

ARCHIVES OF DISEASE IN CHILDHOOD

This issue live
and online
www.archdischild.com

Leading article

Assessing outcomes in twin-twin transfusion syndrome

The incidence of monozygotic twinning is three to five per 1000 births, and around two thirds are monochorionic diamniotic twins resulting from division of the early cell mass some three to eight days after fertilisation. Up to one third of monochorionic twin pregnancies are affected by twin-twin transfusion syndrome (TTTS) and this largely accounts for the three to five times higher perinatal mortality and morbidity in monochorionic twins than dichorionic ones.

The original clinical concept of TTTS was that intertwin vascular anastomoses in the monochorionic placenta caused anaemia and growth restriction in the donor twin, whereas polycythaemia and circulatory overload occurred in the recipient. The diagnostic neonatal criteria were an intertwin haemoglobin difference of > 5 g/100 ml and a birthweight discrepancy of $> 20\%$.

Ultrasound diagnostic criteria are now based on presentation in the second trimester with discordant amniotic fluid volume (oligo/polyhydramnios sequence) in monochorionic placentation. Oliguria in the donor twin results in oligohydramnios, which in extreme cases leads to the fetus becoming tightly enwrapped within its membrane and trapped or stuck against the uterine wall ("stuck twin syndrome"). The bladder and stomach are not visible in anhydramnios. The recipient twin develops hypervolaemia, polyuria, and polyhydramnios with a distended bladder. Hydrops and right sided heart failure with tricuspid regurgitation may occur.

Intertwin vascular anastomoses are normal in monochorionic placentas consisting of superficial artery to artery and vein to vein channels within the chorionic plate, and arteriovenous links within shared cotyledons (deep anastomoses). Up to one third of monochorionic twin pregnancies are affected by TTTS, and the probable reason why most escape this condition is that the shunt of blood between twins is bidirectional and balanced.¹ Indeed, the occurrence of superficial artery to artery anastomoses detected by colour Doppler was lower in monochorionic twin pregnancies affected by TTTS compared with unaffected pregnancies.²

The mortality of untreated TTTS presenting in mid-trimester is 80–100% and includes fetal death and neonatal mortality associated with preterm birth. Neonatal morbidity and longer term neurodevelopmental problems result from complications of preterm birth, and from the haemodynamic disturbance of the syndrome itself. Intra-uterine management options include serial amnioreduc-

tion, amniotic septostomy, laser ablation of placental vessels, and selective fetocide. Given these choices, it is important that short and long term outcomes are carefully monitored, and that we learn more about causal mechanisms of morbidity.

Two papers in this issue of the *Fetal and Neonatal Edition* illustrate some of the difficulties in interpreting outcome data. The study of Cincotta *et al*³ is based on the ultrasound diagnosis of discordance in amniotic fluid volume between the two sacs in monochorionic twin pregnancies, whereas Seng and Rajadurai⁴ rely on neonatal diagnostic criteria.

The use of neonatal criteria to identify TTTS highlights only the mild end of the disease spectrum. More importantly, neonatal criteria may be satisfied in the absence of TTTS. For example, discordant growth may be unrelated to TTTS and can occur in both monochorionic and dichorionic twins, with polycythaemia rather than anaemia as a feature in the growth restricted twin. Even in TTTS correctly diagnosed in mid-trimester the intertwin haemoglobin discrepancy at birth may be less than 5 g/100 ml.

As Cincotta *et al*³ based their diagnosis of TTTS on mid-trimester fetal ultrasound criteria, the liveborn infants in their study were more immature and had a higher neonatal mortality than the infants studied by Seng and Rajadurai.⁴ The use of gestational age matched control infants, however, did not reveal a significant excess of neonatal mortality or respiratory morbidity among their infants with TTTS, indicating the importance of preterm birth in generating neonatal problems.

