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

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ABSTRACT

Objectives: To explore the impact of severity and management (expectant, laser treatment or selective reduction) on perinatal outcome of monochorionic twin pregnancies complicated by selective intra-uterine growth restriction (sFGR).

Methods: Medline, EMBASE, ClinicalTrials.gov and the Cochrane database were searched. Only pregnancies affected by sFGR and categorized according to the Gratacos classification (Type I, II and III) were included. The primary outcome was mortality, including single and double intrauterine (IUD), neonatal (NND) and perinatal death (PND). The secondary outcomes were neonatal morbidity, abnormal post-natal brain imaging, intra-ventricular hemorrhage (IVH), peri-ventricular leukomalacia (PVL), respiratory distress syndrome (RDS), admission to neonatal intensive care unit (NICU) and survival free from neurological complications (intact survival). Meta-analyses of proportions were used to analyze the extracted data.

Results: Fifteen observational studies (784 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) and 97.9% (95% CI 93.6-99.9) had intact survival free from neurological complications. In Type I sFGR treated with laser therapy, IUD occurred in 16.7% (95% CI 0.4-64.1) and with cord occlusion, IUD occurred in 0% (95% CI 0-34.9) co-twins 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), NND in 6.4% (95% CI 0.2-28.2), and 89.3% (95% CI 71.8-97.7) of twins survived without neurological compromise. With laser therapy, IUD occurred in 44.3% (95% CI 22.2-67.7), while none of the affected cases experienced morbidity and survivors were free of neurological complications. In pregnancies undergoing selective reduction, IUD of the co-twin occurred in 5.0% (95% CI 0.03-20.5), NND in 3.7% (95% CI 0.2-11.1) and 90.6% (95% CI 42.3-94.3) of surviving co-twins 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), NND in 6.8% (95% CI 0.7-18.6) and 61.9% (95% CI 38.4-81.9) had intact survival, free from neurological complications. In pregnancies treated with laser therapy, IUD occurred in 32.9% (95% CI 20.9-46.2) and all twins treated with laser survived without neurological complications. Finally, in pregnancies treated with cord occlusion NND occurred in 5.2% (95% CI 0.8-12.8) of co-twins and 98.8% (95% CI 93.9-99.9) had intact survival.

Conclusion: Type I sFGR is characterized by good perinatal outcome with expectant management, which represents the most reasonable management strategy for the large majority of affected cases. Pregnancies complicated by Type II and III sFGR treated with fetoscopic laser ablation had higher mortality but lower morbidity compared to those managed expectantly, supporting the use of fetal therapy at gestations remote from neonatal viability – with scarce data on outcome following selective reduction. However, 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 to the clinical course and prognosis of sFGR has allowed classification by the umbilical artery Doppler findings in the smaller twin (2).In Type I sFGR pregnancies both twins have normal end diastolic flow (EDF) in the umbilical arteries (UA), 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 of sFGR in monochorionic pregnancies has recently been published, but (3)clinical uncertainty regarding the optimal management, particularly at very preterm gestation persists.(3) The particular challenge in monochorionic pregnancies is the risk of acute feto-fetal transfusion in the event of demise or profound hypotension in one twin causing death or neurological injury in the co-twin. Reported perinatal survival in pregnancies affected by Type I sFGRis 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, either fetoscopic laser treatment or selective reduction (SR) of the compromised twin. Selective reduction 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 co-twin.(7)

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

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to a priori designed protocol recommended for systematic reviews and meta-analysis. 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, key words, and word variants for "twin pregnancies", "selective intra-uterine growth restriction" and "outcome" (Supplementary Table 1). The search and selection criteria were restricted to English 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, data collection and data items

The primary outcome was mortality, including intra-uterine death (IUD) of either twin, defined as fetal loss after 20 weeks of pregnancy. We collected data on single IUD, double IUD, neonatal death (NND, defined as the death of either twin up to 28 days of life, perinatal death (PND: defined as IUD and NND), live-birth and survival of at least one twin (up to 28 days).

The secondary outcomes were:

1) Overall neonatal morbidity, defined as the presence in either twin of at least abnormal brain imaging, respiratory distress syndrome (RDS), admission to the neonatal intensive care unit (NICU) or retinopathy of prematurity (ROP)
2) Abnormal brain imaging, defined as the presence of either intra-ventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) of any type on post-natal imaging (ultrasound or magnetic resonance imaging)
3) Severe IVH (grade III and IV)
4) PVL (grade II and III)
5) Respiratory distress syndrome (RDS)
6) Admission to NICU
7) Intact survival, defined as survival free from neurological complications

All these outcomes were explored according to (1) the type of sFGR (Type I, II and III), as described by Gratacos, (2) management adopted (expectant, fetoscopic laser therapy or selective reduction) and (2) fetal size (smaller twin/larger twin). sFGR was defined as

estimated fetal weight (EFW) of one twin <3rd centile, or at least two out of four contributory parameters (EFW of one twin <10th centile, AC of one twin <10th centile, EFW discordance of 25% or more, UA PI of the smaller twin > 95th centile) in the absence of ultrasound signs consistent with the presence of severe TTTS. (3)

