

Neuro-developmental outcome of twins with different birth weights

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Background

Twins as high risk group of children

Twins are at 4-6 times higher risk of perinatal mortality than singletons, and their contribution to all perinatal deaths is disproportionately high.^{1, 2} Prematurity and growth restriction are the main factors leading to high perinatal and infant mortality in twins. Twins have also higher prevalence of neurological morbidity and developmental disability^{3, 4} contributing to approximately 10% of all cerebral palsy cases.³

Birth weight discordancy and pregnancy outcomes

Differences in birth weight (BW) between twin pairs (birth weight discordance) is calculated as $100 \times (\text{BW of larger twin} - \text{BW of smaller twin}) / \text{BW of larger twin}$. International census survey on the definition of growth discordance in twins proposed a two-grade definition: mild (greater than 15% and less than 25% birth weight disparity) and severe (equal to or greater than 25% growth disparity). Birth weight discordance has also been suggested a risk factor for poor perinatal outcomes. Many studies investigated the effect of inter-twin BW discordance on pregnancy outcome and neonatal mortality.^{5,6, 7, 8, 9} but there is no consistency on whether severe twin growth discordance is an independent risk factor for adverse pregnancy outcome.^{5,6,10,11} It is also not clear whether increased perinatal mortality and morbidity in birth weight discrepant twins are mainly attributed to preterm birth

and fetal growth restriction in the smaller twin.⁷ There are few studies which report the effect of growth discordance on the outcomes in twins by the type of placentation^{12,13,14}

Umbilical artery Doppler ultrasound

Umbilical artery Doppler abnormalities (absent or reversed end-diastolic flow - AREDF) are predictive of intrauterine growth retardation which is associated with a higher risk of perinatal mortality due to chronic fetal hypoxia. Studies have shown that abnormal fetal aortic velocity waveform is a significant predictor of minor neurological dysfunction and impaired intellectual development at 7 years of age.^{15, 16} The substantial majority of babies with AREDF are diagnosed in the late second or early third trimester. Optimal management at this stage (< 32 weeks) is a major dilemma for the obstetrician.

Reason for the study

There is lack of population based information on the long-term outcome of growth discordant and growth retarded twins with or without umbilical Doppler artery flow abnormalities. Our follow-up study aims to examine the long-term neurodevelopmental outcome and growth of birth weight discordant twins using data from the population-based Northern Survey of Twins and Multiple Pregnancy (NorSTAMP). The information provided by the study will be of great importance for health professionals and parents in planning antenatal management of twin pregnancies and the future care of children from twin pregnancies and family.

Aims: To assess the growth and neuro-developmental outcomes at age 5-8 years for twins born with significant inter-twin birth weight discordance in the Northern region of England

Objectives

1) To assess the neurodevelopmental outcomes of growth discordant monochorionic twins ($\geq 20\%$ birth weight discrepancy).

2) To ascertain the presence of umbilical artery Doppler abnormalities (absent or reversed end-diastolic flow) and determine the extent to which Doppler abnormalities compared to birth weight discordancy predict growth and developmental outcome of twins. We hypothesise that umbilical artery Doppler ultrasound abnormality is a better predictor of adverse short-term pregnancy outcomes and long-term neurodevelopmental outcomes in twins than birth weight and/or intertwin birth weight discordancy.

3) To investigate the relationship between these outcomes and the gestational age.

Methods

All twin births have already been identified by the NorSTAMP and we plan to utilise data for the years 2000-2004. NorSTAMP is part of the Regional Maternity Survey Office, North East Public Health Observatory (RMSO, NEPHO) which also collects information on all infant deaths (up to one year of age) as part of its routine data capture procedure. Details of any deaths occurring after the first year of life will be obtained for the purpose of this current study by linking with National Health Service Central Register (NHS-CR) for all eligible cases. Thus, we will ascertain all deaths in this group and identify only surviving children.

The NHS-CR will also provide current details of surviving children including details of their general practitioner. We plan to contact the GP of every infant and twin pair known to be alive at 1 year of age to confirm they are still alive, and to inform them of our proposal. We will ask the GP to confirm contact details to approach parents. We will check whether they are currently under paediatric follow up. Parents will then be approached by:

(1) The principal obstetrician involved in the antenatal management of these children (NorSTAMP lead at each unit) or

(2) The lead paediatrician if they are currently under follow-up.

