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Selective Fetal Growth Restriction in Monochorionic Diamniotic Twins: Diagnosis and Management

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Abstract

Selective fetal growth restriction (sFGR) is a severe condition that complicates 10% to 15% of all monochorionic diamniotic (MCDA) twin pregnancies. Pregnancies complicated with sFGR are at high risk of intrauterine demise or adverse perinatal outcome for the twins. Three clinical types have been described according to the umbilical artery (UA) Doppler pattern observed in the smaller twin: type I, when the UA Doppler is normal; type II, when there is persistent absent or reversed end-diastolic blood flow in the UA Doppler; and type III, when there is intermittent absent and/or reversed end-diastolic blood flow in the UA Doppler. Clinical evolution and management options mainly depend on the type of sFGR. Type I is usually associated with a good prognosis and is managed conservatively. There is no consensus on the management of types II and III, but in earlier and more severe presentations, fetal interventions such as selective laser photocoagulation of placental anastomoses or selective fetal cord occlusion of the smaller twin may be considered. This review aims to provide updated information about the diagnosis, evaluation, follow-up, and management of sFGR in MCDA twin pregnancies.

Keywords: Twins; Monochorionic diamniotic twins; Selective fetal growth restriction; Birthweight discordance; Fetal therapy; Placenta

Introduction

Monochorionic diamniotic (MCDA) twin pregnancies account for one in 250 pregnancies.[1] Selective fetal growth restriction (sFGR) is a common complication in about 10% to 15% of MCDA twin pregnancies.[2] However, the reported prevalence varies depending on the diagnostic criteria used. Classically, sFGR was defined as the presence of one twin with an estimated fetal weight (EFW) and/or abdominal circumference below the 10th or 5th percentile (Fig. 1) and a birth weight discordance (BWD) of ≥25%.[1,2] The latest experts' consensus has defined sFGR as the presence of one twin with an EFW below the 3rd percentile as a unique criterion or, alternatively, as the presence of at least three of the following criteria: EFW of one twin below the 10th percentile, abdominal circumference of one twin below the 10th percentile, EFW discordance of ≥25%, and umbilical artery (UA) pulsatility index (PI) of the smaller twin above the 95th percentile.[3] Moreover, before considering a diagnosis of sFGR based on the previous criteria, twin-to-twin transfusion syndrome (TTTS) should be ruled out,[2] since, if the ultrasound diagnostic criteria for TTTS are met, the case should be considered as TTTS and not sFGR.[2]

A clear understanding of the definition and pathophysiology of this disease is fundamental for adequate counseling and management. In this review, we aim to provide updated information about the diagnosis, evaluation, follow-up, and management of sFGR in MCDA twin pregnancies.

Pathophysiology

The main cause of sFGR is an inadequate sharing of the placental territory corresponding to each fetus[4]; fetal weight discordance increases with the increased placental territory discrepancy.[5,6] This is often associated with a very eccentric or velamentous cord insertion of the growth-restricted fetus.[4]

However, the existence of intertwin placental anastomoses and subsequent intertwin blood exchange strongly interfere with the natural history of the growth-restricted fetus, which will not follow the classical pattern seen in singletons. These placental anastomoses can be either arterio-venous, arterio-arterial, or veno-venous, representing direct communications where straightforward intertwin blood exchange occurs. This blood flow exchange differs depending on the fetoplacental volumes and interfetal blood pressure.[7]

The placental anastomoses will have a protective effect on the growth-restricted fetus that receives blood from its co-twin, which may partially balance the placental insufficiency. However, as the pattern of vascular anastomoses may vary widely among MCDA twins even with comparable degrees of fetal growth discrepancy, this will lead to different clinical evolutions and prognoses.[6]

