LETTERS TO
THE EDITOR

Low soluble FcRIII receptor demonstrates reduced neutrophil reserves in preterm neonates

Editor.—Studies of human neonate granulopoiesis have been hampered by the lack of a marker of overall neutrophil cell mass. Assumptions about neonate granulopoiesis have therefore largely been extrapolated from rat data. Direct measurement of total neutrophil cell mass (in terms of neutrophils per g body weight) in newborn rats has shown that they have about one quarter the neutrophil mass of adult animals and that their neutrophil mass increases to adult levels by the time they are 4 weeks old.† In addition, newborn rodents do not have the reserve pool of quiescent granulocyte progenitors, as found in adults, to recruit into production during sepsis. Circumstantial evidence for a similar immaturity of neutrophil production in human neonates comes from the low proportion of quiescent progenitors in cord blood and the frequent occurrence of postnatal neutropenia in preterm infants. Some additional insight comes from a study of mid-trimester abortuses,‡ which showed minimal numbers of neutrophils in haemopoietic tissue before 24 weeks gestation. Until now, direct quantification of total body neutrophil cell mass in human neonates between 24 weeks and term has remained elusive.

In 1992 we reported† that preterm neonates born before 32 weeks gestation have very low plasma concentrations of the soluble FcRIII receptor (sFcRIII), sFcRIII is the plasma form of the neutrophil membrane receptor FcγRIII which, together with other membrane receptors, is responsible for binding to antigens and initiating phagocytosis. We observed that, between 24 and 32 weeks gestation, sFcRIII concentrations are about 15% of normal adult values (mean (SE) 15.3 (1.3)%), while sFcRIII concentrations in fetal samples collected between 19 and 23 weeks are even lower (mean (SE) 8.3 (1.4)%). Between 33 and 36 weeks in utero, sFcRIII increases rapidly so that by term the fetus has concentrations similar to adults. In babies born before 32 weeks, sFcRIII concentrations increase gradually after birth to achieve adult concentrations by the fourth week of postnatal life. At the time, we interpreted these data to indicate reduced FcRIII production by individual cells and thus immaturity of neonate neutrophil function.

Since we published these data, further work has clarified the origins and significance of plasma sFcRIII. These studies have shown that sFcRIII is derived from apoptotic neutrophils, and its concentration in plasma reflects the total body neutrophil mass as well as the overall production of neutrophils in the bone marrow.††

This new understanding of sFcRIII alters the interpretation of our original observation. It is now apparent that our data confirm what was previously only suspected: preterm human infants of less than 32 weeks gestation have reduced neutrophil production and a reduced total neutrophil cell mass at birth. Our data also show that neutrophil reserves remain low for about three weeks after preterm birth. Term infants by contrast, have neutrophil production and stores that are similar to those of adults.

The reduced neutrophil mass of preterm neonates explains the common occurrence of postnatal and sepsis induced neutropenia. The relevance of this finding to the high sepsis incidence associated with prematurity is emphasised by a recent study of patients with idiopathic neutropenia, which has shown that a low sFcRIII concentration is a more accurate predictor of infection risk than the peripheral blood neutrophil count.† Further, this new insight into neonatal immune development suggests that stimulation of neutrophil production by colony stimulating factors early in postnatal life would reduce the incidence and severity of sepsis in preterm neonates by accelerating expansion of their deficient neutrophil reserves.

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Chasing hyponatraemia in preterm infants

Editor,—In a recent issue, Hartnoll et al.1 described preterm neonate sodium supplementation on oxygen dependency and body weight in 25–30 week gestational age infants. Arch Dis Child Fetal Neonatal Ed 2000;85:F160–F164. F160


Suxamethonium is safe in small hands; mivacurium should also be considered

Editor,—We thank Whyte et al3 for detailing the premedication policies for intubation in United Kingdom neonatal units. There is a wide disparity in both the type and dosage of drugs. Whyte et al mention that, as a muscle relaxant, suxamethonium, has important safety benefits. It has a very rapid onset and offset of action, and therefore there is a “get out clause” for the difficult intubation or intubation by an inexperienced operator. However, other considerations need to be taken into account when suxamethonium is used.

