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Perinatal Outcome of Monochorionic Twins With Selective IUGR Compared With Uncomplicated Monochorionic Twins

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Objective: To evaluate the perinatal outcome of MC twins with selective IUGR (sIUGR). *Study design:* A prospective study, which included three groups of MC twins: Group A, uncomplicated MC twin pregnancies (n = 91); group B, sIUGR with normal umbilical artery Doppler (n = 19); and group C, sIUGR with abnormal (absence or reversed EDV) umbilical artery Doppler (n = 18). The latter were routinely hospitalized in the high-risk ward under strict surveillance. *Results:* Neonatal outcome of fetuses complicated with sIUGR and normal Doppler was similar to controls. Neonates born to pregnancies complicated by sIUGR and abnormal Doppler had significantly increased incidence of CNS findings, RDS, NEC, sepsis, and neonatal death compared to controls. Adverse outcome in this group was independently associated only with gestational age at birth. *Conclusion:* The perinatal outcomes of MC twins complicated with sIUGR and normal Doppler are similar to uncomplicated MC pregnancies. MC twins with sIUGR and abnormal Doppler have reasonable outcomes, yet significantly more neonatal complications compared to non-complicated MC twins.

Keywords: monochorionic twins, IUGR, umbilical artery doppler

Selective intrauterine growth restriction (sIUGR) is increasingly recognized as an important complication of monochorionic (MC) twins, involving 7–14% (Acosta-Rojas et al., 2007; Lewi et al., 2008b) of these pregnancies. Uneven placental sharing is thought to be the principal cause of this condition, while the clinical process can depend to some degree on the combination of placental vascular anastomoses (Fick et al., 2006; Chang et al., 2008; 2009). The outcome of MC twin pregnancies with sIUGR without twin-to-twin transfusion syndrome (TTTS) is controversial. Gratacos et al. have described three subgroups of sIUGR patients based on Doppler flow patterns in the umbilical artery (Gratacos et al., 2007). Pregnancies with abnormal Doppler pattern (either absent/reversed flow or intermittent absence/reverse flow) were associated with a poor prognosis and a high incidence of IUFD, neonatal death and cerebral damage (Gratacos et al., 2004; Ishii et al., 2009; 2011). Others report on more favorable outcomes (Hack et al., 2009), even when considering the different Doppler flow patterns in the umbilical artery (Lopriore et al., 2008). Consequently, there is no consensus regarding the optimal prenatal management of MC pregnancies complicated by sIUGR. Furthermore, the prenatal sonographic and clinical prognostic factors of these pregnancies still need to be defined.

The aim of our study was to evaluate the perinatal outcome of MC twins with sIUGR and to assess whether the presence of Doppler flow abnormalities significantly alter the prognosis of such pregnancies even when managed under strict fetal surveillance.

Patients and Methods

This is a prospective cohort study, which included all MC pregnancies after 24 weeks of gestation that were followed at single tertiary center during a 4-year period (between August 2004 and July 2008). The Fetal Medicine Unit at the Sheba Medical Center serves as a referral center for

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fetal therapy, and is the only medical center in Israel performing in utero laser ablation procedures, bipolar cord coagulation or radio-frequency ablation (RFA) according to the medical scenario of complicated MC pregnancies. Patients with TTTS (Quintero, et al., 1999) or major fetal anomalies were excluded from the study. sIUGR was defined as estimated fetal weight (EFW) <10th percentile matched for gender and twin gestation in the local population (Dollberg et al., 2005) and co-twin with EFW >10th percentile. Abnormal umbilical artery Doppler flow was defined as absent or reversed end diastolic flow or intermittent absent end diastolic flow.

Cases were subsequently classified into three groups: uncomplicated MC twin pregnancies (group A), including all MC/BA twin pregnancies without TTTS, fetal anomalies or IUGR; sIUGR with normal Umbilical artery Doppler (group B); and sIUGR with abnormal Umbilical artery Doppler (either absence or reversed end-diastolic flow (a/rEDF) or intermittent a/rEDF) (group C). All pregnancies with sIUGR and abnormal Doppler or fetal weight discordance > 25% were hospitalized routinely after 26 weeks of gestation in the High Risk Pregnancy (HRP) ward for strict surveillance that included nonstress testing three times daily (NST/TID), daily biophysical profile and Doppler examination every other day. Doppler examination included umbilical artery flow measurements, middle cerebral artery (MCA) and ductus venosus (DV) evaluation in cases of suspected fetal deterioration. All pregnancies with selective IUGR that were hospitalized were given antenatal steroids on admission.