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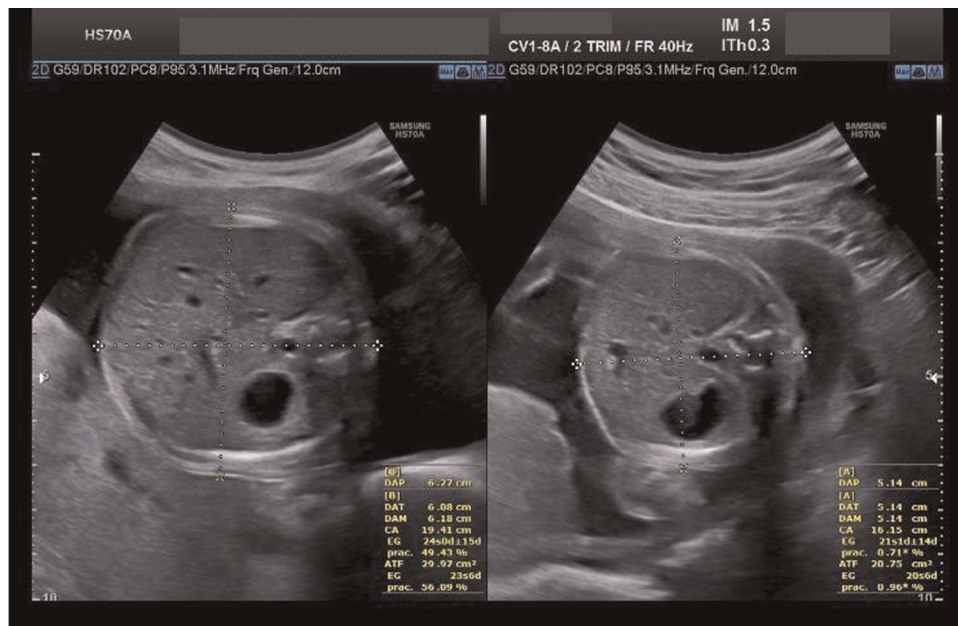
Figure 1. Abdominal circumference discordance in monochorionic twin affected by selective fetal growth restriction.

In the presence of similar placental asymmetry, cases with fewer anastomoses and very little interfetal blood flow interchange will usually tend to present as more severe cases, whereas large interfetal blood flow interchange will usually have a milder clinical expression and better outcome. Nonetheless, there is evidence that the presence of these vascular connections with different volume and pressure puts both fetuses at risk of presenting intrauterine hypoxic-ischemic lesions. The occurrence of acute episodes of hypotension in one fetus lead to a blood transfusion to this fetus from its co-twin, which can lead to the death or neurological damage of its co-twin owing to hypoxia and hypovolemia.[2,8,9] Therefore, not only the placental discordance but also the amount and type of anastomoses will determine the severity, evolution, and management of these pregnancies.

Screening of sFGR

Discordance detected in the crown-rump length (CRL) during the first trimester combined screening may help to predict the outcome in MCDA twin pregnancies.[10,11]

CRL discordance is increased in MCDA twins complicated by fetal death at any gestation, birth of at least one small for gestational age (SGA) neonate, and a BWD of ≥25%.

In MCDA twin pregnancies, the rate of fetal loss or endoscopic laser surgery at <20 weeks is approximately 11%, but in the small subgroups with CRL discordance of ≥10%, ≥15%, and ≥20%, which constitute 9%, <3%, and <1% of the total, respectively, the risk is increased to approximately 32%, 49%, and 70%.[10]

In these cases, parents should be counseled about the increased risk of fetal death and the possible need for early intervention.

Diagnosis and classification

The presence of the previously described vascular anastomoses at the placenta will impact in the UA blood flow of the affected twin as changes in the UA Doppler waveform.

Based on UA Doppler waveform pattern in the affected twin at the time of diagnosis, Gratacós et al.[12] proposed the classification of MCDA twin pregnancies complicated with sFGR into three types (Table 1): type I, when the UA Doppler end-diastolic blood flow is positive; type II, when there is persistent absent or reversed end-diastolic blood flow (Fig. 2); and type III, when there is intermittently absent or reversed end-diastolic blood flow in the UA Doppler (Fig. 3). This last group presents a characteristic pattern seen only in MCDA twins, where the presence of large arterio-arterial anastomoses allows a cyclical compensatory flow from the normally grown twin's circulation

