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Treatment of Types II and III Selective Intrauterine Growth Restriction in Monochorionic Twin Pregnancies: A Systematic Review

Cristiane Emília Dutra Valadão[*1,2], Carolina Soares Barros de Melo[2], Gabriel Bandeira Tofani[3], Luiza Meelhuysen Sousa Aguiar[1,2], Fernanda Magalhães Menicucci[1,2], Raquel Pinheiro Tavares[1,2] and Carlos Henrique Mascarenhas Silva[1,2]

[1]*Department ofFetal Medicine, Hospital Mater Dei, Belo Horizonte, Brazil*
[2]*Department of Obstetrics and Gynecology, Hospital Mater Dei, Belo Horizonte, Brazil*
[3]*Department of Radiology, Hospital Mater Dei, Belo Horizonte, Brazil*

Abstract

Background: Types II and III selective intrauterine growth restriction have worse prognosis than Type I and its treatment are still a challenge. The objective of this study is to discuss the management of selective intrauterine growth restriction types II and III, based on current scientific evidence.

Methods: PubMed, Lilacs/Bireme and SciELO were used as data sources. The following MeSH and DeCS descriptors were used: Twin Pregnancy, Selective Growth Restriction, Fetoscopic Laser Surgery and Cord Occlusion. Articles published in the last five years in Portuguese, English and Spanish were included while meta-analyzes, systematic reviews and case reports with less than three cases were excluded.

Results: 12 articles were selected: a case report, a clinical trial and ten observational studies. Pravastatin and L-arginine prevent the appearance of selective intrauterine growth restriction in pregnancies with changes in the umbilical artery Doppler. Tadalafil increases the weight of the restricted fetuses and prolongs the pregnancies. The survival of the larger fetus after cord occlusion varies between 62% and 93%, with overall survival rates between 31% and 46%, whereas the laser ablation of placental anastomoses has overall survival rates between 53%and90% in pregnancies with types II and III selective fetal growth restriction. Apparently, laser ablation has better results when the restricted fetus has changes in the umbilical artery Doppler and severe oligohydramnios.

Conclusion: Randomized studies are still needed to prove the best treatment for types II and III selective intrauterine growth restriction. Pravastatin + L-Arginine and Tadalafil are promising for prevention and treatment. Fetal survival rates are slightly higher with the laser treatment. Changes in the umbilical artery Doppler and severe oligohydramnios in the restricted fetus seems to be initial indications for management. The parents' desire, local laws, team experience and fetal conditions still interfere in the choice of the surgical method since the results are yet not conclusive.

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Introduction

Selective intrauterine growth restriction (sIUGR) affects 10% to 15% of monochorionic (MC) twin pregnancies [1,2]. This pathology is becoming more common, being responsible for the increase in perinatal and postnatal morbimortality of both fetuses. The unexpected neurological compromise is the main complication associated with this pathology [3].

The currently most accepted definition is that sIUGR occurs when the smaller fetus has an estimated weight below the 10th centile, that is, it is unable to reach its maximum growth potential [3]. The growth discordance between the fetuses (a difference greater than 25%) is an important element for the clinical manifestations and for the prognosis of the pregnancy [4], and although it is often associated with this condition, it is no longer considered to be essential for the diagnosis, according to most authors [3].

There are three factors that can interfere in the intrinsic fetal growth: genetic, environmental (infections, drug usage) and placental [5]. Denbow et al. [5] confirmed that the main cause for sIUGR is an unequal division of the placental mass. However, the various clinical presentations of the disease are intimately correlated to the characteristics of the vascular anastomoses in an inappropriately shared placenta. Acute events during pregnancy, the volume and number of anastomoses, as well as unequal proportion of the shared placenta are the main events responsible for the balance between both circulations and, consequently, for the occurrence of associated complications [1].

There are three types of placental anastomoses in MC pregnancies: arteriovenous (AV), arterio arterial (AA) and venovenous (VV) [5].

