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Selective intrauterine growth restriction in monochorionic twins: pathophysiology, diagnostic approach and management dilemmas

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S U M M A R Y

Selective intrauterine growth restriction (sIUGR) in monochorionic twins is associated with a substantial increase in perinatal mortality and morbidity for both twins. Clinical evolution depends on the combination of the effects of placental insufficiency in the IUGR twin with inter-twin blood transfer through placental anastomoses. Classification of sIUGR into types according to the characteristics of umbilical artery diastolic flow in the IUGR twin permits the differentiation of clinical and prognostic groups. sIUGR type I has normal diastolic flow and relatively good outcome. Type II is defined by persistently absent/reverse end-diastolic flow and is associated with a high risk of intrauterine demise of the IUGR twin and/or very preterm delivery. Type III is defined by the presence of intermittent absent/reverse end-diastolic flow (iAREDF), and is associated with 10–20% risk of unexpected fetal demise of the smaller twin and 10–20% risk of neurological injury in the larger twin. The management strategy for sIUGR with abnormal umbilical artery Doppler (types II and III) remains a challenge, and may include elective fetal therapy or close surveillance with fetal therapy or elective delivery in the presence of severe fetal deterioration. Small clinical series reporting the use of cord occlusion or laser therapy in severe cases suggest that the outcome of the larger twin might be improved. There is probably no single optimal strategy, since decisions will ultimately be influenced by the severity of IUGR, gestational age, parents' wishes and technical issues.

1. Introduction

Selective intrauterine growth restriction (sIUGR) is a common condition associated with monochorionic (MC) pregnancy. It is increasingly considered to be an important complication of MC twins, with potentially significant risks of intrauterine fetal demise (IUFD) or neurological adverse outcome for both twins.[1–5] Introduction of skilled sonographic evaluation, a better understanding of different Doppler patterns and of the anatomy of MC placenta, together with the development of fetoscopic techniques have all contributed to a deeper scientific understanding of this condition. This review summarizes the unique pathophysiology of sIUGR, proposes a classification system which may facilitate to interpret the apparently wide clinical variability observed in this condition, and suggests management approaches according to this classification.

2. Definition and prevalence of sIUGR

The term 'selective intrauterine growth restriction' in monochorionic pregnancies is applicable to cases where the estimated fetal weight (EFW) of the small fetus falls below the 10th percentile. Significant fetal weight discordance is an important element of the clinical picture, which will often accompany this condition, but is not necessary for diagnosis. This is defined by different authors as discordance between the EFW of two fetuses >25%,[6,7] and is calculated as the difference between the EFW of the larger twin and the smaller twin divided by the EFW of the larger twin. The clinical significance of cases when both twins' EFW falls below the 10th percentile without discordance, or cases when discordance exists but the smaller fetus' EFW is above the 10th percentile, remains to be defined.

A definition based on an EFW below the 10th percentile, although not universally established, is widely accepted and tends to be the simplest approach for practical and investigational purposes. However, various diagnostic criteria have been used in the literature, including EFW less than 10th percentile,[1,2,8] fetal weight discordance,[1–3,9] or fetal abdominal circumference,[10] which hamper

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comparison between studies. The reported prevalence of sIUGR based on an EFW below the 10th centile ranges from 10 to 15%.[9,11,12] The reported prevalence of MC pregnancies with an inter-twin birth weight discordance of more than 25% ranges from 11.3% to 19%.[2,9,13]

3. Aspects of the pathophysiology and natural history of sIUGR in MC twins

In recent years the pathophysiological insight of sIUGR has been substantially improved, although the ability to reliably predict the clinical outcome remains elusive – this will probably remain the case, as the clinical presentation and outcome seem to depend on a combination of multiple factors. Until a few years ago the most feared complication of sIUGR in MC twins was the intrauterine demise of the growth-restricted twin, which carries an associated postmortem risk of acute feto-fetal transfusion from the normal to the deceased IUGR fetus. Indeed, death of one MC twin has been reported to be accompanied by concomitant death of the larger twin in 25–30% of cases and neurological damage in 30% of survivors.[14] However, research over recent years has demonstrated that sIUGR is associated with substantial risks for the normally grown twin even if both fetuses are born alive. These risks stem from two main factors. First, since these pregnancies must by definition be delivered before the death of the IUGR fetus, the normal twin is exposed to severe prematurity with its known consequences in terms of neurodevelopmental sequelae. Second, even if prematurity is avoided, there may be an increased prevalence of neurological complications in the normally grown twin due to a high risk of acute feto-fetal transfusion accidents in utero.[1,4,15] The specific risks for these two complications may vary in different types of sIUGR, as discussed later.

