LETTERS TO THE EDITOR

Survival and place of treatment after premature delivery

SIR,—Dr Field *et al* are not justified in concluding from the data presented that there should be a more centralised service for babies of 28 weeks' gestation or less.¹ They found that babies of 28 weeks' gestation or less treated in large centres had higher survival rates than those treated in smaller units. It is likely that this is due to selection in the smaller units of appropriate babies to refer to the large centres.

Data from our unit, which is in the Trent region, were included in the report. We have a policy of transferring babies of 28 weeks' gestation or less to a regional centre. Two categories of babies are not transferred: firstly babies who are so ill that they do not survive long enough to be transferred or are not likely to survive transfer, and secondly babies who are considered pre-viable. During the time of the study, three babies of 28 weeks' gestation or less were not referred from our unit to a large centre, but remained in our unit for terminal care. These were a second twin of 26 weeks' gestation with severe birth asphyxia and asystole at birth who died at 1 hour 20 minutes after unsuccessful resuscitation attempts, an infant of 24 weeks' gestation, and an infant of 21 weeks' gestation.

During the same period we referred post-natally 12 babies of 28 weeks' gestation or less to a large centre for neonatal intensive care. Four of these babies died. Clearly the difference in outcome for these two groups of babies is due to selection bias.

It is likely that similar decisions were taken in other smaller units in the region and comparison of survival in the two types of units is therefore not valid.

We believe that it is in the interest of selected very immature babies in our unit that we should transfer them to a large neonatal centre for intensive care. The results of this policy will be that those infants of 28 weeks' gestation or less who do not transfer may well be receiving terminal care in our unit. It must not be concluded that these babies would have had a better chance of survival or better care had they been transferred to a large centre.

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1 Field D, Hodges S, Mason E, Burton P. Survival and place of treatment after premature delivery. *Arch Dis Child* 1991;66:408-11.

Dr Field and colleagues comment:

We thank Dr Salfield and his colleagues for their comments. Clearly we were concerned that small neonatal units might retain an excess of babies who were considered to have little chance of survival. It was for this reason we employed a method of disease severity scoring.¹ This approach (as reported in the paper) did not indicate that the group of babies treated in small units were at greater risk of death. However more sophisticated

methods of disease severity scoring are now being developed and these should allow this finding to be confirmed. In addition it will then be appropriate to look at mortality in other gestation groups after correction for disease severity.

1 Patterson CC, Halliday HL. Prediction of outcome after delivery for the very low birth-weight (<1500 g) infant. *Paediatric and Perinatal Epidemiology* 1982;2:221-8.

Birthweight ratio

SIR,—In our five centre study of 429 infants under 31 weeks' gestation, birthweight ratio was strongly related to requirement for ventilation, postneonatal mortality and anthropometry at 18 months, and largely unrelated to neurodevelopmental outcome.¹ Birthweight ratio, defined as birth weight divided by the mean reference birth weight for gestation, was proposed as a more useful outcome guide than growth retardation defined using an arbitrary cut off of the 3rd or 10th birthweight centile.

Recently, Brownlee and coworkers re-examined this concept in 436 infants from Leeds and claimed major discrepancies with our observations.² However, the authors agreed with our findings on the lack of relationship with neurodevelopmental scores (we found only a small deficit in language at 18 months), though neither study examined the prognostic value of birthweight ratio in more mature preterm infants. Brownlee and coworkers did not re-examine our data on long term growth and would not have been able to relate realistically birthweight ratio to post-neonatal mortality as in their study the latter was so low.

Thus the only real area of conflict was over the relationship between birthweight ratio and need for ventilation. We found a strong linear trend—the smallest babies at any gestation requiring most ventilation. The Leeds study did not confirm this. We considered this might have been due to a secular trend in neonatal care since our cohort was recruited prior to that in Leeds. Therefore we elected to retest our findings on a new cohort of 231 babies below 31 weeks' gestation that were recruited during 1989-91 into a dietary study in two of our five previous centres. Using birthweight ratio and days of ventilation as continuous variables, and adjusting for gestation, there was a highly significant fall in duration of ventilation with increasing birthweight ratio, corresponding to an average of over seven days' reduction as birthweight ratio climbed from 0.7 to 1.2 ($p=0.002$). Using the same cut off values for ventilatory duration employed by us and by the Leeds group, of more than 7, 14, or 28 days the significance values for reduced ventilatory requirement with increasing birthweight ratio were 0.06, 0.001, and 0.009 (after adjusting for gestation), despite the smaller sample than in our previous study. We were, however, no longer able to confirm that growth retarded babies were more likely to need ventilation in the first 24 hours. Thus, apart from this, our two centre study reaffirms the results of the previous five centre one.

