The article that follows was published in the March 2005 Journal of Obstetrics and Gynecology of Canada. Unfortunately that journal experienced computer theft that resulted in loss of the article in the published form. I do not have a hard copy to scan into a pdf. So I post the pre-publication proof. This reflects the published article except for the following corrections to tables.

table 1. p values for lines 3,4,5 (length stage 1, length stage 2, and length of ruptured membranes) should include a "<" prior to them.

table 1. the variable in line 5 should be "Length of ruptured membranes"

table 1. the variable in line 15 should be "Intervention for failure to progress"

table 1. the variable in line 18 should be "pH < 7.1"

table 2. the second and third variables need units of time to have meaning. length of stage 2 is in minutes and length of rom is in hours.

table 3. the asterix reference should read "P value of 0.04 approached a significant difference from those not receiving acetominophen. All other differences did not approach or achieve significance.

Fever in Term Labour

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Abstract

Objectives: To determine the antecedents, outcomes, and effects of treatment of fever commencing during term labour without prolonged rupture of membranes (ROM).

Methods: A retrospective database and chart review sought associations between maternal, fetal, and labour variables and fever by comparing women whose membranes had been ruptured for less than 24 hours and who were febrile with those who were not. The strength of significant associations was then compared between febrile women who received acetaminophen or antibiotics and febrile women who did not.

Results: We found 16 322 control subjects and 161 cases. On multivariable analysis, fever was associated with epidural analgesia (adjusted odds ratio [AOR] 5.5; 95% confidence interval [CI] 4.0– 7.0), length of stage 2 (AOR 1.003 per minute; 95% CI, 1.001–1.005), length of ROM (AOR 1.15 per hour; 95% CI, 1.10–1.20), meconium in the amniotic fluid (AOR 1.7; 95% CI, 1.2–2.2), intervention for nonreassuring electronic fetal monitoring (EFM) (AOR 5.2; 95% CI, 4.4–6.0), intervention for failure to progress in labour (AOR 3.0; 95% CI, 2.1–3.9), and neonatal intensive care unit (NICU) admission (AOR 5.7; 95% CI, 5.1–6.3). A nonstatistically significant trend toward a decrease in failure to progress with acetaminophen administration was noted.

Conclusions: Fever during labour is associated with longer labour, longer ROM, and use of epidural analgesia. For a given length of labour, women with fever are more likely to experience intervention for failure to progress, intervention for nonreassuring EFM, and infant NICU admission.

Résume

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INTRODUCTION

Clinical chorioamnionitis, diagnosed by the presence of an elevated maternal temperature, uterine tenderness, and foul-smelling amniotic fluid, is a serious complication of pregnancy and threatens the health of both mothers and infants.[1,2] This threat justifies treatment based on the fever alone if the patient has risk factors for chorioamnionitis.[2] The main risk factors for chorioamnionitis are preterm premature rupture of membranes (ROM) and ROM for more than 24 hours.[1,2] Treatment for chorioamnionitis consists of antibiotic therapy and prompt delivery.[2] The management of fever in women in labour, in the absence of other clinical criteria or significant risk factors of chorioamnionitis, is controversial.

If clinical chorioamnionitis is absent, the etiology of fever can be unclear. Fever in women in labour may represent a failure of the homeostatic thermoregulatory system,[3] since fever may be present despite there being no microbiologic or pathological evidence of infection.[4,5] This system failure would explain why fever is associated with epidural analgesia.[6–14] The association of fever with epidural analgesia has also been attributed to selection bias[6]; altered central or vascular thermoregulation[6,10,11]; increased shivering or decreased sweating[6] or other alteration of heat production and dissipation[9]; and increased incidence of chorioamnionitis,[5] which may be due to longer duration of labour.[15]

Regardless of the etiology, fever in labouring women remains a clinical concern because of its association with adverse neurological outcomes in the infant.[14,16,17] This association is independent of neonatal infection[14] and may be mediated by exposure to amniotic and chorionic inflammation[18,19] and (or) an elevation in fetal temperature.[12,20] One author has speculated that infants would benefit if all patients receiving epidural analgesia for more than 5 hours commenced antipyretic therapy.[20]

Since neonatal exposure to maternal fever may be deleterious, it is important to seek a better understanding of risk factors for fever and possible interventions. To determine the antecedents and outcomes of fever in labouring women at low risk of chorioamnionitis, we conducted a database and chart review of febrile women at term without prolonged ROM. We also examined whether treatment of the fever affected the outcomes.

