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Cord Occlusion in Monochorionic Twins with Early Selective Intrauterine Growth Restriction and Abnormal Umbilical Artery Doppler: A Consecutive Series of 90 Cases

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Key Words
Monochorionic pregnancy · Selective intrauterine growth restriction · Cord occlusion · Fetal therapy

Abstract
Objective: To describe perinatal outcomes achieved with cord occlusion (CO) in monochorionic twins with severe selective intrauterine growth restriction (sIUGR) and abnormal umbilical artery Doppler in the IUGR twin (types II and III). ***Methods:*** We studied a consecutive series of 90 cases of sIUGR with abnormal Doppler treated with CO of the IUGR fetus. Abnormal Doppler was defined as continuous (type II, n = 41) or intermittent (type III, n = 49) absent/reversed end-diastolic flow. All cases presented at least one of the following severity criteria: gestational age (GA) <22 weeks, inter-twin estimated weight discordance >35%, reversed end-diastolic umbilical artery flow or ductus venosus pulsatility index >95th centile. We prospectively recorded pregnancy course and perinatal outcome. ***Results:*** Median GA at surgery was 20.6 weeks and mean duration 22.4 min. Miscarriage (<24 weeks) occurred in 3.3% (3/90) and preterm delivery <32 weeks in 7.1% (6/84) of continuing pregnancies. GA at delivery was 36.4 weeks and neonatal survival of the larger twin was achieved in 93.3%. ***Conclusion:*** In a consecutive series studied by an experienced team, CO in monochorionic twins with severe sIUGR type II or III was associated with delivery >32 weeks in 92.9% and neonatal survival of the normal twin in 93.3% of pregnancies.

Introduction

Early-onset selective intrauterine growth restriction (sIUGR) affects about 10% of monochorionic (MC) twins [1] and is associated with an increased risk of perinatal mortality and neurological adverse outcome [2–4]. Although unequal placental sharing is the main cause of sIUGR in MC twins [5], the pattern of placental anastomoses, and consequently of inter-twin blood flow inter-

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change, determines important differences in the clinical evolution and prognosis [6, 7]. The characteristics of diastolic flow in the umbilical artery (UA) Doppler of the fetus with sIUGR classifies three clinical groups with distinct clinical evolution [4]. Type I sIUGR presents with normal UA Doppler and is associated with normally good outcomes. On the contrary, types II and III, which represent different forms of abnormal Doppler, are associated with a high risk of poor outcome, including very preterm delivery, intrauterine fetal death and neurological sequelae for both twins [8–11].

The poor outcomes associated with early-onset sIUGR types II and III may prompt parents to request active therapy. Unfortunately, there is no clear evidence to support a best management strategy for early-onset severe sIUGR [12]. Laser coagulation of placental anastomoses has been attempted to preserve fetal survival and prevent the complications associated with inter-twin acute transfusion episodes occurring in this condition [10, 11, 13, 14]. Clinical series have reported that laser coagulation results in survival rates of roughly 70% for the normally grown and 40% for the IUGR twin. As an alternative to laser coagulation, and particularly in severe cases developing early in pregnancy, parents may request cord occlusion (CO) to maximize outcomes for the normally grown twin. A recent clinical series reported survival in the larger twin of 90% in comparison with 73% in cases treated with laser [11].

The aim of this study was to report a single-center experience in a large consecutive series of MC twins complicated with sIUGR types II and III and managed with CO.

Methods

This clinical series includes a consecutive series of MC pregnancies complicated with sIUGR type II or III and treated with CO during a 6-year period at Hospital Clínic of Barcelona. The study protocol was approved by the institutional ethics committee as part of a large prospective research program for MC twins (QLG1-CT-2002-01632) and signed consent for the use of their clinical data for research studies was obtained by all patients. The cases included in this clinical series have not been reported in any previous study.

