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Outcome following laser surgery of twin–twin transfusion syndrome complicated by selective fetal growth restriction: systematic review and meta-analysis

F. D'ANTONIO[1], D. MARINCEU[2], S. PRASAD[3], N. ELTAWEEL[4] and A. KHALIL[3,5,6,7]

[1]*Center for Fetal Care and High-Risk Pregnancy, University of Chieti, Chieti, Italy;* [2]*Department of Obstetrics and Gynecology, The York Hospital, York, UK;* [3]*Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, University of London, London, UK;* [4]*Division of Biomedical Science, Warwick Medical School, University of Warwick, University Hospital Coventry and Warwickshire, Coventry, UK;* [5]*Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK;* [6]*Twins Trust Centre for Research and Clinical Excellence, St George's University Hospital, St George's University of London, London, UK;* [7]*Fetal Medicine Unit, Liverpool Women's Hospital, University of Liverpool, Liverpool, UK*

KEYWORDS: fetal growth restriction; intrauterine demise; morbidity; mortality; neonatal death; size discordance; small-for-gestational age; stillbirth; TTTS; twin–twin transfusion syndrome

CONTRIBUTION

What are the novel findings of this work?
Monochorionic diamniotic (MCDA) twin pregnancies with twin–twin transfusion syndrome (TTTS) complicated by selective fetal growth restriction (sFGR) had 50% higher odds of fetal loss after laser surgery compared to those with TTTS without sFGR. The risk of neurological morbidity was also significantly higher in pregnancies with both TTTS and sFGR. The risk of fetal loss and neurological morbidity in pregnancies with TTTS and sFGR was significantly higher for the donor but not for the recipient twin.

What are the clinical implications of this work?
sFGR in MCDA pregnancies with TTTS represents an additional risk factor for fetal loss following laser surgery and should be taken into account in individualized risk assessments and tailored counseling of the parents. Long-term follow-up of these children is recommended.

ABSTRACT

Objective *The published literature reports mostly on the outcome of twin pregnancies complicated by twin–twin transfusion syndrome (TTTS) without considering whether the pregnancy is also complicated by another pathology, such as selective fetal growth restriction (sFGR). The aim of this systematic review was to report on the outcome of monochorionic diamniotic (MCDA) twin pregnancies undergoing laser surgery for TTTS that were complicated by sFGR and those not complicated by sFGR.*

Methods *MEDLINE, EMBASE and Cochrane databases were searched. The inclusion criteria were studies reporting on MCDA twin pregnancies with TTTS undergoing laser therapy that were complicated by sFGR and those not complicated by sFGR. The primary outcome was the overall fetal loss following laser surgery, defined as miscarriage and intrauterine death. The secondary outcomes included fetal loss within 24 h after laser surgery, survival at birth, preterm birth (PTB) prior to 32 weeks of gestation, PTB prior to 28 weeks, composite neonatal morbidity, neurological and respiratory morbidity, and survival free from neurological impairment. All outcomes were explored in the overall population of twin pregnancies complicated by sFGR* vs *those not complicated by sFGR in the setting of TTTS and in the donor and recipient twins separately. Random-effects meta-analysis was used to combine data and the results are reported as pooled odds ratios (OR) with 95% CI.*

Results *Five studies (1710 MCDA twin pregnancies) were included in the qualitative synthesis and four in the meta-analysis. The overall risk of fetal loss after laser surgery was significantly higher in MCDA twin pregnancies with TTTS complicated by sFGR (20.90%* vs *14.42%), with a pooled OR of 1.6 (95% CI, 1.3–1.9) (*$P < 0.001$*). The risk of fetal loss was significantly higher*

Correspondence to: Prof. A. Khalil, Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London SW17 0QT, UK (e-mail: akhalil@sgul.ac.uk)

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in MCDA twin pregnancies with TTTS and sFGR for the donor but not for the recipient twin. The rate of live twins was 79.1% (95% CI, 72.6–84.9%) in TTTS pregnancies with sFGR and 85.6% (95% CI, 81.0–89.6%) in those without sFGR (pooled OR, 0.6 (95% CI, 0.5–0.8)) (P < 0.001). There was no significant difference in the risk of PTB prior to 32 weeks of gestation (P = 0.308) or prior to 28 weeks (P = 0.310). Assessment of short- and long-term morbidity was affected by the small number of cases. There was no significant difference in the risk of composite (P = 0.506) or respiratory (P = 0.531) morbidity between twins complicated by TTTS with vs *those without sFGR, while the risk of neurological morbidity was significantly higher in those with TTTS and sFGR (pooled OR, 1.8 (95% CI, 1.1–2.9)) (P = 0.034). The risk of neurological morbidity was significantly higher for the donor twin (pooled OR, 2.4 (95% CI, 1.1–5.2)) (P = 0.029) but not for the recipient twin (P = 0.361). Survival free from neurological impairment was observed in 70.8% (95% CI, 45.0–91.0%) of twin pregnancies with TTTS complicated by sFGR and in 75.8% (95% CI, 51.9–93.3%) of those not complicated by sFGR, with no difference between the two groups.*

