LETTERS TO THE EDITOR

Pitfalls of meta-analysis

EDITOR,—The article by Lacy and Ohlsson clearly shows how statistical manipulation of figures can produce differing results from the same basic data.¹ The authors with their 'cautious use of meta-analysis' find insubstantial evidence of the benefit of IVIG in either prevention or treatment of neonatal sepsis. Using similar data, Weisman *et al*² found the relative risk of infection if IVIG prophylaxis was not given to neonates to be 2.6 (3.2) (mean (SD)), and a relative risk of death in infected neonates not treated with IVIG to be 3.0 (0.7). The authors explain this difference by suggesting use of 'inappropriate statistical methods' by Weisman *et al*.

Lacy and Ohlsson have heavily pruned published data in search of 'good quality' and 'homogeneity'. In the field of IVIG nothing thus far has been homogenous. All the published data – good or poor quality – have not only differed in entry and outcome criteria but also in basic definitions of variables such as the definition of sepsis and mortality from sepsis. Nor have the authors differentiated between mortality from sepsis and that from unrelated causes or weight groups. Babies that weigh 800 g have a higher mortality from causes other than sepsis than those weighing 2500 g. The authors have also failed to discriminate between studies in which a placebo was used for the control group and studies in which there was no intervention in the control group.

Another bias in this analysis was the uncritical use of the large study by Fanaroff³ which accounts for 46% of the total sample. This study was blinded only in phase I and open in phase II.

As the authors themselves pointed out, the studies differed in dose regimen, duration of treatment, and the IVIG preparation used. However, they fail to point out two crucially important differences between preparations: bioavailability which depends on the method of preparation,⁴ and variability in IgG subclass distribution. IgG subclass distribution in the preparations is of greatest relevance, taking into account the organisms which cause infection in the neonatal period.

Second, Clapp *et al*⁵ and ourselves have clearly shown how important it is to attain and maintain serum IgG above at least 400 mg/dl to be protective – very few studies report or measure serum IgG, thus making any comparison extremely difficult, if not impossible.

It may make statistical sense to reject studies which are not prospective, blinded, and controlled, but it makes a nonsense to compare studies without taking into consideration the very principles on which the whole concept of IVIG is based. Information such as bioavailability of the product, serum concentrations obtained, and well defined outcome measure are crucial principles missing from this meta-analysis. Any conclusions drawn on this basis are therefore questionable to say the least. No clinician would use a subtherapeutic dose of antibiotic, for example, and expect it to be effective. It is clear, however, that well designed, large studies with appropriate IVIG are required.

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- 1 Lacy JB, Ohlsson A. Administration of intravenous immunoglobulins for prophylaxis or treatment of infection in preterm infants: meta-analyses. *Arch Dis Child* 1995; 72: F151-5.
- 2 Weisman LE, Cruess DF, Fischer GW. Current status of intravenous immunoglobulin in preventing or treating neonatal bacterial infections. *Clin Perinatol* 1993; 20: 211-24.
- 3 Fanaroff A, Wright E, Korones S, *et al*. A controlled trial of prophylactic intravenous immunoglobulins to reduce nosocomial infections in VLBW infants. *Ped Res* 1992; 31: 202(A).
- 4 Morell A. Characterization and safety aspects of intravenous immunoglobulin preparations. In: Koch C, ed. *Clinical use of intravenous immunoglobulin*. Copenhagen: FADL Publishers, 1988: 9-15.
- 5 Clapp DW, Baley JE, Kliegman RM, *et al*. Use of intravenously administered immunoglobulin to prevent nosocomial sepsis in low birth weight infants: Report of a pilot study. *J Pediatr* 1989; 115: 973-8.

Drs Lacy and Ohlsson comment:

Dr Haque compares our meta-analysis with the review by Weisman *et al*. In our paper we used generally accepted methods for a systematic overview.¹ Our statistical synthesis included a different set of data than those of Weisman *et al*. We stand by our original statement that Weisman *et al* used inappropriate statistical methods to combine study results – that is, they appear to have combined individual study results by using an arithmetic mean of the relative risks, and thus do not account for study variance which depends on sample size and number of outcomes.

