Low Rate of Cerebral Injury in Monochorionic Twins With Selective Intrauterine Growth Restriction

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This study was conducted to determine the incidence of cerebral injury as detected by postnatal brain scan in monochorionic twins with selective intrauterine growth restriction. Having excluded cases complicated with twin-to-twin transfusion syndrome and one co-twin suffering intrauterine fetal death, a total of 73 monochorionic twin pregnancies divided into absence (group I, $n = 46$) or presence (group II, $n = 27$) of selective intrauterine growth restriction. Mild cerebral injury was defined as presenting one of the following abnormal cranial scan findings: intraventricular hemorrhage grade I, grade II, lenticulostiate vasculopathy and/or subependymal pseudocysts, while severe cerebral injury was defined as presenting intraventricular hemorrhage grade III, grade IV, cystic periventricular leukomalacia (PVL) grade II or higher, porencephalic cysts, and/or ventricular dilatation. The incidence of mild cerebral injury was not significantly different between these two groups (eight cases in group I and six cases in group II). Except for one case that later developed a seizure, the majority (13 out of 14) of cases with minor brain scan anomalies were only transient, without significant clinical impact. There was only one case diagnosed with a major brain scan anomaly (periventricular leukomalacia) in group II. One severe brain injury and three neonatal deaths all belonged to group II with abnormal umbilical artery Doppler in the growth restricted twin. In conclusion, the incidence of severe cerebral injury in monochorionic twin pregnancies with selective intrauterine growth restriction was low, at 3.7%.

Keywords: monochorionic twin pregnancy, intrauterine growth restriction, umbilical artery Doppler, cerebral injury, brain ultrasound.

Cerebral palsy is estimated to occur seven times more often in twins than in singleton infants (Adegbite et al., 2005). Among twins, the risk of cerebral injury and subsequent cerebral palsy in monochorionic twins (MC) is much higher than in dichorionic twins (DC) (Blickstein, 2002; Gratacos et al., 2004), because of the characteristic placental vascular anastomoses which are present only in MC placentas. In MC pregnancies, twin-twin transfusion syndrome (TTTS) and one intrauterine fetal death (IUFD) have been recognized as highly susceptible to severe cerebral injury. TTTS, if left untreated, could spell a poor neurological outcome for the fetuses (Gonsoulin et al., 1990), but with laser therapy, the periventricular leukomalacia (PVL) grade III or higher rate reportedly improved to six percent (Senat et al., 2004); in MC with one IUFD the neurological abnormality rate had been estimated as 18% for the surviving fetus due to severe anemia or hypotension caused by exsanguination of one fetus into its co-twin (Ong et al., 2006).

Selective intrauterine growth restriction (sIUGR) occurs in about 12% of twin pregnancies (Gonsoulin et al., 1990; Gratacos et al., 2004; Sebire et al., 1997), with a similar incidence rate for both DC and MC pregnancies (Gratacos et al., 2004). The neurological outcome of MC twins with sIUGR has been reported to be poor (Adegbite et al., 2005; Bejar et al., 1990) or fair (Lopriore et al., 2008). What's even worse, MC with sIUGR with abnormal umbilical artery (UA) Doppler (defined as absence of reverse of end-diastolic velocity) of the IUGR twin could mean more neonatal death and intrauterine fetal demise (Chang et al., 2008; Gratacos et al., 2007; Russell et al., 2007). So, excluding TTTS and MC twins with one IUFD that are known for their close link with neurological impact on the surviving fetuses, the aim of our study was to determine the incidence of severe cerebral injury in MC twins with sIUGR using cranial ultrasound.

Materials and Methods

The data were collected prospectively between March 2006 and December 2008 from women who gave birth to live-born MC twins in Chang Gung memorial

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hospital, where the brain scans could be done within three days of delivery. All women either received antenatal clinic at our hospital or were transferred in because perinatal complications were anticipated. MC pregnancy was diagnosed prenatally by ultrasound as having a single placenta, a thin dividing membrane, and lacking a twin peak sign. An MC pregnancy with sIUGR was defined as an estimated fetal weight below the 10th percentile in one twin of an MC twin pregnancy (Ananth et al., 1998). The exclusion criteria were pregnancies with signs of TTTS, as defined by severe oligohydramnios (maximum vertical pocket of amniotic fluid < 2 cm) in the donor twin and polyhydramnios in the recipient twin (maximum vertical pocket, > 8 cm) (Quintero et al., 1999), and twins with anomalies or at least one intrauterine fetal death or death within 24 hours after delivery, due to the unavailability of their brain scans. The study was approved by the local institutional ethics committee.