Only studies reporting the incidence of the explored outcomes in different types of sFGR according to Gratacos classification 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 is based upon this classification. Studies including cases with fetal anomalies were excluded in view of the higher risk of mortality in affected twins. Only full text articles were considered eligible for the 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 (FS, RT) 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. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author (FDA). 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 assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for case-control studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at the start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of four stars within the Selection category, 3 stars in the Outcome category and a maximum of two stars can be given for Comparability. (10)

Statistical Analysis

First, we performed random-effect meta-analyses of proportions to estimate the pooled rates of each outcome for each type of sFGR (Type I, II or III) according to the type of management reported (expectant, laser or selective reduction). Second, we used random-effect head-to-head meta-analyses to directly compare the risk of each outcome among the smaller versus larger twins, expressing the results as summary odds ratio (OR) and relative 95% Confidence Interval (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 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 the creation of funnel plots for visual inspection. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten, 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 analyse 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 (Table 1, Figure 1, Supplementary Table 2). These 16 studies included 786 monochorionic pregnancies affected by sFGR. The general characteristics of the included studies are reported in Table 1. There was no randomized controlled trial comparing the different management options according to the type of sFGR and all the included studies were observational. Eleven studies reported outcomes for expectant management, although protocols for expectant management varied in monitoring and indications for delivery. Not all authors reported their antenatal management protocols for expectantly managed cases. Outcomes after active management with fetoscopic laser coagulation were reported by 5 studies. SR by cord occlusion was reported in 4 studies and by radiofrequency ablation in 2 studies and these cases were analysed together, because there was not likely to be a significant difference between the two techniques.(8,9) Several studies reported more than one management strategy.

The results of quality assessment of the included studies using Newcastle-Ottawa Scale (NOS) are reported in Table 2. Most included studies scored well regarding the selection and comparability of the study groups and for 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 different management strategies 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 the 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 different types 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 wide heterogeneity in the definition of sFGR among the different studies, with authors variably using EFW, abdominal circumference (AC) and/or the degree of fetal weight discordance (Table 1). We decided to include articles reporting different definitions provided the type of sFGR as described by Gratacos *et al*. 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 perinatal outcome of monochorionic pregnancies affected by sFGR, irrespective of fetal size or weight discordance (2). Sub-analysis according to fetal size was affected by the very small number of included cases for most outcomes which precluded objective risk stratification. The analysis of pregnancy outcomes according to fetal size for pregnancies managed expectantly or by laser therapy are reported in Supplementary Tables 4 and 5.

Synthesis of the results

The results of the pooled analysis are reported in Table 3. Figure 2 summarises the findings for key outcomes. Forest plots for the analysis of individual outcomes are available in the supplementary figures.

Type I sFGR

There were 8 studies (332 twins) of expectant management in Type I sFGR, one study (6 fetuses) reporting the outcome of pregnancies complicated by type I sFGR and treated with laser therapy of placental anastomoses and 2 studies (6 twins) reporting the outcome of type I sFGR treated with SR of the smaller twin. (Table 3a, Figure 2a)

Intra-uterine death

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 cases managed expectantly. After laser in Type I sFGR the overall incidence of IUD was 16.7% (95% CI 0.4-64.1) of cases and there was no case of double IUD. After SRthere were no cases with subsequent intra-uterine death of the larger twin.

Perinatal mortality

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

Neonatal morbidity

Neonatal morbidity occurred in 9.5% (95% CI 0.5-27.7) of cases of Type I sFGR managed expectantly. Of 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) of type I FGR managed expectantly 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 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 Supplementary Table 3.

Finally, 79/80 cases (97.9% (95% CI 93.6-99.9)) of Type I cases managed expectantly and all reported Type I cases managed with laser and SR had intact survival free from neurological complications.

Type II sFGR

Five studies (214 twins) reported the incidence of mortality in monochorionic pregnancies affected by type II sFGR and managed expectantly. Three studies (300 twins) reported the outcome of pregnancies complicated by type II sFGR and treated with laser therapy of placental anastomoses. Three studies (59 twins) reported the outcome of type II sFGR treated with SR of the smaller twin. (Table 3b, Figure 2b)

Intrauterine death

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 Type II cases managed expectantly. In contrast, IUD occurred in 44.3% (95% CI 22.2-67.7) of cases managed with laser therapy. All IUD were single - there were no reported cases of double IUD. After selective reduction, IUD in the surviving twin occurred in 5.0% (95% CI 0.03-20.5) of cases.

Perinatal mortality

Of Type II cases managed expectantly, 81.1% (95% CI 65.4-92.8) of twins 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 cases managed by laser, NND occurred in 15.3% (95% CI 2.7-35.7) of cases and 82.9% (57.8-97.9) pregnancies had at least one twin surviving the neonatal period. After selective reduction, the incidence of NND was 3.7% (95% CI 0.2-11.1).

Neonatal morbidity

Neonatal morbidity occurred in 25.0% (95% CI 10.7-44.9) of cases 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 managed expectantly, and none experienced IVH.