CARDIORESPIRATORY MORBIDITY

Cardiorespiratory morbidity in preterm infants with TTTS embraces diverse problems including surfactant deficiency, structural pulmonary immaturity or hypoplasia, persistent pulmonary hypertension, pulmonary oedema, and hyperviscosity syndrome. The role of TTTS in the pathogenesis is multifactorial and the contribution of the haemodynamic disturbance per se is difficult to assess. The timing, pace, and volume of intertwin transfusion and haemodynamic disturbance probably varies between pregnancies. Indeed, the haemoglobin discrepancy measured by cordocentesis at the time of diagnosis may be surprisingly small or non-existent.^{5,6}

We are hampered by the lack of a suitable experimental animal model to explore the effects of TTTS on cardiorespiratory morbidity. Seng and Rajadurai⁴ have attempted to distinguish an acute form of TTTS based on neonatal

indicators of a haemodynamic disturbance such as tachycardia and hypotension. The validity of this interesting yet simple approach is unclear and it remains to be seen whether it truly distinguishes a group of infants with TTTS whose outcome is driven by a relatively brief and severe intertwin transfusion shortly before delivery.

There may be longer term implications of the haemodynamic disturbance. Recent observations of twins during infancy who had suffered TTTS showed raised pulse wave velocities and presumably reduced arterial distensibility in the brachioradial arteries of the donor twin compared with the recipient. In contrast, co-twin discordance for pulse wave velocities was not observed between the heavier and lighter twin in monochorionic twins who did not have TTTS, nor in dichorionic twins.⁷ The authors hypothesise that cardiovascular adaptation of the fetus to hypovolaemia may alter the physical properties of the artery (vascular remodelling), and this may result in persistent functional vascular abnormalities that increase cardiac afterload and may adversely influence longer term cardiovascular health.

NEURODEVELOPMENTAL OUTCOME

It is the risk of long term neurodevelopmental disability that generates much of the interest in TTTS. The increased risk of cerebral palsy in twins which is not explained solely by preterm birth or low birth weight applies especially to monochorionic twin pregnancies with or without TTTS. It is well known that intrauterine death of one of the pair of monochorionic twins increases the risk of cerebral palsy in the co-twin, and a recent study highlighted the magnitude of that risk.⁸ The prevalence of cerebral palsy in same-sex co-twin survivors where the other had died in utero was 106 per 1000 whereas the corresponding incidence in different-sex survivors was 29 per 1000. The prevalence of other cerebral impairments was substantial but similar in the two groups (114 and 118 per 1000 respectively). The authors concluded that the overall risk of any serious cerebral impairment in a surviving twin when the other has died in utero is at least 20%, and, in truly monochorionic twin pregnancies where one has died in utero, the risk may be as high as 40%. These findings need to be put in perspective in that most twin gestations that culminate in neurodevelopmental disability in one twin are not associated with fetal death of the co-twin.

Epidemiological studies on the long term outcome of twins are important, but they shed only limited light on the role of TTTS in the pathogenesis of neurodevelopmental disability. By the time cerebral impairments become manifest, the brain of the preterm infant has become exposed to an array of possible insults around the time of birth and in the neonatal period.

White matter damage presumed to be of antenatal origin has been observed on early neonatal brain scans in 30% of monochorionic twins compared with only 3% of dichorionic twins.⁹ Although TTTS was not a necessary factor, there was an association between brain lesions and multiple placental anastomoses and intrauterine death of a co-twin. In another series of twin pregnancies complicated by TTTS severe enough to require amnioreduction, 35% (11 of 31) had early lesions that were said to have been acquired antenatally and these were present in both donor and recipients.¹⁰ However, only one infant had cerebral infarction with appreciable tissue loss, the remainder having less severe lesions including subependymal pseudocysts, white matter cysts, basal ganglia echodensity, mild ventricular dilatation, and lenticulostriate vasculopathy which was originally described in association with TTTS by de Vries *et al.*¹¹

In the paper by Cincotta *et al.*,³ periventricular leucomalacia or cerebral atrophy was observed on brain scans in

17% of survivors, but no lesions were present on the initial scans in the first days of life. Therefore some or all of these lesions may have been acquired after birth rather than representing antenatal ischaemic lesions directly attributable to the haemodynamic disturbance of TTTS.