We further divided the MC pregnancies into two groups: MC without IUGR (group I) and MC with sIUGR (group II). Mild cerebral injury was defined as having lesions detected by cranial ultrasound scans with the presence of at least one of the following: intraventricular hemorrhage (IVH) grade I and II, lenticulostriate vasculopathy and subependymal pseudocysts. Severe cerebral injury was defined as having at least one of the following: IVH grade III or grade IV, cystic periventriculoleukomalacia (PVL) grade II or more, porencephalic cysts, and ventricular dilatation. Ventricular dilatation was said to be present when the width of unilateral or both lateral ventricles exceeded the 97th percentile. Neonatal brain scans were done within four days of delivery and serial scans were arranged in case abnormal scans were found or as part of follow-up for preterm babies. A positive finding on a brain scan was established when any one of the serial examinations showed abnormal findings. Neonatal death was defined as death within 28 days of delivery. In order to analyze the effect of abnormal UA Doppler on brain scan-detected anomaly and neonatal outcome of group II MC pregnancies, the neonatal outcomes of group II MC pregnancy were further broken down into two parts: those with the IUGR twin having a normal UA Doppler and those with an abnormal UA Doppler

MC pregnancies without IUGR delivered during the same period of time were used as control subjects. Among the control twins, the smaller twin was the one with lower birth weight and the larger twin was that with higher birthweight. Birthweight discordance was calculated as the difference between the fetal weights of the larger twin and the smaller twin divided by the fetal weight of the larger twin (body weight of larger twin — body weight of smaller twin)/body weight of larger twin ↔ 100%). Neonatal death and major brain scan anomaly were recognized as poor prognostic cases.

Statistical analysis was conducted with SPSS software (version 11.0 for Windows; SPSS Inc, Chicago, IL). Qualitative data were compared by means of χ^2 test or Fisher exact test as appropriate. Two-sample Student *t* test or Mann-Whitney U-test were used to compare between groups for the continuous variables. A probability value of less than .05 was considered statistically significant.

Results

During the study period, three cases of MC pregnancies with sIUGR, originally recruited in this study, later progressed to TTTS and received laser surgery; they were not included in our statistical analysis. Two MC pregnancies with double IUFD at a gestational age of 33 and 36 weeks (without sIUGR) and two MC pregnancies with one IUFD at 18 weeks (without sIUGR) and 28 weeks (with sIUGR, but with the appropriate for gestational age (AGA) twin having IUFD) were also excluded. There were two other cases that were not eligible for analysis; one MC twin with sIUGR with the AGA fetus dying immediately after delivery and another twin set (with sIUGR), both per-

Table 1

Characteristics of Monochorionic Twins (MC) Divided Into Two Groups: Absence of Selective IUGR (Group I) and Presence of Selective IUGR (Group II)

Group	Group I MC (*n* = 46)	Group II MC (*n* = 27)	*p* value
Median gestational age at delivery (weeks) (95% CI)	36.2 (34.3~36.0)	33.4 (31.9~34.9)	.013#
Mean maternal age at delivery (year) ± SD	30.6 ± 4.3	29.4 ± 4.7	.243#
Median birthweight of AGA twin (gm) (95% CI)	2355 (2187~2506)	1870 (1656~2200)	.003#
Median birthweight of IUGR twin (gm) (95% CI)	2173 (1999~2286)	1265 (1084~1518)	< .001#
Median birthweight discordance (%) (95% CI)	8.0 (6.7~10.0)	29.2 (28.3~37.8)	< .001#
Minor brain scan anomaly (per baby number)	8/92 (5 larger and 3 small twins)	6 /54 (4 AGA and 2 IUGR twins)	.772^
Major brain scan anomaly (per baby number)	0/92	1/54 (AGA twin)	0.361^
Neonatal death (per baby number)	0/92	3/54	.049^
Neonatal death or severe cerebral injury (per baby number)	0/92	4/54	.017^

Note: MC: monochorionic twin; IUGR: selective intrauterine growth restriction; SD: standard deviation; Group I: MC without IUGR; Group II: MC with selective IUGR; AGA: appropriate for gestational age; #: Mann-Whitney U test; *: Student t test; ^:Fisher's exact test