After expectant management in type II sFGR, 5.0% (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 selective reduction, 86.2% (95% CI 70.5-96.5) of co-twins 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 pregnancies affected by type III sFGR and managed expectantly. Three studies (50 twins) reported the outcome of pregnancies complicated by type III sFGR and treated with laser therapy of placental anastomoses. Three studies (52 twins) reported the outcome of type III sFGR treated with selective reduction of the smaller twin. (Table 3c, Figure 2c)

Intrauterine death

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 cases managed expectantly. In cases treated with laser therapy IUD occurred in 32.9% (95% CI 20.9-46.2) of cases. All IUD were single, and there were no cases of double IUD. There were no cases of IUD reported after selective reduction. 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 to the larger (pooled proportion 8.0%, 95% CI 3.3-14.5) (p=0.003) twin (p=0.011).

Perinatal mortality

After expectant management 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 cases respectively. There were no NND in the group treated by laser. NND occurred in 5.2% (95% CI 0.8-12.8) of cases managed with selective reduction.

In 87.4% (95% CI 73.3-94.8) of cases managed expectantly, 93.4% (95% CI 74.3-100) managed with laser therapy and 80.2% (37.7-100) of pregnancies managed with antenatal SR reported at least one twin surviving the neonatal period.

Neonatal morbidity

One study (21 twins) reported the incidence of neonatal morbidity, which occurred in 38.1% (95% CI 18.1-61.6) of cases managed expectantly. 38.1% (95% CI 18.1-61.6) of twins had abnormal brain findings on postnatal imaging 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. In analysis according to fetal size, there was increased 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 and 38.5% (95% CI 13.9-68.4) of the larger twin (p=0.679). Abnormal postnatal brain imaging was present in 4.1% (95% CI 0.3-12.0) of the smaller twin and 24.7% (95% CI 14.0-37.3) of the larger twin (p=0.02). Survival free from neurological complications occurred in 80.0% (95% 44.4-97.5) of the smaller twin and 38.5% (95% CI 13.9-68.4) of the larger twin (p=0.09).

Neonatal morbidity was reported by two studies reporting the use of laser therapy (28 twins) with 15.3% (95% CI 4.8-30.4) of the cases having abnormal brain imaging after birth. Intact survival at 28 days of age was reported in all twins managed with laser.

Only two studies reporting SR in type III sFGR reported neurological morbidity. In one study of 2 fetuses neonatal morbidity was 50% (95% CI 12.6-98.7) but in the two studies reporting intact survival after selective reduction, this was 98.8% (95% CI 93.9-99.9).

DISCUSSION

Summary of the main findings

This systematic review confirms that type I sFGR has a generally good perinatal outcome with expectant management representing the most reasonable choice. Type II and III sFGR pregnancies treated with laser or SR have higher perinatal mortality, but lower morbidity, compared to 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, their retrospective, non-randomized design, heterogenous 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 gestation at diagnosis, although cases classified at 16-18 weeks as Type II sFGR may have physiological rather than pathological absent EDF.(10) 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.(11) Finally, it was not possible to explore the association between gestation at delivery and neonatal outcomes, fundamental because gestation is the main determinant of perinatal outcome, irrespective of the severity of sFGR or Dopplers.(12)

Despite these limitations, this study represents the most up-to-date and comprehensive published estimate on the outcome of sFGR by different management options.

Clinical and research implications of our findings

In the present review, PND was rare in type I sFGR cases, all pregnancies in studies reporting neonatal survival had at least one surviving infant and none had severe neurological morbidity. We identified three studies reporting fetal therapy in sFGR (9 pregnancies).(8,13,14) Rustico et al offered cord occlusion to cases classified as Type I with later deterioration,(14) Peng did not report the indication for SR(8) and the Quintero study

predates the Gratacos classification and clarity on the prognostic value of UA Dopplers.(13) The scarcity of studies reporting intervention in Type I and the growing focus of researchers on management of Type II and III point to a developing consensus that Type I sFGR should be expectantly managed.

Weekly sonographic and Doppler surveillance is recommended in expectant management of type I sFGR, because disease progression occurs in up to 25%, (14) with elective delivery between 34-36 weeks.(15) The expectant management of severe sFGR (Types II and III) would benefit from a clear protocol identifying appropriate triggers for intervention. Monitoring of Type III 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 gestation at diagnosis, ductus venosus Z score,(16) cord insertion, (17,18) and fetal weight discrepancy, (19) but further development of prognostic markers in severe sFGR is needed. In general, severe sFGR with normal venous Doppler can be managed expectantly with frequent Doppler, biophysical profile and cardiotocographic evaluation.(1)

Type II sFGR managed with laser is associated with a higher incidence of fetal loss, but all survivors were free from neurological morbidity at follow-up, acknowledging that only small numbers were available for this analysis. Nonetheless, the finding that laser appears to reduce neurological morbidity is consistent with current understanding of the pathophysiology of sFGR, where dichorionisation of the placenta is thought to protect the larger twin from ischaemic events. Similarly, since the smaller twin is known to benefit from vascular anastamoses, dichorionisation is expected to be associated with a higher rate of small twin IUD; an observation confirmed in the pooled analysis (Supplementary Table 5). In the group treated with SR a lower rate of IUD compared to cases treated with laser was observed. This may be explained by technical difficulties in performing laser in the absence of polyhydramnios and with liquor present in the smaller twin, as well as atypical large vascular anastamoses. We have found that where intervention is reported, clinicians more frequently reported the use of SR than laser, suggesting a preference for SR in severe sFGR. Even where laser is preferred it might be precluded by technical factors including placental site or visibility.