To avoid bias, we used explicit criteria for the inclusion of studies and definitions of outcomes. Regarding Dr Haque's criticism of our use of mortality from all causes other than death from sepsis, we believe that the outcome of death from all causes is less subject to bias than disease specific mortality. Feinstein has recently written that: 'An important scientific advance can occur in meta-analysis ... if the outcomes become confined to total deaths, rather than the inconsistencies and occasional fantasies cited as disease-specific causes of death'.²

Our use of the random effects model for pooling of data gave less weight to studies with large sample size than if we had used the fixed effects model.

Correction

Please note that figure 2 of the paper by Lacy and Ohlsson (*Arch Dis Child* 1995; 72: F151-5) was incorrectly reproduced and should have looked like this:

Figure 2 IVIG prophylaxis: effect on sepsis.

In our discussion we emphasised that the lack of benefit for the prophylactic use of IVIG is based on preparations used to date and that 'new preparations of IVIG with other antibodies or other combinations of antibodies might be effective'.

- 1 Ohlsson A. Systematic reviews – theory and practice. *Scand J Clin Lab Invest* 1994; 54 (suppl 219): 25-32.
- 2 Feinstein AR. Meta-analysis: statistical alchemy for the 21st century. *J Clin Epidemiol* 1995; 48: 71-9.

Neonatal meningitis with human parvovirus B19 infection

EDITOR,—We were interested to read two recent papers by Okumura and Watanabe, on the infection of the central nervous system by human parvovirus B19 (B19) infection.^{1 2} In these cases, the disease manifest at around school age and not during the neonatal period. Three years ago, we encountered a newborn infant who presented with meningitis and persistent anaemia, presumably related to B19 infection.

Case report

A 20 day old girl was admitted with high fever (39.8°C). She had been born by normal vaginal delivery, and showed uneventful growth until poor feeding developed on the 17th day of life. On the day of admission, the infant's mother had had low grade fever, joint pains, a rash on all four limbs and headache. Both the infant and the mother had had close contact with the infant's 5 year old brother, who had had erythema infectiosum 17 days previously. Her peripheral leucocyte count was $10.2 \times 10^9/l$, erythrocyte count $3.91 \times 10^{12}/l$, and haemoglobin 127 g/l. A cerebrospinal fluid (CSF) sample indicated severe pleocytosis (861×10^3 leucocytes/ml, with 57% lymphocytes and 43% neutrophils), along with 23×10^3 red cells/ml, protein 0.54 g/l, and glucose 2.7 mmol/l. Serum anti-B19 IgG and IgM tested by enzyme linked immunosorbent assays (SRL commercial assay) were positive in both the infant and the mother. Routine cultures of CSF, blood, and throat swabs yielded no pathogenic growth. Aseptic meningitis were diagnosed, and antibiotics (imipenem, cefotaxime, and amikacin) and gamma globulin were started. Her fever

abated on the 4th day in hospital and her CSF returned to normal on the 12th day. However, her haemoglobin concentration which had been 117 g/l on the 4th day fell to 90 g/l by day 36; the haemoglobin concentration and the reticulocyte count improved gradually and returned to normal on day 73. There were no increases in serum antibody titres for measles, herpes simplex, mumps, rubella, cytomegalovirus, enterovirus 70/71, mycoplasma, toxoplasma, or chlamydia. She was discharged on the 21st hospital day without sequelae.

Unfortunately, we could not make a definitive diagnosis of B19 infection by polymerase chain reaction (PCR), hybridisation, etc, at that time, but we suppose that the acute manifestations of fever, meningitis, and anaemia are more likely to have been related to the B19 infection because B19 IgM was detected in serum, and because the mother simultaneously developed adult type B19 infection. Epidemiologically, the source of infection was thought to be the brother, considering that the incubation period for B19 infection is 17 to 18 days.³

Prenatal B19 infection could cause severe complications such as a hydrops fetalis, but the outcome of primary B19 infection in newborns is still unknown.