All neonates had a transfontanellar cranial ultrasound. Mild cerebral injury was defined by the presence of one of the following findings: intraventricular hemorrhage grade I or II, lenticulostiate vasculopathy and/or subependymal pseudocysts. Severe cerebral injury was defined when one of the following was detected: intraventricular hemorrhage grade III or IV, cystic periventricular leukomalacia (PVL) grade II or higher, porencephalic cysts, and/or ventricular dilatation. Antenatal data were prospectively obtained during each of the antenatal visits and neonatal outcomes were collected from the NICU's medical charts. Neonatal outcomes included respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), CNS abnormalities, sepsis and neonatal death.

The study was approved by the local institutional research ethics committee.

Statistics

Chi-square or Fisher's exact test was used as appropriate for comparison of categorical variables. All continuous data were tested for normality, and are expressed as median (range). One-way ANOVA was used for comparisons among study groups. $P < .05$ was considered significant. All statistical analyses were performed using SPSS version 13.0 (SPSS for Windows; SPSS Inc., Chicago, IL, USA).

Results

One hundred and sixty-nine patients with MC twin pregnancies were evaluated. Thirty-eight pregnancies were excluded due to TTTS ($n = 28$) and anatomical or chromosomal abnormalities ($n = 10$). Three other patients were excluded since both twins were IUGR. One hundred and twenty-eight patients were included in the analysis. Group A included 91 patients with uncomplicated MC pregnancies (control group), group B included 19 pregnancies with sIUGR and normal Doppler and group C included 18 pregnancies complicated by sIUGR and abnormal Doppler in the U/A (6/18 with iAEDV). Three cases of a single Intra Uterine Fetal Death (IUFD) occurred in the uncomplicated MC group (gestational age 29, 34 and 36). All three cases had their last evaluation (prior to fetal death) in an HMO outpatient clinic and presented with IUFD 3–4 days following an apparently normal ultrasound. The prenatal characteristics of our population are shown in Table 1.

Due to our policy, sIUGR pregnancies were hospitalized prenatally for longer period of time compared with controls (which were also hospitalized for other indications such as premature contractions, and so on). Monochorionic twins with sIUGR were delivered earlier compared to controls. However, the incidence of preterm delivery less than 32 weeks of gestation was significantly increased only in the sIUGR twins with abnormal Doppler. The MC twins with sIUGR and abnormal Doppler were more commonly delivered by CS compared to controls and many of them were delivered by an urgent CS due to deterioration of the fetal condition (either nonreassuring fetal heart rate or deteriorating flow pattern).

Two uncomplicated MC pregnancies were electively terminated due to IUFD of a single fetus (gestational age 34 and 36 weeks) and evidence of severe brain injury to the surviving twin. One uncomplicated MC pregnancy continued with a single living fetus. Altogether, 177 neonates were evaluated in the uncomplicated group. None of the sIUGR twin pregnancies was complicated by IUFD, and 74 neonates born to MC pregnancies with sIUGR were available for evaluation (Table 2).

The median cord blood pH were similar among all three groups. The median hematocrit (Hct) of the neonates (comparing larger and smaller neonates separately) did not differ significantly between the three groups; larger twin, group A (44), B (47), and C (45.5), and smaller twin, group A (44), B (44), and C (46). The incidence of neonatal complications was similar among the sIUGR MC pregnancies with normal Doppler (group B) and the controls. One neonate in group C (sIUGR with abnormal Doppler) was born with A low (3) 5-minute Apgar score. Two neonates (5.5%) in group C died during the neonatal period. Both neonates were born at 31 weeks of gestation weighing 720 and 810 grams; both had the highest weight discordancy compared to their co-twin