Table 1

Classification and clinical characteristics of monochorionic diamniotic twin pregnancies complicated with selective fetal growth restriction according to the pattern in the UA Doppler of the growth-restricted twin.[12]

| Type	Doppler pattern of the smaller twin	Clinical characteristics
Type I	Persistently positive end-diastolic blood flow in the UA	Shows the best outcome
Type II	Persistently absent or reversed end-diastolic blood flow in the UA	High risk of poor outcome, presents the worst prognosis
Type III	Intermittently absent or reversed end-diastolic blood flow in the UA	High risk of poor outcome, characterized by an unpredictable clinical evolution

UA: Umbilical artery.
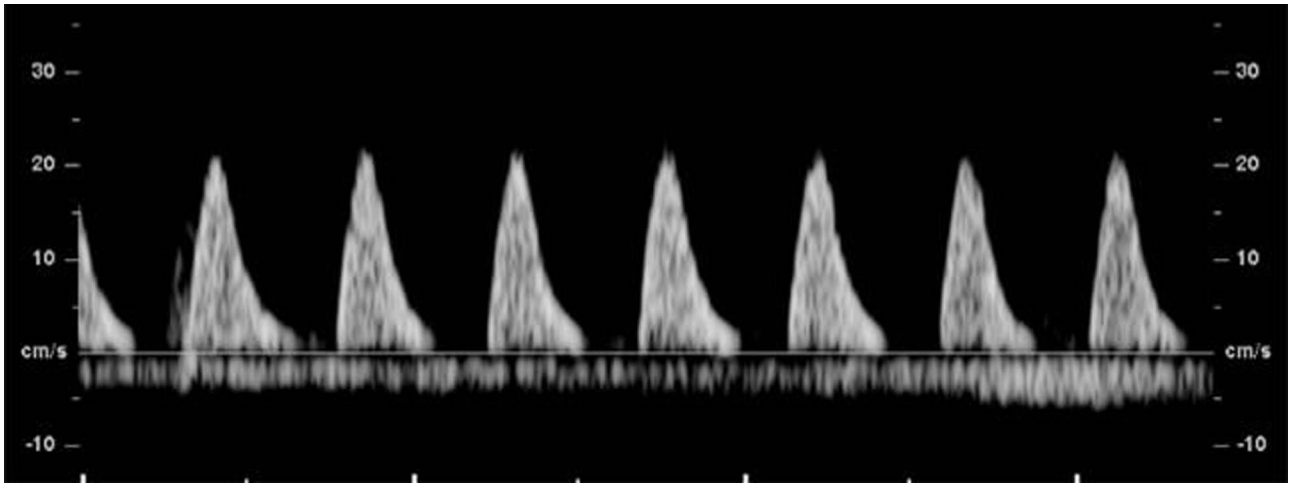
Figure 2. Umbilical artery pulsed Doppler showing persistent absent end-diastolic flow in a case of selective fetal growth restriction type II.

into the smaller twin's cord. This allows longer survival of the growth-restricted twin, but it can facilitate the events that can lead to unexpected demise or neurological compromise in the normally developing fetus.