Conclusions *sFGR in MCDA pregnancies with TTTS represents an additional risk factor for fetal loss following laser surgery. The findings of this meta-analysis may be useful for individualized risk assessment of twin pregnancy complicated by TTTS and tailored counseling of the parents prior to laser surgery.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Monochorionic diamniotic (MCDA) twin pregnancies are at increased risk of complications, including twin–twin transfusion syndrome (TTTS), twin anemia–polycythemia sequence, twin reversed arterial perfusion and selective fetal growth restriction (sFGR)[1–10]. TTTS affects 10–15% of MCDA twin pregnancies, and its severity has been classified using the Quintero staging. Laser surgery is the established method of treating TTTS Stage 2 or higher between 16 and 26 weeks' gestation, which involves coagulating the placental vascular anastomoses between the donor and recipient twins[11–15].

sFGR complicates more than one-third of TTTS cases[6,7]. The rate of survival of both twins following laser surgery has been reported to be lower in pregnancies with TTTS and sFGR compared to those with TTTS without sFGR[16,17]. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines have defined sFGR as a condition in which the estimated fetal weight (EFW) of one fetus is below the 10th centile and the intertwin EFW discordance is greater than 25%[18]. The condition can be further subdivided into Types I, II and III according to end-diastolic flow (EDF) in the umbilical artery (UA) of the smaller fetus. The EDF is positive in Type-I, absent or reversed (AREDF) in Type-II and intermittent AREDF in Type-III sFGR[19].

The majority of the published literature reports on outcomes of twin pregnancies complicated by TTTS without considering whether the pregnancy is also complicated by another pathology, such as sFGR. The aim of this systematic review and meta-analysis was to ascertain the perinatal outcomes of MCDA pregnancies complicated by both TTTS and sFGR undergoing laser surgery.

METHODS

Protocol, information sources and literature search

This review was performed according to an *a-priori* designed protocol recommended for systematic reviews and meta-analyses[20,21]. MEDLINE and EMBASE databases were searched electronically on 24 November 2022, utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'twin–twin transfusion syndrome', 'monochorionic pregnancies', 'ultrasound' and 'outcome' (Table S1). The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were searched manually for additional reports. The PRISMA guidelines were followed[22]. The study was registered with the PROSPERO database (registration number: CRD42022385528).

Outcome measures, study selection and data collection

The inclusion criteria were MCDA twin pregnancy with TTTS complicated by sFGR or not complicated by sFGR undergoing laser therapy[23]. The primary outcome was overall fetal loss following laser surgery, defined as miscarriage and intrauterine death. The secondary outcomes were: fetal loss within 24 h after laser surgery; survival at birth; preterm birth (PTB) prior to 32 weeks of gestation; PTB prior to 28 weeks; composite neonatal morbidity, defined as incidence of respiratory, neurological, infectious morbidity or admission to neonatal intensive care unit; neurological morbidity, defined as the incidence of intraventricular hemorrhage (Grade III and IV) or periventricular leukomalacia (Grade II); respiratory morbidity, defined as the occurrence of respiratory distress syndrome or need for mechanical ventilation; and survival free from neurological impairment.

All these outcomes were explored in the overall population of twin pregnancies complicated by sFGR *vs* not complicated by sFGR in the setting of TTTS, and in the donor and recipient twins separately. Furthermore, we planned subgroup analyses according to TTTS stage, sFGR stage and gestational age (GA) at treatment ($\leq$ *vs* $>$ 24 weeks). sFGR was defined according to the recently published Delphi consensus[23] as the presence of at least two of four contributory parameters (EFW

of one twin $< 10^{th}$ centile, abdominal circumference of one twin $< 10^{th}$ centile, EFW discordance $\geq 25\%$ and UA pulsatility index of the smaller twin $> 95^{th}$ centile) or, in studies published before this consensus paper, as EFW $< 10^{th}$ centile or EFW discordance $\geq 25\%$[24].

Studies reporting the incidence of outcomes only in one arm or those not differentiating between TTTS cases complicated by sFGR and those not complicated by sFGR were not included. Studies including cases affected by sFGR that subsequently developed TTTS, those including monochorionic monoamniotic twin pregnancies and cases with structural or chromosomal anomaly and those from which data could not be extrapolated were excluded. Studies published before 2000 were also excluded, as we considered that advances in prenatal imaging techniques and improvements in the diagnosis and treatment of TTTS made them less relevant. Only full-text articles were considered eligible for inclusion. Case reports, conference abstracts and case series with fewer than five cases were excluded in order to avoid publication bias.