Firstly, intravenous premedication is contraindicated in conditions known to be associated with difficult intubations, such as the Pierre Robin sequence. Further, suxamethonium is a depolarising muscle relaxant and therefore can cause sinus Bradycardia. Atropine can be given in an attempt to avoid this.

Suxamethonium causes depolarisation at the neuromuscular junction, rarely leading to hyperkalaemic induced cardiac arrest.4 Undiagnosed myopathic conditions were found in a number of affected children, and paediatric licensing for this drug was therefore removed in the United States. However, no other very rapidly acting drug has been manufactured, and, because of its popularity, suxamethonium is reinstated. Before its use, a detailed family history for myopathic conditions must be taken.

In our neonatal unit, we have started to use fentanyl, an opioid, with mivacurium as the non-depolarising muscle relaxant and therefore carries no risk of life threatening arrhythmias. The routine use of atropine is not necessary.

Table 1 Summary of the events

<table>
<thead>
<tr>
<th>Day No</th>
<th>Total fluid (ml/kg)</th>
<th>Urinary output (ml/kg)</th>
<th>Sodium input (mmol/kg)</th>
<th>Serum sodium (mmol/l)</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>217</td>
<td>7</td>
<td>3</td>
<td>124</td>
<td>860</td>
</tr>
<tr>
<td>7</td>
<td>248</td>
<td>8</td>
<td>7</td>
<td>120</td>
<td>860</td>
</tr>
<tr>
<td>8</td>
<td>213</td>
<td>7</td>
<td>10</td>
<td>128</td>
<td>870</td>
</tr>
<tr>
<td>9</td>
<td>214</td>
<td>9</td>
<td>9</td>
<td>134</td>
<td>900</td>
</tr>
<tr>
<td>10</td>
<td>203</td>
<td>5</td>
<td>15</td>
<td>131</td>
<td>900</td>
</tr>
<tr>
<td>11</td>
<td>206</td>
<td>6</td>
<td>15</td>
<td>136</td>
<td>940 (PDA)</td>
</tr>
</tbody>
</table>
We agree that a randomised trial needs to be undertaken to prove that premedication has the desirable end point of reducing neonatal morbidity, particularly intraventricular haemorrhage.

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Premedication for intubation in neonates

EDITOR,—We were very interested in the recent papers by Bhatuda et al and Whyte et al on the use of premedication for sedative intubation in neonates. It is now well accepted that term and preterm neonates tolerate awake intubation poorly, often exhibiting hypoxaemia, bradycardia, and systemic and intracranial hypertension during nasotracheal or orotracheal intubation. Analgesia and sedation are still used infrequently in nurseries for intubation and other “routine”, but invasive, therapeutic or diagnostic procedures. We recently performed a randomised, double blind, placebo controlled trial to assess whether sedation with midazolam in premature infants would improve physiological stability and the success rate of endotracheal intubation. Eight premature infants underwent 16 intubation procedures after being randomly assigned to one of three groups: I (n = 6) received placebo; II (n = 7) received atropine and placebo; III (n = 7) received atropine and midazolam. Infants could be randomised again to a different group after completion of each intubation procedure. Heart rate, blood pressure, and oxyhaemoglobin saturation were recorded at 10 minute intervals for each infant. The study was terminated when midazolam was required by the endotracheal intubation in neonates, Arch Dis Child Fetal Neonatal Ed 1997;72:F61–4.

Incidence of severe retinopathy of prematurity

EDITOR,—We were interested to read the article of Vyas et al on the incidence of severe retinopathy of prematurity (ROP) in 11 neonatal units in five cities in England in 1994. We have published similar data from eight neonatal units in New South Wales (NSW) Australia in 1993 and 1994. These data were prospectively collected in the NSW Neonatal Intensive Care Unit’s data collection and is stored and maintained in the NSW Centre for Perinatal Health Services Research, University of Sydney, NSW.

