of term intrapartum fever cases and controls

	Cases (n = 47)	*Controls (n = 47)*	*P value*
Maternal age (y)	25.0 ± 6.0	31.1 ± 7.6	<.0001
Nulliparous	36 (76.6%)	22 (46.8%)	.003
Parity	0 (1 to 6)	1 (0 to 9)	.002
Gravidity	1 (1 to 8)	2 (1 to 1)	.004
Race			.97
Black	9 (19.1%)	9 (19.1%)	
White	25 (53.2%)	26 (55.3%)	
Other	13 (27.7%)	12 (25.5%	
Gestational age (wk)	39.4 ± 1.3	39.6 ± 1.2	.55

Continuous variables expressed as mean ± SD or median (range).

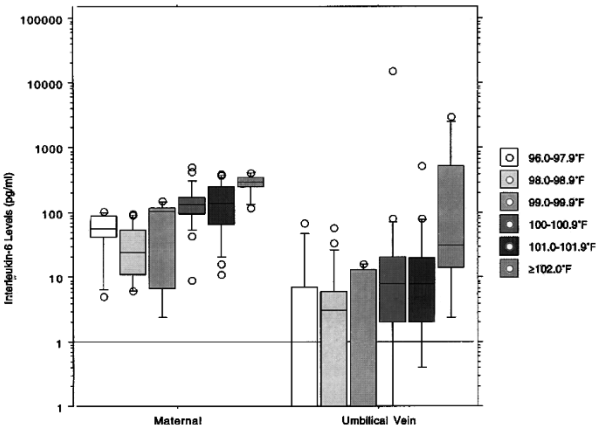

Figure. Box plot of degree of maternal temperature elevation versus maternal and UV IL-6 levels on longitudinal scale (*horizontal line* = 50th percentile; *box* = 25th to 75th percentile; *vertical line* = 10th to 90th percentile). Only 75th and 90th percentiles are shown for UV IL-6 levels when 50th percentile level was undetectable (<0.7 pg/mL).

or Kruskal-Wallis test. Statistical significance was set at $P < .05$ for the univariable analyses. Finally, logistic regression was used to identify important markers of term intrapartum fever after checking for interactions among variables. The presence of multicolinearity in the regression models was assessed and when present, the continuous variables were standardized (subtraction of the mean and dividing by standard deviation). Nonlinear covariate effects were assessed by including standardized second-order polynomials.

Results

Enrollment for this study was halted after 18 months when planned interim analysis demonstrated significance for the three primary outcome variables. There were 82 subjects recruited from Saint Peter's University Hospital. Of these, 4 of the controls had fever develop just before delivery and therefore were not eligible as controls. These 4 controls with their 4 corresponding cases were excluded from the final analysis leaving 37 case-control pairs from Saint Peter's University Hospital. (A separate analysis that included these additional subjects, based on an intent-to-treat principle, showed no meaningful differences from the analyses excluding these subjects. Therefore, they were not included in the reported results.) Ten cases and 10 gestational age–matched controls from the Albert Einstein Medical Center were included for analysis. Of the 47 fever cases, three maternal serum samples and one UV sample were not acceptable for analysis because of errors in collection or processing. Of the 47 control subjects, four maternal serum samples and three UV samples were not acceptable. Placental histologic study was available in 45 cases and 40 controls.

Demographic comparisons are provided in Table I. Febrile cases were younger with lower parity and gravidity than controls. Race distribution and gestational age were similar. Maternal clinical characteristics are reported in Table II. There was a greater duration of labor and duration of ruptured membranes in the febrile cases. There was also an increased number of vaginal examinations and longer time from the initial vaginal examination to delivery for cases. More than 80% of both cases and controls used epidural anesthesia; however, usage was statistically higher in cases (rate ratio 1.1, 95% CI 1.0-1.2). Similarly, the duration of epidural anesthesia was greater for cases. As expected, intrapartum antibiotics were used more commonly in fever cases. Features of clinical chorioamnionitis, except foul-smelling amniotic fluid and a tender uterus, were more common in fever cases. There were no cases of confirmed neonatal sepsis in either group.

