OBJECTIVES: This study was undertaken to investigate the relationship among maternal intrapartum fever, neonatal acidosis, and the risk of neonatal encephalopathy.

STUDY DESIGN: Cohort study of pregnancies at term. Logistic regression was used to estimate the effect of maternal fever and acidosis on the risk of neonatal encephalopathy. The potential interaction between maternal fever and acidosis was included in the models.

RESULTS: Of 8299 women, 25 neonates (0.3%) had encephalopathy develop. These were more often born acidotic (adjusted odds ratio 11.5; 95% CI, 5.0-26.5) or after a maternal intrapartum fever (adjusted odds ratio 8.1; 95% CI, 3.5-18.6). Where both risk factors coexisted, the risk was 12.5% (adjusted odds ratio 93.9; 95% CI, 28.7-307.2). Although this effect is multiplicative, there was no evidence of statistical interaction (P = .93); the effect of maternal fever on the risk of encephalopathy was similar in infants with (adjusted odds ratio 8.7; 95% CI, 2.4-31.7) and without acidosis (adjusted odds ratio 7.4; 95% CI, 2.4-21.9).

CONCLUSION: The combination of a maternal fever with cord acidosis greatly increases the risk of neonatal encephalopathy, but there is evidence against interaction between them, suggesting that they represent 2 separate causal pathways.

Key words: acidosis, labor, maternal fever, neonatal encephalopathy

N


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OBSTETRICS

The relationship between intrapartum maternal fever and neonatal acidosis as risk factors for neonatal encephalopathy

Lawrence W. M. Impey, MD; Catherine E. L. Greenwood, MD; Rebecca S. Black, MD; Peter S-Y. Yeh, MD; Orla Sheil, MD; Pat Doyle, PhD

The presence of maternal fever in labor is a strong risk factor for adverse neonatal and developmental outcomes, including encephalopathy, cerebral palsy, and neonatal death. The mechanism is not understood, but has important implications. The fever may be causal (ie, overheating). This has implications for epidural analgesia, which raises maternal temperature. Or the fever is an epiphenomenon, reflecting a preexisting (ie, antepartum) or intrapartum process, such as infection. Indeed, clinical and histologic chorioamnionitis are also strongly associated with adverse outcomes. The presence of a fever has been labeled “chorioamnionitis,” or equated with infection by the clinician and therefore also in data abstraction. Although infection must be important, not least because prophylaxis against group B Streptococcus reduces neonatal risk, the relationship between fever and adverse outcomes is not entirely attributable to infection. How the fever, or chorioamnionitis, leads to adverse neonatal outcomes remains unclear. Elevated inflammatory cytokine levels have been reported in both mother and fetus. The combination of “potentially asphyxiating” risk...
factors with presumed intrapartum infection dramatically increases the risk of cerebral palsy.\textsuperscript{21} This has been interpreted as possible evidence of synergy between the risk factors.\textsuperscript{12} Alternatively, the effect of a fever, or fever-associated conditions such as chorioamnionitis, is mediated via hypoxia.

Our aim was to investigate the relationship between the intrapartum marker of maternal fever, with neonatal acidosis and the risk of encephalopathy. In particular, we aimed to disentangle the effects of maternal fever and acidosis to determine whether these factors act synergistically or independently.

**Materials and Methods**

A nested cohort study of laboring women with a singleton cephalic fetus was performed by using the database of a large randomized controlled trial (RCT)\textsuperscript{22} which, between Aug. 17, 1998-Apr. 30, 2001, recruited 30.4% of all women delivering in The National Maternity Hospital, Dublin, Ireland. Institutional ethical approval for collection and the use of the data were granted in May 1997. Maternities excluded from this cohort (281) had 1 or more of the following: a breech presentation, gestation less than 37 weeks or more than 41 weeks, a delivery ending in a stillbirth, or a neonate with a major congenital anomaly. All women were afebrile on admission in labor. Maternal temperature was taken orally and hourly in labor: a fever was defined as higher than 37.5°C. Acidosis was defined as a cord arterial or venous pH of below 2 SDs below the mean at delivery: less than 7.05 and less than 7.12, respectively. Neonatal encephalopathy (Sarnat grade 2 or 3) was diagnosed within 7 days.

The RCT was a comparison of cardio-tocography on admission to the labor ward vs the standard monitoring of intermittent auscultation of the fetal heart rate for the prevention of adverse neonatal outcome. No effect of the intervention was found for any of the outcomes studied.\textsuperscript{23} Therefore pregnancies in both the intervention and control arms were included in the cohort analyzed here.