Severe early-onset IUGR was defined as an estimated fetal weight below the 10th centile [15] when the diagnosis was performed after 24 weeks of gestation or abdominal circumference less than the 10th centile [16] together with an inter-twin discordance ≥25% [6]. None of the cases included had signs of twin-to-twin transfusion syndrome (TTTS) or associated abnormalities detected prior to surgery [12]. The type of sIUGR was defined according to the characteristics of diastolic flow in the UA Doppler [4]. Briefly, type II was defined as the continuous observation of absent or reversed end-diastolic flow (AREDF) in UA Doppler. Type III sIUGR was defined by the presence of intermittent AREDF, i.e. the observation of waveforms with AREDF alternating over seconds or minutes with waveforms with positive diastolic flow, following a characteristic intermittent or cyclic pattern as previously described [9, 17]. According to the institutional clinical protocol for the management of MC pregnancies complicated with sIUGR, active therapy (CO or laser) was discussed with parents when any of the following severity criteria was present: early onset (i.e. gestational age [GA] <22 weeks), inter-twin estimated weight discordance >35%, reversed end-diastolic UA flow or ductus venosus (DV) pulsatility index >95th centile. In all cases parents were extensively counseled about the existing evidence and the potential benefits and risks associated with expectant versus active management. The cohort reported here corresponds to all patients requesting CO during the study period.

CO was performed as previously described [13]. Briefly, procedures were performed under maternal sedation with intravascular remifentanil and local anesthesia to allow percutaneous insertion of a 10-F (3.3-mm) Cook cannula. CO was performed preferentially by means of bipolar coagulation (Molly Bipolar Forceps 3.0 mm; Everest Medical, Maple Grove, Minn., USA), but diode laser coagulation was attempted at very early GAs and/or when the diameter of the cord was subjectively small [18, 19]. As the first option, coagulation was performed in the sac of the IUGR twin. Since reduced amniotic fluid is common in these cases, amnioinfusion was used as required to create space allowing to perform the procedure. When the sac of the IUGR was not accessible because it was completely covered by placenta, the trocar was inserted into the sac of the normal fetus and septostomy was performed to access the IUGR sac. Since this entailed creation of a monoamniotic pregnancy, in these specific cases CO was followed by cord section in order to avoid cord entanglement [20]. Patients were normally discharged within 24–48 h after the procedure.

All women were assessed by detailed ultrasound protocols, including placental and fetal Doppler, before the procedure. Postoperative follow-up was conducted 24 h later and then weekly or at closer intervals if indicated by fetal monitoring tests. Pregnancy course and perinatal outcomes were recorded in all cases. Data were obtained from our own records or by contact with the referring physicians and the patients themselves in order to have access to all relevant clinical reports allowing to adequately assess perinatal and neonatal outcomes.

Data were stored in a database and analyzed with the SPSS 17.0 statistical package (SPSS, Chicago, Ill., USA). Normal distribution of the continuous variables was checked by the Kolmogorov-Smirnov test. To determine significant differences between groups, continuous variables were compared by means of Student's t test, Mann-Whitney's U test or ANOVA/Kruskal-Wallis test as appropriate. Categorical variables were compared by χ^2 test or Fisher's exact test as appropriate [21–24].

Results

A total of 142 fetuses with sIUGR type II or III were referred to our Fetal Medicine Service for evaluation at a median GA of 21.6 weeks (range 15.0–34.2). Of these, 24.6% (35/142) did not meet the severity criteria previ-

Table 1. Characteristics of patients and operative features in type II and III sIUGR twin pregnancies managed with CO

Characteristics	Overall	sIUGR	
		type II (n = 41)	type III (n = 49)
Maternal age, years	32.0 (19.0–44.0)	31.7 (19.0–44.0)	32.2 (22.0–39.0)
Nulliparity	69 (76.6%)	34 (82.9%)	35 (71.4%)
GA at therapy, weeks	20.6 (15.1–28.5)	20.0 (15.1–28.5)	21.5 (15.6–28.0)
Estimated fetal weight discordance, %	35.2±5.8	37.6±5.7	33.2±9.8
Anterior placenta	44 (48.8%)	21 (51.2%)	23 (46.9%)
Duration of surgery, min	22.4 (9.0–53.0)	21.8 (9.0–45.0)	23.0 (10.2–53.0)

Data are median (range), n (%) or mean ± standard deviation, as appropriate.

