Readmission of neonates

R Scott-Jupp

Commentary on the papers by Oddie et al (see page 119) and Escobar et al (see page 125)

Two papers coincidentally submitted to Archives from opposite sides of the Atlantic give an opportunity to point out some interesting similarities and differences in the controversial area of hospital readmission shortly after birth. Clinicians in both the UK and the USA are concerned about the knock-on effects of the increasing trend towards earlier neonatal discharge from hospital.

The studies differ significantly in their objectives and methods, so direct numerical comparisons may not be valid. Oddie et al looked at over 10 000 births in the Northern NHS region of the UK in 1998, excluding infants less than 33 weeks gestation. They concentrated on factors associated with early neonatal discharge and readmission, nor did social deprivation have an influence. Indeed, the only significant independent associations they found were breast feeding with reduced readmission rates, and lower gestation with increased rates. They did not study factors such as community support and postnatal visits, but there was considerable variation between the five hospitals in the study. Clinical reasons for readmission were, as expected, a broad range of postnatal problems, probably including a nebulous group of “parental anxiety” admissions with no firm diagnosis; about 9% were primarily because of jaundice.

Escobar et al looked at a different range of factors influencing readmission in the first two weeks. As in the UK study, lower gestations were more likely to be readmitted (including those that had avoided the neonatal intensive care unit), as were those who were sicker at birth. They did not look at feeding mode, but were able to determine which had received home health visits or had attended outpatients: those who had been visited at home in the first 72 hours after discharge were less likely to be readmitted, unless they had also attended outpatients, in which case readmission was more likely. Presumably this latter category reflects a more vulnerable group. Analysis of race revealed that African-American infants were less likely to be readmitted: if, as is often suggested, race in the USA is taken as a proxy for social deprivation, then this represents an interesting difference from the UK study. Asian infants were more likely to be readmitted, but this was almost entirely explained by jaundice. Again, the diagnoses leading to readmission were as expected, but jaundice was the reason in 34%, much more frequent than in the UK study. This difference is unlikely to be completely explained by the inclusion of more preterm infants in the US study.

Management of early neonatal jaundice has been the subject of recent reviews, and clearly practice varies between institutions and between nations. American practice may be much more cautious in preventing high bilirubin levels. However, as discussed by Escobar et al, home phototherapy has an important role here.

A major difference between the two countries is the statutory provision in the UK of a community based midwifery and health visiting service. These two professions are largely non-existent in the USA. The American study found fewer readmissions for those who received a home visit as part of their KPMCP “package”, and this might be analogous to the British postnatal midwife’s visit. Unfortunately the UK study had no data on postnatal visits, nor on their communities’ policies in this area. It cannot be assumed that postnatal home visits will always reduce readmission rates: where the parent’s anxiety exceeds that of the health professional it may do so, but where the parent had been unconcerned and the professional detects a problem, it may have the opposite effect.

A strikingly consistent theme in both studies is the huge variation in readmission rates between neighbouring hospitals. This actually accounts for more of the variation than the “biological” factors already discussed. This is not apparently explained by differences in the degree of social deprivation in the populations served. It is difficult to identify reasons for this: associations with institutional characteristics looked for in the US study were weak and inconsistent, although availability of home phototherapy appears to have some influence. Presumably, in both countries, traditional policies and practices vary between institutions for historical reasons that may have nothing to do with their patient population profile.

From the perspective of a manager or health economist, it might appear that if all institutions could adopt the practices of those with the earliest discharge and lowest readmission rates, then major financial savings could be made. However, we should be cautious about going down this road on the basis of these data, as we know nothing about outcomes, including, possibly, rare but potentially avoidable death and disability; moreover, pressure to send newborns home early, and then to avoid readmission at all costs, may add to the turmoil and anxiety experienced by some vulnerable families that we are unable to quantify.

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The introduction of neonatal screening programmes for congenital hypothyroidism in the 1970s is now regarded as a highly cost effective strategy to detect the commonest congenital metabolic disorder seen in the newborn (1 in around 4000 births). There is no doubt that early diagnosis and treatment of the condition has led to the disappearance of mental retardation, which was the most dramatic long term sequel of congenital hypothyroidism. However, it has been clearly recognised that persistent selective impairments may still occur in these children, such as language delays, minor motor problems, visuospatial defects, and attention problems. Also, postnatal somatic abnormalities including an accelerated cranial growth and delayed bone age to 3 years have been observed, especially in children given high starting doses of levothyroxine. Initially, starting doses of thyroxine were in the range of 8–10 μg/kg/day, but the dose was later revised upwards to 10–16 μg/kg/day.