Explanations of the pathogenesis of white matter damage in TTTS must take into account the fact that both donor and recipient are vulnerable, the incidence of brain lesions is higher in monochorionic twins than dichorionic twins even in the apparent absence of TTTS, and, after intrauterine death, the co-twin in monochorionic twin pregnancy is vulnerable to brain lesions.

Death of a co-twin may be associated with embolism of placental material or detritus to the cerebral circulation of the living fetus, or disseminated intravascular coagulation triggered by thromboplastins from the dead fetus. However, a more likely cause of damage is haemorrhage into the dead twin resulting in severe hypotension and cerebral ischaemia in the survivor.

When both twins survive, antenatal brain damage in the donor twin may occur as a result of cerebral hypoxia-ischaemia triggered by hypovolaemia, hypotension, and anaemia; hyperviscosity in a severely growth retarded donor twin will cause a reduction in cerebral blood flow and may be associated with cerebral venous thrombosis and reduced cerebral perfusion pressure.

The recipient twin is at risk of hypervolaemia and cardiac failure, often with tricuspid regurgitation and right outflow tract obstruction. On first principles, this in itself would probably be sufficient to impair cerebral perfusion pressure especially against a background of raised central venous pressure.

It is possible that the relative abundance of superficial anastomoses in monochorionic pregnancies unaffected by TTTS, while promoting balanced shunting also provides the conduit for relatively acute haemodynamic disturbances which may explain the pathogenesis of cerebral ischaemic lesions in monochorionic twins in the absence of TTTS (or oligo/polyhydramnios sequence).

The extent to which umbilical cord compression or distortion contributes to produce ischaemic white matter damage in oligo/polyhydramnios sequence is unknown. Subtle biological mechanisms may contribute to the pathogenesis of brain damage in monochorionic twin pregnancy with or without overt TTTS. For example, measurement of proinflammatory cytokine activity in donor and recipient twins to explore a possible relation to white matter damage would seem to be a worthwhile study.

Knowing when and how cerebral lesions detected on brain scans arose is an important issue given that specialists in fetal medicine are engaged in a debate about the appropriate management of oligo/polyhydramnios sequence. Intrauterine procedures carry a risk of unintentional fetal loss, and so the possibility of causing harm to survivors should not be lightly dismissed.

If we are to learn anything from randomised trials comparing different management regimens, then firstly there is the need to critically assess the severity of oligo/polyhydramnios sequence before treatment.¹² Secondly, neonatal outcomes should include agreed clinical and Doppler flow criteria for assessing cardiorespiratory adaptation during the first few hours of life, a critical appraisal of the nature and severity of neonatal "respiratory distress", and early ultrasound brain scans to assess antenatally acquired cerebral lesions.

MALCOLM CHISWICK

*St Mary's Hospital for Women and Children, Whitworth Park,
Manchester M13 0JH, UK
m.chiswick@man.ac.uk*

