OBSTETRICS

Cerebral injury in monochorionic twins with selective intrauterine growth restriction and/or birthweight discordance

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OBJECTIVE: The objective of the study was to study the incidence of severe cerebral injury in monochorionic (MC) twins with selective intrauterine growth restriction (sIUGR) and/or birthweight discordance.

STUDY DESIGN: All MC twin pregnancies with 2 liveborn twins were included in the study. We excluded all cases with twin-to-twin transfusion syndrome (TTTS). Sequential cranial ultrasound scans were performed in all MC twin infants.

RESULTS: A total of 117 MC twin pairs were included in the study. The sIUGR of at least 1 fetus was found in 50 twin pregnancies (43%), and birthweight discordance of 25% or greater occurred in 26 twin pregnancies (22%). The overall incidence of severe cerebral injury was 3% (6/218). The incidence of severe cerebral injury in infants from twin pregnancies with and without sIUGR was 2% (2/94) and 3% (4/124), respectively ($P = .62$). The incidence of severe cerebral injury in infants with and without birthweight discordance was 0% (0/48) and 4% (6/170), respectively ($P = .19$).

CONCLUSION: The incidence of severe cerebral injury in MC twin pregnancies not complicated by TTTS with 2 liveborn twins is low. No association could be demonstrated with sIUGR or intertwin birthweight discordance of 25% or greater.

Key words: birthweight discordance, cerebral injury, monochorionic twins, selective intrauterine growth restriction

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The risk of cerebral injury and subsequent cerebral palsy in monochorionic (MC) twins is 7 times higher than in dichorionic twins.[1] This increased risk is related to the characteristic placental vascular anastomoses, which are present only in MC placentas. Vascular anastomoses can lead to various forms of twin-to-twin transfusion syndrome (TTTS). The risk of cerebral injury and neurologic abnormality is increased in particular after chronic TTTS (up to 21%)[2-4] and after single intrauterine fetal demise (IUFD) (up to 18%).[5]

Recently, conflicting results have been reported on 2 additional risk factors in MC twin pregnancies. Increased risk of cerebral injury has been found in MC twins with selective intrauterine growth restriction (sIUGR)[6] and birthweight discordance.[7] However, special care should be taken when interpreting these results because of several methodological limitations. Importantly, the suggestion of a possible association with increased risk for cerebral injury lead authors to speculate that MC twin pregnancies with sIUGR (and persistent absent end-diastolic flow in the umbilical artery of the smaller twin) might benefit from fetoscopic laser treatment, in analogy with MC pregnancies with TTTS.[8] The potential benefit of this invasive approach in MC pregnancies with sIUGR is controversial[9] and is currently being evaluated in a randomized controlled trial.[10]

In a previous study, we were not able to confirm the association between sIUGR and/or intertwin birthweight discordance and severe cerebral injury.[3] However, this lack of association may have been due to the relatively small number of patients included in the study.

The aim of the present study was to investigate the association between sIUGR and/or intertwin birthweight discordance with the presence of severe cerebral injury in a large consecutive series of MC twins without TTTS.

Materials and Methods

Between June 1, 2002, and April 1, 2008, 223 MC twin pregnancies were consecutively examined and delivered at our center. The Leiden University Medical Center is an academic referral center managing all types of complications of MC pregnancies and a national referral center for in utero management of TTTS.

For this study, we included only MC twin pregnancies delivered greater than 24 weeks' gestation, resulting in 2 liveborn twins. MC twins with TTTS, IUFD, and MC triplets were excluded. Diagnosis of TTTS was based on internationally

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accepted standardized antenatal ultrasound criteria.[11]

The primary outcome was the presence of severe cerebral lesions detected on cranial ultrasound scans. A search was performed in our obstetric and neonatal database to retrieve all medical records, including the results of cranial ultrasound investigations during the neonatal period.

The definition of sIUGR was an estimated fetal weight below the 10th percentile in 1 twin, according to the standards provided by Hadlock et al.[12] Gestational age at first ultrasound scan during pregnancy was recorded. Intertwin birthweight discordance was defined as a difference in birthweight of 25% or greater. Birthweight discordance was calculated using the formula: ([birthweight larger twin] − [birthweight smaller twin])/birthweight larger twin × 100%. The cases with sIUGR were retrospectively classified according to the recent classification system proposed by Gratacos et al[13] in relation to the characteristics of the umbilical artery Doppler flow: type I (persistently positive end-diastolic flow), type II (persistently absent or reversed end-diastolic flow (AREDF), or type III (intermittent AREDF). Final classification was done on the last ultrasound examination prior to birth.