Possibly some aspect of respiratory management in Leeds accounts for the differences observed; we understand, for instance, that in Leeds ventilated babies are often paralysed, a procedure which was relatively uncommon in the five centres we investigated. We accept that studies on more centres would be valuable.

Nevertheless, our own data, now based on a substantial cohort, have not led us to change our view on the clinical value of birthweight ratio.

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- 1 Morley R, Brooke OG, Cole TJ, Powell R, Lucas A. Birthweight ratio and outcome in preterm infants. *Arch Dis Child* 1990;65:30-4.
- 2 Brownlee KF, Ng PC, Roussounis SH, Dear PRF. Birthweight ratio revisited. *Arch Dis Child* 1991;66:418-21.

Atrial natriuretic peptide and blood volume during red cell transfusion in preterm infants

SIR,—Rascher *et al* conclude that a slow transfusion of less than 10 ml red cells/kg body weight does not cause volume expansion.¹¹ Their plasma volume measurements are derived by subtracting the red cell mass from the total blood volume. The total blood volume was estimated from the red cell mass divided by the packed cell volume. The accuracy of the plasma volume estimations is obviously not only dependent on the accuracy of the red cell mass measurements but also on the accuracy of the packed cell volume measurements. The authors state that in adults whole blood packed cell volume is usually calculated by multiplication of the measured venous packed cell volume by 0.9. In preterm infants the authors agree the whole body: venous packed cell volume may also vary but do not correct for this. The published conversion factor for neonates is in fact 0.87.^{2,3} Furthermore the measurement of packed cell volume is liable to further error due to trapping of plasma between red cells which is dependent on the flexibility of the red cells. Even a mechanised system, such as a Coulter counter, for measuring packed cell volume by deriving a value from the mean corpuscular volume and red cell count is subject to error.

The method used to measure red cell mass is as described by Phillips *et al*,⁴ which depends upon the dilution of fetal haemoglobin by an infusion of adult haemoglobin. The magnitude of the resulting changes in concentrations of fetal haemoglobin is not specified in either work, although the coefficient of variation of the actual assay technique for measuring fetal haemoglobin is stated to be <3.6%.³ One wonders how accurately the small changes in concentration of fetal haemoglobin can be measured.

The study of Rascher and colleagues would have been more reliable if direct measurements of red cell mass and plasma volume had been made independently of each other. As the study stands the estimation of red cell mass is open to question and the measurement of plasma volume is flawed. A simple measurement of a change in the packed cell volume would have been as informative as the calculated changes in derived plasma volumes.

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1 Rascher W, Lingens N, Linderkamp O. Atrial

- natriuretic peptide and blood volume during red cell transfusion in preterm infants. *Arch Dis Child* 1991;66:395-7.
- 2 Mollison PL, Veall N, Cutbush M. Red cell and plasma volume in newborn infants. *Arch Dis Child* 1950;25:242-53.
 - 3 Lawson HC. The volume of blood—a critical examination of methods for its measurement. In: Hamilton WF, Dow P, eds. *Handbook of physiology*. Vol 1. Washington DC: American Physiological Society, 1962:23-49.
 - 4 Phillips HM, Abdel-Moiz A, Jones JG, et al. Determination of red-cell mass in assessment and management of anaemia in babies needing blood transfusion. *Lancet* 1986;i:882-4.

