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Perinatal Outcome of Monochorionic Twins with Selective Intrauterine Growth Restriction and Different Types of Umbilical Artery Doppler under Expectant Management

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Key Words
Monochorionic twins · Selective intrauterine fetal growth restriction · Umbilical artery · Perinatal prognosis

Abstract
Objectives: To evaluate the prognosis of monochorionic twins with selective intrauterine growth restriction (sIUGR), classified according to the type of umbilical artery Doppler, under expectant management. ***Methods:*** The outcome of 81 cases with isolated sIUGR was evaluated according to a classification based on umbilical artery (UA) Doppler diastolic flow in the IUGR twin (I: present, II: constantly absent/reverse, III: intermittently absent/reverse). Selective feticide was not considered due to legal constraints. Perinatal outcomes included perinatal death and neurological outcome at 6 months of age. ***Results:*** From 81 cases with the diagnosis of sIUGR, twin-twin transfusion was diagnosed in 18 cases. This left 63 cases, of which 23 were classified as type I (36.5%), 27 as type II (42.9%) and 13 as type III (20.6%). Intrauterine death occurred in 4.3% (1), 29.6% (8) and 15.4% (2) among IUGR twins, and 4.3% (1), 22.2% (6) and 0.0% (0) among larger twins. Neonatal death occurred in 0.0% (0), 18.5% (5) and 0.0% (0) among IUGR twins, and 0.0% (0), 11.1% (3) and 23.0% (3) among larger twins. Neurological abnormalities at 6 months were found in 4.3% (1), 14.8% (4) and 23.1% (3) in smaller twins and 0.0% (0), 11.1% (3) and 38.5% (5) in larger twins, respectively. Intact survival at 6 months was recorded in 91% (21), 37% (10) and 61% (8) in smaller twins and 95% (22), 55% (15) and 38% (5) in larger twins, respectively. ***Conclusion:*** The outcome in monochorionic twins with sIUGR and abnormal umbilical artery Doppler is poor under expectant management. Normal Doppler seems to be associated with a good prognosis.

Introduction

The incidence of selective intrauterine growth restriction (sIUGR) is approximately 11–14% among monochorionic (MC) twins [1–3], and this condition has been shown to be associated with substantial perinatal risks for both fetuses [1, 3–7]. 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 [3, 6–8]. Recently, a classification system according to the characteristics of

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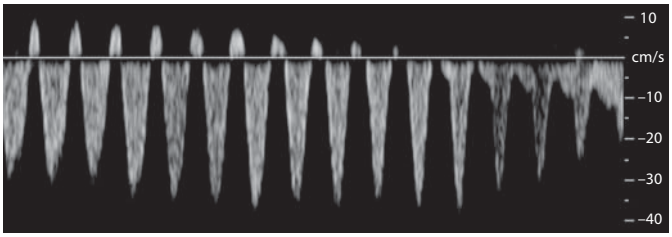

Fig. 1. Typical image of intermittent AREDF in the umbilical artery Doppler waveforms, with cycles intermittently showing AREDF.

diastolic Doppler flow in the umbilical artery (UA) of the smaller twin was advocated by Gratacos et al. [6] to differentiate cases into 3 different clinical forms: type I, normal UA Doppler; type II, persistent absent or reversed end-diastolic velocity flow (AREDF), or type III, intermittent AREDF (iAREDF). While outcomes for type I pregnancies are commonly favorable, IUGR twins in type II cases show in most cases fetal deterioration with a high associated risk of intrauterine fetal death (IUFD) [6]. MC twins with type III sIUGR are characterized by an atypical clinical evolution. About 15% of IUGR twins die unexpectedly and 20% of the larger fetuses show complications of neurological damage due to acute feto-fetal transfusion accidents via arterio-arterial anastomoses [6].

One limitation of previous studies on MC twins with sIUGR is that cord occlusion was performed, either electively [4] or because of fetal deterioration [6]. Therefore, it is unknown whether intervention may have biased the outcome of these clinical series.

In this study, we report the natural history of MC pregnancies complicated with sIUGR in a consecutive series of 81 cases managed expectantly. Perinatal outcome was compared among three study groups established according to the classification system based on the type of UA Doppler in the smaller twin.