The principle cause for the development of sIUGR in MC twins is inadequate placental sharing. The relationship between unequal placental territory and birth weight discordance has recently been revealed in several studies[16–19] showing that discordance increases with increased placental territory discordance. Extremely asymmetric distribution of placental territories is often associated with very eccentric or velamentous cord insertion,[20] although it is unclear whether velamentous insertion is a mere consequence of the asymmetric displacement of the vascular equator or whether it has any implications in the pathophysiology of growth restriction. Aside from placental territory discordance, a second factor largely influencing fetal weight discordance and the natural history of sIUGR in MC twins is the presence of vascular anastomoses in the MC placenta.[18,21] Arterio-venous (AV) anastomoses have unidirectional flow and in reality are vascular AV connections where a placental cotyledon is perfused by an artery from one fetus but drained by a vein going to the other one. Arterio-arterial (AA) and veno-venous (VV) anastomoses are direct connections which can transport blood in either direction, and have therefore an important compensatory role in the event of imbalances in blood volume or pressure at one fetal end.

In general the presence of placental anastomoses has a protective effect on the IUGR fetus, which receives blood from its co-twin that may partially compensate the placental insufficiency. Furthermore, some studies have described that there seems to be a certain degree of correlation between the relative placental discordance and the anastomotic pattern.[18] Thus, inter-twin anastomotic area, net AV transfusion and the diameter of AA anastomoses have been shown to correlate with the degree of inter-twin placental discordance. In other words, larger placental territory discordance is associated with more blood flow interchange that interferes in the natural history of the smaller twin. Whereas this may be protective for the smaller twin, it may carry additional risks to both fetuses as discussed later in this review. In addition, the association between placental size discrepancy and inter-fetal blood flow interchange does not always operate, and in clinical practice it is possible to observe cases with large placental discordance but very few inter-twin anastomoses.

As a consequence of this variability, MC pregnancies with similar degrees of fetal weight discordance may be associated with remarkable differences in clinical course and outcome, and thus different clinical forms coexist within the same diagnosis of sIUGR.[1,10,22] With some degree of simplification several scenarios may be expected. In the presence of similar placental territory discordance, cases with large inter-fetal blood flow interchange will have a milder clinical expression and better outcome, while placentas with few anastomoses and very little blood flow interchange will normally lead to more severe cases. To complicate matters further, there is a third subset comprising cases presenting a large placental AA anastomosis connecting the two fetal circulations. This seems to constitute a characteristic subgroup that is discussed later in relation to proposed clinical classification.

4. Classification of different types of sIUGR on the basis of umbilical artery Doppler: rationale and clinical use

As stated above, the clinical evolution of sIUGR is subject to remarkable variability, and the identification of groups with similar clinical behavior may substantially facilitate clinical management. To date, the clinical technique that best achieves this goal is umbilical artery (UA) Doppler of the IUGR twin. In singleton and DC twin pregnancies, UA Doppler is a key parameter for the diagnosis and surveillance of fetuses with IUGR secondary to placental insufficiency.[23] However, in MC twins with IUGR, the changes observed in the UA Doppler waveforms cannot be interpreted in the same way as in other pregnancies, since they are a combination of the effects of placental insufficiency with those of the inter-twin vascular connections.[10,22,24,25–28] UA Doppler in MC twins with sIUGR may present three main waveform patterns, as defined by the characteristics of diastolic flow: (i) positive, (ii) persistently absent/reverse, and (iii) intermittently absent/reverse end-diastolic flow (iAREDF).[10,22,24,28] The latter has also been defined as cyclical pattern,[24] and refers to a sign unique to MC twins resulting from the presence of transmitted waveforms from the larger into the smaller twin's cord due to the existence of placental large AA anastomoses.[10,24] This pattern is discussed in more detail in the following sections. These Doppler patterns can be observed from very early in pregnancy, usually before the 20th week of gestation, normally remain unchanged until delivery[10,22] and, more importantly, they seem to be strongly associated with marked differences in clinical evolution and outcome.[1,4,10,15]

We have proposed a classification system of sIUGR into three types according to the above Doppler patterns in the fetus with IUGR. Accordingly, pregnancies are defined as type I (normal umbilical artery Doppler), type II (persistent absent or reversed end-diastolic flow, AREDF) or type III (iAREDF). We have shown that these types not only correlate with distinct clinical forms but also with distinct patterns of placental anastomoses.[4] This classification may help to improve the accuracy of current definitions, to understand and predict the distinct clinical evolutions and to plan clinical management. The remainder of the review will discuss the natural history and options for management of the different clinical forms of sIUGR.

