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Perinatal outcome of monochorionic twin pregnancy complicated by selective fetal growth restriction according to management: systematic review and meta-analysis

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KEYWORDS: cord occlusion; laser; meta-analysis; monochorionic; selective fetal growth restriction; systematic review; twins

ABSTRACT

Objective *To explore the impact of severity and management (expectant, laser treatment or selective reduction) on perinatal outcome of monochorionic twin pregnancies complicated by selective fetal growth restriction (sFGR).*

Methods *MEDLINE, EMBASE, CINAHL, Clinical Trials.gov and The Cochrane Library databases were searched for studies on outcome following expectant management, laser treatment or selective reduction in monochorionic twin pregnancies complicated by sFGR. Only pregnancies affected by sFGR and categorized according to the Gratacós classification (Type I, II or III) were included. The primary outcome was mortality, including single and double intrauterine (IUD), neonatal (NND) and perinatal deaths. Secondary outcomes were neonatal morbidity, abnormal postnatal brain imaging, intraventricular hemorrhage, periventricular leukomalacia, respiratory distress syndrome, admission to neonatal intensive care unit and survival free from neurological complications (intact survival). Meta-analyses of proportions were used to analyze the extracted data according to management, severity of sFGR and fetal size (smaller* vs *larger twin).*

Results *Sixteen observational studies (786 monochorionic twin pregnancies) were included. In pregnancies complicated by Type-I sFGR managed expectantly, IUD occurred in 3.1% (95% CI, 1.1–5.9%) of fetuses and 97.9% (95% CI, 93.6–99.9%) of twins had intact survival. In pregnancies complicated by Type-I sFGR treated using laser therapy, IUD occurred in 16.7% (95% CI, 0.4–64.1%) of fetuses and, in those treated using selective reduction, IUD occurred in 0% (95% CI, 0–34.9%) of cotwins, with no evidence of neurological complications in the survivors. In pregnancies complicated by Type-II sFGR managed expectantly, IUD occurred in 16.6% (95% CI, 6.9–29.5%) and NND in 6.4% (95% CI, 0.2–28.2%) of fetuses, and 89.3% (95% CI, 71.8–97.7%) of twins survived without neurological compromise. In Type-II sFGR pregnancies treated using laser therapy, IUD occurred in 44.3% (95% CI, 22.2–67.7%) of fetuses, while none of the affected cases experienced morbidity and survivors were free of neurological complications. Of pregnancies undergoing selective reduction, IUD of the cotwin occurred in 5.0% (95% CI, 0.03–20.5%) and NND in 3.7% (95% CI, 0.2–11.1%), and 90.6% (95% CI, 42.3–94.3%) of surviving cotwins were free from neurological complications. In pregnancies complicated by Type-III sFGR managed expectantly, IUD occurred in 13.2% (95% CI, 7.2–20.5%) and NND in 6.8% (95% CI, 0.7–18.6%) of fetuses, and 61.9% (95% CI, 38.4–81.9%) of twins had intact survival. In pregnancies complicated by Type-III sFGR treated with laser therapy, IUD occurred in 32.9% (95% CI, 20.9–46.2%) of fetuses and all surviving twins were without neurological complications. Finally, in pregnancies with Type-III sFGR treated with selective reduction, NND occurred in 5.2% (95% CI, 0.8–12.8%) of cotwins and 98.8% (95% CI, 93.9–99.9%) had intact survival.*

Conclusion *Type-I sFGR is characterized by good perinatal outcome when managed expectantly, which represents the most reasonable management strategy for the large majority of affected cases. Pregnancies complicated*

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by Type-II or -III sFGR treated with fetoscopic laser ablation have a higher rate of mortality but lower rate of morbidity compared with those managed expectantly, supporting the use of fetal therapy at gestations remote from neonatal viability. Data on outcome following selective reduction are scarce. In view of the lack of evidence from randomized controlled trials, prenatal management of sFGR should be individualized according to gestational age at diagnosis, severity of growth discordance and magnitude of Doppler anomalies.

INTRODUCTION

Selective fetal growth restriction (sFGR) occurs in 10–15% of monochorionic twin pregnancies and represents a management challenge[1] due to the interdependence of twins connected via the placental vasculature. A greater understanding of the relationship of placental share and vascular structure with the clinical course and prognosis of sFGR has allowed classification by umbilical artery (UA) Doppler findings in the smaller twin[2]. In Type-I sFGR pregnancy, both twins have normal end-diastolic flow (EDF) in the UAs, in Type-II there is absent or reversed EDF and, in Type III, the phenomenon of intermittently absent or reversed EDF is observed. A consensus agreement on the diagnostic criteria for sFGR in monochorionic pregnancy was published recently[3], but clinical uncertainty regarding the optimal management, particularly in very preterm gestations persists[4]. The particular challenge in monochorionic pregnancy is the risk of acute fetofetal transfusion in the event of demise or profound hypotension in one twin causing death or neurological injury in the cotwin. Reported perinatal survival in pregnancies affected by Type-I sFGR is 97%, but survival in Types II and III is around 50% and 80%, respectively[4], with a high risk of intrauterine demise that may be particularly unpredictable in Type-III sFGR[5].

Current management options include expectant monitoring with delivery if fetal demise appears imminent, or active fetal intervention, by either fetoscopic laser treatment or selective reduction (SR) of the compromised twin. SR favors the outcome of the larger twin[6], while fetoscopic laser therapy can achieve survival of both twins in select cases at the cost of a higher risk of mortality and neurological complications of the larger cotwin[7].

The aim of this systematic review was to quantify the perinatal outcome of twin pregnancies affected by sFGR according to the type of prenatal management adopted.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to an *a-priori* designed protocol recommended for systematic reviews and meta-analyses. MEDLINE, EMBASE, CINAHL, ClinicalTrials.gov and Cochrane Library databases were searched electronically in February 2018, utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords, and word variants for 'twin pregnancy', 'selective intrauterine growth restriction' and 'outcome' (Table S1). The search and selection criteria were restricted to the English and French language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA[8] and MOOSE[9] guidelines were followed. The study was registered with the PROSPERO database (registration number: CRD42018087121).