The relationship of maternal maximum temperature with maternal and UV IL-6 levels is shown in the Figure. Although higher maternal temperatures were associated with higher IL-6 levels in both maternal and UV samples, the relationship was stronger for maternal levels ($P < .0001$) than UV levels ($P = .02$) with the use of the Kruskal-Wallis test. The median (range) time from initial documented fever to time of delivery was 3 (0.3-13) hours. There was no clinically meaningful association between duration of fever and maternal ($R^2 = 0.13$) or UV ($R^2 = 0.10$) IL-6 levels on the basis of regression analysis using transformed (standardized) IL-6 levels. In all fever cases and all but one of the controls, maternal IL-6 was detected (Table III). Maternal IL-6 levels were significantly higher in cases than controls. IL-6 was detected more commonly and at higher levels in the UV specimens from cases compared with controls. We also examined the degree of elevation of UV IL-6 levels on the basis of previously established cutoff levels suggested to be useful for predicting neonatal infection in preterm infants.[10,11] Fewer than half the cases had IL-6 levels greater than 11 pg/mL and fewer than 25% had UV IL-6 levels greater than 25 pg/mL.

Table II. Clinical characteristics of term intrapartum fever cases and controls

	Cases (n = 47)	*Controls (n = 47)*	*P value*
Cesarean delivery	15 (31.9%)	12 (25.5%)	.49
Induction of labor	14 (29.8%)	19 (40.4%)	.31
Oxytocin administration	37 (78.7%)	33 (70.2%)	.31
Scalp electrode	33 (70.2%)	26 (55.3%)	.12
Intrauterine pressure catheter	14 (29.8%)	11 (23.4%)	.44
Intrapartum antibiotics	39 (83.0%)	12 (25.5%)	<.0001
Epidural anesthesia	46 (97.9%)	39 (83.0%)	.01
Duration of epidural (h)*	7.5 (0-18)	5.5 (0-51)	.003
Duration of labor (h)*	14 (6-78)	9 (1-27)	.0002
Duration of membrane rupture (h)*	10 (1-28)	7 (1-32)	.03
Number of vaginal examinations*	8 (3-16)	6 (1-14)	.0003
Initial examination-to-delivery interval (h)*	14 (5-50)	9 (2-30)	.002
Meconium	15 (31.9%)	11 (23.4%)	.28
Group B *Streptococcus* positive	6 (12.8%)	7 (14.9%)	.52
Urinary tract infection	5 (10.6%)	4 (8.5%)	.73
Maximum temperature†	101.3°F ± 0.7°F	98.5°F ± 0.9°F	<.0001
Admission white blood cell count†	12,000 ± 4,500	10,300 ± 3,200	.05
Tender uterus	1 (2.1%)	0	.99
Maternal tachycardia (≥100 beats/min)	33 (70.2%)	12 (25.5%)	<.0001
Fetal tachycardia (≥160 beats/min)	35 (74.5%)	6 (12.8%)	<.0001
Foul-smelling amniotic fluid	3/45 (6.7%)	1/44 (2.3%)	.61

*Median (range).
†Mean ± SD.

As shown in Table III, fewer than half of the febrile cases and only 20% of the controls had any evidence of histologic chorioamnionitis. Only 14 of 45 (31.1%) of the cases with fever had histologic chorioamnionitis degree categorized as moderate or severe. Chorionic vasculitis, which is an early indicator of fetal inflammatory response, was significantly more common in febrile cases. Funisitis, a more advanced indicator of fetal inflammatory response, was more common in cases, but this did not reach statistical significance. Overall, histologic chorioamnionitis was associated with higher maternal IL-6 levels (median [range] 174 pg/mL [7-508] vs 69 pg/mL [0-301], $P < .0001$) and higher UV IL-6 levels (median [range] 18 pg/mL [0-14,847] vs 2 pg/mL [0-67], $P < .0001$).

We performed a subanalysis on the fever cases to determine whether there was an impact of actual clinical chorioamnionitis on the results. There were 28 of 47 (59.6%) subjects with fever who met criteria for clinical chorioamnionitis (fever plus 2 or more of maternal tachycardia, fetal tachycardia, uterine tenderness, foul or purulent discharge, or leukocytosis). There were no statistically significant differences in maternal IL-6 levels for fever cases meeting criteria for clinical chorioamnionitis when compared with cases lacking the criteria (median [range] 157 pg/mL [9-508] vs 113 pg/mL [38-379], $P = .16$). Similarly, significant differences were not found in UV IL-6 levels in clinical chorioamnionitis cases (median [range] 14 pg/mL [0-14,847] vs fever cases without clinical chorioamnionitis, median [range] 8 pg/mL [0-64], $P = .26$). Among fever cases, differences in histologic chorioamnionitis also did not reach statistical significance between those with and without clinical chorioamnionitis, 15 of 27 (55.6%) versus 6 of 18 (33.3%), respectively, $P = .14$.