In the present review, 62% of twins complicated by type III sFGR and managed expectantly had intact survival with an observed increase in neurological injury in the larger compared to the smaller twin. After laser, while incidence of IUD was three-fold higher than observed in 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 was no IUD in co-twins 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 which can be encountered when performing fetoscopic laser in sFGR. This is a challenging recommendation and not feasible where termination is not an option either because of the legal context or the parents preferences. There is then a role for laser therapy and further study is required to clarify the relative risks of laser compared to SR.

Conclusions

There remains little robust evidence on the optimal management of pregnancies affected by sFGR. Type I 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 selective reduction, fetal therapy may have a role at pre-viable gestations in severe cases in order to preserve the surviving twin from demise or neurological damage. Prenatal management of sFGR should be individualised 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 standardised postnatal follow-up are needed in order to elucidate the optimal management.

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FIGURE LEGEND

Figure 1. Systematic review flowchart (*some studies reported on more than one management.

Figure 2. Results of the pooled analysis for key outcomes in a) Type I b) Type II and c) Type III sFGR according to management.

First author (Year)	Country	Study design	Diagnostic criteria	Type of management	Outcomes reported	Cases (n)	sFGR type	Time to follow up
Rustico (2017) (14)	Italy	Retrospective cohort	EFW <10th centile in one twin OR EFW discrepancy >25%	Expectant (120) Cord occlusion (20)	Mortality, neurological morbidity	140	Type I (65) Type II (62) Type III (13)	12 months – 7 years
Koch (2017)(20)	France	Retrospective cohort	EFW <10th centile in one twin	Expectant (20) Laser (5)	Mortality	25	Type I (16) Type II (2) Type III (7)	7 days
Wang (2017)(21)	China	Prospective case series	Not specified	RFA (4)	Mortality, neurological morbidity,	4	Type II (2) Type III (2)	Up to 3 years
Panciatici (2017) (22)	France	Retrospective case series	Not specified	RFA (2)	Mortality, long term neurodevelopment	2	Type III (2)	Up to 30 months
Peng (2016)(8)	China	Retrospective cohort	EFW <2nd centile in one twin	Cord occlusion and RFA (16)	Mortality, Intact survival,	16	Type I (3) Type II and III (13)	4 - 72 months
Ishii (2015)(23)	Japan	Prospective clinical trial	EFW below <1.5 standard deviations in one twin	Laser	Mortality, neurological morbidity	10	Type II (7) Type III (3)	28 days
Parra- Cordero (2015)(6)	Spain	Prospective cohort	EFW <10th centile or AC <10th centile with EFW discordance >25%	expectant management (2 cases: no outcomes reported); Laser (15 case: no outcomes reported); Cord occlusion (90)	Mortality, intact survival	142	Type II (47) Type III (95)	NS
Pasquini (2015)(24)	Italy	Retrospective cohort	AC <10th centile in one twin	Expectant management (42)	Mortality, neurological morbidity	42	Type I (31) Type II (8) Type III (3)	NS
Peeva (2015)(25)	UK	Retrospective cohort	<22 weeks: AC<5th centile and EFW discrepancy >25% or >22 weeks EFW <5th centile and EFW discrepancy >25%	Laser (142)	Mortality	142	Type II (142)	NS
Machado (2014)(26)	Brazil	Retrospective cohort	EFW <10th centile in one twin	Expectant management (18)	Mortality, neurological morbidity, other morbidities,	18	Type I (2) Type II (11) Type III (5)	NS
Visentin (2013)(27)	Italy	Prospective longitudinal	EFW <10th centile in one twin	Expectant management (24)	Mortality, neurological morbidity, other morbidities	24	Type I (10) Type II (14)	28 days
Weisz (2011)(28)	Israel	Prospective cohort	EFW <10th centile in one twin	Expectant management (37)	Mortality, neurological morbidity, other morbidities, preterm delivery	37	Type I (19) Type II - III (18)	NS
Ishii (2009)(29)	Japan	Retrospective cohort	EFW <10th centile in one twin	Expectant management (81)	Mortality, intact survival, neurological morbidity	63	Type I (23) Type II (27) Type III (13)	6 months
Gratacos (2008)(30)	Spain	Retrospective cohort	EFW <10th centile in one twin	Laser (18), expectant	Mortality, neurological morbidity	49	Type III (49)	28 days

				management (31)				
Gratacos, Carreras (2004)(31)	Spain	Prospective cohort	EFW < 5th centile in one twin and EFW discordance >25%	Expectant management (42)	Mortality, neurological morbidity	42	Type I-II(20) Type III (22)	28 days
Quintero (2001)(13)	USA	Prospective cohort	EFW <10th percentile and AREDF	Expectant management (17); Cord occlusion (2); Laser (11)	Mortality, other morbidities,	30	Type I (6), Type II-III (22), not specified (2)	NS