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Table 2

Characteristics of Brain Scan Anomalies of Monochorionic Twins (MC) Divided Into Two Groups: Absence of Selective IUGR (Group I) and Presence of Selective IUGR (Group II)

Group	Group I MC (n = 46)	Group II MC (n = 27)
IVH grade I (baby number)	5 / 92	5 / 54
Lenticulostriate vasculopathy (baby number)	0 / 92	1 / 54
Subependymal pseudocysts (baby number)	3 / 92	0 / 54
Periventricular leukomalacia (baby number)	0 / 92	1 / 54

Note: MC: monochorionic twin; IUGR: selective intrauterine growth restriction; IVH: intraventricular hemorrhage

ishing within 24 hours after delivery, before the brain scan could be obtained. Therefore, in total, those reaching final comparison statistics were 73 MC pregnancies composed of 46 MCs without IUGR (group I) and 27 MC pregnancies with sIUGR (group II). Our institute is a tertiary referring center specializing in fetal surgery for TTTS. Most of the MCs with sIUGR were referral cases, and consequently, its incidence among MCs was as high as 37.0 % (27/73).

In group I MCs, there were 29 larger babies and 31 smaller babies that received only one brain scan, and 17 larger and 25 smaller babies who received serial scans. In group II MCs, there were 12 AGA babies and 12 IUGR babies who were scanned only once, while 15 AGA and 15 IUGR babies received serial scanning. In summary, 45.7% (42/92) of group I MCs babies and 57.7% (30/52) of group II MCs babies were scanned more than once.

Table I lists the characteristics of the two groups of MCs based on the presence or absence of Siugr; the gestational age of delivery in group I MCs was older than in group II MCs and the birthweight of the larger and smaller twin in group I MC was heavier than the AGA twin and IUGR twin, respectively, in group II MCs. There were three babies suffering from neonatal death in group II MCs. Eight babies in group I and six babies in group II were found with minor brain injury, an incidence not significantly different between the two groups (p = .772). As for severe brain scan anomaly (PVL and ventriculomegaly), there was one case diagnosed in group II, therefore the major injury rate in group I and group II was 0 and 3.7% respectively, although this does not show a significant difference (p = .361).

In group II MCs, between AGA twins and their IUGR counterparts, there were more brain lesions, both major and minor, detected in the former than the latter (five versus two), although the difference was not a statistically significant one (5/27 versus 2/27, p = 0.42). The characteristics of cases with brain injury are listed in Table 2.

We further divided group II MCs into two subgroups; IIa (those showing normal IUGR twin UA Doppler; n = 14) and IIb (with abnormal IUGR twin UA Doppler; n = 13). Comparison parameters between the two subgroups of MCs with sIUGR are displayed in Table 2. The gestational age of delivery was longer in group IIa MCs than in group IIb MCs. The three neonatal death cases and one severe cerebral injury baby all belonged in group IIb MCs; the neonatal death rate might not reach statistical significance, but the poor prognosis rate was higher in group IIb than in group IIa MCs. There were two and four cases found with minor brain injuries in group IIa and group IIb MCs, respectively, a difference not great enough to reach a significant level between the subgroups IIa and IIb MCs.

Among the 14 cases in which only a minor brain anomaly was detected, 13 cases were diagnosed as transient; the remaining case, initially found with IVH grade I, showed evidence by brain scan of the lesion subsiding, later developed a focal seizure at clinical follow-up.

The only case diagnosed with a severe cerebral anomaly was an MC with sIUGR case, delivered by cesarean section at gestational age of 27 weeks 5 days weeks due to repeated late fetal heart beat deceleration in the IUGR twin. The IUGR twin with a birthweight of 680 gm died 15 days after delivery; the AGA twin with birthweight of 1190 gm was found with cystic PVL and ventriculomegaly 12 days after delivery and signs of cerebral palsy and global developmental delay began to show at follow-up.

The median gestational age of delivery in cases diagnosed with and without brain scan anomaly was 32.4 (range from 24.4~40.1) weeks versus 36.0 (range from 27.0~36.9) weeks, a gestation shorter in MCs with brain scan anomaly than without brain scan anomaly (p = .003 by Mann-Whitney U test).