Two authors (D.M. and F.D.A.) 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 outcome. Inconsistencies were resolved through discussion between the two reviewers until consensus was reached or by discussion with a third author (A.K.). If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment and risk of bias

Risk of bias of the included studies was assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool[25]. ROBINS-I provides a detailed framework for assessment and judgement of risk of bias that may arise due to confounding, selection of participants into the study, measurement of interventions, missing data, measurement of outcomes and selection of reported results. The ROBINS-I tool is equally appropriate for cross-sectional and longitudinal non-randomized studies, as quality assessment is independent of study design. Each domain is classified as having low, moderate, serious or critical risk of bias. Low risk indicates that the study is comparable to a well-performed randomized trial in the domain being evaluated. Moderate risk of bias indicates that the study is sound for a non-randomized study, but not comparable to a rigorous randomized trial. Serious risk of bias indicates the presence of important problems, while critical risk of bias indicates that the study is too problematic to provide any useful evidence on the effects of the intervention. If insufficient information was provided to determine the risk of bias of a certain domain, the domain was marked as having no information. All studies were analyzed using this tool regardless of whether the original study design included randomization to other exposures, thus ensuring that the risk of bias was assessed specifically for the comparisons relevant to this review[25].

Statistical analysis

Random-effects meta-analysis was used to combine data and results are reported as odds ratios (OR) with 95% CI. For the purpose of the analysis, the denominator was represented by the number of fetuses per each group for the computation of survivors and morbidity, while the number of pregnancies was used for the assessment of PTB and presence of at least one and two survivors[26,27]. 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 observed heterogeneity, values $< 50\%$ indicate low heterogeneity, whereas I^2 values of $\geq 50\%$ indicate a substantial level of heterogeneity. All analyses were performed using StatsDirect Statistical Software (StatsDirect Ltd, Cambridge, UK). A P-value < 0.05 was considered significant.

RESULTS

Study selection and characteristics

A total of 1045 articles were identified, 16 were assessed with respect to their eligibility for inclusion and five studies were included in the systematic review (Table 1, Figure 1 and Table S2)[28–32]. After removing the studies that included overlapped cases, these five studies included 1710 MCDA twin pregnancies complicated by TTTS undergoing laser surgery. Of these, 886 (51.8% (range, 28.2–65.3%)) pregnancies were complicated by sFGR. The incidence of sFGR in the included studies ranged from 28% in the study by Gibbone *et al.*[28] to 65% in the study by Van Winden *et al.*[32]. Table S3 compares the main pregnancy and disease characteristics between MCDA pregnancies affected by TTTS complicated by sFGR with those not complicated by sFGR. There was no significant difference in the mean GA at the time of laser surgery between the two groups (20.28 ± 1.89 *vs* 20.33 ± 1.98 weeks; pooled mean difference, random-effects, −0.036 (95% CI, −0.664 to 0.592) weeks; $P = 0.910$). TTTS Stage I (11.5% *vs* 18.0%; $P = 0.015$) and Stage II (23.2% *vs* 35.7%; $P < 0.001$) were more common in MCDA pregnancies affected by TTTS without sFGR. Conversely, TTTS Stage III (58.9% *vs* 39.7%; $P < 0.001$) and the presence of AREDF in the UA (25.8% *vs* 17.3%; $P < 0.001$) were more common in pregnancies complicated by TTTS and sFGR. We could not compare the rates of anterior placental position, mean cervical length, use of Solomon technique, velamentous cord insertion or the number of arteriovenous anastomoses between the two groups. Within the twin pair, the donor twin was affected by sFGR in 86.0% (95% CI, 22.9–91.0%) of cases.

Assessment of risk of bias of observational studies according to the ROBINS-I tool is presented in Table 2.

All studies were at moderate risk of bias mainly because their analysis was not stratified according to TTTS stage, severity of sFGR, GA at intervention and Doppler status.

Synthesis of results

One study was excluded from quantitative synthesis because it did not report on the evaluated outcomes[29]. MCDA twin pregnancies with TTTS complicated by sFGR had a significantly higher risk of overall fetal loss after laser surgery, with a pooled OR of 1.6 (95% CI, 1.3–1.9) ($P < 0.001$) (Figure 2), and fetal loss within 24 h after laser surgery (pooled OR, 1.8 (95% CI, 1.2–2.8)) ($P = 0.006$) (Table 3). The risk of fetal loss was significantly higher for the donor twin, overall (pooled OR, 1.9 (95% CI, 1.5–2.5)) ($P < 0.001$) and within 24 h after laser surgery (pooled OR, 2.4 (95% CI, 1.3–4.5)) ($P = 0.008$), but not for the recipient twin ($P = 0.133$ and $P = 0.521$,