A multivariable logistic regression model was applied to the data to determine the best markers associated with maternal fever. Entered into the model were variables that had a significance level on univariable analysis of $P \leq .20$ (nulliparity, scalp electrode, duration of epidural, duration of labor, duration of membranes rupture, number of vaginal examinations, initial examination-to-delivery interval, admission white blood cell count, maternal IL-6, UV IL-6, and histologic chorioamnionitis). Maternal and fetal tachycardia were not included in the model because they were considered signs of fever. After interactions were checked, variables in the final model that did not reach statistical significance ($P < .05$) were removed from the model sequentially. Only three variables remained significant after adjustment for gestational age. These included maternal serum IL-6 levels (odds ratio [OR] 16.2, 95% CI 3.7-72.1, $P = .0003$), nulliparity (OR 9.4, 95% CI 2.3-39.0, $P = .0020$), and the number of vaginal examinations (OR 1.4, 95% CI 1.1-1.9, $P = .0113$).

Comment

Despite the relatively high incidence of term intrapartum fever and the association with adverse outcomes, there are few studies that explore the cause. The data provided from this study highlight the importance of the maternal inflammatory environment as a major contributor to intrapartum fever. We also were able to demonstrate that the fetal inflammatory environment, as measured by UV IL-6 levels and placental histologic study,

Table III. Serologic and histologic markers of inflammation for term intrapartum fever cases and controls

	Cases (n = 47)	*Controls (n = 47)*	*P value*
Maternal IL-6 detected	44/44 (100.0%)	42/43 (97.7%)	.49
Maternal IL-6 levels (pg/mL)*	145 (9-508)	42 (0-298)	<.0001
UV IL-6 detected	40/46 (87.0%)	28/44 (63.6%)	.01
UV IL-6 levels (pg/mL)*	9 (0-14,847)	3.5 (0-81)	.01
UV IL-6 levels ≤11 pg/mL	25 (54.3%)	32 (72.7%)	.07
UV IL-6 levels ≤25 pg/mL	35 (76.1%)	37 (84.1%)	.34
Histologic chorioamnionitis	21/45 (46.7%)	8/40 (20.0%)	.008
Histologic chorioamnionitis severity			.02
Absent	24 (53.3%)	33 (82.5%)	
Mild	7 (15.6%)	4 (10.0%)	
Moderate	8 (17.8%)	2 (5.0%)	
Severe	6 (13.3%)	1 (2.5%)	
Chorionic vasculitis	12/45 (26.7%)	5/40 (12.5%)	.04
Histologic funisitis	7/45 (15.6%)	1/40 (2.5%)	.06

*Median (range) compared with Mann-Whitney *U* test.

has less of an association with intrapartum fevers. Therefore, our data weaken the traditional view that intrapartum fevers are usually a result of ascending intraamniotic inflammation.

A number of studies have suggested a variety of possible noninfectious causes for intrapartum fever.[7,11-13] Leiberman et al[7] has suggested that nearly 90% of maternal intrapartum fevers may be due to epidural anesthesia. Other evidence indicates that epidural anesthesia is associated with intrapartum fever primarily in the presence of placental inflammation.[14] At least one study has suggested that epidural anesthesia is associated with higher maternal serum IL-6 levels after a vaginal delivery.[15] They postulated that regional analgesia results in alterations in the production of various stress hormones that have a direct regulatory effect on IL-6 synthesis. These changes would allow greater production of IL-6, which result in higher maternal intrapartum temperatures and account for the higher rates of fever reported with epidural anesthesia. Our high rate of epidural use in both cases (97.9%) and controls (83.0%) prevented us from examining maternal and UV IL-6 levels on the basis of epidural status.