Discussion

We found that the major cerebral injury rate was 3.7% (1/27) in group II MCs and the minor brain scan anomaly rate was 9.1% in group I MCs and 11.1% in group II MCs. The one case with a major cerebral injury suffered serous neurological sequelae (cerebral palsy). The majority (13/14, 92.9%) of the minor scan anomalies; however, were only transient without clinical significance. In a study of monochorionic diamniotic twins without TTTS (Cordero et al., 2005), it was concluded that monochorionic diamniotic twins had high rates of birthweight discordance, fetal growth restriction, fetal distress, prematurity and

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Table 3

Characteristics of Monochorionic Twins With Selective IUGR Divided Into Two Groups: With And Without Abnormal IUGR Twin UA Doppler

Group	Group IIa MC (n = 14)	Group IIb MC (n = 13)	p value
Median gestational age at delivery (weeks) (95% CI)	35.2 (32.5~37.2)	31.6 (30.1~33.4)	.037#
Median maternal age at delivery (year) (95% CI)	28.3 (25.6~31.0)	28.7 (27.7~33.3)	.308#
Median birthweight of AGA twin (gm) (95% CI)	2160 (1696~2563)	1750 (1371~2502)	.109#
Median birthweight of IUGR twin (gm) (95% CI)	1540 (1268~1904)	995 (777~1212)	.005#
Median birthweight discordance (%) (95% CI)	26.9 (20.7~30.0)	42.9 (35.7~47.4)	< .001#
Minor brain scan anomaly	2/28 (2 AGA)	4/26 (2 AGA and 2 IUGR twins)	.413^
Major brain scan anomaly (per baby number)	0/28	1/26 (AGA twin)	.481^
Neonatal death (per baby number)	0/28	3/26	.105^

Note: MC: monochorionic twin; IUGR: intrauterine growth restriction; CI: confidence interval; UA: umbilical artery
Group IIa: MC with selective IUGR and normal IUGR twin UA Doppler
Group IIb: MC with selective IUGR and abnormal IUGR twin UA Doppler
AGA: appropriate for gestational age
#: Mann-Whitney U test
^:Fisher's exact test

cesarean delivery, but their perinatal mortality was low; in the report, the incidence of grade III and IV IVH was 3% and PVL was 1% in the birthweight discordant group, a finding coinciding with our study results that the severe cerebral injury rate in MC with sIUGR was not as high as previously reported (Adegbite et al., 2005; Bejar et al., 1990).

In a recent report by Lopriore et al. (2008), who also found a low incidence of cerebral injury in MC with sIUGR (or discordant weight), they suspected one of the reasons for the low incidence was a relatively longer gestational age at delivery, 34 weeks in their case series. The incidence of major and minor brain injury was not significantly different between MC with and without sIUGR. However, when further analyzing the gestational age of delivery between cases with and without abnormal brain scan, we discovered cases with abnormal brain scan were delivered at a younger gestation, suggesting that prematurity of the babies and lower birthweight could contribute to some extent to the occurrence of brain scan anomaly in MC pregnancies.

Discordant birthweight has also been recognized as a risk factor for cerebral palsy (Adegbite et al., 2004). In our group II MCs, the mean birthweight discordance was 34.8 %, but the major and minor brain scan anomaly rate was not significantly higher than in group I MC whose birthweight discordance was 8.2%. We further analyzed the birthweight discordance between cases with abnormal brain scan and those without and found the birthweight discordance was 20.1% in the former and 16.7% in the latter, and was not a comparison with statistical significance (Mann-Whitney U test p = .77). One etiology, among others, of a high cerebral injury rate in discordant MCs might be due to inclusion of twins with one IUFD in their study, because the risk of agonal transfusion was high (Fusi & Gordon, 1990; Achiron et al., 1992). In cases without IUFD, the incidence of severe cerebral injury rate was low, as was demonstrated in this study. Another reason for the low major cerebral injury rate in group II MC in our series was that we excluded cases of TTTS, also known for posing a high risk of brain injury for the fetuses (Gonsoulin et al., 1990). Previous studies would include such cases, so the major cerebral injury rate in MC was high (Adegbite et al., 2005). Since the introduction of laser therapy for TTTS, the severe cerebral injury rate in TTTS receiving laser therapy has declined (Senat et al., 2004).