Table 1. General characteristics of the included studies

EFW (estimated fetal weight), pPROM (preterm prelabour rupture of membranes), AREDF (absent or reversed end diastolic flow), RFA (radiofrequency ablation)

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcomes
Rustico	2017	★★	★	★★
Koch	2017	★★★	★	★
Wang	2017	★★		★★★
Peng	2016	★★		★★★
Ishii	2015	★★	★	★★★
Panciatici	2017	★★		★★★
Parra-Cordero	2015	★★★	★★	★★
Pasquini	2015	★★★	★	★★★
Peeva	2015	★★★		★★★
Machado	2014	★★★	★★	★★★
Visentin	2013	★★★	★	★★
Weisz	2011	★★★	★★	★★★
Kennelly	2007	★★	★	★★
Ishii	2009	★★	★	★★★
Gratacos	2008	★★★	★	★★★
Gratacos	2004	★★★★	★	★★
Quintero	2001	★★	★	★★★

TYPE I	Expectant management					Laser therapy					Cord occlusion			
Outcome	**Studies**	**n/N**	**PP (95% CI)**	**I^2(%)**		**Studies**	**n/N**	**PP (95% CI)**	**I^2(%)**		**Studies**	**n/N**	**PP (95% CI)**	**I^2(%)**
IUD (overall)	8	10/332	3.05 (1.1-5.9)	28		1	1/6	16.67 (0.4-64.1)	-		2	0/6	0 (0-34.9)	0
sIUD	8	6/332	2.18 (0.6-4.6)	27.9		1	1/6	16.67 (0.4-64.1)	-		2	0/6	0 (0-34.9)	0
dIUD	7	4/270	1.88 (0.6-3.8)	0		1	0/6	0 (0-45.9)	-		-	-	-	-
NND	5	0/142	0 (0-2.9)	0		1	0/6	0 (0-45.9)	-		1	0/3	0 (0-70.8)	-
PND	5	4/142	3.02 (0.2-8.9)	54.4		1	1/6	16.67 (0.4-64.1)	-		1	0/3	0 (0-70.8)	-
Live born	8	318/332	96.35 (92.6-98.8)	47.7		1	5/6	83.33 (35.9-99.6)3	-		2	6/6	100 (65.1-100)	0
Survival of at least one twin*	5	70/70	100 (94.3-100)	0		1	3/3	100 (29.2-100)	-		2	6/6	100 (65.1-100)	0
Overall morbidity	3	9/86	9.54 (0.5-27.7)	74.4		1	0/5	0 (0-52.2)	-		1	0/3	0 (0-70.6)	-
Abnormal brain imaging	3	4/103	4.13 (0.04-17.3)	73.7		1	0/5	0 (0-52.2)	-		1	0/3	0 (0-70.6)	-
IVH	3	0/103	0 (0-2.9)	0		1	0/5	0 (0-52.2)	-		1	0/3	0 (0-70.6)	-
PVL	3	0/103	0 (0-2.9)	0		1	0/5	0 (0-52.2)	-		1	0/3	0 (0-70.6)	-
RDS	1	4/38	10.53 (2.9-24.8)	-		-	-	-	-		-	-	-	-
Admission to NICU	-	-	-	-		-	-	-	-		-	-	-	-
Intact survival	3	79/80	97.87 (93.6-99.9)	0		1	5/5	100 (47.8-100)	-		1	3/3	100 (29.2-100)	-

Table 3a. Results of the analysis for Type I sFGR pregnancies

TYPE II	Expectant management					Laser therapy					Cord occlusion			
Outcome	Studies	n/N	PP (95% CI)	I^2(%)		Studies	n/N	PP (95% CI)	I^2(%)		Studies	n/N	PP (95% CI)	I^2(%)
IUD (overall)	5	43/214	16.64 (6.9-29.5)	78.2		2	7/16	44.30(22.2-67.7)	0		3	2/59	5.01 (0.03-20.5)	59.6
sIUD	5	17/214	8.15 (3.1-15.3)	58.6		2	7/16	44.30(22.2-67.7)	0		3	2/59	5.01 (0.03-20.5)	59.6
dIUD	4	26/198	10.43 (3.6-20.3)	71.2		2	0/16	0 (0-14.8)	0		-	-	-	-
NND	2	8/82	6.38 (0.2-28.2)	86.1		2	2/16	15.34 (2.7-35.7)	0		2	1/44	3.69 (0.2-11.1)	0
PND	2	22/82	14.96 (3.6-69.5)	96.3		3	140/300	46.69 (41.1-52.3)	21		2	1/44	3.69 (0.2-11.1)	0
Live born	5	162/214	81.09 (65.4-92.8)	83.8		2	9/16	55.70 (32.3-77.8)	-		3	53/59	87.53 (68.9-98.3)	55.4
Survival of at least one twin	1	14	100 (76.8-100)	-		3	110/150	82.89 (57.8-97.9)	53		3	52/59	86.21 (70.5-96.5)	40.1
Overall morbidity	1	7/28	25.0 (10.7-44.9)	-		1	0/8	0 (0-36.9)	-		1	1/3	33.3 (0.8-90.6)	-
Abnormal brain imaging	2	7/40	11.83 (0.1-40.9)	81.3		1	0/8	0 (0-36.9)	-		-	-	-	-
IVH	2	0/40	0 (0-6.6)	0		1	0/8	0 (0-36.9)	-		-	-	-	-
PVL	2	7/40	11.83 (0.1-40.9)	81.3		1	0/8	0 (0-36.9)	-		-	-	-	-
RDS	-	-	-	-		-	-	-	-		-	-	-	-
Admission to NICU	1	21/28	75.0 (55.1-89.3)	-		-	-	-	-		-	-	-	-
Intact survival	1	25/28	89.29 (71.8-97.7)	-		1	8/8	100 (63.1-100)			2	40/41	90.64 (42.3-94.3)	76.4