We used STATA statistical software (STATA, Chicago, IL) for all analyses. All \( P \) values are 2-sided, and we took values less than .05 to indicate statistical significance. The \( \chi^2 \) test, Fisher exact test, and Student \( t \) test were used to compare the characteristics of infants with, and without, neonatal encephalopathy. Logistic regression was used to estimate the effect of maternal fever and acidosis on the risk of neonatal encephalopathy (Breslow and Day\textsuperscript{23}), with the no fever and no acidosis groups used as baseline. In the first model, we adjusted for maternal fever or acidosis (as appropriate), nulliparity, and gender of the neonate as these were shown to be associated with the disease. As neither maternal age nor gestation were found to be associated with the disease, no adjustment was made for these factors. Nor did we adjust for factors we thought were consequences, rather than determinants, of the condition (eg, intrapartum cesarean section). In the second model, we additionally adjusted for induction of labor and epidural anesthesia, although accepting that there may be some degree of overadjustment because of the direction of the causal pathways for these factors. The potential interaction of maternal fever with acidosis was included in the models and assessed through likelihood ratio tests.\textsuperscript{23}

**Results**

The total cohort was 8299 singleton term pregnancies. Almost half the mothers (48%; \( n = 4007 \)) were nulliparous, 3197 (39%) received oxytocin during delivery, 4844 (58%) had epidural anesthesia, 311 (4%) underwent cesarean section, and the mean birthweight of the neonates was 3614 g. Twenty-five infants (0.3%) had neonatal encephalopathy diagnosed.

We found no significant differences in the maternal age or booking weight distributions for infants with encephalopathy and infants without, but the mothers of affected infants were more likely to be nulliparous (Table 1). Affected infants were also more likely to be boys, have had a longer or induced labor, to receive epidural anesthesia, and to be delivered by cesarean section.

There were marked differences in the proportions with maternal fever, and with acidosis, according to disease status: 40% of infants with encephalopathy, compared with 4% of infants without, had acidosis; 44% of infants with encephalopathy, compared with 7% of those without, experienced maternal fever (Table 1). These differences are highly statistically significant (\( P < .0001 \)). The risk of developing encephalopathy after a maternal fever was 1.9% and that where acidosis was present was 2.8%. In situations in which both risk factors were present, the risk was 12.5%. The risk for the whole cohort was 0.3%.

From logistic regression analysis controlling for gender and nulliparity, we estimated that infants with encephalopathy were 11 times more likely be acidicotic (adjusted OR [AOR] = 11.5; 95% CI, 5.0-26.5), and 8 times more likely to have had a mother with fever during labor (AOR = 8.1; 95% CI, 3.5-18.6), than infants without encephalopathy. Infants with encephalopathy were more than 90 times more likely to have experienced both factors (neonatal acidosis and maternal fever) than infants with no encephalopathy (AOR = 93.9; 95% CI, 28.7-307.2; Table 2). In the second analysis, adjusting for induction of labor and epidural as well as gender and nulliparity, the size of the effects reduced slightly, but the pattern remained the same.

There was very strong evidence against interaction between maternal fever and acidosis on the risk of encephalopathy (\( P = .93 \) for analysis adjusting for parity and gender, \( P = .83 \) for analysis adjusting additionally for induction of labor and epidural).

To clarify the independent effect of maternal fever on the risk of encephalopathy, the measures of effect are presented separately for infants with acidosis, and without (Table 3). The stratified estimates of the effect of maternal fever are similar to each other, and remain highly statistically significant (\( P < .001 \)).

**Comment**

In this cohort, both acidosis and a maternal fever are clearly shown to be risk fac-

Maternal fever and neonatal acidosis

There are broadly 3 possible models of the causal pathways of this relationship. First, the effect of maternal fever could be mediated entirely via acidosis. If this is the sole mechanism, the effect of a fever should disappear when adjusted for acidosis.

tors for encephalopathy. In cases in which both are present, the risk is 12.5%. Nevertheless, there is no statistical evidence of interaction between the two. This study was not designed to establish the underlying disease, but to shed light on the role of the 2 risk factors in relation to the risk of encephalopathy.

