

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 $> 37.5^{\circ}$ 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 8.4 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-eclamptics (7.20 *v* 7.24), although severe cord acidaemia 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 acidaemia (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 acidaemia 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 vasoconstriction.

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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.^{1,2} Both outcomes are also linked with infection and maternal fever.^{3,4} As fever may be a risk factor even in the

absence of evidence of infection³, and autoimmune disease may also predispose to cerebral palsy,⁵ 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.⁶ 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 ($\geq 140/90$) with new proteinuria (1+ or more on dipstick testing). Maternal pyrexia in labour was an oral temperature $> 37.5^{\circ}\text{C}$. Severe acidaemia 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 Sarnat⁷ (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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Table 1 Associations of pre-eclampsia in term neonates

Outcome	Pre-eclampsia n (%)	No pre-eclampsia n (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Total	124 (2.0)	6039 (98.0)		
Fever > 37.5°C	25 (20.2)	419 (6.9)	3.39 (2.10 to 5.42)	2.07 (1.24 to 3.47)*
Severe acidaemia	3 (2.4)	51 (0.84)	2.91 (0.72 to 9.85)	
Encephalopathy	6 (4.8)	12 (0.20)	25.5 (8.39 to 74.7)	18.50 (5.92 to 58.13)† 16.56 (5.07 to 54.03)‡ 13.48 (3.21 to 56.70)§

*Adjusted for parity, birth weight, gestation, induction of labour, length 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, in addition, for maternal fever in labour > 37.5°C.

§Adjusted, in addition, for cord arterial pH.

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

Outcome	All babies			Encephalopathic babies	
	Pre-eclampsia	No pre-eclampsia		Pre-eclampsia	No pre-eclampsia
pH					
n*	116	5634		6	12
mean	7.196	7.236	(p<0.001)	7.123	7.059
range	6.82–7.40	6.77–7.53		6.82–7.29	6.83–7.33
Base deficit					
n*	91	5042		3	7
mean	8.826	7.834	(p=0.005)	7.800	15.16
range	19.8–1.5	31.0–1.2		10.8–6.20	21.0–8.20

*Cord blood gases were not measured in all babies; base deficit measurements were more often missing.

ORs were calculated using multiple logistic regression to examine whether the association of pre-eclampsia with both encephalopathy and maternal fever was independent of factors associated with pre-eclampsia that could be determinants of the outcome. In addition, when investigating the association of pre-eclampsia with neonatal encephalopathy, we adjusted for both maternal fever and cord gas acidaemia separately, to ascertain their roles in the causal pathway.

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%). Intrapartum pyrexia was recorded in 419 (6.9%); severe acidaemia 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 reactive protein and positive blood cultures; another born to a pre-eclamptic mother had slightly increased C reactive 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 ($p = 0.51$). Severe acidaemia was significantly associated

with encephalopathy (OR 63.5, 95% confidence interval (CI) 20.3 to 192). The mean cord arterial pH after pre-eclamptic pregnancies was significantly lower, and the base deficit significantly higher, than among other babies (table 2). However, the association between severe acidaemia 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 neonatal encephalopathy was independent of maternal fever and umbilical cord acidaemia (table 1).

Discussion

Our finding that pre-eclampsia is an independent risk factor for maternal fever in labour is consistent with the hypothesis that pre-eclampsia is itself a systemic inflammatory state.⁶

The association between term pre-eclampsia and neonatal encephalopathy, from which more than half the affected babies die or develop severe disability,⁸ confirms previous case-control studies.¹ Indeed, one third of our encephalopathic babies followed pregnancies complicated by pre-eclampsia, as do a significant proportion of cases of cerebral palsy.⁹ In addition, we showed that this relation is not the result of obstetric intervention such as induction, 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 acidaemia. Indeed, there was a trend towards less acidaemia 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 reinforce the belief that antepartum factors are important in the development of neonatal encephalopathy¹ and cerebral palsy.⁸ However, the mechanism by which antepartum factors such as pre-eclampsia lead to encephalopathy remains unexplained.

The association of pre-eclampsia with maternal fever, itself a risk factor for encephalopathy,^{1,4} 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 neonatal outcome. There is compelling evidence of a role for perinatal inflammatory processes not exclusive to infection in the development of long term neonatal handicap.⁵ It is therefore relevant that there is an increased systemic inflammatory response in the newborns of pre-eclamptic women.^{10,11} Whether this is linked in some way to the maternal inflammatory response or has a separate cause is not known.

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

stimuli to localised¹² and systemic¹³ inflammatory responses. The fetuses 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 placenta¹⁴ and fetal blood¹⁵ in pre-eclampsia and is considered to result from poor uteroplacental perfusion.¹⁶

Extreme inflammatory responses lead to vasodilatation and shock as in sepsis. However, vasoconstriction is characteristic of less extreme inflammatory stimuli¹⁷ which could jeopardise tissue perfusion locally. The fetal and neonatal cerebral circulations may be particularly vulnerable, explaining the rare association of pre-eclampsia with neonatal cerebral, particularly parietal lobe, infarcts.¹⁸ Labour may be a complicating factor. Normal spontaneous labour at term is associated with an increased systemic inflammatory response of the newborn.¹⁹ It causes fetal head compression,²⁰ which, even in uncomplicated labour, is associated with disturbed indices of middle cerebral artery flow²¹ and localised hypoxic changes.²² Hence antenatal risk factors may be aggravated by labour, a possibility consistent with the observation that elective caesarean section protects against neonatal encephalopathy.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 autoimmune disease in the development of neurological handicap. We propose that it is also a pathway for pre-eclampsia, and that systemic inflammation leads to localised cerebral ischaemia. 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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Authors' contributions: LI designed the study, performed 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 cowrote the paper. MR and KMcQ collected the data and contributed to the final draft of the paper.

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