Table 3b. Results of the analysis for Type II sFGR pregnancies

TYPE III	Expectant management					Laser therapy					Cord occlusion			
Outcome	Studies	n/N	PP (95% CI)	I^2(%)		Studies	n/N	PP (95% CI)	I^2(%)		Studies	n/N	PP (95% CI)	I^2(%)
IUD (overall)	6	23/170	13.16 (7.2-20.5)	34.6		3	16/50	32.91 (20.9-46.2)	0		3	0/52	0 (0-5.0)	0
sIUD	6	11/170	7.21 (3.8-11.5)	0		3	16/50	32.91 (20.9-46.2)	0		3	0/52	0 (0-5.0)	0
dIUD	5	12/164	5.49 (1.2-12.5)	58.1		3	0/50	0 (0-6.0)	0		-	-	-	-
NND	2	4/70	6.81 (0.7-18.6)	56.7		2	0/14	0 (0-17.6)	0		2	2/50	5.17 (0.8-12.8)	0
PND	2	15/70	22.19 (13.4-32.5)	0		2	4/14	30.71 (10.8-55.5)	0		2	2/50	5.17 (0.8-12.8)	0
Live born	6	145/170	85.08 (78.5-90.6)	16.8		3	11/14	75.34 (51.3-93.1)	0		3	50/52	82.11 (34.3-99.5)	58.6
Survival of at least one twin	2	47/53	87.41 (73.3-94.8)	0		3	24/25	93.39 (74.3-100)	35.1		3	48/52	80.20 (37.7-100)	58.6
Overall morbidity	1	8/21	38.10 (18.1-61.6)	-		2	4/28	15.32 (4.8-30.4)	0.1		1	1/2	50.0 (12.6-98.7)	-
Abnormal brain imaging	1	7/34	20.59 (8.7-37.9)	-		2	4/28	15.32 (4.8-30.4)	0.1		-	-	-	-
IVH	3	3/91	3.46 (0.4-9.3)	20.3		2	2/28	9.01 (1.5-21.9)	0		-	-	-	-
PVL	3	10/91	11.62 (5.5-19.6)	9.5		2	2/28	9.01 (1.5-21.9)	0		-	-	-	-
RDS	-	-	-	-		-	-	-	-		-	-	-	-
Admission to NICU	-	-	-	-		-	-	-	-		-	-	-	-
Intact survival	1	13/21	61.90 (38.4-81.9)	-		1	5/5	100 (47.8-100)	-		2	47/48	98.81 (93.9-99.9)	79.2

Table 3c. Results of the analysis for Type III sFGR pregnancies

Table 3. Pooled proportions (95% CI) for the outcomes observed in the present systematic review in twin pregnancies complicated by a) Type I b) Type II and c) Type III sFGR according to different type of management: expectant, laser or cord occlusion.

