The relation between pre-eclampsia at term and neonatal encephalopathy

L Impey, C Greenwood, O Sheil, K MacQuillan, M Reynolds, C Redman

Abstract

Objectives—To determine whether pre-eclampsia, hypothesised to be an inflammatory condition, is associated with fever in term labour, and confirm and examine the reported association of pre-eclampsia at term with neonatal encephalopathy.

Design—Prospective cohort study.

Setting—A Dublin teaching hospital.

Participants—6163 women in labour with singleton pregnancies at term at low risk for intrapartum hypoxia, recruited to a randomised trial examining the effect of admission cardiotocography on neonatal outcome.

Results—Pre-eclampsia was associated with maternal fever > 37.5°C in labour (odds ratio (OR) 3.39, 95% confidence interval (CI) 2.1 to 5.4); this was independent of obstetric intervention (adjusted OR 2.07, 95% CI 1.24 to 3.47). Pre-eclampsia was associated with neonatal encephalopathy (OR 25.5, 95% CI 5.4 to 74.7); this too was independent of obstetric intervention (adjusted OR 18.5, 95% CI 5.9 to 58.1). Cord arterial pH values were significantly lower in pre-eclampticies (7.20 v 7.24), although severe cord acidemia was not significantly more common (OR 2.91, 95% CI 0.7 to 9.9). The association of pre-eclampsia with encephalopathy was independent of maternal fever (adjusted OR 16.5, 95% CI 5.1 to 54) and cord acidemia (adjusted OR 13.5, 95% CI 3.2 to 56.7).

Conclusions—The association of pre-eclampsia with maternal fever at term supports the hypothesis that pre-eclampsia is an inflammatory condition. The association of pre-eclampsia with neonatal encephalopathy is independent of obstetric intervention and cannot be explained by either acidemia or maternal fever. A systemic inflammatory response in the fetus, perhaps secondary to oxidative stress, could explain the link between maternal pre-eclampsia and neonatal encephalopathy, and this may occur through cerebral vasocostriction.

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Keywords: pre-eclampsia; encephalopathy; fever; labour

Pre-eclampsia affects about 5% of nulliparous women and is a major cause of maternal and neonatal morbidity and mortality. Neonatal effects are not limited to preterm babies, for it is associated with neonatal encephalopathy and cerebral palsy at term. Both outcomes are also linked with infection and maternal fever. As fever may be a risk factor even in the absence of evidence of infection, and autoimmune disease may also predispose to cerebral palsy, the association of an inflammatory state with adverse neonatal outcome is not entirely attributable to infection.

We have provided evidence that pre-eclampsia results from exaggeration of a maternal systemic inflammatory response common to all pregnancies. The theory is consistent with many of the clinical observations and associations of pre-eclampsia, yet fever, a common manifestation of an inflammatory response, is not considered to be a feature of pre-eclampsia. The hypothesis would predict that pre-eclamptic women would at least be more susceptible to fever. This may be most easily detected in labour, but has not been studied.

We therefore determined whether pre-eclampsia at term is associated with maternal fever in labour. When we found that it is, we investigated the association between pre-eclampsia at term and neonatal encephalopathy and analysed whether this is associated with maternal fever.

Methods

The data were prospectively collected from a cohort of women recruited from August 1997 to April 2000 at a Dublin teaching hospital to a randomised, controlled trial determining the effect of admission cardiotocography on the incidence of adverse neonatal outcome. Women with a singleton fetus were eligible if clear liquor was detected at early amniotomy and the fetus was not considered at risk for intrapartum fetal distress—for example, known intrauterine growth restriction, antepartum haemorrhage. In addition, women with a breech presentation, those delivering before 37 and after 42 completed weeks, and those whose babies were anomalous or had inborn errors of metabolism were excluded from analysis.

Pre-eclampsia was defined as new hypertension in pregnancy (≥ 140/90) with new proteinuria (1+ or more on dipstick testing). Maternal pyrexia in labour was an oral temperature > 37.5°C. Severe acidemia was defined as a cord arterial pH < 7.00 with a base deficit > 12 mmol/l. C reactive protein levels and blood cultures were examined in encephalopathic babies only. Neonatal encephalopathy was diagnosed as described by Sarnat and Sarnat (grade 2–3 only). The occurrence of cerebral palsy was not calculated, as our infants are not yet old enough to exclude this diagnosis.