There is clearly a need to define the optimal dose of T4 to initiate therapy as well as the desirable levels of serum T4 to be achieved during long term therapy. This subject was recently discussed by Rovet, who indicated that a number of studies (for example, Bongers-Schokking et al and Dubuis et al) have shown that a higher dose is beneficial in closing the IQ gap between moderate and severe forms of the disease. However, she has previously recorded a possible increase in neurobehavioural disorder in children who have received higher dose regimens of thyroxine. Furthermore, hyperthyroxinaemia in rodents has been associated with adverse neurodevelopmental effects. What current data are available to substantiate the practice of higher dose initial thyroxine therapy? Distinction must be made between the initial serum T4 at diagnosis, the starting dose of T4, and the maintenance serum levels of thyroid hormones in the outcome assessment. Two recent studies emphasise the importance of the initial serum T4. Ng and colleagues found that the initial T4 was an independent factor (inversely related) in the control of head growth in the first three years in 125 subjects with congenital hypothyroidism (CH). In 31 CH subjects studied at 4 years of age, a higher baseline T4 was one of the main predictors of increased verbal IQ but, interestingly, levothyroxine dose at the beginning of treatment and thyroid hormone levels during treatment did not relate to IQ outcome. In relation to the initial starting dose of T4, Gauchard and colleagues showed in 17 patients that early normalisation of TSH (before 3 months) was necessary to allow for normal neurosensorial afferent pathway development (vestibular, proprioceptive), as well as pathways of central integration (cerebellum, vestibular nuclei). The Norwegian study of 49 patients showed that the initial T4 dose predicted verbal IQ at age 20, but the authors have expressed concern at some negative associations between high dose treatment and developmental outcome. Nevertheless, a recent Cuban study of 100 CH children studied at 8.2 years showed that total IQ was related to the initial T4 dose. A careful study by Simonneau-Roy and colleagues showed that children with severe CH treated early with a high dose (median 12 μg/kg/day) of levothyroxine had normal global development and behaviour at school entry. However, as these authors noted, the number of subjects was small, indicating the need for further studies. The Norwegian workers have now extended their study of the 49 subjects referred to above in an attempt to describe the psychological problems in these young adults and to evaluate any negative effects of high dose thyroxine replacement therapy. The results indicate that the CH group, perhaps not surprisingly, had lower performance levels than their sibling controls for some aspects of memory and attention, and had more behaviour problems. Importantly, a high T4 starting dose (≥7.8 μg/kg/day) had no adverse effect on outcome at age 20. Furthermore, there was no deleterious effect of higher T4 levels during infancy, early childhood, or at assessment on the higher order cognitive skills. This study, which divided the initial treatment T4 dose into two groups similar to the Toronto workers, adds significant evidence that a high starting dose of T4 in CH is not harmful in the long term and may be beneficial in some outcome measures.

There are other physiological factors to be considered in relation to thyroxine delivery to developing neural tissue. The fetus with CH derives its T4 mostly from the mother through gestation. Details of the transplacental passage of the hormone are certainly incomplete, but the role of the deiodinase enzymes, particularly type 3, in acting as “a gatekeeper” in this process is under intensive study. Variations in the rate of different areas of brain development during gestation and their detailed response to T4 in marginally hormone deficient situations are further factors which cause abnormal brain morphology at birth. In addition, the complexity of thyroid hormone action in the developing brain is compounded by temporal and regional variations in metabolism, receptor and gene expression. On a practical level the maternal thyroid hormone supply to the fetus is dependent on the iodine supply which may be precarious.

It is probable that the classification of CH into mild moderate and severe, for example, is too simplistic in relation to brain architecture and may account for variation in outcome in children with similar initial hormone levels. Hence it is not surprising that studies in children using psychological outcomes will have differing specificities and sensitivities. From the available clinical evidence, to which the study of Oerbeck et al has contributed significantly, it would appear that the starting dose of levothyroxine should be higher rather than lower. From a cost effectiveness point of view, the higher dose may be justified in the longer term. However, it is important to remember that any increased risk of developing adverse effects is not only dependent on the dose of levothyroxine but is also related to the existing iodine status of the population. Further research is needed to address these issues.
than lower, and that the long term risks of adverse psychological performance are small. A large scale multicentre study is indicated to clarify the concerns of the “low dose” group of investigators. Meanwhile advances in our understanding of thyroid hormone action on the developing brain will improve our ability to make these important clinical judgements.


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Health care

The evolution of paediatric hospitals

R B Goldbloom

Commentary on the paper by Ogilvie (see page 138)

The words “hospice”, “hostel”, and “hospital” share the same etymological root. In ancient times, the aged and infirm were often admitted to a monastic unicellular roots. In health care, as in life, old traditions die hard.