Table 1 Characteristics of studies reporting on outcome of monochorionic diamniotic twin pregnancies with twin–twin transfusion syndrome (TTTS) complicated *vs* those not complicated by selective fetal growth restriction (sFGR) included in systematic review and meta-analysis

Study	*Country*	*Study design*	*Study period*	*Definition of sFGR*	*TTTS stage*	*TTTS* (n)	*TTTS with sFGR* (n)
Gibbone (2022)[28]	Spain	Retro	2007–2021	Delphi†	I–IV	149	42
Kim (2022)[29]*	South Korea	Retro	2011–2018	Delphi†	I–IV	173	103
Donepudi (2021)[30]	USA	Retro	2002–2020	Delphi†	I–IV	492	188
Groene (2019)[31]	Netherlands	Retro	2001–2019	EFW < 10th centile	I–IV	527	312
Van Winden (2015)[32]	USA	Retro	2006–2012	Donor EFW < 10th centile	I–IV	369	241

Only first author given for each study. *Excluded from meta-analysis. †Two out of four contributory parameters (estimated fetal weight (EFW) of one twin < 10th centile, abdominal circumference of one twin < 10th centile, EFW discordance ≥ 25% and umbilical artery pulsatility index of smaller twin > 95th centile). Retro, retrospective.

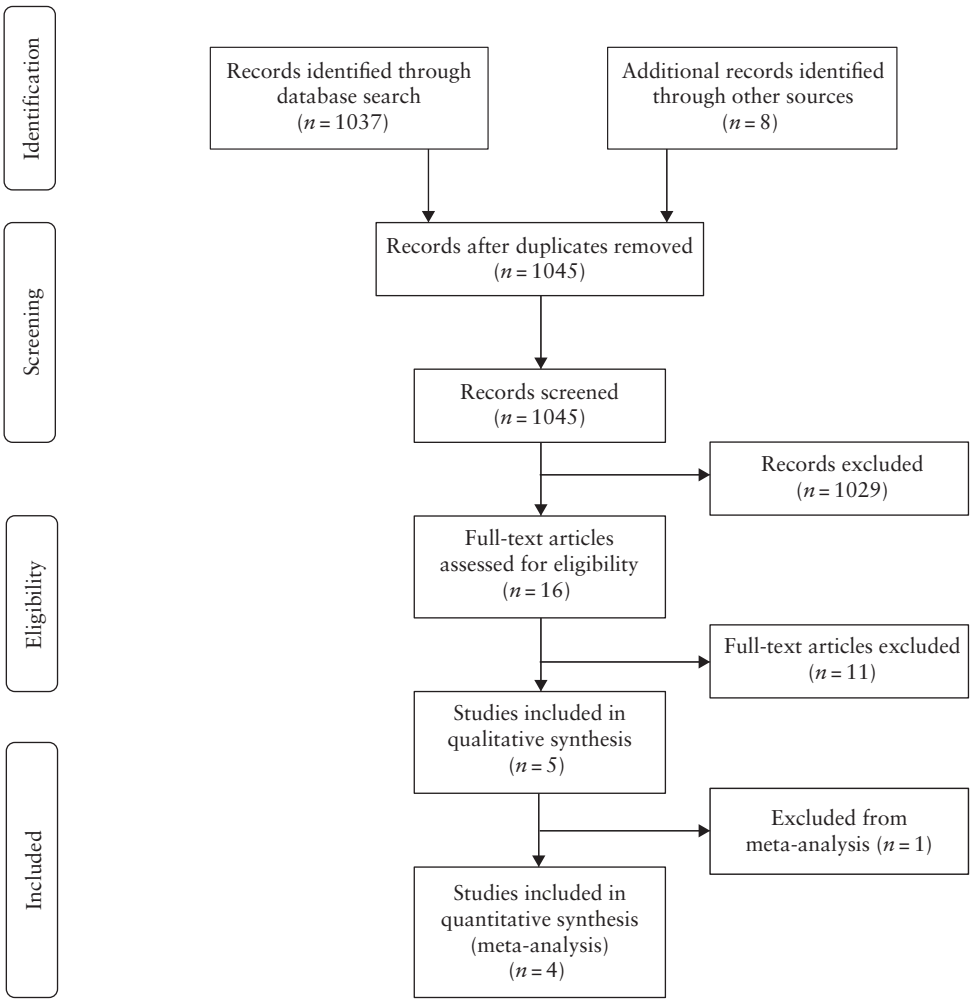

Figure 1 Flowchart summarizing inclusion of studies in systematic review and meta-analysis.

respectively) in pregnancies complicated by TTTS and sFGR. Twin pregnancies complicated by TTTS and sFGR also had a significantly lower rate of live twins at birth (pooled OR, 0.6 (95% CI, 0.5–0.8)) ($P < 0.001$). Table 3 shows the pooled proportions and ORs and their 95% CIs for the investigated outcomes.