5. Type I sIUGR

5.1. Definition and placental features

The type I Doppler pattern is distinguished by positive diastolic flow in the umbilical artery of the small twin. Placental anastomotic patterns in type I pregnancies are similar to uncomplicated monochorionic pregnancies, resulting in a fair number of anastomoses and bidirectional fetal flow interchange. Such interchange favours blood from the larger twin working in a compensatory manner since, even if marginally, it is better oxygenated, and this attenuates the effects of placental insufficiency in the smaller fetus.[4,19] The influence of this transfusion has been demonstrated in several studies and is supported by the observed decrease in the ratio between the degree of fetal and placental discordance in these pregnancies. In a twin pregnancy there should be a linear relation between the discordance in fetal weights and the discordance in placental territories. Thus, this ratio approaches 1 in uncomplicated MC twins. However, in sIUGR type I pregnancies the ratio is lower, which indicates that the actual fetal weight discordance is attenuated with respect to the existing discordance of placental territories.[18]

5.2. Clinical evolution and suggested management

Type I cases are generally associated with good outcomes with reported intrauterine mortality rates of 2–4%.[4,15] As mentioned above, a significant proportion of sIUGR pregnancies are diagnosed early, usually around 20 weeks of gestation, and the UA Doppler pattern in the IUGR fetus observed at diagnosis rarely changes later in pregnancy. Thus, once a case has been assigned to type I it will normally remain in this category until delivery. In a cohort of 39 type I twin pairs parenchymal brain damage in surviving twins was 0%.[4] These results are similar to a recent study from Japan,[15] where neurological abnormalities at 6 months were found in 1 of 23 type I sIUGR cases (4.3%). As clinical evolution of sIUGR type I cases has been shown to be benign in most instances, a policy of expectant management and close follow-up to rule out progression to type II Doppler patterns seems reasonable. In the absence of such progression, bi-weekly or weekly sonographic and Doppler surveillance could be contemplated. In most instances, the IUGR fetus will remain with a normal Doppler until advanced stages of pregnancy allowing elective delivery, which can be performed at around 34–35 weeks.

6. Type II sIUGR

6.1. Definition and placental features

Type II pattern is characterized by persistently AREDF in the UA. As in type I, sIUGR type II pregnancies show a distribution of placental anastomoses quite similar to uncomplicated MC twins, but with a more severe placental discordance.[18] Fetal territory of the IUGR twin is usually extremely small in type II pregnancies, but again the fetal weight/placental discordance ratio is significantly lower than in uncomplicated MC twins,[18] illustrating how inter-twin blood transfusion attenuates the severity of growth restriction.

6.2. Clinical evolution

Unlike type I, the great majority sIUGR type II will show in utero deterioration, but with important differences with respect to singletons or DC twins.[1,10,29] Thus, sIUGR with absent/reverse UA Doppler in MC twins shows a remarkably longer latency time between the onset of AEDF and delivery, on average 10 weeks, compared with the 3–4 weeks reported in singletons with IUGR and similar findings in the UA Doppler.[10,22] Latency time in MC is increased at the expense of an earlier diagnosis of AEDF, normally around 20 weeks versus 27 weeks in singletons.[10] Eventually severe fetal deterioration, as defined by abnormal venous Doppler or biophysical profile, will occur in 90% of type II cases.[4] Elective delivery is indicated in most of these pregnancies earlier than 30 weeks of gestation[4,10] with only a small minority surviving in utero beyond 32 weeks. Thus, placental insufficiency in type II is far more severe than in type I and cannot be fully compensated by inter-twin transfusion.