Study selection and data collection

The primary outcome was mortality, including intrauterine death (IUD) of either twin, defined as fetal loss after 20 weeks of pregnancy, not as a result of planned termination of pregnancy or SR. We collected data on single IUD, double IUD, neonatal death (NND; defined as death of either twin up to 28 days postpartum, perinatal death (PND; defined as IUD or NND), live birth and survival of at least one twin (up to 28 days).

Secondary outcomes were: (1) overall neonatal morbidity, defined as the presence in either twin of at least one of abnormal brain imaging, respiratory distress syndrome (RDS), admission to the neonatal intensive care unit (NICU) or retinopathy of prematurity; (2) abnormal brain imaging, defined as the presence of either intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) of any type on postnatal imaging (ultrasound or magnetic resonance imaging); (3) severe IVH (Grade III or IV); (4) PVL (Grade II or III); (5) RDS; (6) admission to NICU and (7) intact survival, defined as survival free from neurological complications.

These outcomes were explored according to type of sFGR (Type I, II or III), as described by Gratacós *et al.*[2], management adopted (expectant, fetoscopic laser therapy or SR) and fetal size (smaller or larger twin). sFGR was defined as estimated fetal weight (EFW) of one twin $< 3^{rd}$ centile, or at least two out of four contributory parameters (EFW of one twin $< 10^{th}$ centile, abdominal circumference (AC) of one twin $< 10^{th}$ centile, EFW discordance of $\geq 25\%$, UA pulsatility index of the smaller twin $> 95^{th}$ centile) in the absence of ultrasound signs consistent with the presence of severe twin-to-twin transfusion syndrome[3].

Only studies reporting the incidence of the explored outcomes in sFGR classified according to Gratacós *et al.*[2] or from which the type of sFGR could be extrapolated were included. This is justified by the fact that risk stratification, counseling and management of pregnancies complicated by sFGR are based upon this classification. Studies including cases with fetal anomalies were excluded in view of the higher risk of mortality in the affected twin. Only full-text articles were considered eligible for inclusion. Case reports, conference abstracts and case series with fewer than three cases were excluded to avoid publication bias. Studies published before 2000 were not included as advances in diagnosis and management of

twin pregnancies complicated by sFGR make them less relevant.

Two authors (F.G.S., R.T.) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full text copies of those papers were obtained and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcomes. Consensus on inconsistencies was reached by discussion by the reviewers or by discussion with a third author (F.D.). If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) for case–control studies. According to NOS, each study is judged on three broad perspectives: selection of the study groups; comparability of the groups and ascertainment of the outcome of interest. Assessment of the selection of a study includes evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration that the outcome of interest was not present at the start of study. Assessment of the comparability of a study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, assessment of ascertainment of the outcome of interest includes evaluation of the type of assessment of the outcome of interest and length and adequacy of follow-up. According to NOS, a study can be awarded a maximum of four stars within the selection category, three stars in the outcome category and a maximum of two stars can be given for comparability[10].

Statistical analysis

First, random-effects meta-analysis of proportions was performed to estimate the pooled rates of each outcome for each type of sFGR (Type I, II or III) according to the management reported (expectant, laser or SR). Second, random-effects head-to-head meta-analysis was used to compare directly the risk of each outcome among the smaller *vs* larger twin, expressing the results as summary odds ratios and relative 95% CI. Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates that no heterogeneity is observed, while values $> 50\%$ are associated with substantial heterogeneity. A random-effects model was ultimately used for all meta-analyses because of heterogeneity identified between studies. Potential publication bias was assessed using Egger's test and visual inspection of funnel plots. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than 10, as the tests then lack power to detect real asymmetry. StatsDirect 3.0.171 (StatsDirect Ltd, Altrincham) and RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) statistical software was used to analyze the data.

RESULTS

We identified 1859 articles: 61 were assessed with respect to their eligibility for inclusion and 16 studies were included in the systematic review (Tables 1 and S2 and Figure 1). These 16 studies included 786 monochorionic pregnancies affected by sFGR. The general characteristics of the included studies are reported in Table 1. There were no randomized controlled trials comparing the different management options according to type of sFGR, and all the included studies were observational. Ten studies[11–20] reported outcome following expectant management, although protocol for expectant management varied in monitoring and indications for delivery. Not all studies reported the antenatal management protocols used for expectantly managed cases[11,13,14,20]. Outcome after active management with fetoscopic laser coagulation was reported by five studies[11,13,19,21,22]. SR by cord occlusion was reported in four studies[6,11,12,24] and by radiofrequency ablation in three studies[24–26], and these cases were analyzed together because there was not likely to be a significant difference between the two techniques[23,24]. Several studies reported more than one management strategy[6,11–13,19].

The results of quality assessment of the included studies using the NOS are reported in Table 2. Most included studies scored well regarding selection and comparability of the study groups and ascertainment of the outcome of interest. The main methodological weaknesses of these studies were their retrospective design, small sample size, lack of randomization according to management strategy and different gestational ages at assessment, intervention and follow-up.

In view of these limitations, the very small number of studies reporting each individual outcome and lack of comparison between the different types of management in most of the included studies, we decided not to report the risk comparison for each explored outcome according to type of management adopted. The included studies reported a variety of outcomes and no outcome was reported across all included studies, making it difficult to compare the relative importance of different outcomes. For example, the studies that reported double IUD were not included in the analysis for survival of at least one twin.