TABLE 1

Characteristics of 8299 maternitiesa according to encephalopathy status of baby after birth

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Infants with encephalopathy (n = 25)</th>
<th>Infants without encephalopathy (n = 8274)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maternal age (SD) in y</td>
<td>27.6 (5.7)</td>
<td>28.7 (5.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean maternal weight at booking in kg (SD)</td>
<td>65.4 (9.0)</td>
<td>66.5 (11.3)</td>
<td>NS</td>
</tr>
<tr>
<td>% nulliparous (n)</td>
<td>76.0% (19)</td>
<td>48.2% (3988)</td>
<td>.006</td>
</tr>
<tr>
<td>Characteristics of labor and delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean gestation (SD) in completed wk</td>
<td>40.2 (0.9)</td>
<td>39.7 (1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean duration of labor in h (SD)</td>
<td>7.7 (3.8)</td>
<td>5.0 (3.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% maternal fever during labor (n)</td>
<td>44.0% (11)</td>
<td>6.8% (560)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% induction of labor (n)</td>
<td>44.0% (11)</td>
<td>17.7% (1462)</td>
<td>.001</td>
</tr>
<tr>
<td>% epidural anesthesia (n)</td>
<td>84.0% (21)</td>
<td>58.3% (4823)</td>
<td>.009</td>
</tr>
<tr>
<td>% monitoring (EFM) used (n)</td>
<td>72.0% (18)</td>
<td>50.3% (4158)</td>
<td>.03</td>
</tr>
<tr>
<td>% EFM abnormality (n)</td>
<td>48.0% (12)</td>
<td>12.7% (1048)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% LSCS (n)</td>
<td>32.0% (8)</td>
<td>3.7% (303)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neonatal characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight (SD) in g</td>
<td>3627 (519)</td>
<td>3614 (476)</td>
<td>NS</td>
</tr>
<tr>
<td>% male (n)</td>
<td>68.0% (17)</td>
<td>51.1% (4224)</td>
<td>.09</td>
</tr>
<tr>
<td>% admission to SCBU (n)</td>
<td>100% (25)</td>
<td>3.3% (276)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% assisted ventilation (if in SCBU) (n)</td>
<td>33.3% (3)</td>
<td>33.3% (15)</td>
<td>NS</td>
</tr>
<tr>
<td>% acidosis (&gt;2 SD from mean) (n)</td>
<td>40% (10)</td>
<td>4.2% (347)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% acidosis and maternal fever (n)</td>
<td>20.0% (5)</td>
<td>0.4% (35)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

a Singleton term maternities with a cephalic presentation, ending in live births.


TABLE 2

Crude and adjusted odds ratios for the association between acidosis, maternal fever, and risk of encephalopathy

<table>
<thead>
<tr>
<th></th>
<th>Infants with encephalopathy N (%)</th>
<th>Infants without encephalopathy N (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusteda OR (95% CI)</th>
<th>Adjusteda OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal acidosis</td>
<td>10 (40.0%)</td>
<td>347 (4.2%)</td>
<td>15.2 (6.8-34.1)</td>
<td>11.5 (5.0-26.5)</td>
<td>11.8 (5.1-27.0)</td>
</tr>
<tr>
<td>Maternal fever</td>
<td>11 (44.0%)</td>
<td>560 (6.8%)</td>
<td>10.8 (4.9-24.0)</td>
<td>8.1 (3.5-18.6)</td>
<td>6.3 (2.7-14.8)</td>
</tr>
<tr>
<td>Maternal fever and neonatal acidosis</td>
<td>5 (20.0%)</td>
<td>35 (0.4%)</td>
<td>117.5 (37.5-368.30)</td>
<td>93.9 (28.7-307.2)</td>
<td>76.2 (23.1-251.7)</td>
</tr>
</tbody>
</table>

a Adjusted for acidosis or fever (as appropriate), nulliparity, and gender.

b Adjusted for acidosis or fever (as appropriate), nulliparity, gender, induction of labor, and epidural.

c Baseline infants with no maternal fever or neonatal acidosis.