Arteriovenous anastomoses are deeper and allow unidirectional flow; in sIUGR, the direction of the flow happens from the larger twin to the smaller one, acting as a "rescue transfusion" that acts compensating the placental insufficiency of the smaller fetus. For this reason, the progression of the disease is slower [5].

Arterio arterial and venovenous anastomoses are bidirectional and more superficial, causing intermittent flow in the umbilical artery - which can increase the latency period of the disease, but causing an unstable hemodynamic balance, facilitating the occurrence of acute

[*]**Corresponding Author:** Dr. Cristiane Emília Dutra Valadão, Dom Lucio Antunes Street, 381/301, Coração Eucarístico, CEP 30.535-630, Belo Horizonte, Brasil; E-mail: crisvaladao@gmail.com

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fetofetal transfusion episodes in the presence of cardiac frequency or blood pressure variations in any of the fetuses - that can cause intra-uterus sudden death of the restricted fetus or even brain damage in the non-restricted one [3].

Gratacos et al. proposed a classification of sIUGR based on the end-diastolic flow of the umbilical artery (UA) during color Doppler evaluation [3,6,7], representing a combination of the placental insufficiency effects with the effects of the vascular connections between the fetuses. In type I, the end-diastolic velocity of the UA is positive; in type II, the end-diastolic flow is absent or reverses; and in type III the diastole has a cyclic/intermittent pattern [6].

Survival rates in type I sIUGR is greater than 90% without treatment [6], and so, management is expectant in most cases. Types II and III sIUGR have worse prognosis, with high risk of fetal death and brain damage to both twins [3].

Type II sIUGR happens because of severe placental discordance, presenting worse prognosis because of the greater risk of hypoxic deterioration and neurological damage, as well as greater rates of extreme premature birth (usually before 30 weeks), when compared with type III [3]. Clinical deterioration can be predicted in type II by the Doppler study, allowing fetal therapy or interruption of pregnancy depending on the gestational age [3].

Type III sIUGR occurs due to the presence of great AA placental anastomoses associated with an unequally shared placenta, which compensates the restricted fetus but predisposes to acute and unpredicted volemic accidents that can pass unseen in the Doppler, resulting in unexpected fetal death of the restricted twin or brain parenchyma damage on the non-restricted one [8].

Expectant management is acceptable in types II and III, but the worse outcomes associated with the early onset of these types of sIUGR often lead to parents request for active therapy [9,10]. In case fetal therapy is chosen, there are currently two widespread alternatives: umbilical cord occlusion of the restricted fetus (CO) or laser ablation of the inter-placental communicating vessels (LAP), both with still unencouraging results [2]. On the one hand, CO determines the restricted fetus' death, and on the other hand, LAP studies show uncertain and heterogeneous outcomes, being able to increase the risk of the restricted fetus' death by interrupting the protection granted by the interfetal transfusion, and with this, increasing the risk of neurological damage of the non-restricted ones [2,3]. Thus, types II and III management remain as challenge, with optimal conduct yet undetermined.

The present study has the objective of discussing the main alternatives of treatment and control of types II and III sIUGR based in studies published in the last 5 years.

Methods

This systematic review was elaborated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) norms [11]. Searches were undertaken during the month of September 2019 across PubMed, Lilacs/Bireme and SciELO databases. The following MeSH and DeCS descriptors were used: Twin Pregnancy, Selective Growth Restriction, Fetoscopic Laser Surgery and Cord Occlusion. Articles published in the last five years which approached the treatment of selective fetal growth restriction, in English, Portuguese and Spanish, with any epidemiologic design - except meta-analyses, systematic reviews and case reports with less than 3 cases - were accepted.

The primary outcomes analyzed were: (1) Survival rates of the restricted fetus and of the non-restricted fetus and (2) the global number of fetuses born alive.

The secondary outcomes analyzed were: (1) neonatal neurological morbidity (fetal brain image alteration, defined as intraventricular hemorrhage or periventricular leukomalacia), (2) gestational age at delivery and (3) neurological development during infancy.