Two clinical series, managed with different strategies, illustrate the poor outcome associated with type II cases. Gratacós et al.[4] reported the outcome of 30 type II pregnancies, showing an extremely high deterioration rate (90%), as defined by abnormal venous Dopplers or biophysical profile. Mean gestational age at delivery was 30 weeks and the rate of neonatal brain damage of the small twin was 14.4%. The management protocol in this study considered cord occlusion in deteriorating small twins before 28 weeks, and this was performed in 9 of 30 cases. Thus, there were no cases of unexpected IUFD in this group. Ishii et al.[15] reported the outcome of 27 type II patients managed expectantly. In contrast with the previous study, selective feticide was not offered to patients and therefore this study provides a much better picture of the natural history of type II cases. Intrauterine death occurred in 29.6% (8/27) among IUGR twins and 22.2% (6/27) among larger twins. The rate of neonatal brain damage of the small twin at 6 months was 14.8%. Mean gestational age at delivery was 28 weeks. Finally, Quintero et al.[30] reported the outcome of 17 conservatively managed patients with sIUGR compared with that of 11 similar cases treated by placental laser coagulation. Although the authors did not classify cases according to the system here proposed, most of the pregnancies reported had AREDF in the umbilical artery. Expectantly managed IUGR fetuses showed a rate of IUFD of 41%, with a mean gestational age at delivery of 30 weeks, and a rate of severe brain abnormalities of 13.6% (3/22), in the whole group.

6.3. Proposed clinical management

As explained above, the majority of fetuses with type II Doppler diagnosed in the second trimester will deteriorate in utero at or before 30 weeks of gestation.[1,4,15] Although the latency time between diagnosis of AREDF and fetal deterioration may be long, this can be predicted by close fetal monitoring. Since, unlike singleton or DC twins with IUGR, UA Doppler cannot be used as a predictor of imminent fetal death, ductus venosus (DV) Doppler seems the best alternative. In previous series, the appearance of absent or reverse atrial flow in the DV when used as a criterion to indicate selective feticide or delivery has been shown to prevent the occurrence of in-utero death in all cases.[1,4] A weekly follow-up scheme may be reasonable if venous Doppler is normal, and a more frequent follow-up when DV pulsatility index (PI) becomes elevated above two standard deviations. Biophysical profile can be included in the follow-up protocol after viability is reached, although fetal heart monitoring will be of little use since most cases occur in the second or early third trimester.

Management options depend on gestational age and the degree of deterioration of the IUGR fetus. At diagnosis, if there are signs suggesting imminent fetal demise, fetal therapy should be contemplated to protect the larger twin from the death of its co-twin. However, in most cases there are no such signs, and the smaller twin has abnormal UA Doppler but preserved DV atrial flow. Expectant management can be considered along the lines discussed above, with the option of fetal therapy if deterioration occurs before viability is reached or elective delivery beyond 28 weeks. However, some parents may request elective fetal therapy on the grounds of the poor prognosis expected in these cases. Active management may consider two options. Cord occlusion is the most straightforward and less risky procedure, with expected survival rates for the normal twin ranging from 80% to 90%.[31] Fetoscopic laser coagulation may be performed, but it carries higher obstetric risks and is associated with a high risk of demise of the IUGR fetus in any case[30] since the treatment interrupts by definition the relative protection provided by the interfetal transfusion. Technically, laser is more difficult than when performed for twin–twin transfusion syndrome (TTTS) because the placenta is not flattened by a severe polyhydramnios and there is amniotic fluid in the smaller twin's sac which may hamper visualization of the entire vascular equator. Laser might be associated with a small risk of unexplained death of the larger twin, as reported by Quintero et al. in 1 of 11 lasers performed in type II cases, and confirmed later by our group with one case in 17 type III pregnancies treated with laser.[30,32] In summary, laser in sIUGR is a feasible option, but it requires a higher level of experience and surgical skills than in TTTS, and outcome is less certain than with cord occlusion. The potential benefit of this approach is being evaluated in an international clinical trial.

The final decision among therapy options will be influenced by the severity of growth restriction, parents' preferences and technical issues which may include gestational age and placental location. For obvious reasons, the likelihood of fetal deterioration will not be the same when fetal weight discordance is 25% and there is absent end-diastolic flow than in the presence of a 50% discordance and reverse end-diastolic flow. Parents' wishes will also have a strong influence and some parents may regard cord occlusion as an unacceptable option. Finally, a difficult placental location may render laser coagulation more difficult and risky, which in the end might influence the final decision on the type of treatment.