Current understanding of mechanisms of fever suggest that temperature elevations are mediated both locally and centrally by a variety of interacting inflammatory mediators, including cytokines and prostaglandins.[16] It is believed that IL-6 is one of the major circulating pyrogens contributing to fever. IL-6 is found in the circulation of patients after tissue injury and levels correlate significantly with the increase in body temperature.[17,18] There also is animal data to suggest that IL-6 can enter the brain through an active transport mechanism and that it may induce fever by direct action on the brain after crossing the blood-brain barrier.[19] Our data show that maternal serum IL-6 levels have the strongest association with maternal temperature and support the idea that maternal intrapartum fevers may be mediated more through maternal inflammatory processes. However, other hormonal or inflammatory stimuli not studied may also contribute to elevated temperatures.

With respect to placental findings, only about 30% of women with an intrapartum fever had significant histologic chorioamnionitis of moderate or severe degree. This is consistent with our previous retrospective study that showed no placental inflammation in a large proportion of term febrile subjects.[20] Kim et al[21] has suggested that a more important marker of a fetal inflammatory response is the degree of histologic funisitis. We found that only 15% of our fever cases had any evidence of histologic funisitis. These data support the concept that the intrauterine environment and the fetus have a relatively smaller inflammatory contribution that would lead to intrapartum fever at term.

Our UV IL-6 findings are consistent with the histologic data. UV IL-6 levels are considered to represent the fetal inflammatory response.[10] It makes sense that elevations of cord IL-6 would parallel the presence of histologic chorioamnionitis. We found some association of increasing UV IL-6 levels with increasing maternal temperature; however, even when detected, the majority of UV IL-6 levels were relatively low. We examined our term UV samples at two of the lower cutoff levels proposed for identification of sepsis and adverse outcomes in preterm infants (11 pg/mL[10] and 25 pg/mL[11]). The majority of samples from fever cases were below these thresholds indicating a lack of a major IL-6 fetal inflammatory response in the presence of most term intrapartum fevers. Taken with histologic findings, the IL-6 results indicate that the majority of patients with intrapartum fever at term have little, if any, evidence of in utero inflammation.

The only clinical variable that contributed significantly to our prediction model for intrapartum fever was the number of vaginal examinations, but this was less important than maternal IL-6. It may be that some of the clinical characteristics identified as significantly associated

with fever on the univariable analysis may contribute to maternal inflammatory responses and therefore are not independent of the maternal IL-6. It has been suggested that labor itself may increase maternal IL-6 levels.[22] This could increase the likelihood of fever because IL-6 is a pyrogen.[16] In this study, both cases and controls were required to be in labor, which limits the presence of labor as a potential confounder. Nevertheless, the duration of labor in cases was longer, which could, theoretically, increase the chances of having elevated maternal IL-6. In addition, the similar rates of vaginal and cesarean delivery in the study groups reduces the likelihood for route of delivery to be a confounder.

A strength of this study is that there were sufficient subjects to demonstrate significant differences in histologic chorioamnionitis, as well as maternal and UV IL-6 levels based on fever status. There was insufficient power to demonstrate statistical significance in secondary analyses of fever cases having features of clinical chorioamnionitis. Therefore, the lack of significance could be the result of a type II statistical error. However, those analyses were not the primary outcomes of interest for the study. The classic features of clinical chorioamnionitis also may be less reliable predictors of infection or inflammation given the generally liberal intrapartum use of epidural analgesia, antibiotics, and antipyretics.[20]

Finally, the weaker association of fever with markers of inflammation at term, compared with preterm reports, deserves some comment. This can be explained by the different relationship of infection to preterm and term labors. Preterm labor is commonly associated with intraamniotic infection as a cause and therefore these pregnancies probably are more likely to be associated with histologic and serologic markers of inflammation.[22] Conversely, when inflammation occurs at term it may be more likely to be secondary to labor rather than the primary cause of labor.[24] In addition, the immune system response of term and preterm fetuses may differ.[23] Thus, it is not surprising that there are different IL-6 and histologic chorioamnionitis profiles at term compared with preterm pregnancies.