These patterns can be seen very early in pregnancy and are strongly related to the clinical evolution and management.[8,12,13] Although it was previously thought that these patterns remained stable across the pregnancy, latest studies
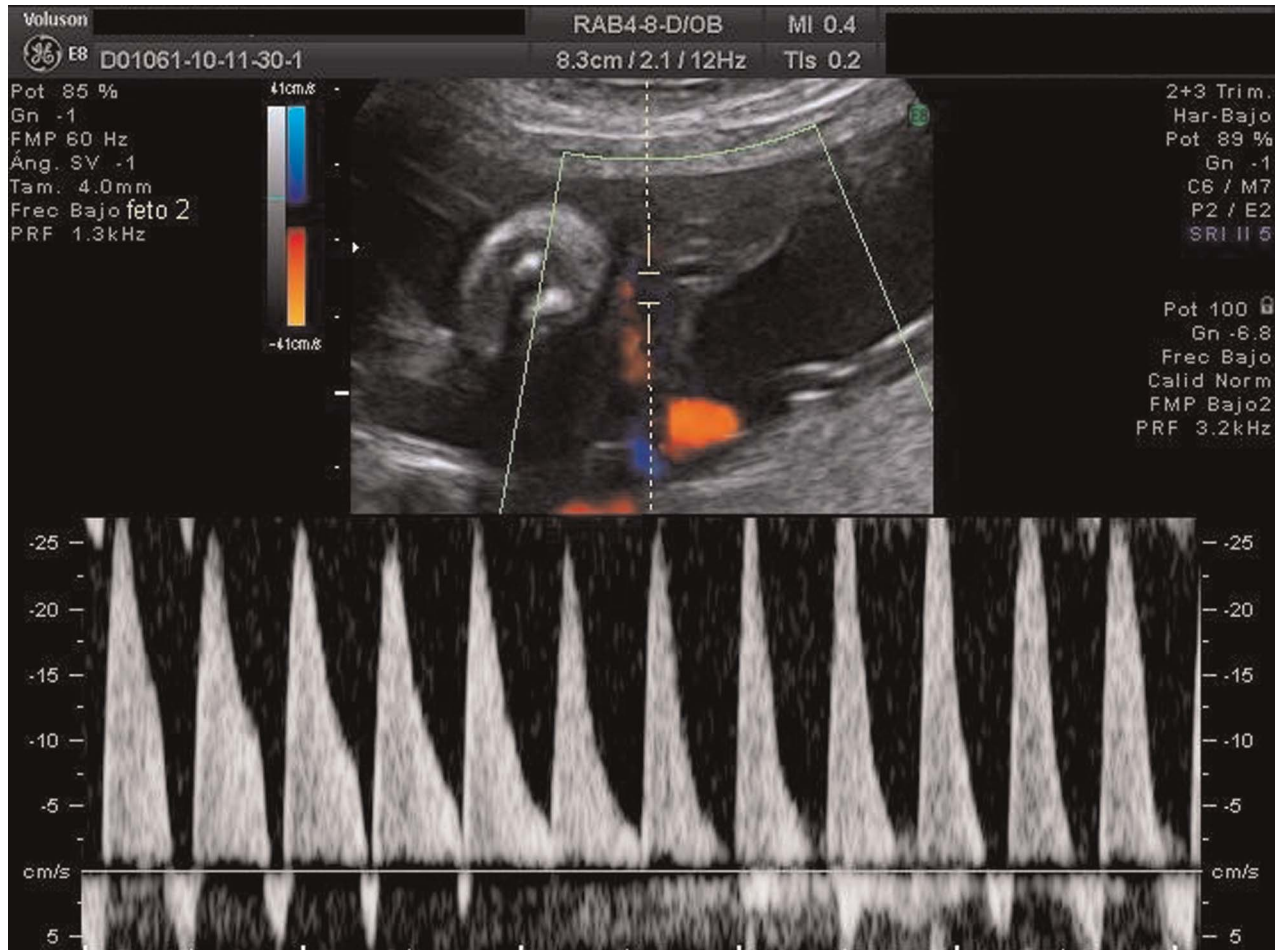
Figure 3. Umbilical artery pulsed Doppler showing intermittently absent or reversed end-diastolic flow in a case of selective fetal growth restriction type III.

showed that it is possible to observe a change in the initial staging.[14]

It is important to emphasize that the UA Doppler patterns should be actively screened for, as they can be easily missed. In order to observe the less pronounced diastolic changes, it is important to set a low sweep speed pulse Doppler, which will also demonstrate the oscillatory changes in the systolic velocities[2] and allow sufficient time for the examination. The intermittent absent or reversed end-diastolic blood flow pattern is more pronounced when the insonation of the UA is performed near the placental insertion of the cord.

Classification of sFGR based on the UA Doppler flow pattern of the smaller twin provides a valuable tool to stratify the obstetric risk of these pregnancies.