Conversely, there was no significant difference in the risk of PTB < 32 weeks of gestation ($P = 0.308$) and < 28 weeks ($P = 0.310$) between MCDA twin pregnancies with TTTS complicated by sFGR *vs* those not complicated by sFGR. Assessment of short- and long-term morbidity was affected by the relatively small number of cases and even smaller number of events, which may have made the systematic review underpowered for such outcomes. We did not observe a significant difference in the risk of composite ($P = 0.506$) or respiratory ($P = 0.531$) morbidity between MCDA twins with TTTS complicated by sFGR *vs* those not complicated by sFGR. Conversely, there was a significantly higher risk of neurological morbidity in the donor twin (pooled OR, 2.4 (95% CI, 1.1–5.2)) ($P = 0.029$), but not in the recipient twin ($P = 0.361$) of MCDA pregnancies complicated by TTTS and sFGR. Only two studies explored the long-term outcome of MCDA pregnancies complicated by sFGR in the setting of TTTS[28,31]. These studies used different diagnostic criteria of sFGR, although they both reported data at 2 years after laser surgery. Overall, there was no significant difference in the rate of survival without neurological impairment between pregnancies with TTTS complicated by sFGR *vs* those not complicated by sFGR ($P = 0.432$).

We could not perform meaningful subgroup analyses according to TTTS Stage, type of sFGR or GA at laser surgery because the original studies did not report this information.

DISCUSSION

Summary of main findings

The findings of this study show that MCDA twin pregnancies with TTTS complicated by sFGR undergoing fetal laser therapy are at a significantly higher risk of fetal loss compared with those not complicated by sFGR. In particular, the risk of loss of the donor twin was significantly higher in pregnancies complicated by TTTS and sFGR compared with those affected only by TTTS. We did not observe a significant difference between the two cohorts in terms of composite neonatal or respiratory morbidity. We observed a significantly higher risk of neurological compromise in the donor, but not in the recipient, twin of pregnancies complicated by TTTS and sFGR. Assessment of morbidity was affected by the small number of included cases, which may have rendered the analysis underpowered for detection of differences in these outcomes.

Table 2 Quality assessment of observational studies according to Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool

Study	*Confounding*	*Selection*	*Measurement of intervention*	*Missing data*	*Measurement of outcomes*	*Reported results*	*Overall*
Gibbone (2022)[28]	Moderate	Low	Low	Low	Low	Moderate	Low
Kim (2022)[29]	Moderate	Low	Low	Low	Moderate	Moderate	Low
Donepudi (2021)[30]	Moderate	Moderate	Low	Low	Moderate	Moderate	Critical
Groene (2019)[31]	Moderate	Low	Low	Low	Moderate	Moderate	Low
Van Winden (2015)[32]	Moderate	Low	Low	Low	Moderate	Moderate	Critical

Only first author given for each study. Risk of bias: low, study is comparable to well-performed randomized trial regarding this domain; moderate, study is sound for non-randomized study with regard to this domain, but cannot be considered comparable to well-performed randomized trial; serious, study has some important problems in this domain; critical, study is too problematic in this domain to provide any useful evidence on effects of intervention.

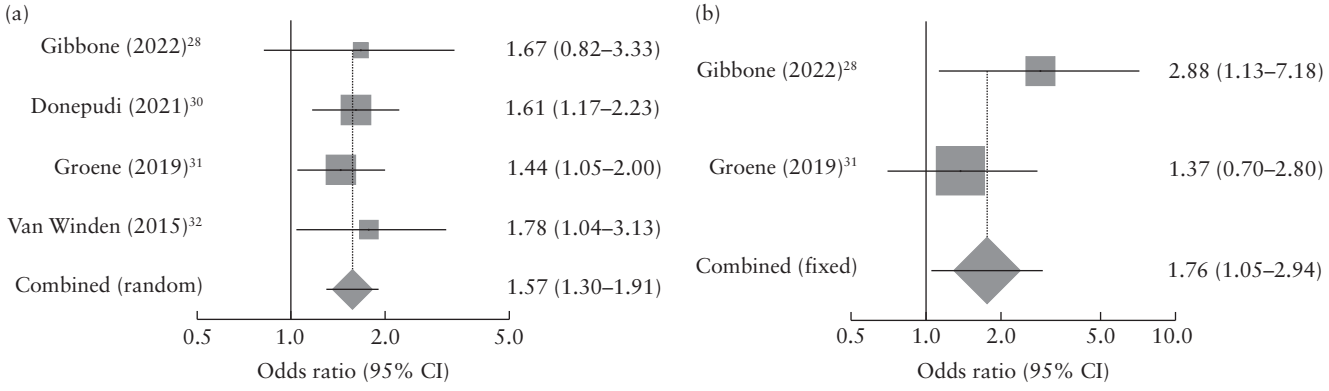

Figure 2 Pooled odds ratios with 95% CI for overall fetal loss after laser surgery (a) and neurological morbidity (b) in monochorionic diamniotic twin pregnancies with twin–twin transfusion syndrome (TTTS) complicated by selective fetal growth restriction (sFGR) *vs* those not complicated by sFGR. Only first author given for each study.