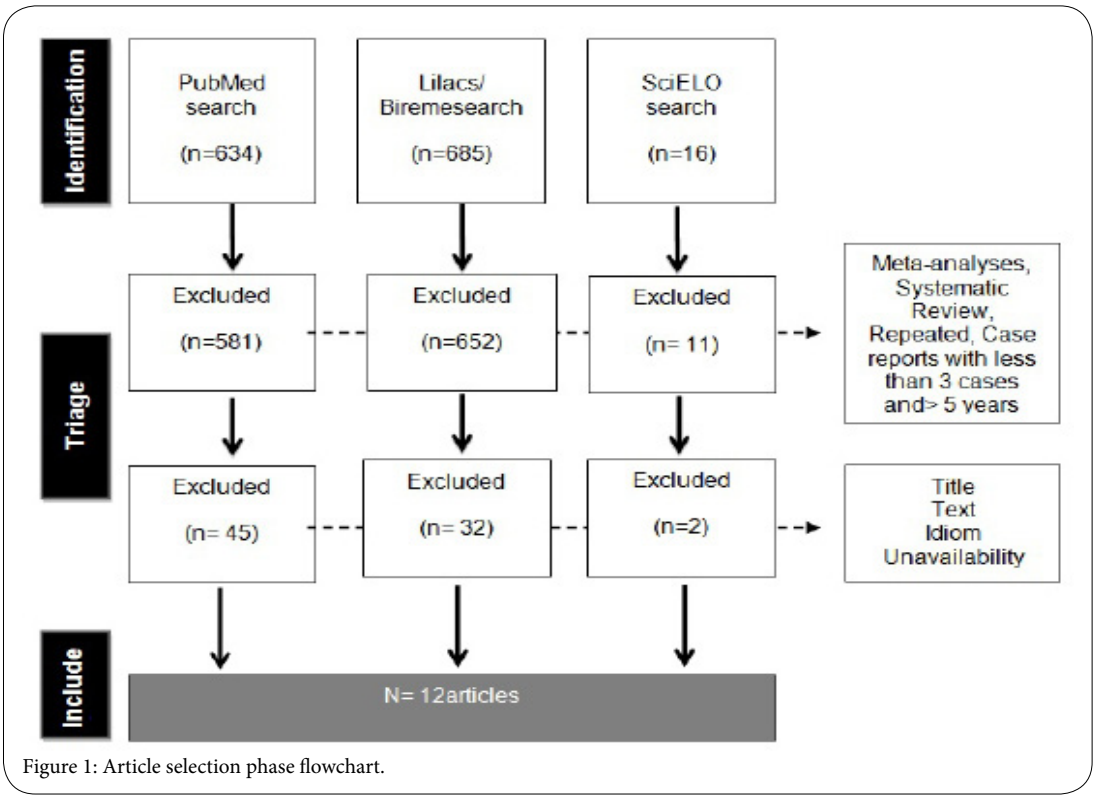

Figure 1: Article selection phase flowchart.

The quality of the included studies was evaluated using the Downs and Black control list for randomized and non-randomized interventional studies in health [12].

Results

Using PubMed's free search with a filter for publications in the last five years, 634 articles were found. Of these, 581 were excluded for being meta-analyses, systematic reviews and/or case reports with less than 3 cases, and another 45 were excluded by their title. In Lilacs/Bireme database, the five years filter was also used and 685 articles were found, of which 652 were excluded for being identical to the articles found in PubMed, 18 were meta-analyses, systematic reviews and/or case reports with less than 3 cases, 27 by the title, 2 due to full text unavailability and other 3 because they were written in different languages than the selected. Sixteen articles were found in the SciELO database, using the same five years filter, of which 11 were excluded for being equal to articles found in PubMed and 9 were excluded after the text was read. Twelve articles were then selected for this review (see Figure 1).