Clinical management, therapeutic options, and survival

The clinical management of sFGR in MCDA twin pregnancies depends on several factors such as the gestational age at diagnosis and parental choices, but is mainly dependent on the Doppler examination results and the type of sFGR.[15] Currently, there is a lack of consensus regarding the management of these pregnancies. The information given below is summarized in Table 2.

sFGR type I

sFGR type I represents the milder form of the growth restriction spectrum in MCDA twins. In these cases, the end-diastolic blood flow in the UA of the growth-restricted twin is positive. The degree of placental asymmetry is less pronounced than for the other types of sFGR, thus presenting less weight discrepancy. Usually, it coexists with a large number of intertwin anastomoses, resulting in a high amount of bidirectional interfetal blood flow exchange, which reduces the effects of placental insufficiency in the growth-restricted twin.[6,16,17]

Essentially, sFGR type I pregnancies are associated with good perinatal outcomes for both twins, with the growth-restricted fetus presenting a stable and linear growth curve. A recent meta-analysis has shown that, without any intervention, 96.4% (95% confidence interval (CI): 92.6–98.8) of sFGR type I were live born.[18] Abnormal brain imaging was reported in

4.1% of live born fetuses with no cases of severe brain abnormalities. A different meta-analysis had previously shown that there is an increased incidence of cerebral injury in sFGR types II and III compared with type I (odds ratio: 7.69; 95% CI: 2.56–25).[19]

Although it is most likely that the course of sFGR type I remains stable, it is possible to see a progression of the initial staging, and therefore, close surveillance of these pregnancies is mandatory.[20] Rustico et al.[20] reported a Doppler pattern change to type II in 26% (17/65) of their cases initially classified as type I, which is much higher than that described in other studies.[16,21]

Therefore, management of sFGR type I is based on a conservative approach with expectant management and weekly sonographic and Doppler surveillance to rule out deterioration of Doppler patterns. Elective delivery is recommended between 34 and 36 weeks of gestation.[22]

sFGR type II

sFGR type II presents a persistent absent or reversed end-diastolic blood flow in the UA. These pregnancies are commonly affected by severe fetal-weight discordance, and they tend to follow a progressive deterioration of the growth-restricted fetus with worsening of the arterial and venous Doppler.

The placental mass of the growth-restricted twin is very small, and the number and diameter of vascular anastomoses in type II are much smaller than in type I.[6] Thus, the compensatory effects that occur in type I still prevail, and the evolution of these pregnancies is less severe than growth-restricted singleton pregnancies.

Therefore, MCDA twins complicated by sFGR type II have a poorer prognosis and are more likely to require active management. Between 70% and 90%[16,21] of these pregnancies are expected to deteriorate before 30 weeks of gestation. However, the UA Doppler is not useful to predict the speed of deterioration in these cases; hence, other ultrasound parameters, such as the ductus venosus Doppler; biophysical profiling; and monitoring of amniotic fluid volume are needed for this purpose.[8,23]

Perinatal mortality in these pregnancies is high. Ishii et al.[21] reported an intact survival of 37% for the smaller twin and

Table 2

Follow-up and management of monochorionic diamniotic twin pregnancies complicated with selective fetal growth restriction according to the pattern in the UA Doppler of the growth-restricted twin.

sFGR Type	Follow-up	Management	Delivery
I	1. Fortnightly fetal biometry and Doppler 2. Weekly Doppler if UA PI >95th centile	Expectant	34–36 weeks

II	1. Fortnightly fetal biometry
	2. Weekly Doppler and BFP
		1. Expectant
		2. Consider active management (SFLC or CC) in severe cases
		  a. <24 weeks
		  b. PI DV >95th centile
		  c. reversed EDF UA Doppler in the smaller twin; and
		  d. BWD >30%
			30–34 weeks—depending on severity (UA EDF pattern, PI DV)

III	1. Fortnightly fetal biometry
	2. Weekly Doppler and BFP
		1. Expectant
		2. Consider active management (SFLC or CC) if signs of deterioration
		  a. change in UA Doppler pattern from predominantly absent to reverse
		  b. PI DV >95th centile; and
		  c. signs of cardiac failure
			32–34 weeks

BFP: Biophysical profile; BWD: Birth weight discordance; CC:Cord coagulation; DV: Ductus venosus; EDF: End-diastolic blood flow; PI: Pulsatility index; SFLC: Selective fetoscopic laser coagulation; UA: Umbilical artery.