Lieberman et al.\(^3\) investigated, albeit obliquely, the possibility of this model. Although they found a clinical diagnosis of “fetal distress” to have occurred in 18.4% of cases of unexplained seizures in which a maternal fever had been noted intrapartum, and in only 2.6% of controls (\(P = .001\)), the effect of a fever nevertheless remained after adjustment for fetal distress and other apparently intrapartum risk factors (AOR = 3.4; 95% CI, 1.03-10.9). The analysis is important but does not disprove model 1 because “fetal distress” is only a surrogate for acidosis, and is a poor predictor of it.\(^4\)

The beneficial effects of cooling in the already encephalopathic neonate\(^25,26\) could go against the possibility of model 1. In these trials, however, some but not all encephalopathic neonates studied were acidic, and dual exposure may be present, as in 20% of our encephalopathic neonates: it is therefore unclear whether the effect of cooling is dependent on the precursors of encephalopathy. That acidic neonates might benefit from cooling does not necessarily mean that any fever was caused by acidosis.

Shalak et al.\(^27\) demonstrated that in 51 severely acidic infants (cord arterial pH < 7.00) admitted to the neonatal unit, histologic chorioamnionitis was present in 51% but had little influence on the risk of encephalopathy. This might support model 1, as well as contrasting with our very high OR in which both risk factors are present. However, with data only from severely acidic, unwell neonates, conclusions about causal pathways involving chorioamnionitis in the majority of neonates are difficult to draw.

In the second model, both risk factors act via different mechanisms and do not influence each other. With this model, although the OR for an adverse outcome in which both risk factors are present would be very high, statistical evidence of interaction would be absent. In the third model, both risk factors act independently when present alone, but act synergistically when both present together, exacerbating the effects of one another. In this model there would be statistical evidence of interaction when both factors are present.

There are also experimental data that appear to support this interaction: much is reviewed by Kendall and Peebles\(^28\); for instance, products of infection or proinflammatory cytokines may reduce the threshold at which hypoxia leads to cellular damage. Epidemiologic data have been similarly interpreted. Nelson and Grether\(^21\) used “potentially asphyxiating conditions” as a surrogate for actual asphyxia or acidosis. They showed significant associations of this, and “infection” (defined clinically and including women with a temperature in labor as well as chorioamnionitis or more robust evidence of infection) with unexplained spastic cerebral palsy. In cases in which both risk factors were present, the OR was 78 (95% CI. 4.8-306), and even higher if only the quadriplegic subgroup was considered. This has led researchers\(^12\) to hypothesize interaction between these risk factors. Wu et al.\(^15\) also found support for model 3. They showed “clinically diagnosed” chorioamnionitis and cerebral palsy to be common among neonates who had birth asphyxia diagnosed, and even with neuroradiologic evidence of “hypoxic-ischemic injury,” and so speculated that chorioamnionitis may have a role in “initiating or exacerbating brain injury from hypoxia-ischemia.”

Our findings, of strong independent effects for both factors but no evidence of statistical interaction when presented together, nevertheless support the hypothesis that it is model 2 that is the most important intrapartum pathway. The experimental evidence does not contradict this: local hypoxic cellular damage, eg, perinatal stroke, may be the end result of a causal pathway manifest as a fever, but this does not imply interaction between this pathway and that involving global hypoxia as reflected in umbilical cord gas changes. With respect to the Nelson and Grether data,\(^21\) the high ORs after exposure to both factors do not prove interaction; indeed these authors do not claim it is present. Their very high risk of cerebral palsy is not dissimilar to our risk of encephalopathy where both a maternal fever and neonatal acidosis are present. A multiplicative effect would be expected where 2 relatively strong but nevertheless independent risk factors co-exist: exposure to 1 risk factor and then, by chance, to another, would lead to an approximate multiplication of the risks. The speculations by Wu et al.\(^15\) rely on clinical and radiologic diagnoses: neonatal signs of injury associated with mater-

### TABLE 3

<table>
<thead>
<tr>
<th>Acidosis (10 infants with encephalopathy, 347 without)</th>
<th>Infants with encephalopathy N (%)</th>
<th>Infants without encephalopathy N (%)</th>
<th>Adjusted(^a) OR (95% CI)</th>
<th>Adjusted(^b) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (5 infants with encephalopathy, 359 without)</td>
<td>5 (50.0%)</td>
<td>35 (10.1%)</td>
<td>8.7 (2.4-31.7)</td>
<td>6.4 (1.7-24.4)</td>
</tr>
<tr>
<td>No acidosis (15 infants with encephalopathy, 7927 without)</td>
<td>6 (40%)</td>
<td>525 (6.6%)</td>
<td>7.4 (2.4-21.9)</td>
<td>5.7 (1.9-17.4)</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for: nulliparity, gender.

\(^b\) Adjusted for: nulliparity, gender, induction of labor, epidural.