For infants of < 29 weeks gestation, there was no significant difference in severe ROP (≥ stage 3) between the five cities in England and NSW (table 1). Unlike Vyas et al., we could not find an association between improved survival and the development of severe ROP. In six of the neonatal units in our study (two have been excluded from this analysis as they are children’s hospitals and have very few small premature infants), survival in infants of < 27 weeks gestation ranged from 51.3% to 68.8%. The percentage with severe ROP for the two units with the lowest and highest survival was 15 (3/20) and 24 (5/21) respectively, while the range of severe ROP in the six neonatal units was 15% (3/20) to 36% (9/25). In infants of 27–28 weeks gestation, survival ranged from 85.1% to 96.7% and the percentage with severe ROP for the two units with the lowest and highest survival was 7 (4/56) and 3 (2/58) respectively, while the range of severe ROP in this group of infants was 2% (1/50) to 7% (4/56) (unpublished observations). We have also shown that, despite an increase in survival of preterm infants following the introduction of surfactant, there was no significant impact on the incidence or severity of ROP.

In infants of 29–31 weeks gestation, six of 443 infants (1.4%) developed severe ROP and one required Cryo/Laser treatment. This infant was 30 weeks gestation with a birth weight of 1305 g. We therefore agree with Vyas et al that there should be no reduction in the upper limit of gestation or birth weight for screening for ROP.

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Blood pressure standards for very low birthweight infants

EDITOR,—Based on careful invasive blood pressure measurements in a cohort of 61 very low birthweight (VLBW) infants in our unit in the first 48 hours of life, Lee et al report on blood pressure standards in this population. The quality of the blood pressure readings was assessed using continuous video recordings during the first wave forms. The inclusion of a relatively large number (n = 28) of extremely low birthweight infants is another strength of this study. In an attempt to define normal blood pressure values in a population that by definition is not “normal”, the authors have excluded very ill infants and infants requiring inotropic support. They have also excluded infants who developed intraventricular haemorrhage (IVH) grades III and IV during the first week of life. They suggest that the lower limits of mean arterial blood pressure (MAP) for infants between 26 and 32 weeks of gestation are numerically similar to the gestational ages. With the exclusion of infants who developed severe IVH, it became impossible to detect any association between blood pressure and IVH. Decreases in cerebral blood flow may play an important role in the pathogenesis of IVH, and, although blood pressure is not a reliable parameter to assess cerebral blood flow, at least two published studies have shown that the incidence of IVH was higher in infants with lower MAP. Perhaps the authors could indicate how many infants...
with IVH grades III and IV were excluded and what blood pressures were recorded in these infants. For similar reasons, it remains uncertain whether the proposed blood pressure standards are applicable to very ill infants or infants who require inotropic support. It is conceivable that cerebral vascular resistance in sick preterm infants differs from that in the study patients, and consequently the application of the suggested blood pressure standards to sick preterm infants would result in different—and possibly inadequate—cerebral blood flows.

The data presented add to our knowledge on blood pressure in VLBW infants, but do not allow the conclusion that the suggested blood pressure standards are safe for all VLBW infants.

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Drs Juin, Rajadurai, and Wee respond:

We would like to thank Dr Berger for his comments. Our objective was to define the different—and possibly would result in different—cerebral blood flows.

The data presented add to our knowledge on blood pressure in VLBW infants, but do not allow the conclusion that the suggested blood pressure standards are safe for all VLBW infants.

PATIENT TRIGGERED VENTILATION IN NEONATAL RESPIRATORY DISTRESS SYNDROME

EDITOR—Baumer reports the results of a large multicentre study comparing the effects of patient-triggered ventilation (PTV) with conventional ventilation (IMV).1 There appears to be no benefit from PTV compared with IMV in death rate, development of chronic lung disease, pneumothorax rates, and cerebral ultrasonographic abnormality. In addition, because of an increased trend toward a higher pneumothorax rate, Baumer concludes that, at present, PTV delivered with either the SLE 2000 or the Dräger babylog 8000 ventilator should be recommended for infants of less than 28 weeks gestation with respiratory distress syndrome (RDS).