The mere idea of a hospital dedicated exclusively to the care of children is a relatively recent concept. In the mid-19th century, Charles Dickens was a vigorous campaigner for the support of such a hospital in London—specifically, for The Hospital for Sick Children, Great Ormond Street. In Our Mutual Friend, published in 1868, he provided one of the first literary references to an exclusively paediatric hospital.1 He describes how Mrs Boffin persuades an elderly woman to seek good care for an ill child:

“We want to move Johnny to a place where there are none but children; a place set up on purpose for sick children; where the good

doctors and nurses pass their lives with children, talk to none but children, touch none but children and comfort and cure none but children.

‘Is there really such a place?’ asked the old woman with a gaze of wonder.”

Dickens later describes how the child was permitted the comfort of bringing favourite toys to the hospital:

“At the Children’s Hospital, the gallant steed, the Noah’s Ark, the yellow bird and the officer in the Guards were made as welcome as their child owner.”

The early ancestors of the modern paediatric hospital (now, in many cases, wisely renamed health centres) included the foundling hospitals, best known for interminable stays, high mortality, and for being the sites where psychosocial deprivation, or “failure to thrive” was first identified as a clinical entity. The paediatric hospital’s ancestry also includes isolation hospitals for
Maternal phenylketonuria: the importance of early control during pregnancy

R Koch

Commentary on the paper by Lee et al (see page 143)

Dr Lee, Ridout, Walters, and Cockburn have reviewed data on 228 pregnancies occurring in women with phenylketonuria (PKU). This paper provides important data which support the main findings of the Collaborative Maternal PKU Study sponsored by the National Institute of Child Health and Human Development in Bethesda, Maryland, USA. Despite the fact that the data of Dr Lee et al are based on pregnancies occurring only in the United Kingdom, the findings verify two of the most important findings in our longitudinal, prospective study, which collected data from three different countries: the United States, Canada, and Germany. In any international study such as the latter, cultural and social differences can always interfere with statistical analyses. Therefore the fact that both studies support and concur that pregnancies in control by the first 10 weeks of pregnancy resulted in normal intellectual development in the offspring at 6–8 years is important information. Furthermore, both studies observed that the occurrence of congenital heart disease in the offspring of women in good metabolic control very early in pregnancy was reduced to 1–2%.
compared to 14–17% in those not in good control.

It is true that the numbers in the British study are smaller than those in the Collaborative Study and alone would not satisfy strong biostatistical evaluation. Only 32 offspring had IQ data at 8 years, whereas in the latter study, follow up data at 6–8 years of age were examined in 231 children.

It is also true that the two studies were organised in a different fashion and yet arrived at similar conclusions. The British study was based on a registry, which was analysed retrospectively for significant outcomes, whereas the Collaborative Study was longitudinal in nature and based on a specific protocol. It is remarkable that the results coincide on the major outcome data.

In reviewing both published studies, it is clear that a public health effort will have to be mounted to further improve outcome. For example, only some 50% of the women were treated before conception. While we currently look on this as significant progress, future studies will undoubtedly show more improvement as we begin to deal primarily with women of normal intelligence. The two reports involve a significant number of women with IQs of 85 or below. For discussion purposes, let us assume that the IQs in the British mothers were similar to those of mothers in the Collaborative Study. If so, 51% of the women with PKU reported in the Collaborative Study had documented IQ assessments of less than 85 on the Wechsler Adult Intelligence Scale. This significant reduction in maternal IQ in both studies is undoubtedly related to the diet discontinuation phase of treatment occurring in many countries during the period between 1965 and 1985. Today diet continuation for women with phenylketonuria is accepted procedure for most countries. Therefore future studies hopefully will be based on outcome in women with normal intelligence. It is my opinion that the availability of mutational data will aid us in selecting women with PKU who definitely must remain on a phenylalanine restricted diet, especially during their childbearing years.

The future use of tetrahydrobiopterin (BH4) in the treatment of pregnancies either alone or in combination with phenylalanine restriction in the mother’s diet also offers hope for improved fetal outcome. The IQ spread in the mothers evaluated in the Collaborative Study was 58–130. There were 48 women in the Collaborative Study who had mild hyperphenylalaninaemia. In the evaluation of the offspring of these 48 women, 40 of whom were untreated and eight of whom were treated with a phenylalanine restricted diet, Levy et al reported that the mean IQ of the 6–8 year old offspring was 102.3. No significant difference in IQ was found between the offspring of the women who were untreated and those who were treated. Future studies may document that treating women with PKU hopefully will produce a better fetal outcome in these pregnancies.

In conclusion, it is for future investigators to verify these new treatment modalities, and perhaps BH4 will prove useful in improving intellectual outcome even in women with classical PKU with two severe mutation of the phenylalanine hydroxylase gene.


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