REFERENCES

1. Petrova A, Demissie K, Rhoads GG, Smulian JC, Marcella S, Ananth CV. Association of maternal fever during labor with neonatal and infant morbidity and mortality. Obstet Gynecol 2001;98:20-7.
2. Leiberman E, Lang J, Richardson DK, Frigoletto FD, Heffner LJ, Cohen A. Intrapartum maternal fever and neonatal outcome. Pediatrics 2000;105:8-13.
3. Adamson J, Alessandri LM, Badawi N, Burton PR, Pemberton PJ, Stanley F. Predictors of neonatal encephalopathy in full term infants. BMJ 1995;311:568-602.
4. Lieberman E, Eichenwald E, Mathur G, Richardson D, Heffner L, Cohen A. Intrapartum fever and unexplained seizures in term infants. Pediatrics 2000;106:983-8.
5. Alexander JM, McIntire DM, Leveno KJ. Chorioamnionitis and the prognosis for term infants. Obstet Gynecol 1999;94:274-8.
6. Gibbs RS, Blanco JD, St. Clair PJ, Castaneda YS. Quantitative bacteriology of amniotic fluid from women with clinical intraamniotic infection at term. J Infect Dis 1983;145:1-8.
7. Leiberman E, Lang JM, Frigoletto F, Richardson DK, Ringer SA, Cohen A. Epidural analgesia, intrapartum fever and neonatal sepsis evaluation. Pediatrics 1997;99:415-9.
8. Porter AE, Auth J, Prince M, Ghidini A, Brenneman DE, Spong CY. Optimization of cytokine stability in stored amniotic fluid. Am J Obstet Gynecol 2001;185:459-62.
9. Naeye RL, Maisels MJ, Lorenz RP, Bottie JJ. The clinical significance of placental villous edema. Pediatrics 1983;71:588-94.
10. Gomez R, Romero R, Ghezzi F, Yoon BH, Mazor M, Berry SM. The fetal inflammatory response syndrome. Am J Obstet Gynecol 1998;179:194-202.
11. Smulian JC, Vintzileos AM, Lai Y-L, Santiago J, Shen-Schwarz S, Campbell WA. Maternal chorioamnionitis and umbilical vein interleukin-6 levels for identifying early neonatal sepsis. J Matern Fetal Med 1999;8:88-94.
12. Marx GF, Loew DA. Tympanic temperature during labour and parturition. Br J Anaesth 1975;47:600-2.
13. Goodlin RC, Chapin JW. Determinants of maternal temperature during labor. Am J Obstet Gynecol 1982;143:97-102.
14. Dashe JS, Rogers BB, McIntire DD, Leveno KJ. Epidural analgesia and intrapartum fever: placental findings. Obstet Gynecol 1999;93:341-4.
15. DeJongh RF, Bosmans EP, Puylaert MJ, Ombelet WU, Vandeput HJ, Berghmans RA. The influence of anaesthetic techniques and type of delivery on peripartum serum interleukin-6 concentrations. Acta Anaesthesiol Scand 1997;41:853-60.
16. Luheshi G, Rothwell N. Cytokines and fever. Int Arch Allergy Immunol 1996;109:301-7.
17. Rothwell NJ. Mechanisms of the pyrogenic actions of cytokines. Eur Cytokine Netw 1990;1:211-3.
18. Rothwell NJ, Hopkins SJ. Cytokines and the nervous system, II: actions and mechanisms of action. Trends Neurosci 1995;18:130-6.
19. Luheshi GN, Gay J, Rothwell NJ. Circulating IL-6 is transported into the brain via a saturable transport mechanism in the rat. Br J Pharmacol 1994;111:146.
20. Smulian JC, Shen-Schwarz S, Vintzileos AM, Lake MF, Ananth CV. Clinical chorioamnionitis and histologic placental inflammation. Obstet Gynecol 1999;94:1000-5.
21. Kim CJ, Yoon BH, Romero R, Moon JB, Kim M, Park SS, et al. Umbilical arteritis and phlebitis mark different stages of the fetal inflammatory response. Am J Obstet Gynecol 2001;185:496-500.
22. Arntzen KJ, Lien E, Austgulen R. Maternal serum levels of interleukin-6 and clinical characteristics of normal delivery at term. Acta Obstet Gynecol Scand 1997;76:55-60.
23. Kim CJ, Yoon BH, Park SS, Kim MH, Chi JG. Acute funisitis of preterm but not term placentas is associated with severe fetal inflammatory response. Hum Pathol 2001;32:623-9.
24. Romero R, Gonzalez R, Baumann P, Behnke E, Rittenhouse L, Barberio D, et al. Topographic differences in amniotic fluid concentration of prostanoids in women in spontaneous labor at term. Prostaglandins Leukot Essent Fatty Acids 1994;50:97-104.