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TABLE 1

Prenatal and Delivery Characteristics of MC Pregnancies

	Group			*p* A:C	*p* A:B
	A Controls (*n* = 91)	B Normal UA Doppler (*n* = 19)	C Abnormal UA Doppler (*n* = 18)		
Prenatal hospitalization					
n (% of group)	21 (23%)	14 (74%)	18 (100%)	< .001	< .001
Days — median (range)	9 (2–64)	11 (2–42)	(2–62)	< .001	27
IUFD *n* (%)	3 (3.3%)	0	0		
GA@Delivery — median (range)					
Gestational age at delivery	36 (28–39)	35 (32–37)	32 (27–35)	< .001	.02
< 32	7 (6.6%)	0 (0%)	10 (55.6%)	< .001	1
< 34	13 (11%)	7 (36.8%)	17 (94.4%)	< .001	.04
Delivery by CS *n* (%)	52 (57.1%)	14 (73.7%)	17 (94.4%)	.001	.32
Urgent CS *n* (%)	26 (28.6%)	7 (36.8%)	10 (55.6%)	.06	.59
Birthweight — median (range)					
Larger twin (grams)	2345 (1410–3630)	2150 (1544–2715)	1550 (760–2275)	< .001	.015
Smaller twin (grams)	2180 (800–3285)	1720 (2005-2035)	1095 (585–1510)	< .001	< .001
Discordance (mean %)	6.90%	22.10%	30.60%	< .01	< .01
> 25% *n* (%)	0	6 (31.5%)	14 (77.7%)	< .01	< .01

Note: N = number of pregnancies, *n* = number, UA = Umbilical Artery, CS = cesarean section

(44% and 43%). Patients in group C had a significantly increased incidence of respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), sepsis and compound morbidity compared to controls.

Twenty-two neonates (8.7%) had abnormal CNS findings on neonatal cranial US. Of those, two thirds were classified as mild and one third as severe (Table 3).

CNS findings on neonatal US were significantly associated with IUGR, flow abnormalities, gestational age at delivery and birthweight (all $p < .01$). However, severe CNS findings were significantly associated with abnormal Doppler (and not IUGR), gestational age at delivery and birthweight. Pregnancies with sIUGR and abnormal Doppler had significantly more neonatal CNS findings (Likelihood ratio of 3.7, 95% CI 2.0–5.7) and specifically more severe findings (likelihood ratio of 3.9, 95% CI 1.8–5.7) compared with controls. Multiple logistic regression analysis was carried out to measure the independent associations between cerebral lesions and various clinical parameters (sIUGR, flow abnormality, sex, birthweight discordance of > 25%, gestational age at birth, and birthweight). Only gestational age at birth ($p < .001$) was independently inversely associated with cranial findings and with severe cranial findings. Neonates with severe neonatal US findings are presented in Table 4.

All IUGR neonates with severe CNS findings were delivered due to non-reassuring fetal heart rate ($n = 4$) or flow deterioration with reversed a-waves in the DV ($n = 1$). Composite bad outcome (defined as either neonatal morbidity or mortality) was significantly ($p < .01$) associ-

TABLE 2

Neonatal Complication of MC Twin Pregnancies

	Group			*p* A:C	*p* A:B
	A Controls (*n* = 177)	B Normal Doppler (*n* = 38)	C Abnormal Doppler (*n* = 36)		
All CNS findings	8	4	10	< .001	.23
Severe CNS findings	2	0	4	.005	1.0
RDS	13	4	18	< .001	.75
NEC	0	0	2	.03	—
SEPSIS	3	1	8	< .001	.56
Any morbidity	20	8	21	< .001	.11
NND	0	0	2	.03	—
Hosp. (d) median (range)	5 (2–99)	19 (3–42)	38 (13–120)	< .001	<.01

Note: *n* = number of neonates, RDS = Respiratory distress syndrome, NEC = necrotizing enterocolitis, NND = neonatal death.