There was also considerable heterogeneity in the definition of sFGR among the different studies, with authors variably using EFW, AC and/or degree of fetal weight discordance (Table 1). We decided to include articles reporting different definitions provided that the type of sFGR classified according to Gratacós *et al.*[2] was reported or could be extrapolated. This choice was based upon the assumption that the type of umbilical flow pattern in the smaller twin is the main determinant of

Table 1 Characteristics of included studies reporting outcome of monochorionic twin pregnancies complicated by selective fetal growth restriction (sFGR)

Reference	*Country*	*Design*	*Cases* (n)	*Diagnostic criteria*	*Management* (n)	*Outcomes reported*	*sFGR type* (n)	*Follow-up*
Gratacós (2004)[20]	Spain	Prosp cohort	42	EFW < 5th centile in one twin and EFW discordance > 25%	Expectant (42)	Mortality, neurological morbidity	Types I & II (20) Type III (22)	28 days
Gratacós (2008)[19]	Spain	Retro cohort	49	EFW < 10th centile in one twin	Expectant (31), laser (18)	Mortality, neurological morbidity	Type III (49)	28 days
Ishii (2009)[18]	Japan	Retro cohort	63	EFW < 10th centile in one twin	Expectant (63)	Mortality, intact survival, neurological morbidity	Type I (23) Type II (27) Type III (13)	6 mo
Ishii (2015)[21]	Japan	Prosp clinical trial	10	EFW < 1.5 SD in one twin	Laser (10)	Mortality, neurological morbidity	Type II (7) Type III (3)	28 days
Koch (2017)[13]	France	Retro cohort	25	EFW < 10th centile in one twin	Expectant (20), laser (5)	Mortality	Type I (16) Type II (2) Type III (7)	7 days
Machado (2014)[15]	Brazil	Retro cohort	18	EFW < 10th centile in one twin	Expectant (18)	Mortality, neurological morbidity, other morbidity	Type I (2) Type II (11) Type III (5)	NS
Panciatici (2017)[26]	France	Retro case series	2	NS	RFA (2)	Mortality, long-term neurodevelopment	Type III (2)	Up to 30 mo
Parra-Cordero (2016)[6]	Spain	Prosp cohort	142*	EFW < 10th centile or AC < 10th centile with EFW discordance > 25%	Cord occlusion (90), expectant (2†), laser (15†)	Mortality, intact survival	Type II (44) Type III (63)	NS
Pasquini (2015)[14]	Italy	Retro cohort	42	AC < 10th centile in one twin	Expectant (42)	Mortality, neurological morbidity	Type I (31) Type II (8) Type III (3)	NS
Peeva (2015)[22]	UK	Retro cohort	142	AC < 5th centile and EFW discrepancy > 25% < 22 weeks or EFW < 5th centile and EFW discrepancy > 25% > 22 weeks	Laser (142)	Mortality	Type II (142)	NS
Peng (2016)[24]	China	Retro cohort	16	EFW < 2nd centile in one twin	RFA (6), cord occlusion (10)	Mortality, intact survival	Type I (3) Types II & III (13)	4–72 mo
Quintero (2001)[11]	USA	Prosp cohort	30	EFW < 10th centile and AREDF	Expectant (17), cord occlusion (2), laser (11)	Mortality, other morbidity	Type I (6), Types II & III (22), NS (2)	NS
Rustico (2017)[12]	Italy	Retro cohort	140	EFW < 10th centile in one twin or EFW discordance > 25%	Cord occlusion (20), expectant (120)	Mortality, neurological morbidity	Type I (65) Type II (62) Type III (13)	12 mo to 7 y
Visentin (2013)[16]	Italy	Prosp longitudinal	24	EFW < 10th centile in one twin	Expectant (24)	Mortality, neurological morbidity, other morbidity	Type I (10) Type II (14)	28 days
Wang (2017)[25]	China	Prosp case series	4	NS	RFA (4)	Mortality, neurological morbidity	Type II (2) Type III (2)	Up to 3 y
Weisz (2011)[17]	Israel	Prosp cohort	37	EFW < 10th centile in one twin	Expectant (37)	Mortality, neurological morbidity, other morbidity, PTD	Type I (19) Types II & III (18)	NS

Only first author of each study is given. *Total number of study referrals: 107 cases included. †No outcomes reported. AC, abdominal circumference; AREDF, absent or reversed end-diastolic flow; EFW, estimated fetal weight; mo, months; NS, not specified; Prosp, prospective; PTD, preterm delivery; Retro, retrospective; RFA, radiofrequency ablation; y, years.

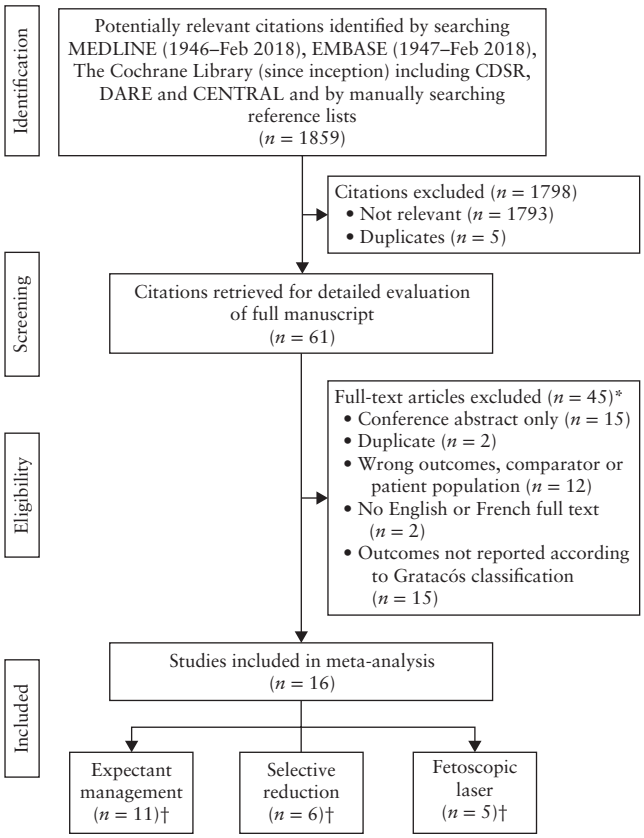

Figure 1 Flowchart summarizing inclusion in systematic review of studies on outcome of monochorionic twin pregnancies complicated by selective fetal growth restriction. *One study had two reasons for exclusion. †Some studies reported on more than one type of management. CENTRAL, The Cochrane Central Register of Controlled Trials; CDSR, The Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effects.