METHODS

The study population comprised all women delivering after planned labour at the Ottawa Hospital General Campus from January 1, 1994, to December 31, 2001, whose pregnancies were of 37 weeks' gestation and whose membranes ruptured less than 24 hours prior to delivery. Planned labour excluded those women whose labour commenced prior to a booked Caesarean. A labour record database for the period from 1994 to 2001 was complete and had been found by internal review to reliably reflect the labour variables noted in the chart. The primary nurse attending the delivery entered data in the labour record database at the time of delivery. Training by the nurse educators ensured standardized data entry. The physician attending the delivery entered diagnoses in the labour record.

After obtaining approval from the Ottawa Hospital Research Ethics Board, we conducted a database and chart review. The labour record database was imported to Microsoft Excel **[REFERENCE].** We deleted records of deliveries prior to 37 weeks' gestation; deliveries after ROM for more than 24 hours; deliveries coded as elective Caesarean section or Caesarean section after 0 hours of labour; and deliveries of the second, third, and fourth infant from the same gestation. The Excel sort function separated the remaining women who were coded to have maternal temperature as a complication of labour (potential cases) from those who did not (control subjects).

A chart review of potential cases selected women who met the criteria for fever in labour (defined as an oral maternal temperature >38ºC or 2 consecutive temperatures >37.5ºC after the onset of active labour) and who did not have uterine tenderness or foul-smelling amniotic fluid. Charts of women who were selected as cases were further reviewed to determine the maximum maternal temperature, time from onset of fever to delivery, presence or absence of chorioamnionitis on placental pathology, and whether antibiotics or acetaminophen had been administered.

Associations were sought between fever and maternal age, nulliparity, induction of labour, use of oxytocin, presence of prelabour ROM, gestational age at delivery, duration of stage 1, duration of stage 2, duration of ROM, infant weight, presence of meconium in amniotic fluid, intervention for nonreassuring electronic fetal monitoring (EFM), failure to progress in labour, umbilical cord pH at delivery, Caesarean delivery, assisted vaginal delivery, stillbirth or neonatal death, and neonatal intensive care unit (NICU) admission. A woman was determined to have failure to progress or intervention for nonreassuring EFM when the obstetrician listed this as the reason for operative delivery. For control subjects, all variables were extracted from the database; for cases, the data were obtained from the maternal chart.

Women who received antibiotics or acetaminophen for treatment of fever were compared with those who did not to determine whether there was a change in the strength of association between outcome variables significantly associated with fever on multivariable analysis. For each significantly associated outcome variable, women who experienced the outcome were compared with those who did not to determine whether the 2 groups differed by maximum maternal temperature, time from onset of fever to delivery, or presence of chorioamnionitis on placental pathology. The rate of postpartum febrile morbidity (defined as fever persisting more than 24 hours after delivery)[3] in women who received antibiotics was compared with the rate in those who did not.

We used the Student's *t* test to make comparisons for continuous variables and relative risk (RR), with 99% confidence intervals (CIs) for nominal and discrete variables. P values were deemed significant if $P < 0.01$, and RR was deemed significant if the 99% CI did not include 1.0. The

Table 1. Results of univariate analysis comparing afebrile (N = 16 322) and febrile (N = 161) patients

Variables	Afebrile (N = 16 322) Average (± SD) or n (%)	Febrile (N = 161) Average (± SD) or n (%)	*P* or RR (99% CI)
Maternal age	29.6 ± 5.3	29.9 ± 5.7	0.42
Gestational age	39.9 ± 1.2	40.1 ± 1.3	0.013
Length of stage 1	8.3 ± 6.3	14.0 ± 7.6	.0001
Length of stage 2	68.6 ± 82.8	175.0 ± 107.9	.0001
Time since ruptured membranes	6.7 ± 5.6	13.8 ± 4.8	.0001
Infant weight	3513 ± 492	3539 ± 561	0.56
Parity = 0	6786 (42)	126 (78)	5.1 (3.1-8.3)*
Induction of labour	2967 (18)	39 (24)	1.4 (0.9-2.3)
Oxytocin	1389 (8.5)	20 (12)	1.5 (0.8-2.8)
Rupture of membranes prior to labour	5960 (37)	79 (49)	1.7 (1.1-2.5)*
Artificial rupture of membranes	9982 (61)	102 (63)	1.1 (0.7-1.7)
Epidural	10 843 (66)	156 (97)	16 (4.9-51)*
Meconium	3544 (22)	68 (42)	2.6 (1.7-4.0)*
Intervention for nonreassuring EFM	273 (1.7)	16 (10)	6.5 (3.2-13)*
Failure to progress	344 (2.1)	51 (32)	22 (14-34)*
Caesarean section	1367 (8.4)	55 (34)	5.7 (3.7-8.8)*
Assisted vaginal birth	2455 (15)	60 (37)	3.4 (2.2-5.1)*
pH 7.1	149 (0.9)	3 (1.9)	2.1 (0.5-9.4)
Neonatal intensive care unit admission	442 (2.7)	35 (22)	10 (6.0-17)*

EFM: electronic fetal monitoring.

