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Postnatal MRI Brain in Infants Treated for Twin–Twin Transfusion Syndrome

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Abstract
Untreated twin-twin transfusion syndrome (TTTS) is associated with significant mortality and neurological impairment. Fetoscopic laser surgery (FLS) is the treatment of choice. We sought to assess intracranial abnormalities in TTTS twins following treatment. In this prospective, blinded study MRI scans were performed on 3 groups; (1) monochorionic diamniotic (MCDA) twins with TTTS who had undergone FLS (n=10), (2) MCDA twins without TTTS (n=8) and (3) dichorionic twins (n=8). Scans were scored as either normal or abnormal. The primary outcome was a composite of abnormal MRI brain or intrauterine fetal demise. The primary outcome occurred in 6/10 (60%) of the TTTS group versus 3/8 (37.5%) in the MCDA group. The primary outcome was significantly different across all study groups [p = 0.029; X^2 = 7.112]. We found that twins treated for TTTS are more likely to have abnormalities on MRI brain at term than other twin groups. This group merits term-corrected MRI as part of their postnatal assessment.

Introduction

Perinatal mortality and morbidity rates are higher in twins than in singleton infants[1]. Monochorionic twins account for the highest risk group[2] and have higher rates of preterm delivery, lower birth weight and neurodisability[3]. A 7-fold increase in neurologic morbidity has been reported in preterm monochorionic twins compared to matched dichorionic twins, the increase attributed to discordant birth weights and co-twin demise in utero[4]. Twin-twin transfusion syndrome (TTTS) affects monochorionic diamniotic (MCDA) pregnancies and represents a severe complication in 10 to 15% of these pregnancies[5]. Unbalanced, interfetal, transplacental blood flow across deep arterial to venous connections results in progressive reduction of amniotic fluid volume and impaired growth in the donor twin, with polyhydramnios and hydrops in the recipient twin[6]. The risk of in-utero demise of untreated twins is 80% to 100%[7] and carries significant risk of neurological impairment in surviving twins. Cerebral palsy rates of 20% in surviving twins have been reported, with the risk significantly higher in the setting of a co-twin demise[8]. Many treatments have been used including, selective fetocide and amniotic septostomy. Current treatment options favour serial amnio reduction and endoscopic laser ablation of the vascular anastomoses. These options have varying success rates, survival outcomes and neurodevelopmental results. Meta-analyses have shown superiority of fetoscopic surgery over other modalities[9,10]. A recent randomised control trial has also shown that fetoscopic laser surgery (FLS) has more favourable survival rates and a significantly reduced risk of neurodevelopmental impairment when compared to amnioreduction[11]. Despite these advances and improved outcomes, significant rates of fetal demise and neurological impairment such as cognitive and motor developmental delay remain[12-14].

Haemodynamic changes resultant to unbalanced blood flow affects many vital organ functions with cardiac, renal and neurological sequelae[15]. Since FLS has become the preferred choice of treatment, some studies demonstrate haemodynamic changes associated with the procedure, distinct from the primary disease process. An increase in peak systolic velocity in the middle cerebral artery is observed in recipient twins post FLS. However, these changes are transient and have uncertain long-termconsequence[16]. Ultrasonographic evidence of severe cerebral lesions in TTTS infants, post laser surgery, suggests that these lesions result from antenatal injury[17]. Fetal magnetic resonance imaging (MRI) identifies areas of cerebral ischaemia, not obvious on antenatal ultrasound[18], but to date there is a paucity of published postnatal MRI brain studies. Term corrected MRI brain imaging is beneficial for risk stratification of ex-premature infants in predicting adverse neurodevelopmental outcome[19]. The purpose of this study was to evaluate intracranial abnormalities in twins following FLS, using term corrected MRI brain and comparing them with both MCDA twins without a diagnosis of TTTS and dichorionic (DC) twins, in which this is not a clinical entity.

Methods

This study was undertaken in the Rotunda Hospital, a national referral centre for FLS in the Republic of Ireland. MRI brain imaging was acquired on 3 twin groups in a prospective, case control manner at term-corrected gestation (37 to 44 weeks). Three study groups were defined as follows (1) twins with an ultrasound diagnosis of twin-to-twin transfusion syndrome who had previously undergone fetoscopic laser surgery, (2) Monochorionic diamniotic twins with normal antenatal ultrasounds outruling a diagnosis of TTTS and (3) Dichorionic twins. Twin infants who had delivered in the study centre having previously undergone FLS were included; matched pairs of MCDA and DC twins were consecutively enrolled for each TTTS case. Cases on whom FLS had been performed but that delivered elsewhere were excluded, as were infants with an antenatal diagnosis of complex congenital anomalies (cardiac, gastrointestinal tract or respiratory), chromosomal disorders or primary brain abnormalities. TTTS was diagnosed using antenatal ultrasound and staged according to Quintero criteria[20]. MRI's were performed on a General Electric (United Kingdom) 1.5T Signa MRI system a departmental neonatal brain protocol. Chloral hydrate (50mg/kg) was used for sedation.