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nal fever or chorioamnionitis have much in common with those after severe acidosis and have consequently been erroneously labeled as evidence of birth asphyxia.\textsuperscript{10, 14} Even with neuroradiologic imaging, no findings are specific to hypoxia: a problem these authors point out. Further, quadriplegic cerebral palsy is considered the usual subtype after an intrapartum event,\textsuperscript{7} but as Wu et al\textsuperscript{15} show, is also associated with chorioamnionitis. The clinical and neuroradiologic findings attributed to hypoxia may therefore simply be because this has historically been considered the mechanism of intrapartum injury.

Our figures are similar to those of Nelson and Grether,\textsuperscript{21} and our conclusions are similar to Lieberman et al.\textsuperscript{17} We go further, however, by testing for statistical interaction, and by using acidosis rather than surrogate markers. The very high risk of neonatal encephalopathy when both maternal fever during labor and neonatal acidosis were present together is explained by the multiplicative effect of dual exposure compared with no exposure. These risk factors therefore appear to operate largely independently and represent 2 separate causal pathways.

Global hypoxia manifests as acidosis is thought to be the principal mechanism of intrapartum damage; although meconium aspiration and fetal trauma can occur, they are rare causes of adverse outcome. It is widely assumed that if acidosis is absent, then labor has little role.\textsuperscript{7} It is not known if the intrapartum maternal fever observed in our or other studies is a purely intrapartum process or is a reflection or exacerbation of an existing antepartum process. Certainly, our cohort were afebrile at the start of labor; and the diagnosis “chorioamnionitis,” is rare in the antepartum period at term, except when the membranes have ruptured.\textsuperscript{5} We can also not exclude the possibility of a causal relationship between acidosis and postnatal or neonatal temperature: for instance, acidosis could lead to an inflammatory response, or fever, but the duration of labor prevents its detection. This might have caused the slight reduction in the OR of fever (Table 3) for encephalopathy when adjusted for acidosis. Therefore, although model 2 is the most important behind the intrapartum fever, there remains the possibility that the effects of acidosis are causally related to temperature or an inflammatory response but these are largely manifest outside labor.

We acknowledge other potential limitations. First, absence of evidence regarding interaction is not evidence of absence. In our tests for interaction, however, our values were close to 1.00 and a type II error is unlikely. Second, we consider only a maternal fever, rather than chorioamnionitis. Although this limits our interpretations, definitions of chorioamnionitis differ greatly, and a maternal fever is an established and definable risk factor that can be assessed on large numbers. Third, we consider only intermediate term morbidity. Nevertheless, encephalopathy is one of the best available predictors of cerebral palsy in term neonates: about a third of neonates with encephalopathy Sarnat grade 2 or worse will have cerebral palsy develop or die.\textsuperscript{29} Furthermore, both an intrapartum fever\textsuperscript{8, 10} and fetal acidosis\textsuperscript{8, 11} are associated with both conditions. The advantage of the outcome encephalopathy is that it allows the analysis of prospectively collected data, because it presents shortly after birth. Aside from the implications on our understanding of the role of labor, there are practical uses of these data. The first is clear from the high risk (12.5%) of an adverse outcome if both acidosis and a maternal fever coexist: a maternal fever identifies a “high-risk” labor. Evidence regarding the use of cardiotocography or electronic fetal monitoring to detect fetal acidosis in labor suggests it should at least be restricted to high-risk women.\textsuperscript{30} Risk is currently poorly assessed by using antenatal factors, meconium-stained liquor, or the admission cardiotocograph, although maternal temperature monitoring is haphazard. The finding of a maternal fever identifies a labor at high risk for adverse neonatal consequences, particularly if acidosis occurs as well. Second, because a fever represents a largely independent pathway, the potential exists to integrate risk factors for adverse outcomes in a manner similar to that used to screen for chromosomal defects.\textsuperscript{31} This might allow, for instance, alteration of the threshold of pH for delivery of a fetus according to whether the mother had a fever.

Maternal fever in labor is strongly associated with serious adverse neonatal and long-term outcomes. Whatever the underlying mechanism, it represents a causal pathway that appears to be largely separate from acidosis. If acidosis is not the only common intrapartum mode of brain injury, the contribution of labor to brain injury could have been considerably underestimated. Targeting only the prevention of intrapartum fetal acidosis in research and clinical practice, risks missing an important other mechanism.

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12. Peebles DM, Wyatt JS. Synergy between antenatal exposure to infection and intrapartum


