‘Perinatal infection is an important risk factor for cerebral palsy in very-low-birthweight infants’

SIR–The report by Wheater and Rennie that perinatal infection is a preventable risk factor for cerebral palsy (CP) leaves us unconvinced on several grounds.

First, the comparative data relate to neonatal infection rather than perinatal infection. This may seem a minor point but the word ‘perinatal’ implies an earlier event and timing of the onset of cortical damage is all important. There are already a number of robust studies which show chorioamnionitis as a risk factor; one explanation of their results is that intrauterine infection predisposes both to postnatal infection and to CP.

Second, the population was heterogeneous and appears to have included even babies referred in late for neurosurgical management. As the authors’ data makes clear, these babies are more likely to develop CP. This may introduce systematic bias because the controls are effectively from a different population to the cases.

Third, the most obvious alternative explanation of the results is that infection is confounding an underlying relationship between gestation and CP. The smallest, most immature babies are more likely both to get infected and to develop CP. If the authors bad controlled for either gestational age or birthweight in a logistic regression analysis the results would have been more credible.

Fourth, Table III does not report odds ratios, as stated in the text, but relative risks. For conditions with a high prevalence, as CP has in this sample of very-low-birthweight infants, the odds ratios are considerably different to the relative risks. Although this does not make much difference to the implications of the results, it is a basic epidemiological error which confuses comparisons with other studies.

Fifth, it is inappropriate to state that ‘one or more episodes of infection trebled the risk of neonatal cranial ultrasound abnormality’. It is likely that in many of these cases the ultrasound abnormality preceded the onset of infection. This strengthens our assertion that what is being reported in this study are two separate underlying relationships, one between immaturity and CP and one between immaturity and infection.

Our main criticism is of the final paragraph. To proceed from such debatable evidence by asserting that antibiotic prophylaxis of the very-low-birthweight baby might be a cost effective way of reducing the incidence of CP is a speculation which seems to have been plucked out of thin air. Even if we were to accept their evidence of a possible causal relationship, there is no evidence that antibiotic prophylaxis would prevent such infections, nor that any possible benefit would outweigh potential harms of widespread antibiotic prophylaxis.

The authors have been poorly served by the editors and reviewers of the journal who should at least have addressed our final point. The peer review system is not just a filter; it can be an intrinsic part of the process which helps authors produce the best paper from the data available. It has failed on both counts in this case.

‘Wheater and Rennie Reply’

SIR–Doctors Reading and Eason are correct that our Table III gives relative risks rather than odds ratios. We apologise for this error. They are also correct that the corresponding table of odds ratios (see below) is qualitatively similar and that the implications are the same: we referred to relative risks in the abstract.

We make no secret of the fact that our population was from such debatable evidence by asserting that antibiotic prophylaxis of the very-low-birthweight baby might be a cost effective way of reducing the incidence of CP is a speculation which seems to have been plucked out of thin air. Even if we were to accept their evidence of a possible causal relationship, there is no evidence that antibiotic prophylaxis would prevent such infections, nor that any possible benefit would outweigh potential harms of widespread antibiotic prophylaxis.

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Revised Table III: Odds ratios

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<tr>
<th></th>
<th>n</th>
<th>Odds ratio (95%CI)</th>
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<tbody>
<tr>
<td>Babies with brain injury and:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>41/78</td>
<td>4.7 (2.9,7.8)</td>
</tr>
<tr>
<td>No neonatal sepsis</td>
<td>39/350</td>
<td>4.7 (2.9,7.8)</td>
</tr>
<tr>
<td>Babies with CP and:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal cranial ultrasound</td>
<td>39/41</td>
<td>12.6 (7.1,22.4)</td>
</tr>
<tr>
<td>Normal cranial ultrasound</td>
<td>30/398</td>
<td>12.6 (7.1,22.4)</td>
</tr>
<tr>
<td>Babies with CP and:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>38/81</td>
<td>5.4 (3.2,9.2)</td>
</tr>
<tr>
<td>No neonatal sepsis</td>
<td>31/358</td>
<td>5.4 (3.2,9.2)</td>
</tr>
<tr>
<td>Babies with CP, normal cranial ultrasound and:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>14/64</td>
<td>4.5 (2.1,9.8)</td>
</tr>
<tr>
<td>No neonatal sepsis</td>
<td>16/334</td>
<td>4.5 (2.1,9.8)</td>
</tr>
<tr>
<td>Babies with CP, abnormal cranial ultrasound and:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>24/17</td>
<td>2.3 (0.9,5.5)</td>
</tr>
<tr>
<td>No neonatal sepsis</td>
<td>15/24</td>
<td>2.3 (0.9,5.5)</td>
</tr>
<tr>
<td>Babies with CP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Products of multiple pregnancy</td>
<td>25/128</td>
<td>1.2 (0.7, 2.1)</td>
</tr>
<tr>
<td>Singletons</td>
<td>46/511</td>
<td>1.2 (0.7, 2.1)</td>
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</tbody>
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heterogeneous. We did not believe, however, that arbitrary exclusions would make our data more reliable or easier to interpret.

It is true that many of our data relate to early neonatal infection. But in view of the fact that our results confirm those of others regarding the association between chorioamnionitis (and/or maternal pyrexia) and later cerebral palsy (CP), we thought it better to use the term perinatal. We agree that one explanation of our results is that antenatal infection, which may precipitate delivery, may predispose both to early infection and to CP. Karin Nelson’s group has shown high levels of interleukins and tumour necrosis factor alpha to be present in archived neonatal blood spots of children born at term who later developed CP, particularly those with spastic diplegic CP1. The implication of these results is that an in utero infection increases the risk of CP. Preterm babies are, of course, ex utero at a time when their brains are at the same vulnerable stage of development, which may be one explanation for our finding that post-natal sepsis also increased the risk in our group.

Their main objection is to our final paragraph, in which we point to the methodological weaknesses of our study, summarise our interpretation of the association between infection and outcome, and speculate on the ‘possibility of reducing CP by preventing infection’. Speculation is an accepted component of the discussion section of a scientific paper. We agree with Skelton and Edwards2 that if authors do not go beyond their results, their discussion is tautological. No one expects the medical reader to act on such speculation except in the context of a controlled trial. We await with interest the results of the Oracle trial of antibiotics in preterm labour3, although at present the outcome includes only abnormal neonatal ultrasound scans at discharge. The high number of ‘ultrasound normal’ CP cases in our study shows that this may underestimate the incidence of CP by about half.

Mary Wheater
Janet Rennie

References

POEM

Today our main concern...

Today I would have talked about amygdala, almond-shaped clusters of inter-connected structures perched above the brain stem –

but today was ominous:
inner and outer weather mingled around the campus in a tide of cobalt clouds.

Amygdala, little almond,
I would have told them it was you who runs these loops of low-grade melodrama –

but a gull was crying
above the concrete temple of the Arts Block
as if it had forgotten the sea.

I would have taken them through the limbic system
and the ancestral environments of our feelings,
explained the neural hi-jackings

but feared I might be mad myself,
sing turmoil at them,
sing the syrupy vernacular of the heart

and they’d be waiting
faceless, rising tier on tier like placid saints,
the dispassionate white screen waiting
to be scrawled with the graffiti of frets and angst,
the pa system sense the drowning hollows

of my voice and boom uncertainty.

Today our main concern...our main concern will be the cohorts of our intimate enemies,
the toxic thoughts, the case of love...

Judy Gabagan