Table 1 sums up the main characteristics of the selected articles, including Downs and Black score [12]. Two studies include drug

Reference	Country	Type of Study	Sample (N)	Sample Characteristics	Diagnostic Criteria	Conduct	Reported Results	Score (12)
Magawa et al. [13]	Japan	Pros Phase I Clinical Trial	6	MC or DC twin pregnancy with sIUGR	EFW < -1,8 SD	Tadalafil per oral	Adverse effects, fetal growth, GA at delivery; weight at birth, maternal and fetal Tadalafil concentration, fetal Doppler evaluation	17
Jurisic et al. [14]	Serbia Greece UK	Pros Case report	5	DC twin pregnancy with UA PI changes and sIUGR	Undefined	Prevastatin and L-arginin per oral	Mortality, fetal growth, GA at delivery, neurological morbidity, adverse effects	--
Miyadahira et al. [15]	São Paulo	Retro cohort	67	MCDA twin pregnancy with types II and III sIUGR	EFW < 10th centile and EFW discordance > 25%	Laser (39), expectant (28)	Mortality	15
Wang et al. [16]	China	Pros Cohort	4	MCDA twin pregnancy with types II and III sIUGR	Undefined	Radiofrequency ablation	Mortality, fetal and postnatal neurological morbidity, GA at delivery	14
Peng et al. [17]	China	Retro Cohort	13	MCDA twin pregnancy with types II and III sIUGR	Undefined	Radiofrequency ablation (8), cord coagulation (5)	Mortality, neurological morbidity, GA at delivery, others	19
Peeva et al. [18]	UK	Retro Cohort	14	DCTA triplets and sIUGR	EFW or AC < 5th centile EFW discordance > 25%	Laser	Mortality, GA at delivery	16
Parra-Cordero et al. [9]	Spain	Pros Cohort	90	MCDA twin pregnancy with types II and III sIUGR	EFW < 10th centile; ou CA < 10th centile and EFW discordance > 25%	Cord coagulation	Mortality, GA at delivery, others	14
Ortiz et al. [19]	Spain	Retro Cohort	68	MCDA twin pregnancy with types II and III sIUGR	EFW < 10th centile and EFW discordance > 25%	Fetoscopy (laser, cord occlusion)	Chorioamniotic membrane separation	18
Ishii et al. [20]	Japan	Pros Cohort	10	MCDA twin pregnancy with type II sIUGR and severe oligohydramnios of the restricted twin	EFW < -1,5 SD	Laser	Mortality, neurological morbidity, others	12
Yinon et al. [21]	Israel	Retro Cohort	23	MCDA twin pregnancy with types II and III sIUGR	EFW < 10th centile and EFW discordance > 25%	Radiofrequency ablation (19), cord coagulation (4)	Mortality, neurological morbidity, others	16
Peeva et al. [22]	UK	Retro Cohort	547	MCDA twin pregnancy with sIUGR with and without FFTS	EFW ou CA < 5th centile and EFW discordance > 25%	Laser	Mortality	20
Ishii et al. [8]	Japan	Retro Cohort	52	MCDA twin pregnancy with type II sIUGR and severe oligohydramnios of the restricted twin	EFW < -1,5 DP and/ or EFW discordance > 25%	Laser	Mortality, neurological morbidity, others	19

Table 1: General characteristics of the selected studies.
Caption: Pros: Prospective; Retro: retrospective; sIUGR: selective fetal growth restriction; MC: monochorionic; DC: dichorionic; EFW: estimated fetal weight; PI: pulsatility index; UA: umbilical artery; MCDA: monochorionic diamniotic; DCTA: dichorionic triamniotic; AC: abdominal circunference; FFTS: fetofetal transfusion syndrome.

treatments: one is a clinical essay (Tadalafil) and the other is a case report (pravastatin and L-arginine). The remaining articles were observational studies of surgical treatments; one study reported results after expectant management, six after laser therapy, three after radiofrequency ablation and three after cord coagulation. Various of these observational studies reported more than one strategy of treatment. There were no randomized studies comparing the different treatments.

The main methodological weaknesses of these studies are the observational design, small samples, lack of randomization and different gestational ages in the evaluation, intervention and monitoring. There is also a considerable heterogeneity in the definition of selective fetal growth restriction between different studies.