Clinical and research implications

TTTS is among the main determinants of perinatal mortality and morbidity in monochorionic gestations[1,9–12,33]. Several factors can affect the prognosis of monochorionic pregnancies undergoing laser surgery for TTTS, such as GA at intervention, a more advanced Quintero stage at diagnosis and short cervical length[33]. Although TTTS is predominantly a hemodynamic condition induced by unbalanced blood flow through placental anastomoses, it is associated commonly with a certain degree of size discordance between the two fetuses[34]. In the present systematic review, the prevalence of sFGR complicating TTTS ranged between 28.2% and 65.3%. The presence of sFGR in the setting of TTTS can pose additional risks, which can impact on short- and long-term outcomes of the pregnancy[35–37]. Increased discordance in placental sharing leads to an increase in the net volume flow between the twins, leading to more interdependent circulations, and it is not uncommon to have twins with significantly different placental shares presenting with a similar weight at birth as a result of chronic compensatory perfusion from the larger to the smaller twin. Placental dichorionization secondary to photocoagulation of placental anastomoses

Table 3 Pooled proportions and odds ratios (OR) for outcomes following laser surgery of monochorionic diamniotic twin pregnancies with twin–twin transfusion syndrome (TTTS) complicated by selective fetal growth restriction (sFGR) *vs* those not complicated by sFGR

		Pregnancies with TTTS and sFGR			*Pregnancies with TTTS and no sFGR*					
Outcome	*Studies (n[ref])*	*Fetuses (n/N)*	*Pooled proportion (95% CI)*	I^2 *(%)*	*Fetuses (n/N)*	*Pooled proportion (95% CI)*	I^2 *(%)*	*Pooled OR (95% CI)*	I^2 *(%)*	P
Fetal loss (overall)	4[28,30–32]	326/1566	20.90 (15.07–27.42)	87.9	234/1508	14.42 (10.37–19.01)	82.0	1.57 (1.30–1.91)	0	< 0.001
Donor twin	4[28,30–32]	200/783	25.65 (19.27–32.61)	75.7	127/754	16.08 (12.06–20.56)	61.7	1.89 (1.45–2.45)	0	< 0.001
Recipient twin	4[28,30–32]	126/783	16.17 (8.83–25.21)	88.9	107/754	13.32 (8.90–18.46)	72.4	1.25 (0.93–1.67)	0	0.133
Fetal loss within 24 h*	2[31,32]	85/1106	7.66 (6.17–9.30)	81.3	31/686	4.62 (3.18–6.32)	0	1.81 (1.19–2.77)	0	0.006
Donor twin	2[31,32]	47/553	8.65 (6.45–11.13)	0	13/343	4.04 (2.22–6.37)	0	2.36 (1.25–4.45)	0	0.008
Recipient twin	2[31,32]	38/553	6.15 (1.15–14.71)	91.4	18/343	5.46 (2.22–8.11)	0	1.29 (0.59–2.83)	33.9	0.521
Live twins	4[28,30–32]	1240/1566	79.10 (72.58–84.93)	87.9	1274/1508	85.58 (80.99–89.63)	82	0.64 (0.52–0.77)	0	< 0.001
Donor twin	4[28,30–32]	583/783	74.35 (67.39–80.73)	75.7	627/754	83.92 (79.44–87.94)	59.3	0.53 (0.41–0.69)	0	< 0.001
Recipient twin	4[28,30–32]	657/783	83.83 (74.79–91.17)	88.9	647/754	86.68 (81.54–91.10)	72.4	0.80 (0.59–1.07)	0	0.126
Preterm birth < 32 weeks	3[28,30,32]	206/471	44.31 (31.24–57.81)	86.5	220/539	36.24 (22.33–51.45)	91.4	1.29 (0.94–1.76)	0	0.308
Preterm birth < 28 weeks	3[28,30,32]	78/471	15.89 (9.51–23.55)	73.6	80/539	12.42 (5.71–21.25)	85.61	1.21 (0.85–1.72)	0	0.310
Composite neonatal morbidity	2[28,31]	123/478	39.76 (6.68–79.68)	97.4	136/462	31.12 (15.99–48.67)	93.2	1.41 (0.52–3.82)	87.7	0.506
Donor twin	2[28,31]	53/233	36.05 (4.74–76.83)	94.8	66/230	30.41 (15.16–48.29)	86.9	1.21 (0.43–3.39)	76.5	0.722
Recipient twin	2[28,31]	70/245	42.39 (8.49–81.20)	94.9	70/232	31.69 (16.83–48.78)	85.8	1.52 (0.57–4.06)	75.2	0.401
Neurological morbidity	2[28,31]	42/499	12.36 (2.56–28.01)	88.6	29/471	6.27 (3.84–9.58)	38.3	1.76 (1.05–2.94)	47.5	0.034
Donor twin	2[28,31]	20/242	12.22 (2.04–29.19)	80.2	12/235	5.62 (1.86–11.125)	58.9	2.39 (1.09–5.22)	0	0.029
Recipient twin	2[28,31]	22/257	11.92 (2.71–26.42)	76.1	17/236	7.55 (4.54–11.24)	0	1.56 (0.60–4.05)	45.5	0.361
Respiratory morbidity	2[28,31]	108/489	37.29 (3.40–81.67)	98.0	128/472	29.35 (10.57–52.85)	96.3	1.36 (0.52–3.60)	0	0.531
Donor twin	2[28,31]	46/238	33.68 (2.06–78.96)	95.9	65/236	29.91 (10.93–53.51)	92.5	1.09 (0.38–3.12)	76.4	0.866
Recipient twin	2[28,31]	62/251	39.91 (4.74–83.18)	96.0	63/236	28.74 (10.26–52.02)	92.5	0.58 (0.34–3.92)	70.1	0.327
Survival without neurological impairment†	2[28,31]	305/500	70.83 (44.99–90.95)	91.4	322/447	75.80 (51.91–93.28)	93.4	0.80 (0.60–1.07)	0.13	0.432
Donor twin	2[28,31]	152/257	69.37 (41.14–91.35)	84.9	162/221	76.30 (55.37–92.08)	90.5	0.68 (0.46–1.04)	0	0.076
Recipient twin	2[28,31]	153/243	69.75 (48.27–87.46)	77.5	160/226	74.75 (48.40–93.81)	93.9	0.93 (0.62–1.39)	0	0.719