Note: Fetal lung maturation and fetal neuroprophylaxis is recommended before delivery.

55% for the larger twin, with a mean gestational age at delivery of 28 weeks in the absence of any intervention. Interestingly, Colmant et al.[14] have recently documented a large series of 108 pregnancies complicated with sFGR type II, where 41.6% cases were managed expectantly, and in half of those cases, the staging improved to type I. The overall survival rate > 28 days after birth was 77.8%. In these series,[14] they found that the best predictors for survival of the smaller twin were a positive a-wave in the ductus venosus and a discordance in the EFW of <30%. A recent meta-analysis reported that 89.3% (95% *CI*: 71.8–97.7) of live born twins managed expectantly survive without neurological compromise.[18]

The clinical management of MCDA twins complicated with sFGR type II will depend on gestational age and pattern of fetal deterioration. If a conservative approach is decided, weekly monitoring must be carried out and this may be even more frequent if the ductus venosus PI increases above the 95th centile.[2,16] After fetal viability is reached, biophysical profiling and fetal heart monitoring could be included in the follow-up protocol.[22]

Active management, such as umbilical cord coagulation (CC) of the growth-restricted twin or intrauterine selective fetoscopic laser coagulation (SFLC) of placental anastomoses, can be considered according to the severity of the condition, the anticipated surgical difficulties, and parental desire.[14] Intervention is usually considered in severe cases when the diagnosis is made before 24 weeks' gestation or when there are signs of fetal deterioration and imminent fetal demise such as an abnormal a-wave in the ductus venosus or abnormal biophysical profile.[2,24] Rustico et al.[20] reported that the risk of intrauterine death is higher for type II-sFGR twins in the presence of reversed end-diastolic flow pattern when compared with the absent pattern.

Selective termination via CC (Figs. 4, 5) of the smaller twin is a relatively straightforward procedure that can protect the normally growing fetus against neurological injury


Figure 5. The targeted umbilical cord is visualized and grasped with the diathermy forceps.

or death in case of intrauterine demise of its co-twin. A series of 90 cases of severe sFGR types II and III showed a survival rate of 93.3% of the normally growing fetus, with a mean gestational age at delivery of 36.4 weeks.[25]

SFLC is a well-established treatment for TTTS. In theory, the ablation of vascular anastomoses protects the normally grown twin in case of deterioration or demise of the smaller twin. However, this may also leave the smaller twin without the compensatory circulation provided by the normally grown twin.[26] Peeva et al.[27] reported a large series of 142 MCDA twin pregnancies complicated with sFGR type II where SFLC was performed. The survival rates were 39.5% and 69.3% for the smaller and the normally grown fetus, respectively, with an average gestational age at delivery of 32 weeks. A recent series[14] documented 13 cases of SFLC carried out in sFGR type II twins and showed the poorest neonatal survival rate at 28 days (23.1%) and the earliest gestational age at birth (29 weeks; range, 29–32) when compared with cases managed expectantly or with CC. By contrast a recent meta-analysis reported an 82.9% survival rate of at least one twin, a 44.3% rate of intrauterine demise, and a 15.3% rate of neonatal death when SFLC was performed.[18]

The principal difficulty of performing SFLC for sFGR is to clearly identify and selectively coagulate the placental anastomoses. Unlike in cases complicated with TTTS, in sFGR twins, the placenta is not flattened by the severe polyhydramnios, and there is amniotic fluid in the sac of the smaller twin. Therefore, visualization of the entire vascular equator is highly challenging. All these facts may determine a longer intraoperative time and risky procedure.[28] In addition, the presence of an absent or reversed end-diastolic flow in the UA Doppler from very early in the pregnancy could also mirror the poor capacity to cope with SFLC. Finally, the procedure itself carries a risk of premature rupture of membranes, preterm labor, and chorioamnionitis.[26]