However, we are concerned that this may be a premature conclusion given the significant difference in PTV delivered by the two main ventilators used and the potential heterogeneity of clinical practice within the different centres involved, despite agreed ventilation protocols. Dimitriou et al showed that neonates and infants trigger a significantly lower proportion of breaths using the SLE 2000, an airway pressure triggered ventilator that provides synchronised intermittent positive pressure ventilation (SIPPV). Attempts to optimise the trigger rate of the SLE 2000 ventilator by increasing pressure sensitivity often results in an altered trigger rate as discussed by Baumer. Therefore the PTV modes of the two ventilators are substantially different. This prompts us to ask whether the findings of this multicentre study are only applicable to PTV provided by SLE 2000? Would there have been a different outcome if all the triggered babies had received SIPPV?

It is not known how many of the 40/213 babies of less than 28 weeks gestation who had pneumothoraces were receiving SIPPV. As only 11% (52/465) of all triggered babies ever received SIPPV, we surmise that very few of the 40 were ventilated in this way. Is it fair to conclude that the Dräger babylog 8000 has a trend to pneumothorax on SIPPV? In a separate smaller study, Baumer also reports 120 patients in three centres randomly assigned to either the Dräger babylog 8000 or the SLE 2000 ventilator, and found a non-significant trend to higher pneumothorax rate, chronic lung disease, and death for the former group. But we are not told how many of the babies were actually on trigger mode (PTV or SIPPV). Those would all have been receiving IMV or SIMV, or intermittent mandatory ventilation where the baby's breaths, selected during a “time window”, trigger the ventilator with the preset number of breaths.

The results were reported in the way that they were for a reason. The original study design allowed a four way randomisation between the two makes of ventilator and the two modes of ventilation. As was reported, only three centres had enough of both ventilators to allow this to occur. Other centres ventilating infants with the Dräger babylog had a two way randomisation between PTV and IMV.

Therefore the possibility of confounding by differences in practice between centres needed to be excluded. If the centres using the Dräger as well as the SLE 2000 were different, and I agree with their implied statement that, as each trigger ventilator performs differently, results obtained using one ventilator cannot be extrapolated to another. However, both ventilators were used in PT mode (sometimes referred to as SIMV or intermittent mandatory ventilation) where the baby's breaths, selected during a “time window”, trigger the ventilator with the preset number of breaths.

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PTV, patient triggered ventilation; IMV, intermittent mandatory ventilation.

Table 1 Rates of pneumothorax in infants of less than 28 weeks gestation using two different makes of ventilator

<table>
<thead>
<tr>
<th>Ventilator Make</th>
<th>PTV mode</th>
<th>IMV mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dräger without pneumothorax</td>
<td>19 (20%)</td>
<td>20 (%)</td>
</tr>
<tr>
<td>Dräger with pneumothorax</td>
<td>5 (20%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>SLE without pneumothorax</td>
<td>154 (68%)</td>
<td>114 (52%)</td>
</tr>
<tr>
<td>SLE with pneumothorax</td>
<td>35 (14%)</td>
<td>14 (6.5%)</td>
</tr>
</tbody>
</table>

PTV, patient triggered ventilation; IMV, intermittent mandatory ventilation.

during the SLE 2000 in PTV mode in infants less than 28 weeks gestation, but not extend this caution to ventilating infants with the Dräger babylog 8000.

Given that none of these differences were statistically significant, no clear recommendation can be given. This is why the wording used in the publication was “it might be prudent to avoid….”

As regards the number of infants departing from their assigned mode of ventilation, several points should be emphasised. The study protocol permitted changing the mode of ventilation at the discretion of the attending clinicians. This was inevitably interpreted differently by each clinical team. Departure from the assigned mode of ventilation was not an intended outcome, and it is evident that this occurred more commonly in the more immature infants and those that subsequently died. High rates of departure from the assigned mode cannot therefore readily be interpreted as evidence of failure of the assigned mode. Table 2 shows the numbers of infants of all gestations departing from the assigned mode of ventilation.

There was therefore a higher crude rate of departure from the assigned mode of ventilation in infants ventilated with the Dräger babylog 8000, with a similar proportion departing with the SLE 2000 in PTV mode in infants less than 28 weeks gestation, but not extend this caution to ventilating infants with the Dräger babylog 8000.