7. Type III sIUGR

7.1. Characteristic Doppler findings and placental features

Type III sIUGR is defined by the presence of iAREDF in the UA Doppler of the IUGR twin. The characteristic feature of this Doppler pattern, unique to monochorionic twins, is the alternation of phases of positive with phases of absent/reverse diastolic flow, normally but not always in a cyclical fashion (Figure 1). The observation of this sign indicates the presence of a large placental AA anastomosis,[22,26] which facilitates transmission of the systolic waveforms of one twin into the umbilical cord of the other one. Indeed, observing the characteristic bidirectional flow pattern of AA anastomoses (Figure 2) facilitates the understanding that iAREDF is a distant reflection of such a pattern in the umbilical cord of the IUGR fetus.[24,29,33] Transmission of the AA pattern into the UA of the smaller twin is explained by the large inter-twin fetal weight discordance, in combination with a large diameter AA vessel, a shorter distance between placental cord insertion sites, or both.[22,26] When these three factors are all present one can observe cases with extremely prominent reversed waveforms in the IUGR twin.

In type III pregnancies, AA anastomoses behave as functional arterio-venous anastomoses with a strong influence in the natural history of the IUGR fetus.[19] Such influence is expressed in the particular clinical evolution of these cases, as discussed below, and in the ratio between placental and fetal weight discordances, which on average can be below 0.5, the lowest among pregnancies with sIUGR.[4] Indeed, it is common to find extreme differences in the ratio between placental territories, which not rarely may be 10-fold or beyond.[18]

iAREDF is normally diagnosed in MC pregnancies complicated with sIUGR, but it is not an exclusive sign of such pregnancies. Although rare, it can be observed in uncomplicated MC pregnancies (normally in cases with very close cord insertions and large AA anastomoses) and even in pregnancies complicated with TTTS.[26] In addition, the presence of a large AA in MC pregnancy does not presuppose that iAREDF will be observed, particularly if the cords are far from each other and fetal weights are similar.

7.2. Clinical evolution and pathophysiological basis

Type III pregnancies are, like the previously discussed types, characterized by a long latency time between diagnosis and delivery. In most cases, the compensating effect of the large AA allows survival of the IUGR fetus until advanced stages of pregnancy, without showing clear signs of hypoxic deterioration. In these respects, this behavior may resemble that of type I. However, contrary to type I cases these pregnancies are associated with a significant increase in the risk of unexpected IUFD of the IUGR fetus and of brain injury in the normally grown twin. These adverse outcomes are explained by the high risk of acute feto-fetal hemorrhagic accidents through the large AA vessel, which may lead to death of the smaller twin or acute hypovolemia in the larger one. Such acute feto-fetal transfusion episodes may occur in the presence of transient bradycardic episodes in the smaller twin, and are facilitated by the large diameter of the AA anastomosis, which facilitates direct and rapid transfusion over a period of seconds. In large AA connections, the increase in vessel diameter results in exponential increases in the volume flow per second. Wee et al.[28] have reported that the mean diameter of the AA anastomoses was more than double in cases presenting iAREDF in UA Doppler, as compared to those without this sign (4.3 mm vs 2.1 mm). A two-fold increase in the diameter results in a four-fold increase in the

Figure 1. Pulsed Doppler insonation of the umbilical artery of the small twin in a monochorionic pregnancy with selective intrauterine growth restriction type III. The photograph represents the most typically observed image, with a cyclical pattern of positive, absent and reversed end-diastolic flow.

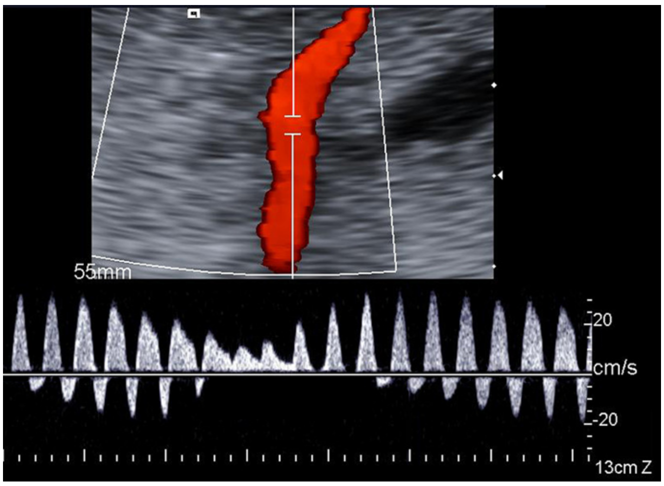

Figure 2. Pulsed Doppler insonation of a large placental arterio-arterial anastomosis, showing the characteristic bidirectional periodic pattern resulting from the collision of two opposite systolic waveforms.