Data were analysed using SPSS 9.0 (Chicago, Illinois, USA) and Epi-Info, and crude odds ratios (ORs) were calculated. Adjusted

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Cord blood gases were not measured in all babies; base deficit measurements were more often
adjusted, in addition, for cord arterial pH.

†Adjusted, in addition, for maternal fever in labour > 37.5
analgesia, use of oxytocin, and instrumental delivery.
‡Adjusted for parity, birth weight, gestation, induction of labour, length of labour, epidural
analgesia, use of oxytocin, and instrumental delivery.
*Adjusted for parity, birth weight, gestation, induction of labour, length of labour, epidural
anaesthesia, use of oxytocin, and instrumental delivery.

Results
Of 6163 women in labour who met the study
criteria, 124 (2.0%) had pre-eclampsia; labour
was induced in 87 of these (70.2%). Intra-
partum pyrexia was recorded in 419 (6.9%);
severe acidemia occurred in 54 (0.9%), and
neonatal encephalopathy in 18 (0.3%). Among
the encephalopathic neonates, one born to
a non-pre-eclamptic mother had raised C reac-
tive protein only. Pre-eclampsia was associated
with shorter gestation, induction of labour, lower
parity, lower birth weight, epidural analgesia, longer
labour, use of oxytocin, and instrumental
delivery.

Neonatal encephalopathy was associated
with pre-eclampsia; this was independent of
these variables (table 1). Maternal pyrexia was
also significantly associated with pre-eclampsia
(table 1); this was also independent of the
above covariates (instrumental delivery was not
analysed as it could not cause intrapartum
fever).

Cord gas values were obtained in 116 (94%) of
pre-eclamptic deliveries and 5634 (93%) of
non-pre-eclamptic deliveries (p = 0.51). Se-
vere acidemia was significantly associated
with encephalopathy (OR 63.5, 95% confi-
dence interval (CI) 20.3 to 192). The mean
cord arterial pH after pre-eclamptic preg-
nancies was significantly lower, and the base deficit
significantly higher, than among other babies
(table 2). However, the association between severe
criteria and pre-eclampsia (table 1) did not reach statistical significance. Among
the encephalopathic babies, there was a trend
towards a higher pH and lower base deficit in
those born to mothers with pre-eclampsia
(table 2).

The association of pre-eclampsia with neo-
natal encephalopathy was independent of
maternal fever and umbilical cord acidemia
(table 1).

Table 1  Associations of pre-eclampsia in term neonates

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-eclampsia</th>
<th>No pre-eclampsia</th>
<th>Crude odds ratio (95% CI)</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>124 (2.0%)</td>
<td>6039 (98.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever &gt; 37.5°C</td>
<td>25 (20.2%)</td>
<td>419 (6.9%)</td>
<td>3.39 (2.10 to 5.42)</td>
<td>2.07 (1.24 to 3.47)*</td>
</tr>
<tr>
<td>Severe acidemia</td>
<td>3 (2.4%)</td>
<td>51 (0.8%)</td>
<td>2.91 (0.72 to 9.85)</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>6 (4.8%)</td>
<td>12 (0.2%)</td>
<td>25.5 (8.39 to 74.7)</td>
<td>18.50 (9.92 to 58.13)†</td>
</tr>
</tbody>
</table>

*Adjusted for parity, birth weight, gestation, induction of labour, epidural analgesia, and use of oxytocin.
†Adjusted for parity, birth weight, gestation, induction of labour, length of labour, epidural analgesia, use of oxytocin, and instrumental delivery.
‡Adjusted for parity, birth weight, gestation, induction of labour, length of labour, epidural analgesia, use of oxytocin, and instrumental delivery.

Table 2  Relation between cord arterial pH/base excess and pre-eclampsia in term neonates

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All babies</th>
<th>Encephalopathic babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>7.196</td>
<td>7.236 (p&lt;0.001)</td>
</tr>
<tr>
<td>range</td>
<td>6.77-7.53</td>
<td>6.77-7.53</td>
</tr>
<tr>
<td>Base deficit</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>91</td>
<td>5042</td>
</tr>
<tr>
<td>mean</td>
<td>8.826</td>
<td>7.834 (p=0.005)</td>
</tr>
<tr>
<td>range</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*Adjusted for parity, birth weight, gestation, induction of labour, epidural analgesia, use of oxytocin, and instrumental delivery.