Table 2 Quality assessment of included studies on outcome of monochorionic twin pregnancies complicated by selective fetal growth restriction, according to Newcastle–Ottawa Scale (NOS)

Reference	*Selection*	*Comparability*	*Outcome*
Gratacós (2004)[20]	★★★★	★	★★
Gratacós (2008)[19]	★★★	★	★★★
Ishii (2009)[18]	★★	★	★★★
Ishii (2015)[21]	★★	★	★★★
Koch (2017)[13]	★★★	★	★
Machado (2014)[15]	★★★	★★	★★★
Panciatici (2017)[26]	★★		★★★
Parra-Cordero (2016)[6]	★★★	★★	★★
Pasquini (2015)[14]	★★★	★	★★★
Peeva (2015)[22]	★★★		★★★
Peng (2016)[24]	★★		★★★
Quintero (2001)[11]	★★	★	★★★
Rustico (2017)[12]	★★	★	★★
Visentin (2013)[16]	★★★	★	★★
Wang (2017)[25]	★★		★★★
Weisz (2011)[17]	★★★	★★	★★★

Only first author of each study is given. Maximum of one star for each numbered item within selection and outcome categories. Maximum of two stars can be given for comparability.

perinatal outcome of monochorionic pregnancies affected by sFGR, irrespective of fetal size or weight discordance[2]. Subanalysis according to fetal size was affected by the very small number of included cases for most outcomes, which precluded objective risk stratification. The analyses of pregnancy outcome according to fetal size for those managed expectantly and those treated using laser therapy are reported in Tables S3 and S4.

Synthesis of results

The results of the pooled analysis are reported in Table 3. Figure 2 summarizes the findings for key outcomes. Forest plots for the analysis of individual outcomes are available in Figures S1–S3.

Type-I sFGR

There were eight studies (332 twins) on expectant management in Type-I sFGR[11–18], one study (six fetuses) reporting the outcome of pregnancies complicated by Type-I sFGR treated with laser therapy of placental anastomoses[11], and two studies (six twins) reporting the outcome of Type-I sFGR treated with SR of the smaller twin[12,24] (Table 3, Figure 2a).

Overall, single and double IUD occurred in 3.1% (95% CI, 1.1–5.9%), 2.2% (95% CI, 0.6–4.6%) and 1.9% (95% CI, 0.6–3.8%) of fetuses in pregnancy complicated by Type-I sFGR managed expectantly. After laser therapy in Type-I sFGR, the overall incidence of IUD was 16.7% (95% CI, 0.4–64.1%) and there was no case of double IUD. After SR, there were no cases with subsequent intrauterine death of the larger twin.

Of twins affected by Type-I sFGR managed expectantly, 96.4% (95% CI, 92.6–98.8%) were liveborn, while none of the reported cases experienced NND. PND occurred in 3.0% (95% CI, 0.2–8.9%) of fetuses, while all Type-I pregnancies managed expectantly had at least one twin that survived to the neonatal period (100%; 95% CI, 94.3–100%). In pregnancies with Type-I sFGR managed using fetoscopic laser surgery, 83.3% of fetuses (95% CI, 35.9–99.6%) were liveborn and all pregnancies had at least one twin surviving the neonatal period. In cases in which SR was used, no perinatal deaths occurred.

Neonatal morbidity occurred in 9.5% (95% CI, 0.5–27.7%) of fetuses in pregnancy complicated by Type-I sFGR managed expectantly. In those studies that reported RDS as an outcome, 10.5% (95% CI, 2.9–24.8%) of liveborn fetuses were affected. Abnormal postnatal brain imaging was observed in 4.1% (95% CI, 0.04–17.3%), but no cases were reported with the specific severe brain anomalies on imaging such as IVH or PVL. None of the included surviving twins of Type-I sFGR pregnancy managed with laser or SR experienced morbidity or had abnormal brain imaging after birth. A detailed description of the different neurological outcomes reported by each included study is presented in Table S5. Finally, 79/80 (97.9% (95% CI, 93.6–99.9)) fetuses affected by Type-I sFGR managed expectantly and all of those managed with laser therapy or SR had intact survival.