Therefore, to monitor the IUGR twin in order to decrease the rate of IUFD is important in MC with sIUGR, especially those with an abnormal IUGR twin UA Doppler. The UA Doppler finding of the sIUGR twin could itself serve as a prognostic indicator for neonatal outcome. After we divided group II MC by the IUGR twin UA Doppler, we found the cases of major cerebral injury and neonatal death were all in the group IIb MCs. In MC with sIUGR and normal IUGR twin UA Doppler, there was no neonatal death and severe cerebral injury found in our series. So the prognosis in group IIb MCs was poorer than group IIa MCs due to more cases of neonatal death or severe cerebral injury.

In our study, the rate of cerebral lesions was not significantly different between AGA and IUGR twins in group II MCs; more AGA twins (n = 5) than their IUGR counterparts (n = 2) developed brain lesions, and the only one case of severe brain lesion was in an AGA twin. These findings were compatible with what was reported by Gratacos et al. (2004) where the larger babies were at higher risk for cerebral injury in MC with sIUGR and intermittent abnormal IUGR twin UA Doppler.

Fetoscopic placental laser coagulation for MC with sIUGR had been performed as clinical trials (Gratacos et al., 2008; Quintero et al., 2001). Due to the fact that MC pregnancies with IUFD have a very high risk of cerebral injury to the surviving twin, fetoscopic

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surgery is beneficial in terms of reducing the neurological risk in cases where the IUGR twin was very likely to die in utero; it can prevent the agonal transfusion. The value of fetoscopic surgery in MC with sIUGR is mainly determined by two factors; what percentage of IUGR twins would become IUFD and what percentage of fetuses would die after fetoscopic surgery? In the large prospective study by Lewi et al. (2008), they report only 1 double IUFD and 1 single IUFD in 29 pairs of MC twins with severe discordant growth (IUFD rate 5% (3/58) and single IUFD rate 1.7%,(1/58)). If we multiply 1.7% by 18% (an estimated neurological injury rate for the surviving twin in an MC with one IUFD situation as proposed by Ong et al. (2006)), the total cerebral injury rate imposed on MC with sIUGR twins will be an extremely low 0.3% contributed by single IUFD. However, Quintero et al. (2001) reported that 5/11 (45.5%) of IUGR twins would die in utero after surgery (with abnormal IUGR twin UA Doppler) and 12/18 (66.6%) by Gratacos et al. (2008) in cases where IUGR twins had intermittent abnormal UA Doppler. Owing to the high percentage of IUGR twins that would likely die as a result of surgery, and a very small chance of encountering single IUFD and low risk of developing severe cerebral lesions in group II MCs as discovered by our study, routinely subjecting cases of MC with sIUGR to fetoscopic placental laser coagulation is not justified.

There were some limitations to this study: First of all, the case numbers were too small to tell the influence of intermittent abnormal UA Doppler of IUGR twin on the brain scan; according to a report bv Gratacos et al., there was a high incidence of neurological impairment in MC with sIUGR associated with intermittent abnormal UA Doppler in the IUGR twin (Gratacos et al., 2004). We had three cases of intermittent abnormal UA Doppler in group II MC and two cases in group I MCs, but none of them suffered from neurological abnormality. Secondly, this study used brain scans to evaluate the brain injury, but the ultrasound technique is far from perfect as a predictor of neurodevelopment outcomes. There were three babies suffering from neonatal death in group IIb MCs; they died within 2, 7 and 15 days of delivery. Though the brain scans were done after delivery, they revealed no evidence of cerebral injury. Several studies have shown that 95% of all IVHs can be detected by a cranial ultrasound performed on the seventh postnatal day, but severe brain injury like slowly progressive low pressure cerebral ventriculomegaly may not be noted until the infant approaches 40 weeks' conceptional age and PVL may not appear until the second postnatal week (Ment et al., 2000). Severe brain scan anomaly is strongly associated with neurological abnormality (Hack et al., 2000). But the role of minor brain scan anomaly is still not clear; perhaps low-grade hemorrhages more affect cognitive disability when compared with their nonhemorrhage gestation age-matched peers (Whitaker et al., 1996). Such babies will need a long term follow-up of their neurodevelopment. Thirdly, the injection study of the placenta was not performed, so the influence of the intertwined anastomoses on the brain injury could not be evaluated in this study.

In conclusion, after excluding cases of IUFD and TTTS, the incidence of major and minor brain scan anomaly rate in babies of MC with sIUGR was not significantly different from that in MC without IUGR cases; the incidence of major cerebral injury in MC with sIUGR was found to be relatively low.

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