Those agreeing will be asked to return a stamped addressed envelope and will then be contacted by the principal investigator and an appointment will be made either at the local hospital or at home depending on parental preference. Funds will be made available to cover local public transport costs.

Data will be collected on

- Birth weight, sex and gestational age at birth, inter-twin birth weight discordance will be calculated
- chorionicity (antenatally diagnosed, postnatally confirmed or determined)
- pregnancy outcome: preterm birth, intrauterine growth retardation, stillbirth or neonatal death, congenital anomalies, admission to SCBU, caesarean section, induced labour
- Maternal information - age, parity, obstetric history, medical/social history (Smoking)
- umbilical artery Doppler ultrasound parameters along with the gestation (after linking with fetal medicine database/ antenatal case notes)
- estimated fetal weight by gestational age (at ...weeks gestation)
- Sociodemographic information from parents will include educational level and occupation of both parents, language spoken at home, and family structure

At the time of the child's assessment, following details will be collected:

- Height, weight, head circumference, mid-arm circumference and waist/hip ratio. These will be expressed as proportions below the 50th, 10th, and 3rd centile.
- Blood pressure (mmHg)
- Cognitive function assessment will be assessed using the revised British Ability Scales (BAS II), in which the total score is made up as the calculated mean of three clusters: verbal ability, non-verbal reasoning, and spatial ability. Each cluster consists of two subtests. The BAS has an ability score (general conceptual ability, GCA) standardised to a mean of 100 and an SD of 15.
- Neuromotor function, balance, and coordination will be assessed with the Quick Neurological Screening Test (QNST-II). The QNST was constructed to identify persons as young as 5 years old who have minor neurological signs that are frequently associated with learning disabilities. The QNST consists of a series of 15 observed tasks. To accommodate younger subjects, age sensitive modifications have been made in administering the test (for two tasks) and for scoring (for five tasks). Typically, neuromotor function tasks that are age dependent and merely reflect development are scored 1 point, but tasks that reflect a clear neuromotor dysfunction are scored 3 points. A score of 25 or less

on the QNST is considered in the normal range, 26–49 is considered a moderate discrepancy, and 50 or more is considered a severe discrepancy.

- Visual function will be tested by acuity testing of each eye separately at 6 metres and at 30 cm using the Snellen chart. Visual abnormalities are defined as an acuity of 6/9 or worse for near or far in one or both eyes.
- Hearing will be tested with a handheld pure tone diagnostic audiometer at 500, 1000, 2000, and 4000 Hz. Each threshold will be determined by crossing it three times. The average loss for these four frequencies will be calculated. Significant hearing loss is defined as a loss in one or both ears of >25 dB.
- Behaviour is rated using the Strengths and Difficulties Questionnaire (SDQ). This is completed by parents. The questionnaire consists of 25 items. The total behaviour deviance score is calculated as the sum of four of the five subscales: emotional symptoms, conduct problems, hyperactivity, and peer problems. A total of 0–13 is considered a low score, a total score of 14–16 is considered borderline, and a score of 17–40 is high. This form will also be completed by respective school teachers if parents are happy with it.

Statistical methods – The initial statistical analysis will be carried out by consultants within the study group. Previous studies have suggested that infants born with severe growth retardation and abnormal umbilical Doppler studies may have a cognitive outcome 1 standard deviation (SD) below the mean. In this study we hypothesise that the growth retarded twin will have a cognitive outcome half a SD (equivalent to 7.5 IQ points) lower than their twin pair. Using a paired analysis, and assuming a mean IQ of 100, 50 twins pairs would be able to document a difference of half a SD at a significance level of 95% with 70% power. We plan to approach parents sequentially and have assumed that approximately 60-70% will agree to take part in the study.

The χ^2 test with continuity correction will be used for dichotomous outcome variables. Continuous outcome variables will be tested for normal distribution using the Kolmogorov–Smirnov test for normality. In variables with a normal distribution, means will be compared using Student's *t* test; in variables where distribution is not normal, the Mann–Whitney U test will be used. Associations between continuous variables will be assessed using analysis of variance and linear regression. All

analyses will be conducted using SPSS. An independent statistician will be consulted at this stage.

Ethics and Confidentiality

We will apply for MREC approval. All electronic data will be kept password protected on NHS trust PCs or server. Data will not be shared with those outside the NHS or held on University or personal computer. The database will be registered with the Caldicott Guardian.

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