Drs Rascher and Linderkamp comment:

Dr Anthony and Professor Levene have raised important questions concerning the blood volume method used in our study. They point to the following possible pitfalls: (1) the method of red cell mass measurement may not be reliable. We used a method described by Phillips *et al* (that is, dilution of fetal haemoglobin by transfused adult red blood cells).¹ Phillips *et al* report a maximum coefficient of variation of less than 3.6%.¹ In 20 double measurements of fetal haemoglobin we found a mean variability ($V = [A-B]/[A+B]/2$) of 3.4%. This variability may have caused a mean error of a single red cell mass determination of 7%. This is in the range of other red cell mass methods.^{2,3} The variability of fetal haemoglobin measurement and thus the error of red cell mass increases with decreasing fetal haemoglobin. (2) the microfuge packed cell volume has to be corrected for trapped plasma. Trapped plasma is about 2% for neonatal and adult red cells⁴ and can thus be neglected. (3) the whole body packed cell volume differs from the venous (central) packed cell volume. In adults, the body:venous packed cell volume ratio is about 0.91. In full term neonates ratios of 0.87⁵ and 0.90² have been reported, and in severely ill preterm infants ratios of 0.82 to 0.89 have been determined.³ The use of a mean body:venous packed cell volume ratio derived from another study merely changes the blood volumes by a constant factor. The maximum error for blood volume calculation from red cell mass and packed cell volume using a constant ratio of 0.855 for preterm infant is 4%.

As plasma volume measurements may be associated with an error of 6%,⁶ a double label technique using a red cell and a plasma indicator probably does not appreciably increase the reliability of whole blood volume estimation. On the other hand, we agree with Dr Anthony and Professor Levene that the use of a plasma protein label would have been more reliable for plasma volume measurement. However, determination of plasma volume was not the primary purpose of our study. Moreover, Evans blue is no longer commercially available and radioactively labelled proteins are not used any more in newborn infants for ethical reasons.

We conclude that the fetal haemoglobin dilution technique is a reliable method for red cell mass measurement and whole blood volume estimation. As blood volume did not change during transfusion, the increase in red cell mass was certainly associated with a decrease in plasma volume. A simple measurement of a change in packed cell volume would not have been as informative as the estimation of blood volume from red cell mass and packed cell volume.

- 1 Phillips HM, Abdel-Moiz A, Jones JG, et al. Determination of red-cell mass in assessment and management of anaemia in babies needing blood transfusion. *Lancet* 1986;i:882-4.
- 2 Bratteby LE. Studies on erythro-kinetics in infancy VIII. Mixing, disappearance rate and

- distribution volume of labelled erythrocytes and plasma proteins in early infancy. *Acta Soc Med Upsal* 1967;72:249-56.
- 3 Linderkamp O, Betke K, Fendel H, et al. Tc-99m-labelled red blood cells for red cell mass measurement in newborn infants. *J Nucl Med* 1980;21:637-40.
 - 4 Linderkamp O, Meiselman HJ, Wu PYK, Miller FC. Blood and plasma viscosity and optimal hematocrit in the normal newborn infant. *Clinical Hemorheology* 1981;1:575-85.
 - 5 Mollison PL, Veall N, Cutbush M. Red cell and plasma volume in newborn infants. *Arch Dis Child* 1950;25:242-53.
 - 6 Linderkamp O, Mader T, Butenandt O, et al. Plasma volume estimation in severely ill infants and children using a simplified Evans blue method. *Eur J Pediatr* 1977;125:135-41.

Non-invasive assessment of pulmonary arterial pressure in healthy neonates

SIR,—We read with interest the study by Skinner *et al*.¹ We would however, take issue with the statement that the method we used in our study to assess pulmonary artery pressure,² the inverse relationship with the ratio of the time to peak velocity (TPV) of pulmonary artery flow and the right ventricular ejection time (RVET), is less suitable for study of the newborn. The advantage of TPV:RVET ratio as a means of studying physiological changes is that we obtained quantitative data in 100% of our studies. Using tricuspid regurgitation, Dr Skinner *et al* obtained quantitative data in only 22% of term studies and 45% of preterm studies.