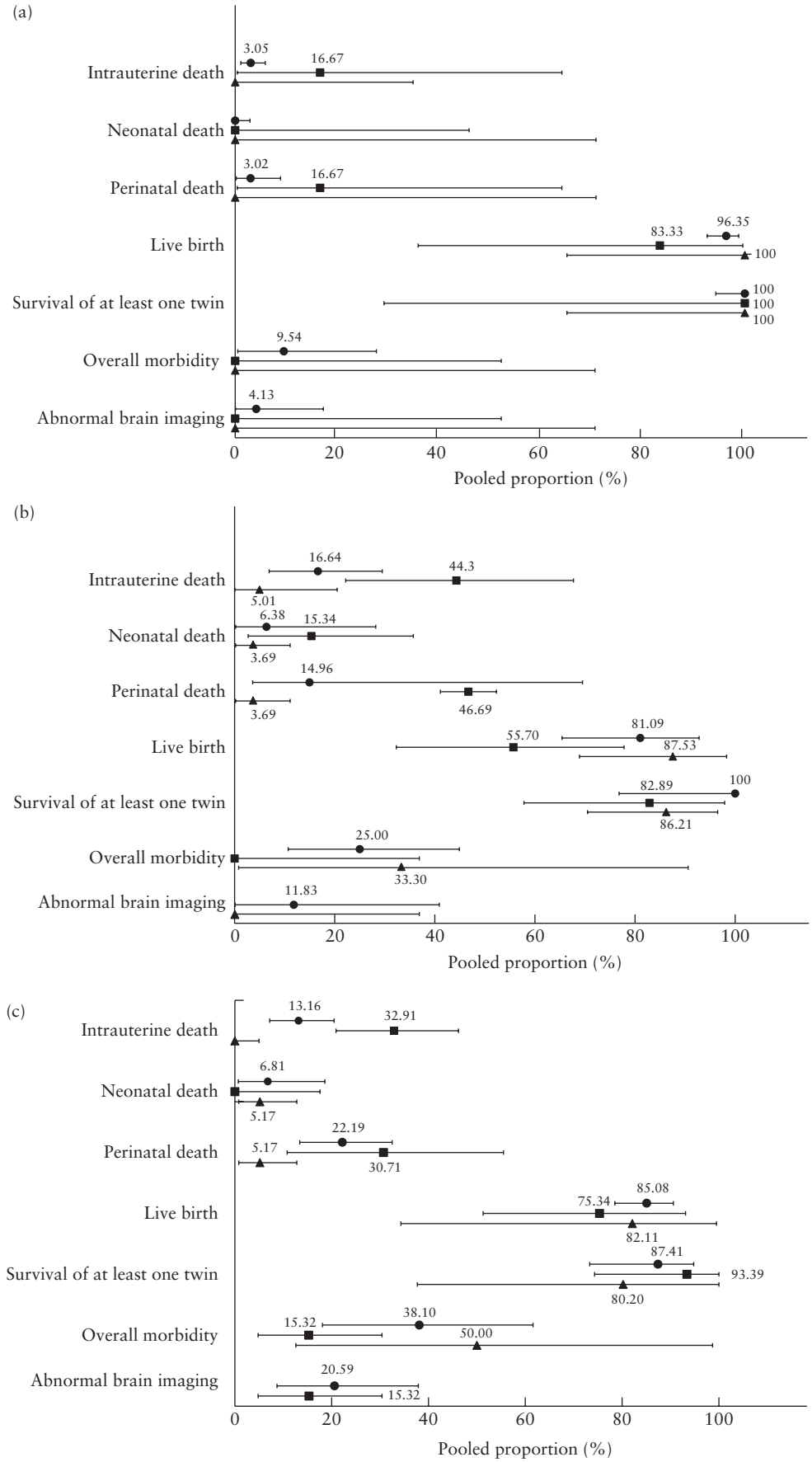

Figure 2 Results of pooled analysis for key outcomes in pregnancies complicated by Type-I (a) Type-II (b) and Type-III (c) selective fetal growth restriction, according to management (expectant, ●; laser treatment, ■; selective reduction, ▲).

Table 3 Pooled proportions (PP) of outcomes in monochorionic twin pregnancies complicated by selective fetal growth restriction (sFGR) according to type of management (expectant, laser or selective reduction) and severity of sFGR

	Expectant management				*Laser therapy*				*Selective reduction*			
Outcome	*Studies* (n^{ref})	*Fetuses* (n/N)	*PP (95% CI)*	I^2 *(%)*	*Studies* (n^{ref})	*Fetuses* (n/N)	*PP (95% CI)*	I^2 *(%)*	*Studies* (n^{ref})	*Fetuses* (n/N)	*PP (95% CI)*	I^2 *(%)*
Type I												
IUD												
Overall	$8^{11–18}$	10/332	3.05 (1.1–5.9)	28.0	1^{11}	1/6	16.67 (0.4–64.1)	—	$2^{12,24}$	0/6	0 (0–34.9)	0
Single	$8^{11–18}$	6/332	2.18 (0.6–4.6)	27.9	1^{11}	1/6	16.67 (0.4–64.1)	—	$2^{12,24}$	0/6	0 (0–34.9)	0
Double	$7^{11–13,15–18}$	4/270	1.88 (0.6–3.8)	0	1^{11}	0/6	0 (0–45.9)	—	—	—	—	—
NND	$5^{11,13,16–18}$	0/142	0 (0–2.9)	0	1^{11}	0/6	0 (0–45.9)	—	1^{24}	0/3	0 (0–70.8)	—
PND	$5^{11,13,16–18}$	4/142	3.02 (0.2–8.9)	54.4	1^{11}	1/6	16.67 (0.4–64.1)	—	1^{24}	0/3	0 (0–70.8)	—
Liveborn	$8^{11–18}$	318/332	96.35 (92.6–98.8)	47.7	1^{11}	5/6	83.33 (35.9–99.6)	—	$2^{12,24}$	6/6	100 (65.1–100)	0
Survival of at least one twin*	$5^{11,13,16,17,20}$	70/70	100 (94.3–100)	0	1^{11}	3/3	100 (29.2–100)	—	$2^{12,24}$	6/6	100 (65.1–100)	0
Overall neonatal morbidity	$3^{11,17,18}$	9/86	9.54 (0.5–27.7)	74.4	1^{11}	0/5	0 (0–52.2)	—	1^{24}	0/3	0 (0–70.6)	—
Abnormal brain imaging	$3^{11,14,17}$	4/103	4.13 (0.04–17.3)	73.7	1^{11}	0/5	0 (0–52.2)	—	1^{24}	0/3	0 (0–70.6)	—
IVH	$3^{11,14,17}$	0/103	0 (0–2.9)	0	1^{11}	0/5	0 (0–52.2)	—	1^{24}	0/3	0 (0–70.6)	—
PVL	$3^{11,14,17}$	0/103	0 (0–2.9)	0	1^{11}	0/5	0 (0–52.2)	—	1^{24}	0/3	0 (0–70.6)	—
RDS	1^{17}	4/38	10.53 (2.9–24.8)	—	—	—	—	—	—	—	—	—
NICU admission	—	—	—	—	—	—	—	—	—	—	—	—
Intact survival	$3^{11,13,18}$	79/80	97.87 (93.6–99.9)	0	1^{11}	5/5	100 (47.8–100)	—	1^{24}	3/3	100 (29.2–100)	—
Type II												
IUD												
Overall	$5^{12,14–16,18}$	43/214	16.64 (6.9–29.5)	78.2	$2^{13,21}$	7/16	44.30 (22.2–67.7)	0	$3^{6,12,25}$	2/59	5.01 (0.03–20.5)	59.6
Single	$5^{12,14–16,18}$	17/214	8.15 (3.1–15.3)	58.6	$2^{13,21}$	7/16	44.30 (22.2–67.7)	0	$3^{6,12,25}$	2/59	5.01 (0.03–20.5)	59.6
Double	$4^{12,15,16,18}$	26/198	10.43 (3.6–20.3)	71.2	$2^{13,21}$	0/16	0 (0–14.8)	0	—	—	—	—
NND	$2^{16,18}$	8/82	6.38 (0.2–28.2)	86.1	$2^{13,21}$	2/16	15.34 (2.7–35.7)	0	$2^{6,25}$	1/44	3.69 (0.2–11.1)	0
PND	$2^{16,18}$	22/82	14.96 (3.6–69.5)	96.3	$3^{13,21,22}$	140/300	46.69 (41.1–52.3)	21	$2^{6,25}$	1/44	3.69 (0.2–11.1)	0
Liveborn	$5^{12,14–16,18}$	162/214	81.09 (65.4–92.8)	83.8	$2^{13,21}$	9/16	55.70 (32.3–77.8)	41	$3^{6,12,25}$	53/59	87.53 (68.9–98.3)	55.4
Survival of at least one twin*	1^{16}	14/14	100 (76.8–100)	—	$3^{13,21,22}$	110/150	82.89 (57.8–97.9)	53	$3^{6,12,25}$	52/59	86.21 (70.5–96.5)	40.1
Overall neonatal morbidity	1^{18}	7/28	25.0 (10.7–44.9)	—	1^{21}	0/8	0 (0–36.9)	—	1^{25}	1/3	33.3 (0.8–90.6)	—
Abnormal brain imaging	$2^{14,16}$	7/40	11.83 (0.1–40.9)	81.3	1^{21}	0/8	0 (0–36.9)	—	—	—	—	—
IVH	$2^{14,16}$	0/40	0 (0–6.6)	0	1^{21}	0/8	0 (0–36.9)	—	—	—	—	—
PVL	$2^{14,16}$	7/40	11.83 (0.1–40.9)	81.3	1^{21}	0/8	0 (0–36.9)	—	—	—	—	—
RDS	—	—	—	—	—	—	—	—	—	—	—	—
NICU admission	1^{16}	21/28	75.0 (55.1–89.3)	—	—	—	—	—	—	—	—	—
Intact survival	1^{18}	25/28	89.29 (71.8–97.7)	—	1^{21}	8/8	100 (63.1–100)	_	$2^{6,25}$	40/41	90.64 (42.3–94.3)	76.4