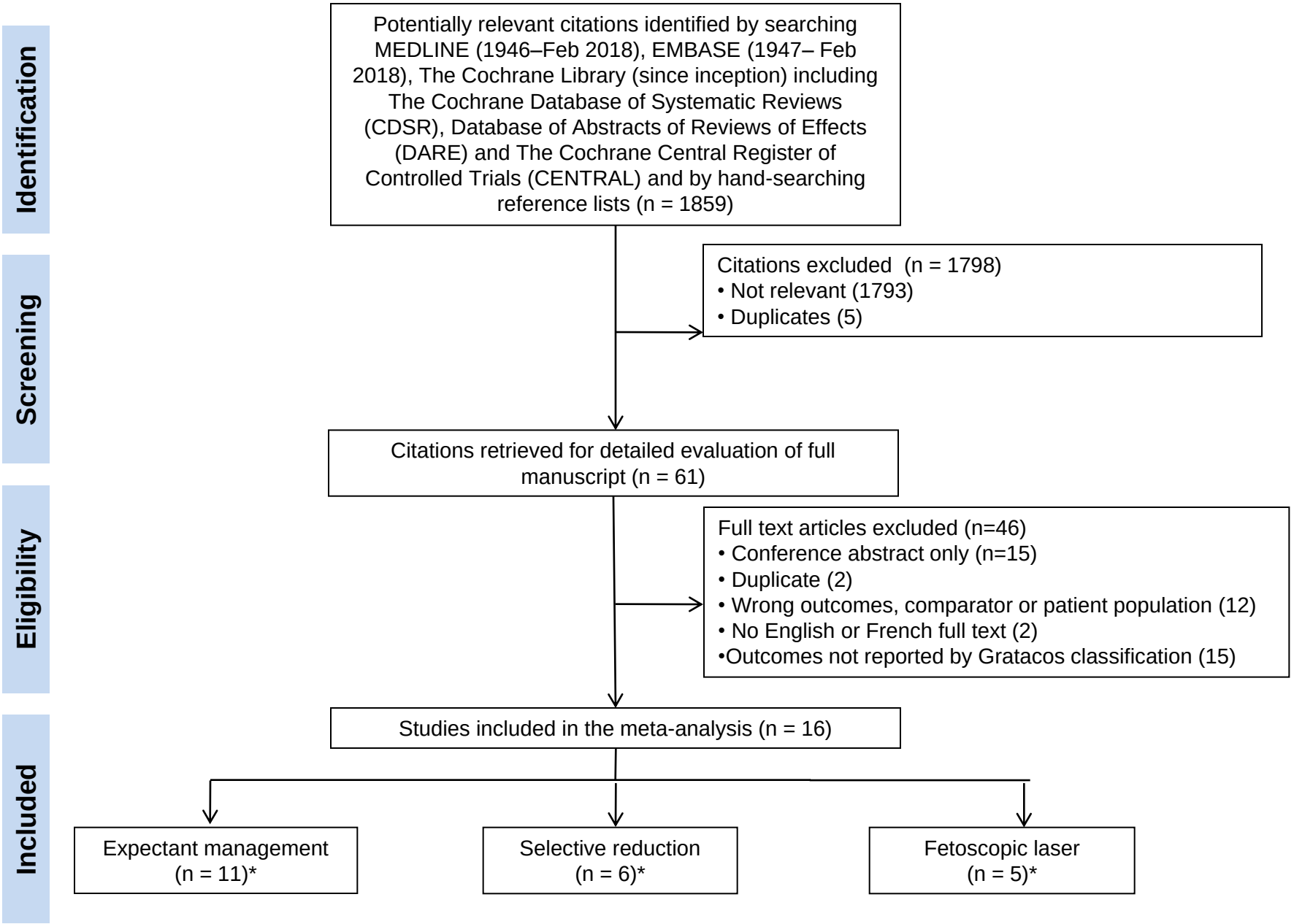

Figure 1 Flow chart illustrating identification of studies included in this systematic review. *some studies reported on more than one management.

Figure 2a.