In summary, there is no evidence from this study of any trend towards better outcomes with the Dräger babylog 8000 ventilator, although the small numbers enrolled make any conclusions less robust. There is evidence that suggests there may have been a short term reduction in pneumothorax rates from the educational package offered at the start of the trial.

In conclusion, there was no convincing evidence of a beneficial effect of a policy of using PTV in preterm infants with RDS with the ventilators used. Regular attention to staff education on ventilator techniques is recommended.

I would like to use this opportunity to pay tribute to the two trial coordinators (Sue Ellis and Tom Mill), to the trial statistician (David Wright), and to the data monitoring committee (David Field and Diana Elfelbourne), whose details were inadvertently omitted from the final paper and without whom, together with the trial collaborators, the study would not have been possible.

Pyridoxine dependent epilepsy: a suggestive electroclinical pattern

EDITOR,—There are several problems with describing the electroclinical pattern in pyridoxine dependent seizures. One is defining the electroclinical features. Until now all published reports (including four of the five cases of Nabbout and colleagues) have described the electroencephalogram (EEG) in neonates who have received other anticonvulsants beforehand. It seems possible that anticonvulsants could affect the EEG, as suggested by the infant with the most pronounced burst suppression pattern in the paper of Nabbout and colleagues. This method of assessing the electrical pattern is on withdrawal, when we, like others, found that a continuous or intermittent high volt slow wave pattern with or without spikes was typical. It would be very useful to know the EEG features of the patient who did not receive any other drugs before pyridoxine, as this would be the first description of the true electrical pattern in pyridoxine dependent seizures.

This study showed that use of EEGs in neonatal units. Very few of the neonates reported in the literature or in the UK study had EEGs before receiving pyridoxine. Presumably this reflects difficulties in obtaining EEGs out of hours or in the absence of a facility attached to the neonatal unit, as well as the desire to treat without delay. As a result, for some neonatal units it may be misleading and (b) early treatment does appear to be beneficial.

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Parental visiting in neonatal units

EDITOR,—We read with interest the paper by Cuttini et al. Although policy on parental visiting is an easier issue to evaluate, parental participation in decision making, particularly in decisions with strong ethical overtones, is much more complex. It is difficult to evaluate with accuracy, and by its nature is much more controversial. The paper does not stress that data collected from each participating unit, through a structured questionnaire completed by the unit coordinator, represent policies—that is, the intention and stance of each unit towards the particular issue for evaluation. Data collected through questionnaires and interviews involving both unit staff and parents would have provided a better understanding of the actual practice of each participating unit.

No unit from Greece took part in the study by Cuttini et al., but Greece is briefly mentioned in the Discussion, using results from a previous study in which, in a sample...
of 38 units from 11 European countries, it was shown that the nine units that imposed visiting restrictions were in France, Greece, Italy, and Portugal.

We would like to provide further information on visiting policy in Greek neonatal intensive care units (NICUs). There are 15, two of which are private; 12 are attached to maternity hospitals and the remaining three are in children’s hospitals and accept distant referrals. Amongst these, only one (Aglaia Kyriakou Children’s Hospital), visiting restrictions are imposed. These allow parents only, and the usual practice is 30 minutes to one hour visiting time in the morning and afternoon (except during mothers). The most common reasons given for imposing restrictions are increased danger of infection and a disruptive effect on the unit.

We conducted a survey, through questionnaire and interview, of parents with a baby who had been cared for in another NICU that imposed visiting restrictions before it was transferred to our NICU and/or parents who had had a previous baby in another NICU that imposed restrictions. The overwhelming majority (98.6%) said that they preferred our liberal policy on visiting. One mother of a preterm baby with bronchopulmonary dysplasia said that “if I had delivered at term I would be with my baby; if I had not delivered prematurely I would also be with my baby (in my womb); now that I have delivered prematurely why can’t I be with my baby?”

We conclude that in Greece there is a demand for unrestricted parental visiting, but most Greek NICUs do not meet this demand for reasons not based on medical or sociological evidence.