*After laser surgery. †2 years after laser surgery.

leads to a functional and hemodynamic separation of the circulations of the two fetuses by interrupting the hemodynamic exchange and making each twin dependent on its own placental share. Therefore, the fetus with a reduced placental share may be at increased risk of complication, mainly intrauterine death, due to placental insufficiency. In the present systematic review, the risk of fetal loss in MCDA twin pregnancies with TTTS and concurrent sFGR was significantly higher in the donor but not in the recipient twin. The donor twin was more likely to be affected by a smaller placental share compared with the recipient, thus making it more susceptible to the consequences of placental insufficiency after dichorionization.

Twins affected by TTTS are at higher risk of abnormal neurodevelopmental outcome compared with unaffected twins. sFGR represents another independent risk factor for impaired neurodevelopmental outcome after birth[33]. The occurrence of abnormal brain imaging after birth is about 3% in twins with Type-I sFGR and 12–14% in those with Type-II and -III. Therefore, sFGR in twin pregnancies with TTTS is an additional risk factor for neurodevelopmental delay[14]. In the present systematic review, we report an increased risk of adverse neurological outcome at birth in the donor twin of pregnancies complicated by TTTS. We did not observe a significant difference in the incidence of survival free from neurological impairment at 2 years of age. However, these results should be interpreted with caution. Only two studies were included in the analysis, and they used different definitions of sFGR and type of postnatal assessment. Furthermore, the relatively small number of pregnancies included may have made the analysis underpowered to evaluate this outcome. In view of the high risk of impaired neurodevelopmental outcome, twins affected by TTTS, irrespective of the coexistence of sFGR, should receive long-term dedicated neurological follow-up[36]. More evidence is needed to elucidate the burden and type of neurocognitive delay in pregnancies complicated by TTTS and sFGR.

Given this increased risk of demise and neurological morbidity, there is scope to improve counseling regarding pregnancy outcome in TTTS cases with concurrent sFGR, especially regarding survival, GA at delivery and long-term neurological outcome. This additional information may help parents to make decisions for their care that are best suited to them. In cases of severe donor sFGR, a discussion about selective termination should be considered, taking into account the legal regulations in view of the high risk of neurological morbidity. The findings of this meta-analysis may be useful for individualized risk assessment of twin pregnancy complicated by TTTS and tailored counseling of the parents prior to laser surgery.