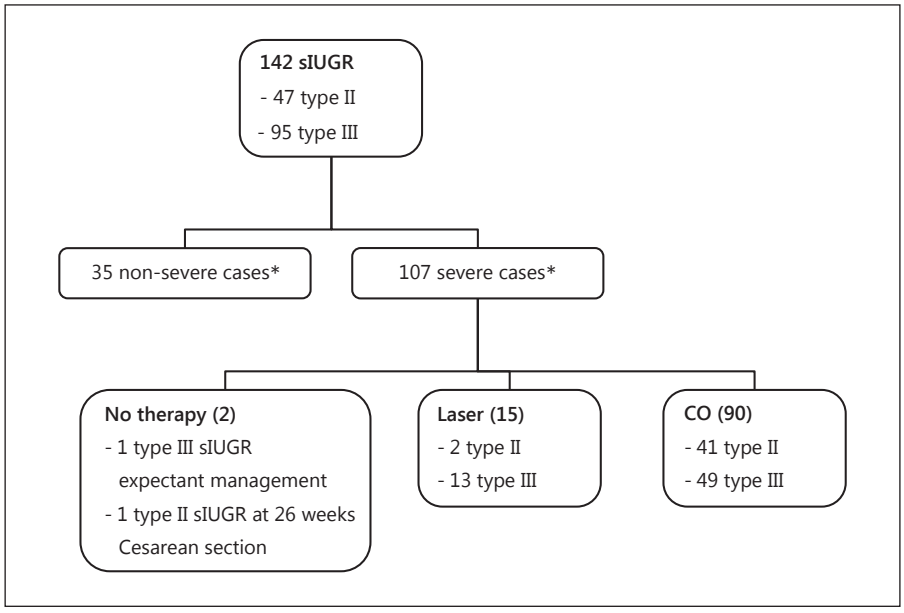

Fig. 1. Flow chart of referred type II and III sIUGR. * Severity defined as the presence of any of the following criteria: early onset (i.e. GA <22 weeks), inter-twin estimated weight discordance >35%, reverse end-diastolic UA flow or DV pulsatility index >95th centile.

ously described, while the remaining 75.4% (107/142) presented at least one severity criterion and fetal therapy was offered. Laser photocoagulation of vascular anastomosis and CO were performed, at the parents' request, in 15 and 90 cases, respectively (fig. 1). Therefore, a total of 90 MC twins, 41 (45.6%) with sIUGR type II and 49 (54.4%) with sIUGR type III, in whom CO was performed, were included in the study. Table 1 summarizes the baseline and operative features of the patients reported. The characteristics of fetoplacental Doppler at the time of treatment are displayed in table 2. As expected, the rate of abnormal DV pulsatility index was high in both groups. Overall, 48.8% (20/41) of type II and 40.8% (20/49) of type III patients had either elevated pulsatility index or reversed atrial flow in the DV of the smaller fetus. The operation was performed entirely in the sac of the smaller twin in 85 (94.4%) cases, whereas in 5 (5.6%) the trocar was entered into the sac of the normal fetus and a septostomy was required, as explained above. Bipolar CO was used in 79 (87.8%) of cases, while diode laser coagulation was attempted in the remaining 11 (12.2%) cases, all performed before 18 weeks gestation.