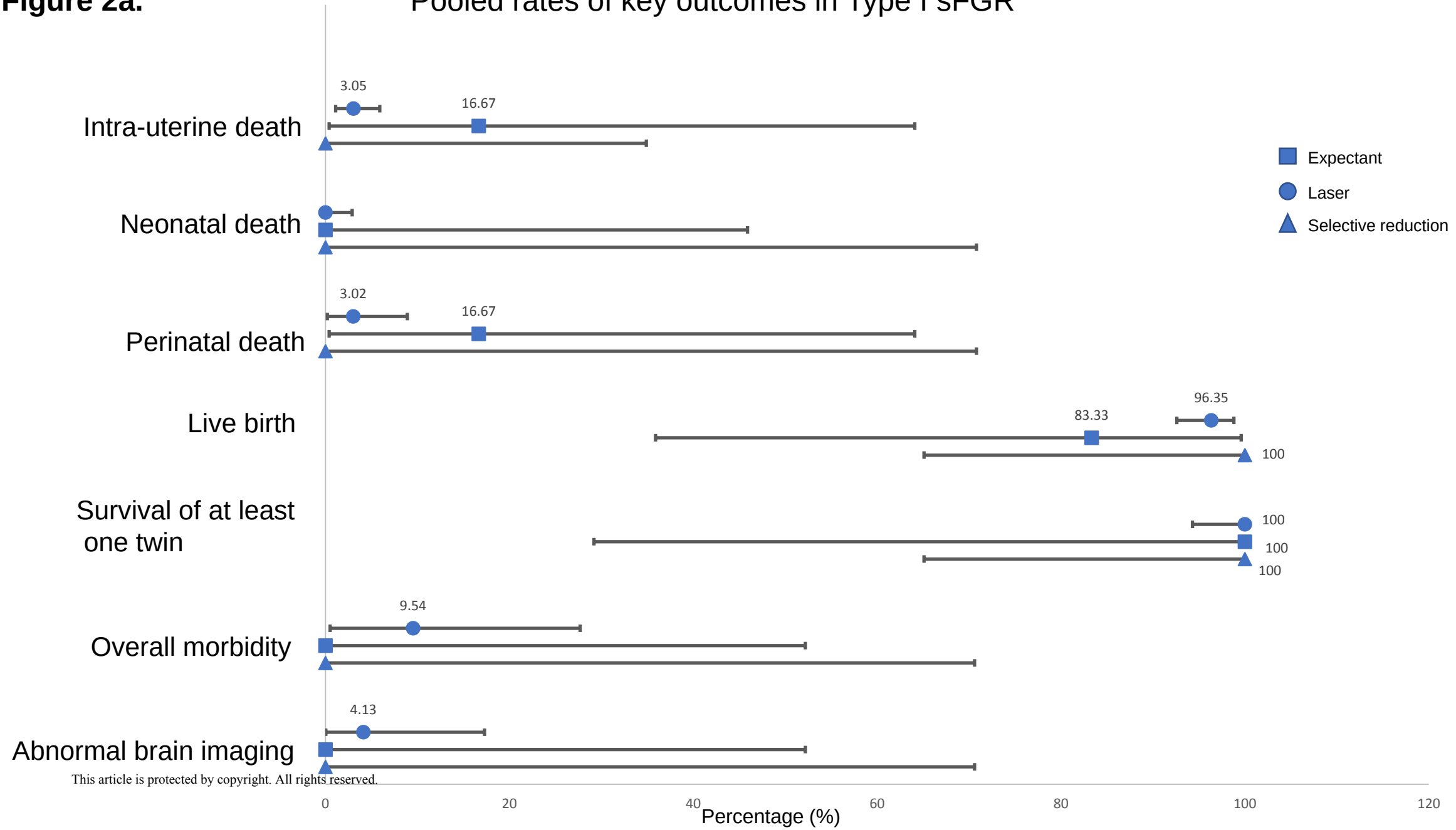

Figure 2b. Pooled rates of key outcomes in Type II sFGR

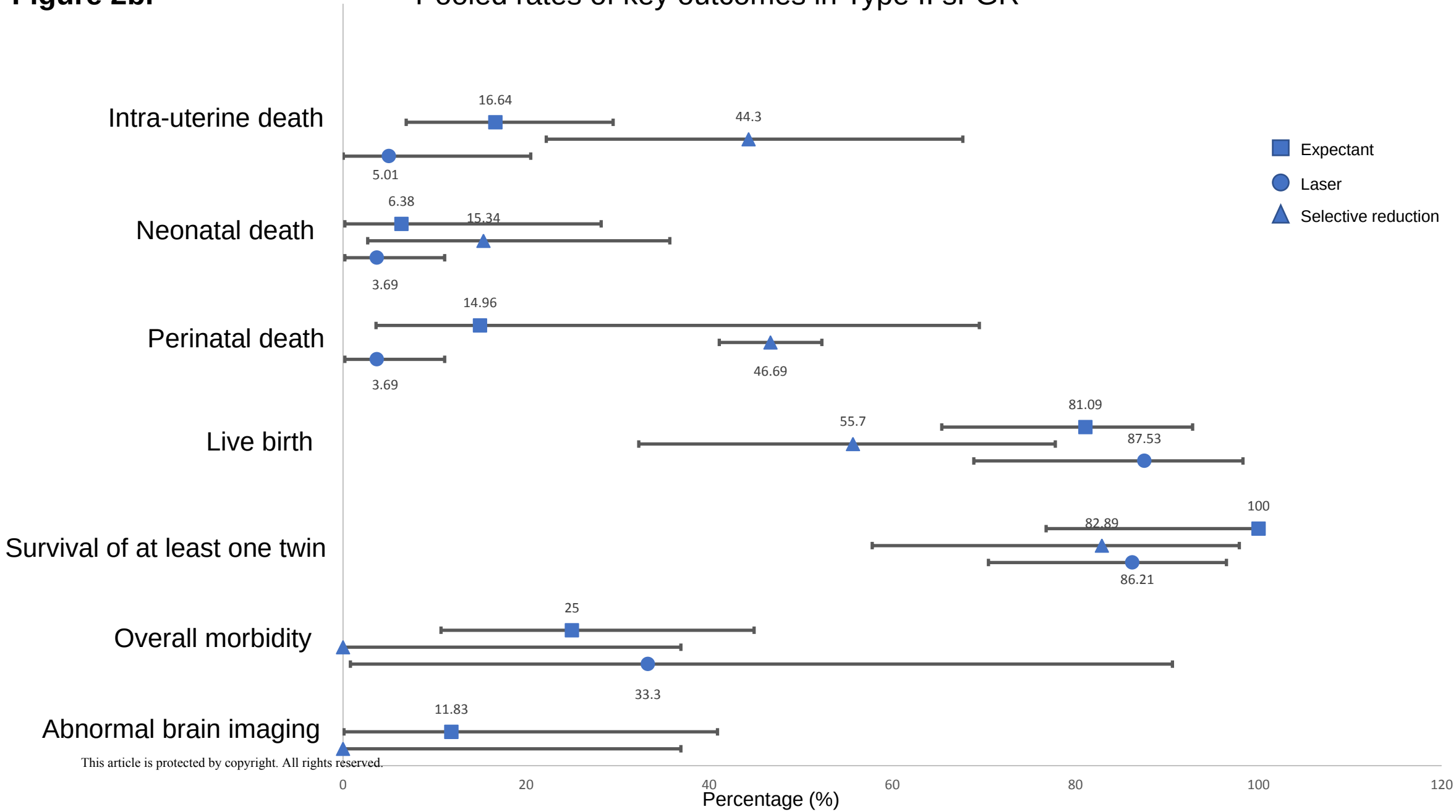

Figure 2c. Pooled rates of key outcomes in Type III sFGR