*Febrile patients had a significantly greater relative risk than afebrile patients.

CIs were set at 99%, and the value of *P* was set at < 0.01 to minimize the risk of finding a spurious association owing to the large number of comparisons undertaken in this study. All significant associations were subjected to binary logistic regression using SPSS version 11 **[reference]**. We ran the regression analysis with fever as the dependant variable and associated variables as covariants. For associations surviving multivariable analysis, we used SPSS version 11 **(reference)** to calculate an adjusted odds ratio (AOR) with 95% CI.

RESULTS

The database contained 16 505 adequate records, matching the criteria for the study population. Of these, 16 322 women without fever were used as control subjects. We reviewed 183 records noted "maternal temperature." Twelve women did not meet criteria for fever commencing in labour. Three women had ROM for longer than 24 hours, and 7 charts were not available. None of the women had uterine tenderness or foul-smelling amniotic fluid. There were 161 cases available for analysis. The incidence of fever in women in labour at term with ROM for less than 24 hours was 1.0%.

There were no cases with stillbirth or neonatal death. Cases and control subjects did not differ by maternal age, gestational age, or infant weight, but the stages of labour and the duration of ROM were longer in cases than in control subjects (Table 1). Univariable analysis found significant associations between fever and nulliparity, prelabour ROM, use of epidural analgesia, presence of meconium in amniotic fluid, intervention for nonreassuring EFM, intervention for failure to progress in labour, operative vaginal delivery, Caesarean delivery, and NICU admission **(Table 1)**.

Table 2. Adjusted odds ratios (with 95% CIs) for variables that remained associated with fever after binary logistic regression

Variable	Adjusted odds ratio (95% CI)
Epidural	5.5 (4.0–7.0)
Length of stage 2	1.003 (1.001–1.005)
Length of ROM	1.15 (1.10–1.20)
Meconium	1.7 (1.2–2.2)
Intervention for non-reassuring EFM	5.2 (4.4–6.0)
Failure to progress	3.0 (2.1–3.9)
NICU admission	5.7 (5.1–6.3)

ROM: rupture of membranes; EFM: electronic fetal monitoring; CI: confidence interval; NICU: neonatal intensive care unit.

On multivariable analysis, the only associations that remained significant were between fever and epidural analgesia, length of stage 2, length of ROM, presence of meconium in amniotic fluid, intervention for nonreassuring EFM, failure to progress in labour, and NICU admission (**Table 2)**.

The analysis of the effect of treatment with acetaminophen and antibiotics was limited by the small sample size and low statistical power. Physician preference determined whether antibiotics (either monotherapy for group B streptococci or broad spectrum therapy) or acetaminophen were given. Neither treatment with antibiotics nor treatment with acetaminophen changed the incidence of meconium in amniotic fluid, failure to progress in labour, intervention for nonreassuring EFM, or NICU admission significantly (**Table 3).** However, with acetaminophen use, the difference in the incidence of failure to progress in labour approached significance.

In 29 cases, acetaminophen was administered and a temperature reading was taken within 4 hours. In 20 (69%) of these cases, there was a decrease in temperature; in 6 (21%) there was no change; and in 3 (10%) the temperature increased with use of acetominophen. The maternal temperature was not observed to decrease consistently after antibiotic administration.

Whether there was meconium in the amniotic fluid, failure to progress in labour, intervention for nonreassuring EFM, or NICU admission made, there was no significant difference in average maximum fever, average time from fever to delivery, or the finding of chorioamnionitis on histological examination of the placenta **(Table 4)**. Placentas were sent, according to physician preference, for pathological assessment in 41 cases, and chorioamnionitis was noted in 26 (63%).

Postpartum febrile morbidity occurred in 7 cases. Of these women, 5 had received antibiotics prior to delivery. The postpartum febrile morbidity rate among women who received antibiotics (4.2%) did not differ significantly from the rate among those not given antibiotics (4.9% $P = 0.79$). Additional postpartum morbidity among cases included 1 afebrile wound infection and a uterine dehiscence after vacuum extraction that led to a hysterectomy.

DISCUSSION

In this study, fever developing in women in labour at term with less than 24 hours ROM was associated with epidural analgesia, longer stage 2, longer duration of ROM, meconium in the amniotic fluid, intervention for nonreassuring EFM, intervention for failure to progress in labour, and NICU admission. These associations indicate that if a woman receives epidural analgesia, she is at fivefold increased risk of developing a fever. Longer labour also increases the risk of fever, as the AORs indicate a 15% increase in risk for each hour of stage 1 and an 18% increase in risk for each hour of stage 2. If a patient develops a fever, the clinician needs to observe her closely as she is at threefold increased risk of intervention for failure to progress in labour, at fivefold increased risk of intervention for nonreassuring EFM, and at 70% increased risk of meconium in the amniotic fluid.