Pregnancy courses and perinatal outcomes are displayed in table 3. Fetal demise occurred in 3 (3.3%) cases, all within 1 week of the procedure. Death occurred prenatally in 1 case with complete chorioamniotic detachment and retrochorionic hematoma. The remaining cases were due to preterm delivery before 24 weeks gestation. A total of 87 (96.7%) fetuses were born alive, while 3 newborns died within the neonatal period due to extreme pre-

Table 2. Fetal Doppler characteristics of the UA and DV in the study groups

Doppler	sIUGR	
	type II (n = 41)	type III (n = 49)
UA reversed end-diastolic flow		
Larger twin	0	0
Smaller twin	12 (29.3%)	9 (18.4%)[a]
DV PI >95th centile		
Larger twin	7 (17.1%)	4 (8.1%)
Smaller twin	20 (48.8%)	20 (40.8%)*
Absent or reversed A wave DV at diagnosis		
Larger twin	1 (2.4%)	0 (0.0%)
Smaller twin	15 (36.6%)	7 (14.3%)*

PI = Pulsatility index.
[a] Predominantly reversed end-diastolic flow.
* $p < 0.05$; χ^2 test and corrected with Fisher's exact test.

Table 3. Pregnancy courses and perinatal outcomes after CO in sIUGR type II and III (n = 90)

Characteristics	sIUGR	
	type II (n = 41)	type III (n = 49)
Survival of larger twin	38 (92.7%)	46 (93.4%)
GA at delivery, week	36.4 (28.5–41.1)	36.5 (26.0–41.0)
Birth weight of live-born twin, g	2,696±768	2,599±828
Miscarriage <24 weeks	2/41 (4.9%)	1/49 (2.0%)
PPROM <32 weeks	5/39 (12.8%)	5/48 (10.4%)
Preterm delivery <37 weeks	12/39 (30.8%)	15/48 (31.3%)
Preterm delivery <32 weeks	3/39 (7.7%)	3/48 (6.3%)
Membrane detachment	5/41 (12.2%)	4/49 (8.1%)
Septostomy	4/41 (9.8%)	2/49 (4.1%)

Data are median (range), n (%) or mean ± standard deviation, as appropriate.
PPROM = Preterm premature rupture of membranes.

maturity and a severe Ebstein's anomaly detected during follow-up, respectively. Thus, overall neonatal survival was 93.3% (84/90). Septostomy was observed in a total of 6 cases, 3 cases where septostomy was intentional plus 3 further cases where septostomy was discovered on follow-up.

Discussion

This clinical series describes the outcomes of sIUGR MC twins with abnormal Doppler and managed with CO. Survival rates in the normal fetus were in the higher range of previously reported figures for MC pregnancies undergoing CO using bipolar and/or laser coagulation. Thus, individual studies have reported rates of 70–87% [25–28]. A recent meta-analysis, including 12 studies and various techniques, reported a 79% overall survival rate [29]. However, the majority of case series included procedures performed during the learning curve of the team. When the current series started, the team had over 450 previous fetoscopic procedures. In this respect, the survival rates were fairly similar to the 91% reported by Chalouhi et al. [11] and the 88% reported by Bebbington et al. [25] in sIUGR managed by CO by an experienced team.

Management of type II and III sIUGR MC pregnancies is a challenge because sIUGR is not a single condition such as TTTS. While clinical series end to include early-