Discussion
Our finding that pre-eclampsia is an independ-
ent risk factor for maternal fever in labour
is consistent with the hypothesis that pre-
eclampsia is itself a systemic inflammatory
state.5 The association between term pre-eclampsia
and neonatal encephalopathy, from which
more than half the affected babies die or
develop severe disability,6 confirms previous
case-control studies.7 Indeed, one third of our
encephalopathic babies followed pregnancies
complicated by pre-eclampsia, as do a signifi-
cant proportion of cases of cerebral palsy.8 In
addition, we showed that this relation is not the
result of obstetric intervention such as induc-
tion, epidural analgesia, or augmentation. The
lower mean cord arterial pH and higher base
deficits in pre-eclamptic pregnancies were
compatible with relative hypoxaemia. Yet the
risk of encephalopathy was independent of
cord acidemia. Indeed, there was a trend
towards less acidemia in encephalopathic
neonates delivered to pre-eclamptic women.

These data are consistent with the consensus
that neonatal encephalopathy does not depend
on severe intrauterine hypoxaemia. They rein-
force the belief that antepartum factors are
important in the development of neonatal
encephalopathy7 and cerebral palsy.6 However,
the mechanism by which antepartum factors
such as pre-eclampsia lead to encephalopathy
remains unexplained.

The association of pre-eclampsia with ma-
ternal fever, itself a risk factor for encephalo-
pathy,4 could not entirely explain the increased
risk of encephalopathy in this group of
pre-eclamptic women. Hence it is likely that
fever itself is not causal, and that some other
feature of the disease leads to the adverse neo-
natal outcome. There is compelling evidence of
a role for perinatal inflammatory processes not
exclusive to infection in the development of
long term neonatal handicap.9 It is therefore
relevant that there is an increased systemic
inflammatory response in the newborns of pre-
eclamptic women.9,10 Whether this is linked to
some way to the maternal inflammatory
response or has a separate cause is not known.

The origin of the fetal inflammatory re-
sponse in pre-eclampsia is likely to be hypoxia
and oxidative stress. These are well recognised

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stimuli to localised\(^{12}\) and systemic\(^{11}\) inflammatory
to responses. The fates of pre-eclamptic 
women may be hypoxaemic, which is consistent 
with our finding of a greater mean base 
deficit and lower mean pH. Such hypoxaemia is 
reflected in increased markers of oxidative stress in the placenta\(^{16}\) and fetal blood\(^{15}\) in 
pre-eclampsia and is considered to result from poor 
uteroplacental perfusion.\(^{16}\)

Extreme inflammatory responses lead to 
vasoconstriction and shock as in sepsis. However, 
vasoconstriction is characteristic of less ex- 
ductive stimuli\(^1\) which could 
jeopardise tissue perfusion locally. The fetal 
and neonatal cerebral circulations may be par- 
ticularly vulnerable, explaining the rare associ- 
ation of pre-eclampsia with neonatal cerebral, 
particularly parietal lobe, infarcts.\(^{18}\) Labour 
may be a complicating factor. Normal sponta- 
eous labour at term is associated with an 
increased systemic inflammatory response of 
the newborn.\(^{19}\) It causes fetal head compres- 
sion,\(^{20}\) which, even in uncomplicated labour, is 
associated with disturbed indices of middle 
cerebral artery flow\(^{21}\) and localised hypoxic 
changes.\(^{22}\) Hence antenatal risk factors may be 
aggravated by labour, a possibility consistent 
with the observation that elective cesarean 
section protects against neonatal encephalopa- 
thy.\(^{23}\) Whether labour is implicated or not, 
localised cerebral vasoconstriction, hypoxia, 
and neuronal damage could occur. The key 
point is that this need not be in the context of 
global asphyxia nor even reflected in changes in 
umbilical blood gas analyses.

An inflammatory response appears to be a 
common pathway for infection and auto-
immune disease in the development of neuro-
logical handicap. We propose that it is also a 
pathway for pre-eclampsia, and that systemic 
inflammation leads to localised cerebral ischa- 
mia. Future research could address indices of 
perinatal systemic inflammation rather than 
gas analysis in cord blood, and relate the results 
of fetal and neonatal brain imaging to these and 
antenatal risk factors.

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statistical analysis, and wrote the paper. OS was principal grant 
holder, and contributed to the study design and the final draft of 
the paper. CR and CG contributed to the study design, analysis, 
and wrote the paper. MR and RMcQ collected the data and 
contributed to the final draft of the paper.

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