Our data suggested that pulmonary artery pressure falls slightly but significantly more slowly in healthy preterm than in term infants.² Dr Skinner *et al* did not find this difference and suggested that factors other than pulmonary artery pressure which can affect TPV:RVET might have influenced our results. We do not believe that to be the case for the following reasons, taking each of these factors in turn. Firstly, that the positioning of the pulsed Doppler sample is critical. We used a constant site in the centre of the artery distal to the pulmonary valve, not technically difficult in early life. Secondly, myocardial function, which if poor will prolong TPV. All infants in the study referred to were healthy and had good myocardial function. Any reduction in contractility resulting from lower gestational age would cause the difference which we found between preterm and term infants to be an underestimate. Thirdly, tricuspid regurgitation, here Dr Skinner *et al* have misread the reference cited. Kitabatake *et al* could find no statistically significant effect of tricuspid regurgitation on the relationship between TPV and pulmonary artery pressure.³ Finally, heart rate, which will slightly reduce TPV:RVET as it increases.⁴ The term babies in our study had a mean heart rate of 129 compared with 143 in those preterm. From the regression analysis provided by the data of Akiba *et al*,⁴ this difference would cause a change in TPV:RVET of 0.005, not likely to affect the significance of our data. For example, between 25 and 36 hours after birth mean TPV:RVET was 0.36 in the term infants compared with 0.29 in the preterms. In addition the difference in heart rate between the two groups remained constant through the study period while the differences in TPV:RVET did not.

Tricuspid regurgitation is a good method for estimating pulmonary artery pressure, so why did Skinner *et al* not find the same differences? While lack of longitudinal data may be part of the problem, the important information missing from this paper is the distribution of gestation within the wide range quoted (28 to 35 weeks) and even more

importantly the gestation of the seven infants in whom longitudinal quantitative analysis was possible. Healthy infants of less than 31 weeks are not common, this tends to bias the selection of infants in this type of study towards higher gestations. Thirty seven percent of the preterm infants in our study were of less than 31 weeks, this may be why we were able to demonstrate a difference.

Tricuspid regurgitation, when present, and TPV:RVET are both good methods for non-invasively assessing pulmonary artery pressure. Like all Doppler methods they both have limitations. Within the practice of paediatric cardiology, where both methods were developed and validated, tricuspid regurgitation has advantages particularly in children with large intracardiac left to right shunts. However, we would argue that a method which allows data collection in only a minority of normal subjects may not be the best for describing physiological changes.

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- 1 Skinner JR, Boys RJ, Hunter S, Hey EN. Non-invasive assessment of pulmonary arterial pressure in healthy neonates. *Arch Dis Child* 1990;66:386-90.
- 2 Evans NJ, Archer LNJ. Postnatal circulatory adaptation in healthy term and preterm neonates. *Arch Dis Child* 1990;65:24-6.
- 3 Kitabatake A, Inoue M, Asao M, et al. Non invasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation* 1983;68:302-9.
- 4 Akiba T, Yoshikawa M, Otaki S, et al. Prediction of peak pulmonary artery pressure by continuous wave Doppler echo cardiography in infants and children. *Pediatr Cardiol* 1988;9:225-9.

Dr Skinner *et al* comment:

We thank Drs Evans and Archer for their comments. There are now three Doppler techniques for assessing neonatal pulmonary arterial pressure: the TPV:RVET ratio, regurgitant tricuspid flow, and the analysis of ductal flow.¹ The TPV:RVET ratio can be measured serially in all infants, but is it as accurate a measure as that provided by tricuspid regurgitation when present and measurable?

If the TPV:RVET ratio is influenced by pulmonary arterial pressure only and it is valid to compare subjects of different size, absolute values can be obtained by imposing Evans' ratios on Kitabatake's regression from adults, which correlates TPV:RVET with pulmonary arterial pressure. However, Evans' ratio of 0.2:1 in preterm infants at six hours implies a mean arterial pressure of 100 mmHg; almost three times average systemic pressure! Similarly, the lower ratios seen in the preterm babies imply higher pressures than in term babies.

As aortic TPV is shortened by mitral regurgitation,² Kitabatake postulated that pulmonary TPV might be shortened by tricuspid regurgitation, and found nine of 11 adult patients with tricuspid regurgitation had TPV values below the regression line for the whole group. Although the regression for patients with tricuspid regurgitation did not differ significantly from this regression, a third of the whole group had tricuspid regurgitation. No comparison was reported between those with and without tricuspid regurgitation.

Serial measurement is clearly the best way to assess the speed with which pulmonary arterial pressure falls, and we presented our serial data on seven preterm babies graphically. They were the same mean gestational age