Although there is no consensus agreement on how these pregnancies should be managed, in cases presented before 24 weeks, with BWD >30%, PI of ductus venosus above
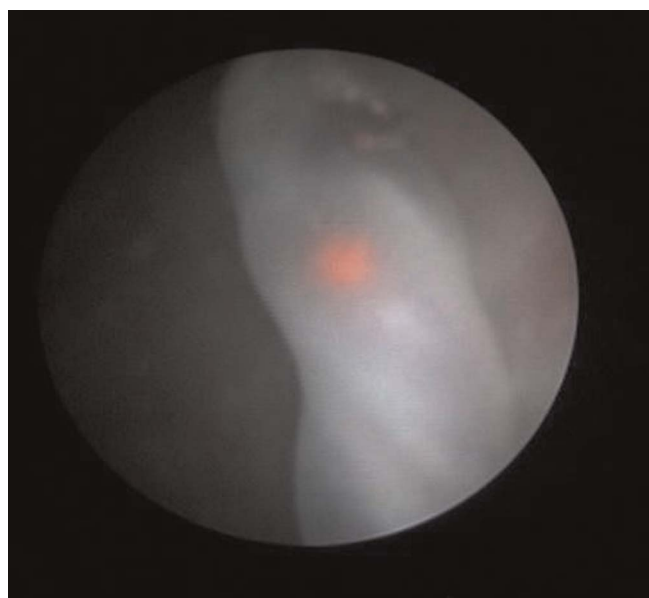
Figure 4. Fetoscopic view of umbilical cord before cord occlusion.

the 95th percentile, reversed end-diastolic blood flow in the UA Doppler, and/or oligohydramnios, an active management with either CC or SLF should be discussed. The counseling must include a thorough explanation of the risks and benefits of every procedure, along with the technical difficulties, and prioritize the parents' wishes.[2,14]

sFGR type III

sFGR type III accounts for about a fifth of all sFGR twins[29] and is characterized by the presence of an unequal placental sharing and a large intertwin artery-to-artery anastomoses,[17] which allows acute hemodynamic exchanges from one twin to the other. This is recognized by the presence of intermittent positive, absent, and reversed end-diastolic blood flow[1] in the UA Doppler of the smaller twin.[2,30] Imbalance of blood flow through artery-to-artery anastomoses is explained by a combination of different factors: different arterial size diameter, intertwin BWD, and distance between placental cord insertion sites.[31] The existence of these large artery-to-artery anastomoses leaves each twin susceptible to ischemic brain damage through transient episodes of bradycardia and hypotension owing to bleeding in their co-twin placental territory. This is why these type of twins are the ones with a higher risk of unpredictable intrauterine demise and neurological damage.[26]

MCDA twins complicated with sFGR type III have the highest degree of placental discrepancy among the three types of sFGR,[6] but the artery-to-artery anastomoses compensate for this disparity allowing considerable exchange of blood from the larger to the smaller twin. Somehow, the normally grown fetus behaves like a pump twin, and this may be the explanation for the development of hypertrophic cardiomyopathy-like changes in up to 20% of the cases, contrary to the 2.5% seen in types I and II.[32]

The optimal prenatal management in these pregnancies is yet to be established and remains a challenge. sFGR type III twins present an apparent benign evolution, and in most of the cases, they survive beyond 32 or 34 weeks. However, because of its unpredictability, literature describes a wide variability in the clinical management,[1,33,34] and many studies reported a high incidence of 11% to 20% of unexpected fetal demise, with a high risk of up to 20% for parenchymal brain lesions in the normally grown twin.[8,18,35] A recent meta-analysis reported an incidence of severe intraventricular hemorrhage (grade III and IV) and periventricular leukomalacia of 3.5% and 11.6%, respectively.[18]

In a recent large series that documented 328 twin pregnancies complicated with sFGR type III, fetal death occurred in 11% of the pregnancies, but was less than 2% at 28 weeks.[35] Delivery at 32 weeks was associated with a high rate of adverse neonatal outcomes, approximately 29%, which substantially decreased at 34 weeks to 11%, with a very low risk of fetal death approximately 0.7% at this later gestational age.