Discussion

Multiple pregnancies represent 1% of all pregnancies, although their incidence has been increasing due to the various fertilization techniques. Dizygotic twins represent 70% of twins, while monozygotic represent only 30%. Chorionicity is, however, a risk factor because monozygotic twins present greater prevalence of prematurity, low weight, perinatal death and neurological sequelae in consequence mainly of sIUGR, that happens in 20% to 25% of these pregnancies due to inequality in the division of the placental mass and to new or pre-existing anastomoses between placental territories [9,23,24].

In the past, several studies were designed to show the results of expectant management on types II and III sIUGR. Quintero et al. [25] in 2001 reported overall survival rate of 58.5% after expectant management in type II sIUGR, with a rate of neurological damage of 13.6% and mean gestational age at delivery of 30.6 weeks. Huber et al. [26] reported a survival rate of 60% in 19 pregnancies of MC twins with type II sIUGR and expectant management, with high rates of premature delivery before 32 weeks. In a series of expectant management of twin pregnancies with type II sIUGR in Japan, Ishii et al. [27] reported in 2009 an overall survival rate of 58.5%, an overall intact survival rates (no death or neurological morbidity) of 37% for restricted infants and of 55% for the normal ones, with 28 weeks of mean gestational age at delivery. In fetuses with type III sIUGR after expectant conduct, two series previously described intrauterine mortality of 15% for restricted twins and of 7% to 24% for the normal twin, but with a rate of brain parenchyma damage in the normal twin of 19% to 38%, independently if the restricted twin survived or not [7,27]. Miyadahira et al. [15] in 2018 also studied expectant management in types II and III sIUGR, reporting mortality rates of the restricted twin of 83.3% and 22.7%, with an overall survival of 41.7% and 84.1% for types II and III, respectively. The neurological morbidity wasn´t mentioned in this last study. Table 2 summarizes these articles of expectant management and its data.

In types II and III sIUGR, hypoxic deterioration of the restricted fetus and changes in the neurological damage predictors of the normal growth fetus associated with the volume of amniotic fluid and gestational age will be determinant to decide if intrauterine interventions will be performed or not.

Until the present study, drug interventions were still not viable options for the treatment of this pathology. Two studies were highlighted in this revision as promising proposals for drug therapies in the future.

The use of Pravastatin and L-arginin (PRAV + L-Arg) seems to prevent the development of sIUGR in twin pregnancies that present with early onset (24-28 weeks) changes in the UA Doppler of the restricted fetus due to their vasodilator, anti-inflammatory and anti-thrombotic effects [14]. Improvement in the Doppler study of UA was observed after two weeks of the beginning of the treatment, followed by improvement in the fetal growth pattern after 9 weeks of treatment. PRAV + L-Arg prevented restricted fetus demise, enabling extension of the pregnancy for 9 weeks after detection of changes in Doppler, also reducing the risks of extreme prematurity. No adverse effects were observed in the fetuses and neonates; they were born alive and had normal neurological development until they were 4 years old. However, it was an observational study with small sample, sIUGR in dichorionic (DC) pregnancies only - which cannot be freely extrapolated to MC pregnancies. Maybe after randomized studies with adequate samples and population of patients with MC pregnancies this treatment could become the prevention of early onset sIUGR.

Another promising drug is Tadalafil, a long duration vasodilator that acts as inhibitor of 5-Phosphodiesterase. It would not act as a prevention, but as a treatment of sIUGR in MC pregnancies. Animal studies showed it can increase placental growth factor, facilitating fetal growth [28]. In 2017, Kuboet al. [29] showed, in a retrospective study comparing the use of tadalafil versus expectant management in single pregnancies with fetal growth restriction, that the Tadalafil group presented fetal growth rates and fetal weight at birth greater than in the control group. In 2019, with six cases of MC and DC twin pregnancies with sIUGR and mean gestational age of 26 weeks, Magawa et al. [13] demonstrated that Tadalafil can be safely used in these groups of patients, and in addition it increased the weight of the restricted fetuses after two weeks of use, extended the pregnancies for a mean of 8 weeks, leading to a mean gestational age at birth of 34 weeks. A randomized study for single pregnancies with fetal growth restriction, TADAFER II, is already ongoing in Japan, with estimated end date for data collection in 2021 [28]. It is also necessary the organization of a randomized study for MC twin pregnancies so that this therapeutical effect of Tadalafil can be proved in this population, and check in what subgroup of sIUGR it will be more beneficent, potentially avoiding an invasive fetal procedure that can result in several complications.