area and consequently flow volume per second. Thus, even a short episode of bradycardia or hypotension in the smaller twin could result in considerable blood exchange in a matter of seconds, as compared to cases with smaller AA vessels.[1]

In a clinical series of 65 type III sIUGR cases, up to 89% IUGR fetuses progressed until 32 weeks or later without abnormal venous Doppler or biophysical profile changes suggestive of fetal deterioration. In spite of this apparently benign evolution, 15.4% of IUGR fetuses died unexpectedly hours or days after a normal examination. In addition, even if both twins were alive, the larger twin had a significantly increased incidence (19%) of abnormal neonatal brain scans, suggesting white matter injury. These results were later confirmed in the Japanese series,[15] reporting type III cases to be associated with 15.4% of IUFD in the smaller twin and 38.5% of surviving larger twins showing brain damage at 6 months.

7.3. Practical aspects for the evaluation of the iAREDF Doppler pattern

iAREDF is relatively common in sIUGR pregnancies. However, the sign must be actively sought; otherwise it can easily be missed and may lead to under-ascertainment, particularly in retrospective studies. This may partially explain differences in the reported incidence of iAREDF in sIUGR fetuses (20–45%) in prospective studies[22,26] and it is the reason for retrospective studies reporting not a single case of iAREDF in relatively large series of sIUGR pregnancies. The sign is often more pronounced near the placental cord insertion site. If required, maternal breathing must be withheld during Doppler recording to rule out any influence of maternal movements. A low sweep speed pulse Doppler setting is much better to identify less pronounced cyclic changes, and allows observation of the oscillatory changes in systolic velocities that characteristically accompany diastolic changes. AA anastomosis involves only one umbilical artery, but in most cases it can be observed in either artery due to the presence of the Hyrtl anastomosis, a placental vessel connecting both umbilical artery at the placental umbilical cord insertion and present in virtually all pregnancies.[34]

7.4. Clinical management of type III sIUGR pregnancies

Management of type III sIUGR represents a challenge. Left to its natural evolution the prognosis would in general be better than in type II cases, but clinical decisions are more difficult due to the unpredictability of adverse outcomes. In a similar manner to what has been discussed for type II, there is not a single option. Certainly, the severity of growth discrepancy and of the Doppler anomalies will influence counseling and the final decision about the type of management, although parents' wishes and technical issues may also play an important role. It is reasonable to believe that the risk increases with greater diameter of the AA and EFW discordance and less distance between the cords. Thus, the most prominent and clear forms of iAREDF should be expected to carry the worst prognosis. However, there is no clear evidence to support this notion. We have observed cases of poor outcome in all clinical forms of iAREDF, including some cases with mild features and distant cords.

If expectant management is chosen, follow-up schemes should be similar to those discussed above for type II cases, i.e. weekly follow-up if venous Doppler is normal, and closer follow-up with consideration of active management if venous Doppler becomes abnormal. Unfortunately, in type III the IUGR fetus will rarely show signs of fetal deterioration in venous Doppler, and therefore one reasonable option may be to deliver electively around 32 weeks of gestation. This is clearly an arbitrary decision and, although not based on any evidence, in our opinion it makes sense to adjust the timing according to the prominence of the intermittent flow. Thus, where clear intermittent reverse flow is observed in combination with large estimated fetal weight discordance, a large AA anastomosis should be expected and it seems wise to deliver the pregnancy at 32 completed weeks. The reasons are probably similar to those used for decisions in monoamniotic pregnancies, i.e. to reduce the opportunity for unexpected adverse outcomes to occur. Those type III pregnancies with milder forms of intermittent absent end-diastolic flow and moderate EFW discordance could probably be prolonged until 34 weeks.