Continued over.

Table 3 *Continued*

Outcome	Expectant management				Laser therapy				Selective reduction			
	Studies (n^{ref})	*Fetuses* (n/N)	*PP* *(95% CI)*	I^2 *(%)*	*Studies* (n^{ref})	*Fetuses* (n/N)	*PP* *(95% CI)*	I^2 *(%)*	*Studies* (n^{ref})	*Fetuses* (n/N)	*PP* *(95% CI)*	I^2 *(%)*
Type III												
IUD												
Overall	6[12,14,15,18–20]	23/170	13.16 (7.2–20.5)	34.6	3[13,19,21]	16/50	32.91 (20.9–46.2)	0	3[6,12,26]	0/52	0 (0–5.0)	0
Single	6[12,14,15,18–20]	11/170	7.21 (3.8–11.5)	0	3[13,19,21]	16/50	32.91 (20.9–46.2)	0	3[6,12,26]	0/52	0 (0–5.0)	0
Double	5[12,15,18–20]	12/164	5.49 (1.2–12.5)	58.1	3[13,19,21]	0/50	0 (0–6.0)	0	—	—	—	—
NND	2[18,20]	4/70	6.81 (0.7–18.6)	56.7	2[13,21]	0/14	0 (0–17.6)	0	2[6,26]	2/50	5.17 (0.8–12.8)	0
PND	2[18,20]	15/70	22.19 (13.4–32.5)	0	2[13,21]	4/14	30.71 (10.8–55.5)	0	2[6,26]	2/50	5.17 (0.8–12.8)	0
Liveborn	6[12,14,15,18–20]	145/170	85.08 (78.5–90.6)	16.8	3[13,19,21]	11/14	75.34 (51.3–93.1)	0	3[6,12,26]	50/52	82.11 (34.3–99.5)	58.6
Survival of at least one twin*	2[19,20]	47/53	87.41 (73.3–94.8)	0	3[13,19,21]	24/25	93.39 (74.3–100)	35.1	3[6,12,26]	48/52	80.20 (37.7–100)	58.6
Overall neonatal morbidity	1[18]	8/21	38.10 (18.1–61.6)	—	2[19,21]	4/28	15.32 (4.8–30.4)	0.1	1[26]	1/2	50.00 (12.6–98.7)	—
Abnormal brain imaging	1[20]	7/34	20.59 (8.7–37.9)	—	2[19,21]	4/28	15.32 (4.8–30.4)	0.1	—	—	—	—
IVH	3[14,19,20]	3/91	3.46 (0.4–9.3)	20.3	2[19,21]	2/28	9.01 (1.5–21.9)	0	—	—	—	—
PVL	3[14,19,20]	10/91	11.62 (5.5–19.6)	9.5	2[19,21]	2/28	9.01 (1.5–21.9)	0	—	—	—	—
RDS	—	—	—	—	—	—	—	—	—	—	—	—
NICU admission	—	—	—	—	—	—	—	—	—	—	—	—
Intact survival	1[18]	13/21	61.90 (38.4–81.9)	—	1[21]	5/5	100 (47.8–100)	—	2[26]	47/48	98.81 (93.9–99.9)	79.2

N is total number of fetuses (or pregnancies) in studies reporting particular outcome, and *n* is number of those fetuses (or pregnancies) with that outcome. *For survival of at least one twin, *n/N* refers to number of pregnancies rather than number of fetuses. IUD, intrauterine death; IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit; NND, neonatal death; PND, perinatal death; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome.

Type-II sFGR

Five studies (214 twins) reported the incidence of mortality in monochorionic pregnancies affected by Type-II sFGR managed expectantly[12,14–16,18]. Three studies (300 twins) reported the outcome of pregnancies complicated by Type-II sFGR treated with laser therapy of placental anastomoses[13,21,22]. Three studies[6,12,25] (59 twins) reported the outcome of Type-II sFGR treated with SR of the smaller twin (Table 3, Figure 2b).