Reference	Sample	Survival rate of the restricted twin	Survival rate of the non restricted twin	Neurological Morbidity	Overall Survival	GA at delivery, weeks, median
Quintero et al. [25]	17 Type II sIUGR	59%	58%	13,6%	58.5%	30.6
Huber et al. [26]	19 Type II sIUGR	63%	78%	NR	60%	32
Ishii et al. [27]	27 type II sIUGR 13 type III sIUGR	51% 85%	66% 76%	12,9% 30% (38,5% of the larger twin)	58.5% 80%	28 31
Gratacós et al. [7]	65 Type III sIUGR	85%	93%	19,7% (larger twin)	89%	31,6
Miyadahira et al. [15]	6 Type II sIUGR 22 Type III sIUGR	16.7% 77.3%	66.7% 90.9%	NR NR	41.7% 84.1%	NR NR

Table 2: Results of Expectant Management.
Caption: GA: Gestational age; sIUGR: selective intrauterine growth restriction; NR: not rated.

Among surgical interventions currently available, there are two main options performed under fetoscopy, which are umbilical cord occlusion (CO) of the restricted fetus and laser ablation of communicating placental vessels (LAP).

Fetoscopy, a minimally invasive surgery, is a well stablished procedure for various fetal conditions, such as fetofetal transfusion syndrome, mielomenigocele, inferior urinary tract obstruction and congenital diaphragm herniation [30,31]. However, there are still doubts regarding to when and which would be the best way to intervene in case of MC pregnancy with sIUGR. Besides, fetoscopy is not a procedure completely free of complications. In 2016, Ortiz et al. [19] observed the occurrence of chorioamniotic membrane separation in 20.7% of MC twin pregnancies with types II and III sIUGR after fetoscopy (LAP or CO), concluding that early gestational age (below 18 weeks) in the moment of the procedure is the only factor associated to the severity of this condition and that this chorioamniotic membrane separation increases the risk of gestational complications and decreases the chances of neonatal survival in approximately 10%, especially if this separation is complete.

Cord occlusion has been for a long time the surgery of choice for the treatment of types II and III sIUGR because, despite determining the death of the restricted fetus, it presented global survival rates greater than LAP, with lower rates of brain damage in the survivor fetus. Intra-cardiac injection of potassium chloride in the restricted fetus is contra-indicated in MC pregnancies due to the risk of passage of cardiotoxic agents through the placental anastomoses to the other fetus [21]. Thus, selective feticide in MC pregnancies is reached by interruption of blood flow to the restricted fetus. There are numerous ways to perform this interruption, such as cord ligation, laser coagulation, ultrasound guided cord coagulation with bipolar, radiofrequency ablation, microwaves ablation and high intensity focal ultrasound [16].

Coagulation with bipolar and radiofrequency ablation are the most used techniques for CO in types II and III sIUGR fetuses. In the studies analyzed in this systematic review, there is no superiority of one technique over the other regarding global survival rates, perinatal outcomes and secondary outcomes, although there is a tendency for more premature births and lower weights at birth in the group of coagulation with bipolar [17,21]. Wang et al. [16] obtained survival rates of the bigger fetus after radiofrequency ablation of 75% and there were no cases of neurodevelopment delay (until they were 3 years old). Peng et al. [17] had survival rates of the bigger fetus of 62,5% and 71,1% for coagulation with bipolar and radiofrequency ablation, respectively; they realized also that outcomes are better when the procedure is performed after 18 weeks and that delivery before 28 weeks is the most important independent predictor for the morbimortality of the survivor fetus. Yinon et al. [21] also compared cord coagulation and radiofrequency ablation, reaching the rates of survival of the normal twin of 84.5% and 89.5%, respectively. Parra-Cordero et al. [9] obtained survival rates of 93,3% of the bigger fetus, a similar rate reported by other authors such as Chalouhi et al. (91%) [32] and Bebbington et al. (88%) [33]. For Parra-Cordero, the high survival rates of the recent studies are related to the greater experience of the surgical team and probably the series that had lower rates have surgeons still in the learning curve [9].