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TABLE 3

CNS Findings on Neonatal Cranial US

	(A) Control (*n* = 177)	(B) sIUGR Normal Doppler (*n* = 38)	(C) sIUGR Abnormal Doppler (*n* = 36)
Infants with mild CNS findings *n* (%)	6 (3.3%)	4 (10.5%)	6 (16.6%)
Resolved periventricular hyperechogenicity	3	2	4
Resolved mild ventricular asymetry	1	0	1
Periventricular hyperechogenicity	1	0	1
IVH grade I	1	0	0
Lenticulostriate vasculopathy	0	2	0
Infants with severe CNS findings *n* (%)	2 (1.1%)	0	4 (11.1%)
IVH grade III	1	0	0
PVLw	0	0	3
Significant ventricular dilatation	1	0	0
Poroencephalic cyst	0	0	1

ated with IUGR, flow abnormalities, gestational age at diagnosis, low birthweight and lower Apgar scores (both 1` and 5`). However, on logistic regression analysis only gestational age at birth was independently associated with composite bad outcome.

Discussion

The outcome of MC pregnancies with sIUGR is not clear for both the smaller and the larger fetuses, and conflicting results have been reported (Chang et al., 2010; Ishii, 2009; Gratacos, 2007; Gratacos et al., 2004; Lopriore, 2008). Our study presents the prenatal and neonatal outcome of MC pregnancies with sIUGR managed prospectively under strict surveillance and hospitalization of patients with Doppler abnormalities or severe discordancy.

The rate of intra-uterine fetal death (IUFD) is five times higher in MC (7.6%) vs. DC (1.5%) twin pregnancies (Hack et al., 2008). IUGR and growth discordance might further increase the risk of IUFD (Lewi et al., 2008a). In our study, 3/182 (1.6%) non-complicated MC fetuses and none of the 74 fetuses in the IUGR group (0%) died in utero. This is in contrast to previous studies, which have showed a higher incidence of IUFD in sIUGR cases with or without umbilical artery flow abnormalities. Our study is under-powered to evaluate the risk of IUFD; however, the lower rate of IUFD in our study might also be due to including only cases that continued the pregnancy beyond 24 weeks of gestation. In studies with relatively higher rates of IUFD (Gratacos et al., 2004; 2007) about half of IUFD cases occurred prior to 24 weeks' gestation. The inconsistent data regarding incidence of IUFD might also be explained by the differences in definition of IUGR and inclusion criteria used by different studies. In our study, we defined sIUGR when one of the twins had EFW < 10th percentile, whereas Gratacos et al. used more strict criteria and defined sIUGR as EFW < 5th percentile and discordancy of ≥ 25%.

Our low rate of IUFD might also be explained by the close surveillance protocol starting at 26–27 weeks' gestation (including daily BPP and Doppler studies and non-stress test every eight hours) and policy of elective delivery at 34 weeks in cases of flow abnormalities. However, this cannot be concluded from our study since all patients with Doppler abnormalities were hospitalized and proper comparison cannot be made.

Cranial findings in MC twin pregnancies complicated by sIUGR were described in several cohorts of patients (Adegbite et al., 2005; Chang et al., 2010; Gratacos et al., 2004; 2007; Ishii et al., 2009; Lopriore et al., 2008).

TABLE 4

Characteristics of Neonates with Severe CNS Findings

	GA at delivery	Mode of delivery	Cause of delivery	S/L twin	Weight	Discordancy	Ab. flow	CNS findings to co-twin
Control								
IVH grade III	28+1	EmCS	PTL, cord prolapse	Similar weight	1000	0%	N	No
Ventricular dilatation	28+3	EmCS	Labor, breech	Similar weight	800	0%	N	No
sIUGR								
BL PVL	31+0	EmCS	Flow deterioration	L'	1445	36%	Y	Mild
BL PVL	29+3	EmCS	NRFHR	L	1470	30%	Y	No
PVL	31+0	EmCS	NRFHR	S	740	44%	Y	Mild
Poroencephalic cyst	31+5	EmCS	NRFHR	L	1680	26%	Y	No

Note: EmCS = Emegency cesarean section, NRFHR = Non-reassuring fetal heart rate, PVL = Periventricular leukomalacia