- 1 Bajoria R, Wigglesworth J, Fisk NM. Angioarchitecture of monochorionic placentas in relation to the twin-twin transfusion syndrome. *Am J Obstet Gynecol* 1995;172:856-63.
- 2 Denbow ML, Cox P, Talbert D, Fisk NM. Colour Doppler energy insonation of placental vasculature in monochorionic twins: absent arterio-arterial anastomoses in association with twin-to-twin transfusion syndrome. *Br J Obstet Gynaecol* 1998;105:760-5.
- 3 Cincotta RB, Gray PH, Phythian G, Rogers YM, Chan FY. Long term outcome of twin twin transfusion syndrome. *Arch Dis Child Fetal Neonatal Ed* 2000;83:F171-6.
- 4 Seng YC, Rajadurai VS. Twin transfusion syndrome: a five year review. *Arch Dis Child Fetal Neonatal Ed* 2000;83:F168-70.
- 5 Fisk NM, Borrell A, Hubonont C, Tannirandorn Y, Nicolini U, Rodeck CH. Fetofetal transfusion syndrome: do the neonatal criteria apply in utero? *Arch Dis Child* 1990;65:657-61.
- 6 Saunders NJ, Snijders RJ, Nicolaidis KH. Twin-twin transfusion syndrome during the 2nd trimester is associated with small intertwin hemoglobin differences. *Fetal Diagn Ther* 1991;6:34-6.
- 7 Cheung YF, Taylor MJO, Fisk NM, Redington AN, Gardiner HM. Fetal origins of reduced arterial distensibility in the donor twin in twin-twin transfusion syndrome. *Lancet* 2000;355:1157-8.
- 8 Pharoah POD, Adi Y. Consequences of in-utero death in a twin pregnancy. *Lancet* 2000;355:1597-602.
- 9 Bejar R, Vigliocco G, Gramajo H, et al. Antenatal origins of neurologic damage in newborn infants. II. Multiple gestations. *Am J Obstet Gynecol* 1990;162:1230-6.
- 10 Denbow ML, Battin MR, Cowan F, Azzopardi D, Edwards AD, Fisk NM. Neonatal cranial ultrasonographic findings in preterm twins complicated by severe fetofetal transfusion syndrome. *Am J Obstet Gynecol* 1998;178:479-83.
- 11 de Vries L, Beek F, Stoutenbeek P. Lenticulostriate vasculopathy in twin-to-twin transfusion syndrome: sonographic and CT findings. *Pediatr Radiol* 1995;25:41-2.
- 12 Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. *J Perinatol* 1999;19:550-5.

John Emery Tribute Evening

Time: 6pm followed by drinks reception
Date: Wednesday 29 November 2000
Place: The Manson Lecture Theatre, The London School of Hygiene and Tropical Medicine, Keppel Street, London WC1
Tickets: Free; donations to FSID welcome
Information: Call FSID on 020 7222 8001

The Foundation for the Study of Infant Deaths (FSID), the UK's leading cot death charity, is hosting an evening of lecture and discussion in tribute to the life and work of the late Professor John Emery.

This tribute evening has been organised in recognition of the enormous contribution Professor Emery made to the understanding of sudden and unexpected deaths in infancy. The evening will focus on three aspects of his work and their impact on the suture of sudden infant death.

Lectures are:

- Paediatric Pathology, presented by Dr Margaret Evans, Consultant Paediatric and Perinatal Pathologist, Sheffield Children's Hospital
- Care of the Next Infant (CONI), presented by Dr Robes Coombs, Consultant Neonatologist, Northern General Hospital
- Risk related intervention, presented by Professor Robert Carpenter, Visiting Professor, Department of Epidemiology and Public Health, London School of Hygiene and Tropical Medicine.

The evening will be introduced and chaired by Lady Sylvia Limerick.
 To reserve a place call Amy Mellor at FSID on 020 7222 8001.



Assessing outcomes in twin-twin transfusion syndrome

MALCOLM CHISWICK

Arch Dis Child Fetal Neonatal Ed 2000 83: F165-F167

doi: 10.1136/fn.83.3.F165

Updated information and services can be found at:

<http://fn.bmj.com/content/83/3/F165.full.html>

These include:

References

This article cites 12 articles, 1 of which can be accessed free at:

<http://fn.bmj.com/content/83/3/F165.full.html#ref-list-1>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

- [Epidemiologic studies](#) (529 articles)
- [Pregnancy](#) (844 articles)
- [Reproductive medicine](#) (795 articles)
- [Clinical diagnostic tests](#) (437 articles)
- [Radiology](#) (420 articles)
- [Radiology \(diagnostics\)](#) (389 articles)
- [Drugs: cardiovascular system](#) (172 articles)
- [Urology](#) (62 articles)
- [Stomach and duodenum](#) (22 articles)
- [Valvar diseases](#) (17 articles)

Notes

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>