Expectant management with close surveillance monitoring is usually the most accepted recommendation, but it will depend on the severity of the condition and the gestational age at diagnosis. If expectant management is decided, weekly follow-up is recommended with elective delivery at approximately 32 to 34 weeks. Doppler evaluation, biophysical profile, and, once viability is reached, fetal heart rate monitoring could be included in the follow-up protocol.[2] In addition, it seems reasonable to include a fetal echocardiography during the follow-up as the increased overload of the normally grown twin could lead to cardiomegaly and cardiac failure.[32]

If any sign of deterioration appears, elective delivery or active management needs to be discussed with the parents. These signs include changes in the UA Doppler from predominantly absent to reverse, worsening in BWD, PI of the ductus venosus above the 95th percentile, or signs of cardiac failure.[2]

Active therapy such as CC and SFLC is considered when signs of imminent fetal death are present.[12,28,36] In view of the lack of ability to predict fetal deterioration in this type of twins, the separation of the placental anastomoses by SFLC was thought to be beneficial. However, this procedure is associated with even more technical difficulties than in sFGR type II cases, owing to the closer insertion of the umbilical cords and the large artery-to-artery connexions.[2] A cohort study comparing 18 sFGR type III cases treated with SFLC with 31 cases that were managed expectantly reported a 75% intrauterine demise of the smaller twin in cases in the former treatment group. However, the normally grown twin in the laser group was less likely to die in the event of its co-twin's death. This protective effect may also work in terms of neurological affection.[12] Despite earlier studies proving the feasibility of SFLC in complicated sFGR twins, difficulties in technical aspects are well-described, and there is scarce data reporting on perinatal outcomes after SFLC for sFGR type III sFGR.

Parents should also be counseled about the option of selective cord occlusion of the smaller twin as a treatment option. This may be contemplated for cases of very early diagnosis and cases with extreme BWD or extreme forms of intermittent absent or reversed end-diastolic flow in the UA Doppler.[15] Results of clinical series suggest that the CC is associated with better survival rates for the normally grown twin and a mean gestational age at delivery of 36.4 weeks.[24]

Long-term outcomes

Long-term neurological outcomes

Beyond survival, the quality of life that these children will have is equally important. Perinatal outcomes in sFGR twins have been largely reported with high rates of perinatal mortality (16%–29%) and neonatal morbidities, especially adverse neurological outcome (0%–33%).[18,20,37] A systematic review and meta-analysis by Buca et al.[24] based on 13 studies concluded that children with sFGR type II and III are at higher risk of abnormal brain imaging when compared with type I. In a systematic review by Inklaar et al.,[19] an abnormal UA Doppler pattern and a lower gestational age at delivery are the main risk factors for brain injury.

Only five studies reported long-term neurological outcome beyond two years of age, but the results were so heterogeneous that meta-analysis was prevailed,[37] manifesting the lack of evidence and scarce literature relating to long-term neurological outcomes with different types of sFGR and other prenatal findings.

Usually, it is assumed that the majority of the neurodevelopmental adverse outcomes are related to prematurity. However, approximately 60% of MCDA pregnancies will deliver close to term without any complications.[38] Nevertheless, even in uncomplicated pregnancies, neurodevelopmental impairment has been identified in up to 7% children.[39]

In addition, most of the reported neurological outcomes are based solely on neonatal brain imaging, and although the predictive value of the neuroimaging is increasing, its predictive accuracy remains controversial.[37]

Conclusions

sFGR is a severe condition that complicates MCDA twin pregnancies. The risks of intrauterine demise or adverse perinatal outcome for both twins are high. The disease is classified into three types according to the Doppler pattern of the UA in the small fetus, and this classification is essential to stratify the risk of the pregnancy and predict evolution and perinatal outcome.

sFGR type I is associated with a good prognosis, and therefore, expectant management is the preferred option. sFGR types II and III have a relatively poor prognosis; due to the lack of robust data, clinical management of these pregnancies is controversial, and it should be individualized considering gestational age at the time of the diagnosis, surgical difficulties, local service capabilities, and preferences of the parents.

Large-scale trials comparing different management options and assessing long-term neurodevelopmental outcomes are essential.

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Conflicts of Interest

None.

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