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TABLE 5

Cranial Findings in the Literature and in Our Study

Study	Definitions of study group vs. control group	Cranial findings in study group	Cranial findings in control group	*p*
Adegbite et al. (2005)	Retrospective — MC discordant (> 20%) twins vs. MC concordant twins	All 14/30 (46.6%)	All 12/76 (15.7%)	.002
Gratacos et al. (2004)	Prospective — sIUGR MC twins (birthweight < 5th% and discordancy > 25%) vs. monochorionic twins without IUGR	IVH 4/75 (5.3%) Parenchymal brain damage 9/75 (12%)	IVH 10/64 (15.6%) Parenchymal brain damage 0/64 (0%)	0.13 < .002
Lopriore et al. (2008)	sIUGR MC twins (with birthweight < 10th%) vs. uncomplicated MC twins	Mild lesions 20/94 (21.2%)	Mild lesions 12/94 (12.7%)	NS
	Mild lesions 20/94 (21.2%)	Severe lesions 4/94 (4.2%)	Severe lesions 2/94 (2.1%)	
	Severe lesions 4/94 (4.2%)			NS
Ishii et al. (2009)	Prospective — sIUGR MC twins (with birthweight < 10th%) with vs. without flow abnormalities	II — A/R EDV 7/52 (13.4%) III — iA/R EDV 8/26 (30.7%)	I — (+) EDV 1/46 (2.1%)	0.06 .001
Chang et al. (2010)	Retrospective — sIUGR MC twins (with birthweight < 10th%) vs. uncomplicated MC twins	IVH (I) 5/54 (9.2%) LSV 1/54 (1.8%) PVL 1/54 (1.8%)	IVH (I) 5/92 (5.4%) LSV 0/92 (0%) PVL 0/92 (0%)	0.5 .37 .37
Current study	sIUGR MC twins (with EFW < 10th %) with and without flow abnormalities vs. uncomplicated MC twins	Normal flow Mild lesions 4/38 (10.5%) Severe lesions 0/38 (0%)	Uncomplicated Mild lesions 5/177 (2.8%) Severe lesions 3/177 (1.7%)	 NS NS
		Abnormal flow Mild lesions 6/36 (16.6%) Severe lesions 4/36 (13.8%)		 .005 .005

However, these studies included a limited number of patients and vary in their methodology. Our study, as others (Adegbite et al., 2005; Gratacos et al., 2004; Ishii et al., 2009) found a higher incidence of both mild and severe cranial findings in the sIUGR group. The difference was statistically significant only in the sIUGR group with flow abnormalities. Multivariate regression analysis found that cranial findings were independently associated only with gestational age at birth. Similar results were found when analyzing other complications of prematurity (RDS, NEC, and sepsis). It is possible that strict follow-up might decrease the rate of IUFD by early intervention (delivery) on one hand, but on the other hand may result in increased incidence of neonatal complications due to prematurity.

In this study, the outcome of pregnancies with sIUGR and normal Doppler was similar to uncomplicated MC pregnancies. However, those with Doppler abnormalities (characterized as type II or type III by Gratacos et al. (2007)) were more prone to significant prematurity (< 32 weeks), delivery by CS, CNS findings (both mild and severe), RDS, sepsis and neonatal death. Our study has the strength of all women being evaluated and hospitalized in a single department. Another advantage is the strict follow-up (since diagnosis as sIUGR) that decreases the cases 'lost to follow-up'. However, due to the small number of cases, we did not separate sIUGR patients according to the type of flow abnormality (i.e., type II or type III AEDV (Gratacos et al., 2007)) and therefore we could not associate the outcome to either type II or III flow pattern.

The management of MC pregnancies complicated by sIUGR and abnormal flow is challenging. Comparing the outcomes from different studies is difficult due to the different methodologies (retrospective vs. prospective, interventional vs. observational, and so on). While some consider selective feticide or laser coagulation in order to protect the appropriately grown twin, others advocate a conservative expectant management (Gratacos et al., 2008; Quintero et al., 2001). We believe that the results of our study shed some light on this issue; however they are not conclusive enough to favor one management over the other. There is no doubt that more prospective studies and preferably randomized trials in this field should be presented in order to establish a more solid management algorithm.

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