The AOR of 5.5 for fever in labour and epidural analgesia use was consistent with previous studies, which have noted ORs ranging from 4.17 to 14.5.[8] While previous work noted an association with nulliparity,[7,14] our study found this association was not significant when controlling for length of labour. The finding that longer stage 2 of labour and ROM were associated with fever was consistent with previous reports.[7,13,14]

An association between maternal fever and operative deliveries has been noted in 2 previous studies.[10,14] One of these found that the higher rate of intervention was partly owing to a higher rate of failure to progress in labour.[10] Given that fever was independently associated with interventions for failure to progress in labour, it is possible that fever causes uterine dysfunction.

The association between maternal fever and NICU admission is consistent with previous reports of an association between maternal fever and an increased frequency of sepsis investigations and antibiotic treatment in the infant.[7,8]

Both this study and previous work[13] found that antibiotic treatment, in the absence of clinical signs of chorioamnionitis, did not change the frequency of outcomes associated with fever in labour or the incidence of postpartum febrile morbidity. Our study is the first to demonstrate a possible benefit of antipyretic therapy with

Table 3 Incidences of outcomes associated with fever on multivariate analysis

Outcome	Any antibiotics	Broad-spectrum antibiotics only	No antibiotics	Acetaminophen	No acetaminophen
	n (%)	n (%)	n (%)	n (%)	n (%)
Meconium	51 (43)	10 (56)	17 (41)	16 (42)	52 (43)
Failure to progress	38 (24)	5 (28)	13 (32)	7 (18)*	44 (32)
Intervention for non-reassuring EFM	14 (12)	3 (17)	2 (5)	5 (13)	11 (9)
NICU admission	27 (23)	4 (22)	8 (20)	7 (18)	28 (21)

Patients who received any antibiotics (N = 120) and those who received broad-spectrum antibiotics (N = 18) were separately compared with those who received no antibiotics (N = 41). Patients who received acetaminophen (N = 122) were compared with those who did not (N = 38).

*Significantly different from those not receiving acetominophen. All other differences were not significant.

Table 4 Length of time (hours) from onset of fever to delivery, maximum maternal temperature, and incidence of chorioamnionitis on placental pathology patients who experienced each outcome to those who did not

Outcome	Length of fever prior to delivery			Maximum temperature			Chorioamnionitis[a]		
	mean ± SD			mean ± SD			n (%)		
	Outcome present	Outcome absent	*P*	Outcome present	Outcome absent	*P*	Outcome present	Outcome absent	*P*
Meconium	4.7 ± 2.9	4.6 ± 3.1	0.81	38.5 ± 0.6	38.4 ± 0.5	0.19	13 (50%)	5 (33%)	0.30
Failure to progress	4.8 ± 2.6	4.6 ± 3.1	0.65	38.5 ± 0.6	38.5 ± 0.5	0.72	9 (35%)	6 (40%)	0.73
Intervention for nonreassuring EFM	5.1 ± 2.9	4.6 ± 3.0	0.44	38.7 ± 0.6	38.5 ± 0.5	0.25	1 (4%)	1 (7%)	0.69
NICU admission	4.4 ± 3.2	4.7 ± 2.9	0.71	38.6 ± 0.6	38.5 ± 0.5	0.29	7 (27%)	8 (53%)	0.09

[a]Histology was available on 41 placentas, and chorioamnionitis was noted in 26 patients.

acetaminophen. If maternal fever does lead to uterine dysfunction, then it is biologically plausible that an intervention that decreases the degree of fever would also decrease the degree of uterine dysfunction. However, the present study lacked the power to demonstrate a significant benefit.

This was an observational study and was therefore unable to determine causality. The results are also dependant on the quality of the database. Relying on the database to define cases accurately resulted in 4 potential cases (2.2% of 183 women) being misclassified, as they had ROM for more than 24 hours. Control subjects may have been similarly misclassified. Nevertheless, while a 2.2% error rate may be significant in a sample of 183, it loses significance in a sample of 16 322. The main limitation of this study arises from the small number of cases and the consequent difficulty obtaining sufficient statistical power to determine whether clinically relevant benefit results from antibiotic or acetaminophen treatment of fever in labour.

Fever in labour is associated with detrimental maternal and fetal outcomes. Interventions that reduce these outcomes are needed. The use of acetaminophen and antibiotic to treat fever in women in labour with no other markers of chorioamnionitis merits a sufficiently powered, randomized, placebo-controlled study. Until such a study is undertaken, clinicians should be sensitive to the increased risks that a woman in labour with fever faces and must carefully consider offering such a woman antibiotics and acetaminophen.

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