onset severe cases, there are still differences in the GA at onset, the magnitude of fetal weight discrepancy and the severity of Doppler changes. In addition, parents' preferences may strongly determine their decision as to the preferred attitude. Previous series have consistently reported that these pregnancies are at substantially high risk of preterm birth, perinatal death and neurological sequelae. In a study performed in Japan, where selective termination is not allowed, Ishii et al. [8] reported an intact survival rate of 37% for the smaller and of 55% for the larger twin in type II sIUGR, with a mean GA at delivery of 28 weeks. Quintero et al. [10] reported a 41% intrauterine death rate in type II sIUGR in cases managed conservatively, with 42% complicated by concomitant death of the co-twin and a rate of neurological damage of 13.6%. Huber et al. [30] reported a 60% survival rate in 19 MC twin pregnancies with sIUGR and persistent AREDF in the UA (type II), with a high rate of preterm delivery <32 weeks. Finally, in type III fetuses two series have described a 15% in utero mortality for the IUGR twin, with a 19–38% rate of parenchymal brain damage in the normally grown twin, irrespective of whether the IUGR co-twin was born alive or dead [4, 8]. A relevant clinical question is how CO compares with laser coagulation in MC twins with sIUGR. Peeva et al. [14] recently published the largest series of type II sIUGR treated by endoscopic placental laser coagulation, with a survival rate of the normal twin of 67.6% (96/142), 38.7% of the IUGR fetuses (55/142) and an overall survival rate of 53.2% (151/284). In a previous smaller series, Quintero et al. [10] treated MC twins with sIUGR and UA AREDF (type II) with laser and reported a 63.6% survival rate (7/11) of the normal twin and 45.5% survival rate (5/11) of the IUGR fetus. In a series mentioned above, Chalouhi et al. [11] reported CO but also placental laser coagulation in 23 cases with either type II or III sIUGR. Survival was 74% in the normal twin and 30% in the IUGR twin. Finally, we have previously reported 18 cases with sIUGR type III treated with laser, with survival rates of 94 and 33% for the normal and IUGR twin, respectively [13]. However, we must stress that this series represented selected cases of sIUGR where the operation was deemed technically feasible. It is likely that when all consecutive cases are treated with laser, survival for the normal twin is closer to figures reported by Chalouhi et al. [11] and Quintero et al. [10]. Reduced survival of the IUGR fetus treated with laser is logical considering that laser coagulation discontinues the protective blood supply from the larger fetus. The apparently lower survival in the larger twin could result from a combination of factors, including the need to operate in the sac of the larger twin and the fact that, as previously described, the operation can be considerably more challenging as compared with laser in TTTS [13]. As mentioned above, the decision on the type of therapy will remain essentially a decision of parents. Although the decision to perform CO may seem clearly more radical to parents, average overall survival rates (i.e. newborns surviving in relation with the initial total number of fetuses) in the series quoted above were around 55% with laser and 46% with CO. This means that for every 50 pregnancies treated (with 100 fetuses), laser would result approximately in 35 normal twins and 19 IUGR twins surviving, while CO would lead to 46 normal twins alive. These figures might be of help when counseling parents with this condition.

This study represents the largest reported clinical series of sIUGR managed with CO. This series should not be regarded as representative of the true population of sIUGR whatsoever. The cases reported here represent the most severe end of the spectrum, since the sample size was made up of cases referred to a fetal therapy center. Consequently, the proportion of cases presenting with severity criteria is overrepresented and should not be considered as a reflection of the true proportions in a nonselected population of sIUGR. Despite being the largest reported sample, we acknowledge that there still remains a relatively small sample size, so that the smaller size of the resulting subgroups may have prevented the detection of uncommon complications. Likewise, all cases were selected on the basis of severity criteria defined a priori. However, we acknowledge that the criteria to define 'severity' were arbitrary since there is no conclusive evidence in this respect. Finally, follow-up in this study was not complete for all cases. We used medical reports and information from managing physicians, and this might result in under ascertainment of mild cases of neurological impairment. However, previous studies on 1-year follow up in patients treated with CO, with a significant proportion of cases with sIUGR, reported no increase in morbidity aside from that associated with prematurity [28].

CO in MC twins, and particularly in sIUGR, is a challenging procedure. The operation very often requires previous amnioinfusion and working in a relatively reduced operative space. Short operative times and minimal manipulation are critical to achieve optimal results. We must stress that fetoscopic techniques should only be performed in tertiary centers by teams with consolidated experience. The results reported here represent the performance of CO in experienced hands. This information can be of value for counseling parents affected by this condition.

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