For Type-II sFGR pregnancies managed expectantly, overall, single and double IUD occurred in 16.6% (95% CI, 6.9–29.5%), 8.2% (95% CI, 3.1–15.3%) and 10.4% (95% CI, 3.6–20.3%) of fetuses, respectively. In contrast, IUD occurred in 44.3% (95% CI, 22.2–67.7%) of fetuses in cases managed with laser therapy, all of which were single IUDs. After SR, IUD of the surviving twin occurred in 5.0% (95% CI, 0.03–20.5%) of cases.

Of fetuses in Type-II sFGR pregnancies managed expectantly, 81.1% (95% CI, 65.4–92.8%) were liveborn, while NND occurred in 6.4% (95% CI, 0.2–28.2%) and PND in 15.0% (95% CI, 3.6–69.5%). Of fetuses in pregnancies managed by laser, NND occurred in 15.3% (95% CI, 2.7–35.7%), and 82.9% (57.8–97.9%) of pregnancies had at least one twin surviving the neonatal period. After SR, the incidence of NND was 3.7% (95% CI, 0.2–11.1%).

Neonatal morbidity occurred in 25.0% (95% CI, 10.7–44.9%) of fetuses in Type-II sFGR pregnancies managed expectantly, while 11.8% (95% CI, 0.1–40.9%) had abnormal postnatal brain imaging. Severe PVL complicated 11.8% (95% CI, 0.1–40.9%) of twins in pregnancies managed expectantly, and none experienced IVH. After expectant management in Type-II sFGR, 75.0% (95% CI, 55.1–89.3%) of twins were admitted to NICU and 89.3% (95% CI, 71.8–97.7%) survived without neurological compromise. None of the cases affected by Type-II sFGR and treated with laser therapy experienced morbidity or had abnormal brain imaging after birth, and all twins survived without neurological complications. After SR, 86.2% (95% CI, 70.5–96.5%) of cotwins survived the neonatal period and 90.6% (95% CI, 42.3–94.3%) were free from neurological complications.

Type-III sFGR

Six studies (170 twins) reported the incidence of mortality in monochorionic pregnancy affected by Type-III sFGR managed expectantly[12,14,15,18–20]. Three studies (50 twins) reported the outcome of pregnancy complicated by Type-III sFGR treated with laser therapy of placental anastomoses[13,19,21]. Three studies[6,12,26] (52 twins) reported the outcome of Type-III sFGR treated with SR of the smaller twin (Table 3, Figure 2c).

Overall, single and double IUD occurred in 13.2% (95% CI, 7.2–20.5%), 7.2% (95% CI, 3.8–11.5%) and 5.5% (95% CI, 1.2–12.5%) of fetuses, respectively, in Type-III sFGR pregnancies managed expectantly. In cases treated with laser therapy, IUD occurred in

32.9% (95% CI, 20.9–46.2%) of fetuses: all IUDs were single. There were no cases of IUD reported after SR. When stratifying the analysis according to fetal size, in cases managed expectantly, the incidence of overall IUD was higher in the smaller (pooled proportion 20.7%; 95% CI, 12.3–30.6%) compared with the larger (pooled proportion 8.0%; 95% CI, 3.3–14.5%) twin ($P = 0.0267$) (Table S3).

After expectant management in Type-III sFGR, 85.1% (95% CI, 78.5–90.6%) of twins were liveborn, while NND and PND occurred in 6.8% (95% CI, 0.7–18.6%) and 22.2% (95% CI, 13.4–32.5%) of fetuses, respectively. There were no NNDs in the group treated using laser therapy. NND occurred in 5.2% (95% CI, 0.8–12.8%) of fetuses in cases managed by SR. In 87.4% (95% CI, 73.3–94.8%) of cases managed expectantly, 93.4% (95% CI, 74.3–100%) of those managed with laser therapy and 80.2% (95% CI, 37.7–100%) of those managed with antenatal SR, at least one twin survived the neonatal period.

One study[18] (21 twins) found the incidence of neonatal morbidity of fetuses with Type-III sFGR pregnancies, when managed expectantly, to be 38.1% (95% CI, 18.1–61.6%). Abnormal brain findings on postnatal imaging were observed in 20.6% (95% CI, 8.7–37.9%) of twins in pregnancies managed expectantly, while the incidence of severe IVH and PVL was 3.5% (95% CI, 0.4–9.3%) and 11.6% (95% CI, 5.5–19.6%), respectively. Analysis according to fetal size showed there was increased rate of morbidity in the larger twin in Type III cases managed expectantly. Neonatal morbidity affected 27.3% (95% CI, 6.0–61.0%) of the smaller twins and 38.5% (95% CI, 13.9–68.4%) of the larger twins ($P = 0.679$) (Table S3). Abnormal postnatal brain imaging was present in 4.1% (95% CI, 0.3–12.0%) of the smaller twins and 24.7% (95% CI, 14.0–37.3%) of the larger twins ($P = 0.02$). Survival free from neurological complications occurred in 80.0% (95% 44.4–97.5%) of the smaller twins and 38.5% (95% CI, 13.9–68.4) of the larger twins ($P = 0.09$).

Neonatal morbidity was described by two studies (28 twins) reporting the use of laser therapy, with 15.3% (95% CI, 4.8–30.4%) of fetuses having abnormal brain imaging after birth[19,21]. Intact survival at 28 days of age was reported in all twins of Type-III sFGR pregnancies managed with laser therapy.

Only one study reporting SR in Type-III sFGR described neurological morbidity. In this study of two fetuses, neonatal morbidity occurred in 50% (95% CI, 12.6–98.7%)[26], but intact survival was reported in 98.8% (95% CI, 93.9–99.9%) of fetuses in the two studies reporting this outcome following SR[6,26].

DISCUSSION

Summary of main findings

This systematic review confirms that Type-I sFGR generally has a good perinatal outcome when managed expectantly, which represents the most reasonable choice for management. Type-II and -III sFGR pregnancies treated with laser therapy or SR have a higher rate of perinatal mortality but a lower rate of morbidity, compared with those managed expectantly.

Strengths and limitations

The strengths of this review are the thorough search and assessment of clinical outcomes stratified by classification and management. The small number of studies and their retrospective, non-randomized design, heterogeneous populations and dissimilar management protocols for sFGR are major limitations. The findings are also subject to potential publication bias because the nature of some outcomes and the small number of studies limit the reliability of formal tests.