It is worth noting that, in Greece, infants beyond the neonatal period have been admitted to children’s wards with their mothers for many years.

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Ureaplasma colonisation and chronic lung disease in neonates

EDITOR.—We read the article by Hannaford et al1 with interest. We would like to point out that in our recent retrospective analysis,2 our finding of the colonisation rate of genital mycoplasmas (Ureaplasma urealyticum and Mycoplasma hominis) in the respiratory tract of premature infants of 27% were similar to those of Mycoplasma hominis


The authors of the paper “Risk adjusted and population based studies of the outcome for high risk infants in Scotland and Australia” Arch Dis Child Fetal Neonatal Ed 2000;82:118-123 have asked us to publish the following corrected version of table 6. The authors apologise for the error.

<table>
<thead>
<tr>
<th>500–999 g</th>
<th>Relative risk of neonatal death</th>
<th>95% confidence interval</th>
<th>1000–1499 g</th>
<th>Relative risk of neonatal death</th>
<th>95% confidence interval</th>
<th>500–1499 g</th>
<th>Relative risk of neonatal death</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scotland vs Australia 1993–94</td>
<td>1.24</td>
<td>1.09–1.42</td>
<td>1.20</td>
<td>0.90–1.61</td>
<td>1.22</td>
<td>1.08–1.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scotland vs Australia 1993–96</td>
<td>1.48</td>
<td>1.35–1.63</td>
<td>1.34</td>
<td>1.09–1.65</td>
<td>1.30</td>
<td>1.18–1.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>England and Wales vs Australia 1994</td>
<td>1.15</td>
<td>1.07–1.24</td>
<td>1.18</td>
<td>1.01–1.39</td>
<td>1.17</td>
<td>1.09–1.25</td>
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<tr>
<td>England and Wales vs Australia 1993–96</td>
<td>1.25</td>
<td>1.19–1.32</td>
<td>1.23</td>
<td>1.09–1.39</td>
<td>1.22</td>
<td>1.16–1.28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dr Gilbert et al respond:

EDITOR.—We thank Drs Bhandari and Hussain for their interest in our paper. We too were intrigued by the apparently contradictory effects of ureaplasma colonisation on the lungs of affected infants and acknowledge that our hypothesis is unsubstantiated. The possibility that a subacute intrauterine infection could stimulate endogenous surfactant production is a plausible explanation for the significantly lower incidence of respiratory distress syndrome (RDS) in these infants. The fact that intrauterine infection is low grade, may also mean that delivery is delayed for long enough for exogenous steroids to take effect.

The development of chronic lung disease (CLD) is dependent on many factors, and, in our study, it correlated less closely with ureaplasma infection than did RDS. We suggested that other effects of multiple gestation outweighed those of ureaplasma infection on the development of CLD in twins. Presumably, the lower rate of RDS in ureaplasma infected singleton infants reduced their risk of CLD, directly or indirectly. If so, there must be other respiratory insults severe enough to offset this effect. We were unable to identify factors associated with CLD beyond from RDS and ureaplasma infection. In particular, the incidence of PDA did not differ between infants with and without CLD.

We postulate that the low grade inflammatory effect of intrauterine ureaplasma infection could cause significant irreversable lung damage and predispose to CLD, as well as stimulating the production of surfactant. The outcome is unlikely to be affected by erythromycin therapy after birth, except in the minority of infants in whom there is frank pneumonitis, with progression after birth.

We have not studied the effects of postnatal steroids, but this is unlikely to be a significant confounding factor than did RDS. We also noted that the time the study was done, steroid therapy was not given until about four weeks of age, when CLD was already established.

Although we agree that further research is needed to confirm our findings, we believe that the inverse relationship between ureaplasma colonisation and RDS was too strong to be dismissed as a statistical aberration.

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EDITOR’S note
References 22–30 of the paper by Hannaford et al were incorrect, and each correlate with the number below in the text. Thus reference 22 in the reference list corresponds with reference 23 in the text, and so on. This correction appears online [lancet.bmj.com/ cgi/content/full/fetalneonatal;81/3/F162/DC1].

The journal would like to apologise for this error.