Because in many countries CO is not a legal procedure, many studies arose to better understand the laser effects in the placental anastomoses of sIUGR and its complications. The first series of studies with laser showed survival rates of the normal fetus of 63% to 94%, of the restricted fetus between 30% and 45% and a global survival rate between 43% and 63%; but those were small studies with well selected severe cases [9]. Miyadahira et al. [15] showed afterwards that in types II and III sIUGR with changes in the ductus venosus Doppler, laser had similar outcomes to expectant management in less severe cases, reaching an overall survival rates of 58.3% and 66.7% after laser procedure in types II and III, respectively.

Ishii et al. [20] showed that, in a small study with 10 cases of sIUGR and umbilical artery changes in Doppler associated with severe oligohydramnios, survival rates of the restricted fetus was 30% and of the normal fetus was 100% (with global survival rates of 65%) and all of them with no signs of abnormal neurological abnormalities 28 days after birth and mean gestational age of 32 weeks at delivery. They concluded that the best indication for laser would be severe oligohydramnios of the restricted fetus, which would potentially benefit the prognosis of the normal fetus.

Peeva et al. [22] published in 2015 the biggest series of type II sIUGR treated with laser, reaching survival rates of the normal twin of 67,6% and 38,7% in the restricted fetus, with global survival rates of 53,2%. In another study, Peeva et al. [18] showed that in triplet dichorionic triamniotic pregnancies coursing with sIUGR, results were similar to their study with monochorionic diamniotic pregnancies, presenting with survival of one of the fetuses in 79% of pregnancies and global survival rates of 52% of all babies. In 2018, Ishii et al [8] again published a series with types II and III sIUGR pregnancies with umbilical arterial Doppler changes and severe oligohydramnios, but now with 52 cases that received laser as treatment. In this study, global survival rate for type II was 64,5%, with the restricted fetus survival rate of 36% and the larger fetus of 93%. Mortality rate was significantly higher in type II sIUGR (64% versus 20%). No cerebral abnormalities were observed in the fetuses and neonates in this study. This study proved that the severity criteria (changes in Doppler and oligohydramnios) maybe are more precise indications for laser in types II and III sIUGR, showing that laser reduces the impact of AA anastomoses that can cause brain lesion and cardiomyopathies in the normal fetus and that interruption of such anastomoses also prevent those lesions in the normal fetus after death of the restricted fetus. The lower survival rate of the restricted fetus treated with laser as observed in the aforementioned studies is logical, considering that laser coagulation leaves a smaller placental area for the restricted fetus and interrupts the protection of the blood supply from the larger one. The apparent lower survival of the normal twin can result from a combination of factors, including the fact that fetoscopy occurs through the amniotic sac of the bigger twin and that this procedure can be considerably more challenging compared with the laser in the fetofetal transfusion syndrome [9].

Regarding surgical options, survival rates are heterogeneous among the different methods, although somewhat better in those cases which were carefully selected for the treatment with laser ablation of placental anastomoses. The results obtained by Ishii et al. [8] in 2018 are encouraging and can enlighten the best indications for this procedure in types II and III sIUGR. However, all studies which had surgical option were observational and with small samples. Randomized studies that compare both surgical options are still necessary so that we can choose the best treatment safely. Table 3 summarizes the results of all the surgical studies described in this article.

Conclusions

Despite new researches has appeared in the last five years to try to elucidate which is the best treatment for types II and III sIUGR, its management is still challenging, as shown by the analysis of the studies mentioned above.