Methods

A total of 81 MC twin pregnancies were diagnosed with sIUGR before gestational week 26 in three institutions in Japan from 2001 to 2008. Patients provided informed consent to have their data recorded for clinical studies, which were approved by the Institutional Review Boards at the respective institutions. The definition of sIUGR was an estimated fetal body weight below the 10th percentile in the smaller twin. Twin-twin transfusion syndrome (TTTS) was defined as the presence of ultrasound findings of polyhydramnios in one twin and oligohydramnios in the other, together with markedly discordant bladders, as previously defined [9]. Cases with TTTS or the diagnosis of a fetal malformation at the time of initial diagnosis were not included in this study. Cases with sIUGR were classified into 3 groups based on UA Doppler flow: type I, positive end-diastolic velocity in UA; type II, AREDF constantly observed, or type III, iAREDF defined as the clear observation of abnormal diastolic flow waveforms following an intermittent pattern within a short interval (fig. 1) [6]. Doppler waveforms were recorded using a minimum of three measurements at a free loop in each UA in the absence of fetal or maternal movement. Doppler sampling was performed using a 3.5- or 5-MHz curved array transducer with spatial peak temporal average intensities of <100 mW/cm^2. The angle of insonation was 0° or as close to 0° as possible. The pictures of Doppler exams were available and of good quality from all cases. The diagnosis was established by the characteristics of Doppler at enrolment, but a minimum of two consecutive examinations confirming the initial findings were required at each participating institution.

Fetal condition was monitored by ultrasonography, including fetal growth curves, amniotic pocket and UA Doppler, in combination with fetal heart rate (FHR) monitoring on non-stress test or fetal biophysical profile at these three centers or the referring hospitals. If a case was diagnosed with TTTS before gestational week 26 after the initial diagnosis of sIUGR, laser therapy was contemplated. Selective feticide by cord occlusion was not an option in our clinical setting, and therefore all cases not diagnosed as having TTTS during the observation period were managed expectantly. Indications and route of delivery were decided at the discretion of the attending physicians. Principally, delivery was considered by fetal indications, including fetal deterioration defined by abnormal FHR and/or abnormal biophysical profiling (BPP) score, and by estimated fetal growth arrest at least for 2 weeks after 32 weeks of gestation. Abnormal Doppler waveforms including reversed flow in ductus venosus and reversed flow in umbilical artery were used in some cases, but since the study period was long they were not used consistently for clinical decisions throughout the whole study period.

The occurrence of TTTS was recorded. Perinatal outcome, including the rate of intrauterine and neonatal death, and the rate of neurological morbidity at 6 months of age was recorded in all twins. All neonates were assessed by neonatologists and ultrasonographic brain scan was performed normally and investigation by MRI was indicated when ultrasonography revealed abnormal brain scans within the 6 months' observational period. Any significant abnormal findings on brain ultrasonography or MRI, including intraventricular hemorrhage (grade III or IV), cystic periventricular leukomalacia, blindness, deafness were regarded as neurological morbidity as defined before [9]. The absence of the above mentioned neurological morbidity at 6 months of age was defined as intact survival. Infants were not assessed by any developmental tests in this study.

Results

A total of 81 cases were recorded during the study period, comprising 26 cases of type I, 40 cases of type II and 15 cases of type III. The incidence of TTTS before gestational week 26 after an initial diagnosis of sIUGR was

Table 1. Perinatal outcome according to a classification based on umbilical artery Doppler

	Type I (n = 23)	Type II (n = 27)	Type III (n = 13)
GA at delivery, weeks, median (range)	36 (26–38)	28 (18–40)	31 (25–37)
Fetal indication for delivery, % (n)	30.4 (7)	70.4 (19)	69.2 (9)
Fetal deterioration in smaller twins, % (n)	8.7 (2)	25.9 (7)	15.4 (2)
Growth arrest in smaller twins, % (n)	3 (13.0)	11.1 (3)	7.7 (1)
Fetal deterioration in larger twins, % (n)	4.3 (1)	7.4 (2)	38.5 (5)
Growth arrest in larger twins, % (n)	0.0 (0)	0.0 (0)	0.0 (0)
Fetal deterioration in both twins, % (n)	4.3 (1)	0.0 (0)	7.7 (1)
Intrauterine both fetal demise, % (n)	0.0 (0)	14.8 (4)	0.0 (0)
Miscarriage, % (n)	0.0 (0)	7.4 (2)	0.0 (0)
IUFD of smaller twins, % (n)	4.3 (1)	29.6 (8)	15.4 (2)
IUFD of larger twins, % (n)	4.3 (1)	22.2 (6)	0.0 (0)
NND of smaller twins, % (n)	0.0 (0)	18.5 (5)	0.0 (0)
NND of larger twins, % (n)	0.0 (0)	11.1 (3)	23.1 (3)
NM of smaller twins, % (n)	4.3 (1)	14.8 (4)	23.1 (3)
NM of larger twins, % (n)	0.0 (0)	11.1 (3)	38.5 (5)