Table 1. Clinical Demographics and Primary Outcomes

	Group 1 ***TTTS*** (n=10)	Group 2 ***MCDA*** (n=8)	Group 3 ***DC*** (n=8)	
Gestational age (weeks)	32+0 (4)	28+3 (3)	34+3 (2)	P<0.01
Birth Weight (grams)	1796 (737)	1028 (443)	2019 (687)	p=0.13
Male Sex	60% (6)	50% (4)	55% (5)	
Antenatal Steroids	80% (8)	100% (8)	75% (6)	p=0.34
LSCS Delivery	80% (8)	100% (8)	100% (8)	p=0.18
Cranial Ultrasound Abnormal*	75% (6) 16.6% (1)	100% (8) 12.5% (1)	50% (4) 0	
Age at MRI (weeks)	42 (7)	43 (10)	50 (2)	p=0.60
Primary Outcome (Abnormal MRI or Fetal Demise)	60% (6)	37.5% (3)	0	p=0.03

Results expressed as mean (SD) or %. P values to 2 decimal places and / or <.01

Twin-Twin transfusion syndrome (TTTS), Monochorionic Diamniotic (MCDA), Dichorionic (DC), Lower segment Caesarean Section (LSCS), Standard deviation (SD)

Abnormal Cranial ultrasound = evidence of intraventricular haemorrhage (IVH) grade II to IV or cystic periventricular leukomalacia (PVL)

A single attending radiologist (SR), who was blinded to the study groups, analysed each scan and, with the other authors, graded the findings in a pragmatic fashion as either normal or abnormal. The primary study outcome was abnormal findings on MRI brain or fetal demise. Abnormal findings were subsequently subclassified as either a minor (unlikely to be of clinical significance) or major abnormality (likely to have a clinical effect). A comparison of diagnostic efficacy between MRI brain and cranial ultrasound was then performed. A cranial ultrasound was deemed abnormal if an intraventricular haemorrhage of grade III – IV or periventricular leukomalacia was documented[21]. Comparison of proportional differences between groups was performed using Chi squared analysis.

Continuous variables were expressed as means and 95% confidence intervals (expressed in parenthesis). Comparison between continuous variables was made using the analysis of variance (ANOVA), followed by Post Hoc Tukey's analysis, where appropriate. Statistical significance was accepted for alpha< 0.05. The Research Ethics Committee of the Rotunda Hospital granted study approval.

Results

From July 2008 to December 2011, 28 cases of twin-to-twin transfusion syndrome had fetoscopic laser surgery performed at the study centre. 10 cases were eligible for inclusion and 5 subsequently enrolled. The patient sample obtained was representative of the TTTS cases treated with FLS and delivered in this institution during the study period. 4 MCDA twin pairs were enrolled in Group 2 and 4 sets of DC twins in Group 3. Mean gestational age at which FLS was performed was 19 weeks (18.1, 19.9) in line with usual practice. Demographic perinatal data and cranial ultrasound results are presented. There was no significant difference in birth weight between the TTTS and MCDA [mean difference 769g (-32, 1569); p=0.61] or DC [mean difference-223g (-1023, 578); p=0.766] groups. Chi squared test showed a difference in primary outcome between MCDA and TTTS groups [c2= 7.112; p =0.029]. No primary outcome event was recorded for the DC group. 60% of the TTTS group (6/10) had an abnormal scan or either died in-utero versus 37.5% (3/8) of the MCDA group. The TTTS group accounted for 66.7% of patients experiencing the primary outcome. Individual MRI abnormalities across twin groups were heterogeneous.

Table 2. MRI abnormalities recorded

Patient	MRI Result	Group	Significance	Gestation at Delivery
Twin A (1)	Focal cortical migration abnormality – Posterior inferior left frontal lobe	1 Q.2	Major	32+6
Twin B (2)	Focal area T1 hyper-intensity – left deep white matter adjacent to body of left lateral ventricle	1 Q.1	Minor	34+2
Twin D (1)	Thin corpus callosum, Dilatation of lateral and third ventricles	1 Q.2	Minor	35+0
Twin E (1)	Area of haemorrhage in posterolateral right thalamus	1 Q.4	Minor	24+3
Twins H (1)	Small focus of haemorrhage in posterior horn right lateral ventricle	2	Minor	27+6
Twins H (2)	Cystic encephalomalacic change in left cerebellar hemisphere; little remaining parenchyma	2	Major	27+6
Twins J (1)	Foci of blooming artifact in lateral ventricles laterally – prior IVH	2	Minor	25+3

Quintero stage (Q.), Intraventricular Haemorrhage (IVH)