After birth, cranial ultrasound scans were performed routinely in all MC twins according to our clinical protocol. Cranial ultrasounds were performed by experienced neonatologists not blinded to whether the infants had sIUGR or intertwin growth discordance. The cranial ultrasound protocol at our neonatal intensive care unit requires a minimum of 3 scans during the first week of life (days 1, 3, and 7), followed by at least 1 scan weekly until discharge. If cerebral abnormalities were detected, scanning frequency was intensified around the date of detection and repeated at the time of the estimated date of confinement.

In term infants (gestation of ≥ 37 weeks), repeat cranial ultrasound scans were not performed if scans were normal at birth. Cranial ultrasound scans were performed with an Aloka 5000 scanner (Biomedic Nederland BV, Almere, The Netherlands) with a multifrequency (5-10 MHz) transducer. The cerebral anatomy was visualized in the standard coronal and sagittal planes.[14]

Intraventricular hemorrhages (IVH) were classified according to Volpe[15] and periventricular leucomalacia (PVL) was graded according to de Vries et al.[16] Severe cerebral lesions on cranial ultrasound scans were defined as the presence of at least 1 of the following findings: IVH grade III, periventricular hemorrhagic infarction (previously known as IVH grade IV), PVL grade II or greater, porencephalic cysts, and ventricular dilatation. Ventricular dilatation was present when the width of 1 or both lateral ventricles exceeded the 97th percentile.[17] Other severe cerebral abnormalities associated with adverse neurological outcome were also recorded. In addition, PVL grade I, subependymal pseudocysts and lenticulostriate vasculopathy were recorded and classified as mild cerebral lesions.

Placental injection with colored dye was performed routinely in all MC placentas to record the presence and type of vascular anastomoses and determine the intertwin placental sharing discordance. The placental territory of each fetus was measured by following the margins demarcated by the presence of color-specific dye. Individual placental territories were measured using Image Tool for Windows version 3.0 (Image Tool, San Antonio, TX). The placental sharing discordance was calculated by dividing the larger placental territory by that of the smaller territory. Details on the technique used for placental injection have been described previously.[18]

Statistics

The results of categorical variables were compared using the χ^2 test. A Student t test was used to compare normally distributed values between 2 groups. Multiple logistic regression analysis with random twin effect was used to measure the independent effects of potential prognostic factors on outcome. A model with random twin effect was applied to adjust for possible correlated effects within twins. The results of the logistic models were expressed as an odds ratio and 95% confidence intervals. $P < .05$ was considered to indicate statistical significance.

We calculated that group sizes of 103 infants were required to demonstrate a 10% difference in severe cerebral lesions (13% vs 3%) with a significance of 0.05 and a power of 80%, by 2-tailed analysis. Analysis was performed using SPSS version 14 (SPSS Inc, Chicago, IL). Multiple logistic regression analysis was performed with EGRET version 2.0.1 for Windows (Cytel Software Corp, Cambridge, MA).

RESULTS

Of the 223 MC twin pregnancies consecutively examined and delivered at our center during the study period, 106 were excluded because of TTTS (n = 102), single IUFD (n = 3), or MC triplet pregnancy (n = 1). Single IUFD occurred in 2 MC pregnancies without sIUGR and in 1 MC pregnancy with sIUGR, classified as type I.

A total of 117 MC twin pregnancies with 2 liveborn twins were included in the study; sIUGR was found in 50 pregnancies (43%) and occurred in 73 fetuses (31%). Birthweight discordance of 25% or greater occurred in 26 twin pregnancies (22%). Birthweight discordance of 25% or greater was found in 50% (25/50) of MC pregnancies with sIUGR, whereas sIUGR was present in 96% (25/26) of pregnancies with birth weight discordance of 25% or greater. Of the 50 pregnancies with sIUGR, 26 were classified as type I (52%), 15 as type II (30%), and 9 as type III (18%). Mean gestational age at first ultrasound scan was 15.8 weeks (± 5.2).

Placental injection study was successfully performed in 86% (101/117) of placentas. Placental sharing discordance was higher with sIUGR than in MC pregnancies without sIUGR, 1.9 vs 1.4 respectively ($P < .01$). Arterioarterial anastomoses were detected more frequently in MC pregnancies with sIUGR than without sIUGR, 93% vs 79%, respectively ($P = .05$). Baseline characteristics and placental characteristics of MC twin pregnancies with and without sIUGR are summarized in Table 1.