Selective intrauterine growth restriction is not a unique condition like the fetofetal transfusion syndrome. Although studies usually

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Reference	Sample Characteristics	Management	Survival rate of the restricted twin	Survival Rate of the non-restricted twin	Neurological Morbidity	Overall Survival	GA at delivery, weeks, median
Wang et al. [16]	3 Type II sIUGR 1 Type III sIUGR	Radiofrequency ablation	0%	75%	0%	37.5%	37 26
Peng et al. [17]	13 Types II and III sIUGR	Radiofrequency ablation (8) cord coagulation (5)	(RA) 0% (CC) 0%	71.1% 62.5%	NR NR	35.5% 31.25%	31.4 31
Yinon et al. [21]	23 Types II and III sIUGR	Radiofrequency ablation (19) cord coagulation (4)	(RA) 0% (CC) 0%	89.5% 84.5%	NR NR	44.7% 42.2%	37 33
Parra-Cordero et al. [9]	41 Type II sIUGR 49 Type III sIUGR	Cord coagulation	(Type II) 0% (Type III) 0%	92.7% 93.4%	NR NR	46.3% 46.7%	36.4 36.5
Miyadahira et al. [15]	30 Type II sIUGR 9 Type III sIUGR	Laser	(Type II) 30% (Type III) 55.6%	86.7% 77.8%	NR NR	58.3% 66.7%	NR NR
Peeva et al. [22]	142 Type II sIUGR without FFTS 405 Type II sIUGR with FFTS	Laser	(without FFTS) 38,7% (with FFTS) 39,7%	67.6% 69.8%	NR NR	53.2% 54.8%	32 32.3
Peeva et al. [18]	14 DCTA triplets and sIUGR	Laser	NR	NR	NR	52,4%	32
Ishii et al. [20]	10 Type II sIUGR with severe oligohydramnios	Laser	30%	100%	0%	65%	32,4
Ishii et al. [8]	42 Type II sIUGR 10 Type III sIUGR (with severe oligohydramnios)	Laser	(Type II) 36% (Type III) 80%	93% 100%	0% 0%	64.5% 90%	32 34

Table 3: Comparison of surgical managements.
Caption: GA: gestational age, sIUGR: selective fetal growth restriction, NR: not rated, RA: Radiofrequency ablation, CC: cord coagulation, DCTA: dichorionic triamniotic, FFTS: fetofetal transfusion syndrome.

include severe cases with early onset, there are differences in the gestational age of the beginning of the disease, in the magnitude of the discrepancy between the fetal weights and in the severity of the Doppler changes.

Drug treatment arises as promising options in this scenario, especially for the early onset cases. PRAV+L-Arg would enter as prevention and tadalafil as a treatment. Randomized trials are still necessary with both drugs, though.

Regarding surgical treatments (laser ablation of placental vessels and cord occlusion), which previously had very uncertain results in types II and III sIUGR, in the last years they have proved to be reasonable options, with higher overall survival rates and less chance of neurological morbidity than in the initial studies. The biggest bioethical problem involved in these options is the certain death of one of the fetuses-the main objective of these techniques.

Laser ablation of placental vessels has presented slightly better results than cord occlusion in terms of overall survival. It seems that choosing the cases by its severity has an influence on the results; the cases of types II and III sIUGR with changes in umbilical artery Doppler associated with severe oligohydramnios in the restricted fetus seems to be the cases that benefit the most out of the laser, with survival rates (and free of brain damage) much higher than cord occlusion. Perhaps criterious selection of the indications for each procedure may be the path in the evolution of the treatment.

However, all of the studies analyzed that involved fetal surgery were also observational, requiring further randomized trials to prove these findings. Therefore, the prenatal management of types II and III sIUGR must still be individualized according to the gestational age of the diagnosis, to the severity of the growth discrepancy, to the degree of Doppler abnormalities, to the local laws, to the technical difficulties, to the team's experience and to the parents' desire. The prognosis and the survival chances expected for each fetus after each procedure must be discussed with the couple before making any decisions, since the results involving the best surgical technique are not yet conclusive.

Competing Interests

The authors declare that they have no competing interests.

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