GA = Gestational age; IUFD = intrauterine fetal death; NND = neonatal death; NM = neurological morbidity.

11.5% (3/26) in type I, 32.5% (13/40) in type II and 13.3% (2/15) in type III. All 18 patients with TTTS were treated by laser surgery. This left 63 patients with isolated sIUGR, distributed in 23 type I patients, 27 type II patients and 13 type III patients (table 1).

Median gestational age at delivery was 36 weeks (range, 26–38 weeks) in type I, 28 weeks (range, 18–40 weeks) in type II and 31 weeks (range, 25–37 weeks) in type III. The rate of intrauterine death was 4.3% (1), 29.6% (8) and 15.4% (2) in the IUGR twins, and 4.3% (1), 22.2% (6) and 0.0% (0) in the larger twin (table 1). Delivery was indicated for fetal reasons as defined above in 30.4% of type I cases, 70.4% of type II cases, and 69.2% of type III cases. In the remaining patients delivery occurred due to spontaneous labor or it was indicated for maternal reasons.

Data on postnatal evolution are summarized in table 1. The rate of neonatal mortality in types I, II and III was 0.0% (0), 18.5% (5) and 0.0% (0) among smaller twins, and 0.0% (0), 11.1% (3) and 23.0% (3) among larger twins, respectively. There was no infant death after the neonatal period in any of the three study groups. Neurological morbidity within 6 months after birth, as defined above, was found in 4.3% (1), 14.8% (4) and 23.1% (3) of smaller twins and in 0.0% (0), 11.1% (3) and 38.5% (5) of larger twins in pregnancies defined as type I, II and III, respectively.

When the totality of cases with and without intact survival was analyzed, among the 23 type I twins, 91.3% (21) smaller twins and 95.7% (22) larger twins were defined as having intact survival (IS). Among 27 type II pregnancies, 37.0% (10) smaller and 55.6% (15) larger twins had IS. Finally, among 13 type III twins, 61.5% (8) smaller and 38.5% (5) larger infants were defined as having IS. The distribution of cases within each pregnancy type according to the presence of IS in both fetuses, only one or none are displayed in figure 2.

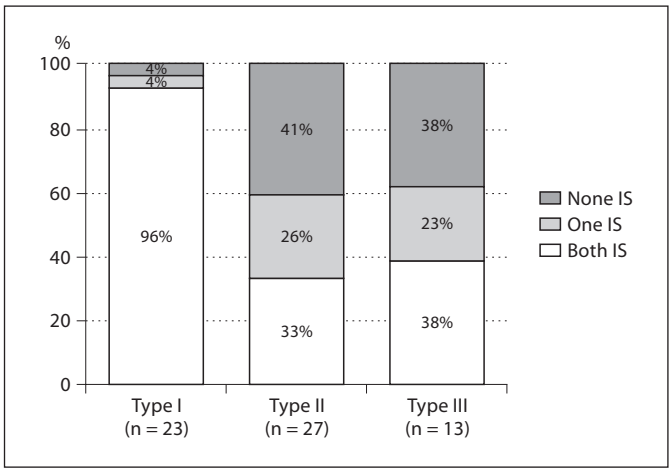

Fig. 2. Pregnancy outcome per mother; the number of infants with intact survival. IS = Intact survival; not IS = death or neurological morbidity.