Parenthesised number in Patient column refers to birth order

Group 1 (TTTS) Group 2 (MCDA)

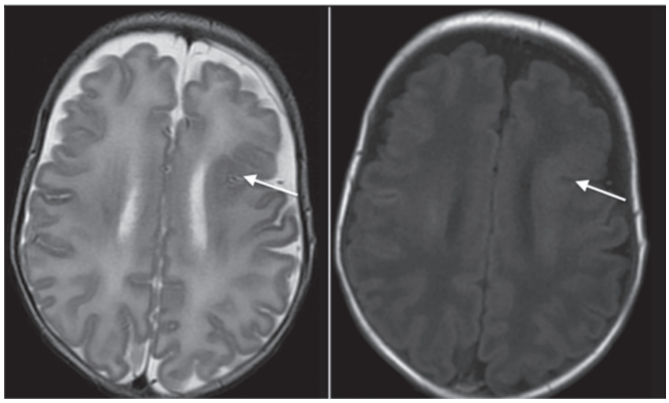

Figure 1 Twin A(1) focal cortical migration abnormality (arrow). T1 (right), T2 (left)

Discussion

In this study, we investigated abnormal term-corrected MRI brain or death as a primary outcome in twin-to-twin transfusion syndrome versus matched MCDA twins and DC twins and demonstrate that this primary outcome occurs with greater frequency in the TTTS group. 1/4 (25%) of the abnormal MRI's in the TTTS group showed a major finding of immediate clinical significance, with the remainder of undetermined clinical significance. The focal cortical dysplasia identified is likely to have occurred during brain development before 24 weeks gestation and not as a consequence of prematurity. Focal cortical dysplasias may occur secondary to abnormal post migrational development caused by injury to the developing cortex and have been reported in twin-twin transfusion syndrome[22,23]. The MRI with a major finding in Group 2 was most likely secondary to complications of prematurity as there was evidence of haemorrhage on cranial ultrasounds during the first 3 days of life. The heterogeneous abnormal MRI findings are not all of equal significance. These range from evidence of prior haemorrhage such as intraventricular

haemorrhage to subtle structural abnormalities such as a thin corpus callosum. This cohort is not large enough to correlate findings with particular twin groupings; however, the long-term consequences and their associations merit investigation. Cranial ultrasound, a readily available bedside imaging tool, is the mainstay of routine imaging in neonatal intensive care units. The finding of the focal cortical migration abnormality, (Twin A1), was not detected on ultrasound and hence would have been missed if ultrasound was used as the sole imaging modality, and in this case was falsely reassuring.

Spruijt et al recently presented the incidence of cerebral injury in twin-twin transfusion syndrome post fetoscopic surgery using cranial ultrasound as the primary imaging modality. These authors present data showing that the rate of injury did not differ between the TTTS group and the matched controls, with an incidence of cerebral injury documented in 8.6% of survivors[24]. We observed that MRI was superior when compared to cranial ultrasound in detecting abnormalities in this group. If cranial ultrasound alone was utilised our rate of abnormalities in the TTTS group, 16.6%, is in keeping with previous reported rates of 3 – 16%[24]. Whilst our numbers are small, we present a similar rate of injury using cranial ultrasound, but show that use of this imaging modality alone can miss significant lesions and under call the true rate of injury as shown using MRI. Merhar and colleagues have previously published an uncontrolled case series, which demonstrates an MRI abnormality rate of 68% in TTTS twins[25]. We present herein a study, which demonstrates a similar abnormality rate of 60% in TTTS twins, a rate that is significantly higher than that of their non-TTTS counterparts. Moreover, we present data, which suggests superior sensitivity of MRI over ultrasound as an imaging modality in this specific clinical situation. While it is difficult to directly infer the underlying cause for the reported outcome from the current dataset, a number of pathogeneses may underlie these findings.

These twins are exposed to a hostile intra-uterine environment pre-treatment and also potential risks and haemodynamic changes, which may ensue from the FLS procedure itself. Fetuses, as with newborns, are vulnerable to changes in blood pressure, blood flow and heart rate. These changes place a demand on fetal cerebral auto regulatory mechanisms to ensure stability and protect the developing brain from injurious consequences. It is known that preterm infants are particularly susceptible to dysregulation of cerebral blood flow, which can result in intracerebral haemorrhages and periventricular leukomalacia (PVL)[26,27]. The preceding stresses of the twin-to-twin transfusion may predispose the twin pair to a reduced ability to regulate cerebral blood flow during and after the fetoscopic laser surgery. Whilst extensive antenatal data has been presented in this high-risk group, formal outcome data from MRI brain studies are scarce. Within the context of this limited study sample, we have shown a clear and definite trend identifying a higher risk for abnormal MRI brain or death in TTTS twins versus other twin groups. These results suggest that there is indeed an increased risk of neurologic injury in TTTS twins, which was already known, but MRI shows this injury in better detail. In successful cases of FLS the pregnancy may continue to delivery at term in the referring unit without need for neonatal intervention or monitoring after delivery. These infants would not routinely have cranial ultrasounds or receive neurodevelopmental follow up at discharge. Identifying infants at risk at the earliest time point affords an opportunity to maximise the neurodevelopmental outcome.