In case fetal therapy is considered, cord occlusion is a straightforward treatment. It seems reasonable that this therapy should normally be reserved for cases with extreme forms of iAREDF and/or extreme EFW discordance, or if fetal deterioration of the IUGR fetus is observed. Laser coagulation is also feasible in type III pregnancies, but it is associated with even more technical difficulties than in type II. In a small clinical series by our group, the procedure resulted in a 75% risk of IUFD for the smaller fetus, normally within the first week after therapy.[32] As a trade-off, the procedure suggested beneficial effects in the larger twin, and a significant reduction in the risk of concomitant death of the AGA twin after intrauterine demise of the IUGR fetus was observed.[32] In any event, laser is a complex procedure and it might even be unfeasible, particularly when factors such as an anterior placenta, an exceedingly large AA and/or umbilical cord insertions very close to each other. Actually, when these factors are identified before surgery it would be wise to reconsider laser coagulation since the chances for failure or serious complications, such as a placental vessel perforation, may be high. In summary, laser coagulation in type III sIUGR pregnancies should be performed only by surgeons with a consolidated track record in fetoscopic operations in monochorionic pregnancies, and in any case parents should be informed that placental coagulation might fail. However, it may constitute a reasonable alternative for parents requesting active management and not accepting a cord occlusion.

8. Cardiac consequences of selective IUGR

The particular hemodynamic situation created by the existence of vascular anastomoses between two fetuses with discordant weights may entail cardiovascular consequences for the larger twin. This situation is most evident in type III pregnancies, where hypertrophic cardiomyopathy-like changes are observed in the normal twin in a substantial proportion.[35] Thus, an enlarged heart in the normally grown fetus should be regarded as part of the normal spectrum of findings in type III pregnancies. These cardiac changes seem to be reactive and have not been associated with a poorer neonatal prognosis for the normal fetus, but the impact on long term cardiac function remains to be evaluated.[35] We have postulated that this situation might reflect a state of high output cardiac failure produced by the larger twin pumping part of the fetoplacental volume of the smaller one. In these respects one might say that type III pregnancies with extreme fetal weight discordances might constitute the latest step in which a viable fetus is preserved before the development of an acardiac twin in monochorionic pregnancies. Therefore, sIUGR with abnormal Doppler seems to be associated with a state of subclinical high output cardiac dysfunction in the larger twin, which is most pronounced and may even lead to hypertrophic-like changes in type III cases.

9. Late-onset SIUGR

A recent study has described the clinical outcome and placental characteristics of late-onset sIUGR. This was defined as birth weight discordance of $\geq$25% first diagnosed after 26 weeks of gestation and thus not observed at 20 weeks.[5] The rate of late-onset sIUGR was reported to be 6.3%, 13 in a cohort of 208 MC pregnancies. Clinically, it was characterized by a benign course with almost concordant growth until the late second trimester, with discordance developing progressively from then onwards and reaching on average of 30%. Mean gestational age at delivery was 35 weeks. UA Doppler was normal in all cases and there was only one case of IUFD (8%) in this series. There rate of severe inter-twin hemoglobin differences at birth, meeting the criteria for twin anemia–polycythemia sequence, was 38% (5/13), which suggests that measurement of MCA peak systolic velocity should be performed in these cases. The clinical significance and long term consequences of late-onset IUGR remain to be determined.

Conflict of interest statement

None declared.

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Practice points

- MC twin gestations complicated by sIUGR are at high risk of perinatal complications and should be managed in dedicated high risk pregnancy units.
- Clinical evolution of early-onset sIUGR is a function of placental sharing discordance and inter-twin blood flow determined by the anastomotic pattern, and this may lead to substantial clinical differences in apparently similar cases.
- UA Doppler evaluation in MC twins with sIUGR allows definition of three types: (I) positive, (II) persistently absent/reverse, and (III) intermittently absent/reverse diastolic flow. In most cases, these Doppler types are apparent from early in pregnancy and do not change once the diagnosis is established, which may be of help for parents' counseling and clinical decisions.
- Type I is associated with a fairly good prognosis. Types II and III are associated with a higher risk of intrauterine demise of the smaller twin, a high rate of delivery at less than 32 weeks of gestation. Type III is associated with increased risk of neurological injury of the larger twin.
- Management in type II and III remains a challenge. Fetal therapy may be an option to improve the prognosis of the larger twin, but the decision must also be weighed against the risks of fetal therapy and parents' wishes.

Research directions

- There is a need for larger prospective series, with careful characterization of cases in terms of umbilical artery Doppler, to:
  - determine the prognosis and risk factors associated with poor outcome in sIUGR types II and III;
  - describe the long term neurological outcome in survivors of different types;
  - compare management strategies in observational trials.
- Although clinical randomized trials would be highly desirable, the chances of success are limited in view of the substantial number of factors affecting outcome, which may constitute an insurmountable limitation to define homogeneous populations, and the strong influence of parents' preferences among management options.

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