Discussion

Perinatal prognosis has previously been described for 134 MC twins with sIUGR according to a classification system based on UA Doppler waveforms, with umbilical cord occlusion performed for some cases with abnormal UA based on predicted poor outcome [6]. On the contrary, the present study described perinatal outcomes in a clinical series of cases complicated with sIUGR and managed expectantly with early delivery if warranted, since selective feticide was not applicable due to legal constraints. Among the limitations which must be considered as potential biases in this clinical series is the retrospective nature of the study, and the fact that subjects included patients referred from scattered hospitals, although patients were diagnosed and classified on UA Doppler by specialists at each of the three participating centers. Nevertheless, these results could be of value in clarifying the natural history of twins with sIUGR.

It was noteworthy that the incidence of TTTS before gestational week 26 in the observational period was around one-third in type II cases, while that in type I or III cases was around 12%. This finding could indicate that cases with continuously abnormal UA Doppler in the smaller twin might be at higher risk for TTTS. Type I cases could be relatively protected from TTTS because of a higher number of placental anastomoses, which might allow a more efficient inter-twin blood exchange [3]. Likewise, type III could also be relatively protected from the occurrence of TTTS by the presence of large artery-to-artery anastomoses [6, 10]. Unfortunately, this study did not analyze in detail placental vascular anastomoses preventing any comparison in these respects.

Perinatal outcomes for type I twins were in general favorable, with an intact survival rate in both smaller and larger twins over 90%. The findings are in line with previously reported data [6]. In the light of this evidence, it might seem reasonable that type I patients be managed conservatively until late in gestation. Conversely, type II patients showed the worst prognosis among the three study groups. IS in type II was only 37.0% in smaller twins and 55.6% in larger twins. Of note was the fact that 48.1% of the smaller fetuses showed perinatal death including fetal and neonatal death. Our findings are in line with those of Quintero et al. [4], reporting a high rate of IUFD in type II fetuses managed expectantly. This complication may have remarkable consequences on the outcome of the other twin, due to the risk of acute feto-fetal hemorrhage [11–13]. In a previous report, in utero deterioration of the sIUGR fetus was found in 90.0% of type II [6]. Although in the present study we used a different definition for fetal deterioration, 70% of the type II pregnancies here reported needed delivery due to fetal indications.

The clinical evolution of type III twins presenting with iAREDF has been reported to be atypical. Although sIUGR fetuses differ from type II by failing to show signs of fetal hypoxic deterioration, some sIUGR fetuses may die unexpectedly. More importantly, the proportion of larger twins presenting neurological abnormalities such as PVL may be high in spite of both fetuses being born alive [5, 6]. Only a small number of type III cases were included in the present study. However, the results appear similar to those previously reported [5, 6], with 15.4% of smaller twins presenting IUFD and 38.5% of larger twins showing brain damage.

As the outcome of MC pregnancies with sIUGR and abnormal UA Doppler seems to be clearly unfavorable, some sort of intervention could be considered for these cases at the time of diagnosis. Umbilical cord occlusion for selective feticide has been extensively reported as an option for complicated or discordant MC twins [14, 15], and this procedure could be considered as an option for type II and III pregnancies. However, the use of this technique may be controversial. Selective feticide reduces by definition the survival rate to 50%, and in some cases the remaining twin can also present perinatal death or neurological morbidity [14]. For this reason, and particularly in countries such as Japan where feticide is usually ethically unacceptable, the application of laser coagulation for placental communicating vessels may be an option. The overwhelming advantage that this therapy represents for TTTS [9] has not been reproduced in preliminary clinical series reporting the use of laser placental coagulation in type II [4] or type III cases [4, 16]. Although the number of cases included in these studies has so far been small and further experience may be required, the results suggest that laser may increase the chances of fetal death of the smaller twin, but it might protect the larger twin from the consequences of fetal death of the IUGR fetus [4, 16].

In conclusion, clinical evolution and perinatal outcome with expectant management was different in MC twins with sIUGR classified according to the type of UA Doppler flow in the sIUGR fetus. In general, the outcome in MC twins with sIUGR and abnormal umbilical artery Doppler was markedly poor under expectant management, while normal Doppler seemed to be associated with a good prognosis. Fetal intervention such as cord

occlusion or laser therapy might be considered as a management option for sIUGR cases with abnormal Doppler findings, but the benefit of this options remains to be evaluated in further clinical studies.

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