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- 1 Okumura A, Ichikawa T. Aseptic meningitis caused by human parvovirus B19. *Arch Dis Child* 1993; 68: 784-5.
- 2 Watanabe T, Satoh M, Oda Y. Human parvovirus B19 encephalopathy. *Arch Dis Child* 1994; 70: F71.
- 3 Anderson MJ, Higgins PG, Davis LR, et al. Experimental parvovirus infection in man. *J Infect Dis* 1985; 152: 257-65.

Outcome of triplet pregnancies

EDITOR,—The incidence of triplet and higher order pregnancies has more than doubled since 1980 as a result of new techniques for the treatment of infertility. Because of the high incidence of prematurity, triplets are at a high risk of neonatal complications and death. The poor reproductive histories of some mothers treated for infertility has led to the suggestion that such triplets carry a poorer prognosis than those naturally occurring, possibly as the result of earlier delivery.

Since 1980, 41 sets of liveborn triplets have been admitted to the Mersey Regional Neonatal Unit, Liverpool. Twenty eight sets were natural, and 13 the result of fertility treatments (six ovulation induction, six IVF, and one GIFT). The mean gestational age at delivery was 30.2 weeks in the natural triplets and 30.3 weeks in the others. There were five deaths in both groups; seven infants in the natural group and two in the infertility group have survived with major disabilities (cerebral palsy and/or blindness). Survival without major disability was not significantly different between the two groups (86% natural *v* 82%). However, only 75% and 61% triplet pregnancies admitted, respectively, resulted in three live children without subsequent disabilities.

It remains important to counsel couples undertaking infertility treatments concerning the morbidity and mortality associated with

higher order pregnancies, but such risks are probably not greater as the result of mode of conception, but, rather, relate mainly to prematurity.

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Acute blood pressure response to surfactant administration

EDITOR,—Saliba *et al* reported a significant increase in cerebral blood flow velocity (CBFV) and transcutaneous carbon dioxide tension (TcPCO₂) following rapid instillation of surfactant.¹ The rise in CBFV was related to, but not solely explained by, the increase in TcPCO₂. They found no alteration in one minute averages of mean arterial blood pressure (MABP). It is reasonable to expect that swings in systemic blood pressure could be caused by rapid intratracheal administration of surfactant and we would like to offer an explanation as to why the current method of measuring short term blood pressure change may obscure potentially important information.

All infants in our neonatal intensive care unit have continuous physiological variables transferred from a multiparameter monitor to a cotside computer,² and displayed in real time. Using this system to display second by second data during surfactant administration, we often detect significant blood pressure surges which can be biphasic in character and could therefore be obscured by looking at the mean change in pressure over a selected time period.

The figure shows the blood pressure trace from an infant receiving Exosurf as an infusion over five minutes. Each data point is a one second value and a total of 21 minutes is displayed. The trace is analysed as three equal time periods: before, during, and after

surfactant administration. If analysis were confined to mean values for each period of five minutes, the finding would be a 1 mm Hg fall in MABP during, and a rise of 4 mm Hg after, administration. These findings would not be impressive. However, detailed analysis within the time periods of administration shows a drop in MABP of 10 mm Hg below the pre-treatment baseline followed by a rise in MABP of 12 mm Hg above the baseline. An overall swing in MABP of 22 mm Hg against a background MABP of 33 mm Hg would certainly be considered important.

It is our frequent observation that administration of surfactant can provoke significant fluctuations in blood pressure which may be overlooked when examining mean changes alone.

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1 Saliba E, Nashashibi M, Vaillant M-C, et al. *Arch Dis Child* 1994; 71: F174-8.

2 Bass C, Badger P, McIntosh N. Mary 3 - a new generation computerised neonatal monitoring system. In: Lafeber HN, ed. *Fetal and neonatal physiological measurement*. Amsterdam: Elsevier Science Publishers, 1991: 187-90.

Dr Grantly Dick-Read

EDITOR,—Grantly Dick-Read's contribution to obstetrics was not limited to the labour ward.¹ His books shifted the emphasis in antenatal education from mothercraft to preparation for childbirth, with its emphasis on physiology and informed choice. These, together with the antenatal classes developed by his second wife, Jessica Bennett, are the basis of most antenatal preparation today.

In 1956 a group of mothers influenced by Dick-Read's work formed a charity to