Twin-twin transfusion syndrome is associated with significant rates of neurodevelopmental impairment. Twins who survive without treatment, post conservative treatment and surviving twins post co-twin demise are at the greatest risk[8,28]. Despite improvements in neurodevelopmental outcomes post FLS in recent years, significant rates of neurodisability persist[29]. Further studies are necessary to fully explore the consequences of intrauterine interventions and any correlation with specific MRI findings that may exist. Though larger studies are required both to definitively answer the clinical question, and to incorporate comprehensive long-term neurodevelopmental follow up, we feel that this specific high-risk patient group merit term-corrected MRI brain imaging, as opposed to cranial ultrasound, as part of their postnatal assessment model and ongoing clinical neurodevelopmental assessment.

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Advanced Maternal Age and Assisted Reproductive Technologies in an Irish Population

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Abstract
In recent decades the amount of women over 40 seeking assisted reproductive technology (ART) interventions in order to become pregnant has dramatically increased, both in Ireland and worldwide. This is due to an increase in the average age at which women are choosing to have their first child while additionally, many couples are choosing to have a second family later in life. However, as with natural conception, ART success rates decrease with maternal age. In the present study, we perform a 16 year retrospective analysis on our clinical data of women between 40 and 45 years of age, who have undergone ART at a tertiary referral ART clinic. The percentage of patients in this age group was analysed over time, in order to determine follicle recruitment, % oocyte yield, embryonic quality, positive hCG (pregnancy rate), clinical pregnancy rate and rate of preclinical pregnancy loss. Results from our clinic show that women greater than 43 years of age have a significantly reduced reproductive potential compared to women in the 40 to 42 years age group. Woman in the 43-45 age group showed reduced fertilization rates (53.73% versus 58.82%), reduced positive hCG rates (11.51% versus 19.03%) and clinical pregnancy rates (5.04% versus 12.52%) and increased rates of preclinical pregnancy loss (56.23% versus 34.23%), compared to women in the 40-42 age group. With the age at which couples are choosing to have children constantly increasing, novel ART treatment strategies need to be developed.

Introduction

There is a well-established link between advanced maternal age and reduced reproductive potential. This natural decrease in fertility in women is caused by several factors including reduced oocyte numbers, diminished oocyte and embryo quality and an increase in miscarriage rate[1-3]. In addition, pregnancy at this later stage in life involves increased maternal and fetal risks including: miscarriage, hypertension, preeclampsia, gestational diabetes, placenta praevia, placental abruption, caesarean section, genomic disorders, premature birth, low foetal birth weight and neonatal morbidity[4]. In recent decades the amount of women over 40 seeking assisted reproductive technology (ART) interventions, in order to become pregnant, has dramatically increased. This is due to an increase in the average age at which women are choosing to have children; while additionally, many couples are choosing to have a second family later in life[5]. However, as with natural conception, ART success rates decrease with maternal age. In addition to a reduction in oocyte numbers retrieved during a standard ART cycle, maternal age has a detrimental effect on oocyte competence[6-8]. One major factor evident in aged oocytes is an increase in aneuploidy[9,10]; with chromosomal abnormalities being a major determinant of subsequent embryonic development. Nondisjunction during meiosis is the principle cause of aneaploids. If normal disjunction (chromosome separation) process fails to happen, and two chromosomes go to only one pole n+1 and n-1 gametes are produced. The aim of the present study was to perform detailed analysis of our clinical data on women greater than 40 years of age, who have undergone ART at a tertiary referral ART clinic, between 1997 and 2013.

Methods

A retrospective analysis of clinical and laboratory data was performed by collecting data from our tertiary referral ART academic program. All IVF/ICSI cycles carried out on women between 40 and 45 years of age, at the Human Assisted Reproduction Ireland (HARI) clinic, Rotunda Hospital, Ireland between January 1997 and January 2013 were identified. This clinic has an age cut-off limit for ART of 45 years of age. Patients between 40 and 45 years of age at egg collection were selected for analysis. We also split our patients into two age groups for comparative analysis; 40-42 and 43-45. The following parameters were then analysed: follicle recruitment, % oocyte yield (oocyte follicle ratio), positive hCG, clinical pregnancy rate (ultrasound confirmation of a gestational sac at 7 weeks) and preclinical pregnancy loss (absence of intrauterine sac at 7 week ultrasound scan following previously positive urinary hCG test).There were