Few studies reported gestational age at diagnosis, although cases classified at 16–18 weeks as Type-II sFGR may have physiologically rather than pathologically absent EDF[27]. Additionally, practice varies in local availability of fetal intervention, neonatal services and legal restrictions on termination of pregnancy. In several centers, expectant management included offering SR for fetal deterioration < 26 weeks. Furthermore, variation in outcome reporting precludes meta-analysis of infrequently reported but important outcomes[28]. Finally, it was not possible to explore the association between gestational age at delivery and neonatal outcome, which is fundamental because gestational age is the main determinant of perinatal outcome, irrespective of the severity of sFGR or Doppler abnormalities[29]. Despite these limitations, this study represents the most up-to-date and comprehensive published estimate on the outcome of sFGR according to management option.

Clinical and research implications

In the present review, PND was rare in Type-I sFGR cases, since all pregnancies in studies reporting neonatal survival had at least one surviving infant and none had severe neurological morbidity. We identified three studies (nine pregnancies) reporting fetal therapy in Type-I sFGR[11,12,24]. The study by Quintero *et al.*[11] predates the Gratacós classification and clarity on the prognostic value of UA Doppler, Rustico *et al.*[12] offered cord occlusion in cases classified as Type-I sFGR with later deterioration and Peng *et al.*[24] did not report the indication for SR. The scarcity of studies reporting intervention in Type-I sFGR and the growing focus of research on management of Type-II and -III sFGR point to a developing consensus that Type-I sFGR should be managed expectantly.

Weekly sonographic and Doppler surveillance is recommended in expectant management of Type-I sFGR because disease progression occurs in up to 25%[12], with elective delivery between 34–36 weeks[30]. Expectant management of severe sFGR (Types II and III) would benefit from a clear protocol identifying appropriate triggers for intervention. Monitoring of Type-III sFGR

is particularly challenging since IUD is unpredictable and the risk of neurological injury to the larger twin is substantial. Known adverse predictors in sFGR include earlier gestational age at diagnosis, ductus venosus *Z*-score[31], cord insertion site[32,33] and fetal weight discrepancy[34], but further development of prognostic markers for severe sFGR is needed. In general, severe sFGR with normal venous Doppler can be managed expectantly with frequent Doppler, biophysical profile and cardiotocographic evaluations[1].

Type-II sFGR managed with laser therapy is associated with a higher incidence of fetal loss, but all survivors were free from neurological morbidity at follow-up, although it is acknowledged that only small numbers were available for this analysis. Nonetheless, the finding that laser therapy appears to reduce neurological morbidity is consistent with current understanding of the pathophysiology of sFGR, in which dichorionization of the placenta is thought to protect the larger twin from ischemic events. Similarly, since the smaller twin is known to benefit from vascular anastomoses, dichorionization is expected to be associated with a higher rate of IUD of the smaller twin, an observation confirmed on pooled analysis (Table S3). In the group treated with SR compared with cases treated with laser therapy, a lower rate of IUD was observed. This may be explained by technical difficulties in performing laser therapy in the absence of polyhydramnios and with amniotic fluid present in the smaller twin, as well as atypical large vascular anastomoses. We have found that, when intervention was reported, clinicians more frequently reported the use of SR than laser therapy, suggesting a preference for SR in severe sFGR. Even when laser treatment is preferred, it might be precluded by technical factors such as placental site or visibility.

In the present review, 62% of twins in pregnancies complicated by Type-III sFGR managed expectantly had intact survival with an observed increase in neurological injury in the larger compared with in the smaller twin. After laser treatment, while incidence of IUD was three-fold higher than that observed following expectant management, < 16% of survivors had abnormal brain imaging and all reported survivors were free from major neurological complications. Likewise, in pregnancies undergoing SR, there were no cases of IUD in cotwins and over 98% had intact survival at follow-up. Fetal therapy may therefore represent a reasonable approach in Type III cases diagnosed remote from term.

If fetal therapy is chosen, SR should be the approach of choice in view of the significant technical difficulties and surgical complications that can be encountered when performing fetoscopic laser surgery for sFGR. This is a challenging recommendation and not feasible when termination of pregnancy is not an option because of the legal context or the parents' preferences. As such, there is a role for laser therapy and further study is required to clarify the relative risks of laser therapy compared to those of SR.

Conclusions

There remains little robust evidence on the optimal management of pregnancies affected by sFGR. Type-I sFGR is characterized by a good perinatal outcome and expectant management is appropriate for most cases. Type-II and -III sFGR are affected by a higher burden of perinatal mortality and morbidity. Although our findings do not support intervention with either laser therapy or SR, fetal therapy may have a role at previable gestational ages in severe cases in order to protect the surviving twin from demise or neurological damage. Prenatal management of sFGR should be individualized according to gestational age at diagnosis, severity of growth restriction and magnitude of Doppler anomalies. Large multicenter trials sharing objective protocols of prenatal management and standardized postnatal follow-up are needed in order to elucidate the optimal management.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Search strategy for studies reporting outcome in monochorionic twin pregnancies complicated by selective fetal growth restriction

Table S2 Studies excluded from systematic review and reason for exclusion

Table S3 Perinatal mortality and morbidity in monochorionic twin pregnancies complicated by selective fetal growth restriction (sFGR) managed expectantly, in smaller *vs* larger twin, according to severity of sFGR

Table S4 Perinatal mortality and morbidity in monochorionic twin pregnancies complicated by selective fetal growth restriction (sFGR) treated with laser surgery, in smaller *vs* larger twin, according to severity of sFGR

Table S5 Summary of studies reporting neurological outcome in monochorionic twin pregnancies complicated by selective fetal growth restriction (sFGR)

Figure S1 Forest plots of outcome in monochorionic twin pregnancies complicated by Type-I selective fetal growth restriction, according to management.

Figure S2 Forest plots of outcome in monochorionic twin pregnancies complicated by Type-II selective fetal growth restriction, according to management.

Figure S3 Forest plots of outcome in monochorionic twin pregnancies complicated by Type-III selective fetal growth restriction, according to management.