This review has also highlighted the lack of large-scale prospective studies with quality data comparing MCDA twin pregnancies complicated by TTTS with *vs* without sFGR. The retrospective studies identified had relatively small sample sizes and heterogeneous antenatal management and stratification. There is need for further extensive research on sFGR in the context of TTTS, as it is an important additional risk factor and has an impact on pregnancy outcome.

Strengths and limitations

Thorough literature search and multitude of outcomes explored represent the main strengths of this review. Retrospective non-randomized design of the included studies, their small sample size, dissimilarity in prenatal management of pregnancies complicated by both TTTS and sFGR and lack of stratification of the analysis according to the type of sFGR, TTTS stage and GA at intervention represent its main weaknesses. Lack of stratification of the analysis according to TTTS stage represents one of the major weaknesses of the present review. Perinatal outcome after laser surgery is influenced by TTTS stage, with higher survival rates for earlier (I and II) compared with more advanced (III–IV) Quintero stages at laser surgery. We could not formally perform a subgroup analysis considering different Quintero stages separately because the original studies did not report information on the observed outcomes stratified according to disease staging. Furthermore, the incidence of sFGR in pregnancies complicated by sFGR was highly heterogeneous among the included studies adopting the same definition, and it is likely that overdiagnosis of sFGR may have affected the reported results. Assessment of neonatal and long-term outcome was also challenging and was affected by potential bias. Only two studies with different types of postnatal assessment explored the long-term outcome of twin pregnancies with sFGR coexisting with TTTS, and we could perform a pooled analysis on the outcome only at 2 years of age, which may be insufficient to delineate the actual neurological outcome[28,31]. Another limitation of the present review lies in the fact that we could not stratify the analysis according to severity of sFGR. Fetal growth is a continuous phenomenon and many factors can affect its severity, including the degree of fetal smallness, Doppler findings and hemodynamic changes affecting the fetal cardiovascular system. Finally, although similar, different definitions of sFGR were adopted by the different studies and stratifying the analysis according to definition would have further limited the power of the analysis.

Conclusion

sFGR in the setting of TTTS increases the risk of mortality, especially in the donor twin. Prospective large multicenter studies are needed to confirm these findings and to elucidate whether sFGR in the setting of TTTS represents an additional risk factor not only for mortality, but also for short- and long-term morbidity.

REFERENCES

1. D'Antonio F, Khalil A, Dias T, Thilaganathan B; Southwest Thames Obstetric Research Collaborative (STORK). Early fetal loss in monochorionic and dichorionic twin pregnancies: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2013; **41**: 632–636.
2. D'Antonio F, Thilaganathan B, Dias T, Khalil A; Southwest Thames Obstetric Research Collaborative (STORK). Influence of chorionicity and gestational age at

single fetal loss on risk of preterm birth in twin pregnancy: analysis of STORK multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2017; **50**: 723–727.
3. Saccone G, Khalil A, Thilaganathan B, Glinianaia SV, Berghella V, D'Antonio F; MONOMONO, NorSTAMP and STORK research collaboratives. Weight discordance and perinatal mortality in monoamniotic twin pregnancy: analysis of MONOMONO, NorSTAMP and STORK multiple-pregnancy cohorts. *Ultrasound Obstet Gynecol* 2020; **55**: 332–338.
4. Pagani G, D'Antonio F, Khalil A, Papageorghiou A, Bhide A, Thilaganathan B. Intrafetal laser treatment for twin reversed arterial perfusion sequence: cohort study and meta-analysis. *Ultrasound Obstet Gynecol* 2013; **42**: 6–14.
5. D'Antonio F, Khalil A, Dias T, Thilaganathan B; Southwest Thames Obstetric Research Collaborative. Crown–rump length discordance and adverse perinatal outcome in twins: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2013; **41**: 621–626.
6. Buca D, Pagani G, Rizzo G, Familiari A, Flacco ME, Manzoli L, Liberati M, Fanfani F, Scambia G, D'Antonio F. Outcome of monochorionic twin pregnancy with selective intrauterine growth restriction according to umbilical artery Doppler flow pattern of smaller twin: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017; **50**: 559–568.
7. Townsend R, D'Antonio F, Sileo FG, Kumbay H, Thilaganathan B, Khalil A. Perinatal outcome of monochorionic twin pregnancy complicated by selective fetal growth restriction according to management: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2019; **53**: 36–46.
8. D'Antonio F, Odibo A, Prefumo F, Khalil A, Buca D, Flacco M, Liberati M, Manzoli L, Acharya G. Weight discordance and perinatal mortality in twin pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2018; **52**:11–23.
9. D'Antonio F, Odibo A, Berghella V, Khalil A, Kack K, Saccone G, Prefumo F, Buca D, Liberati M, Pagani G, Acharya G. Perinatal mortality, timing of delivery and prenatal management of monoamniotic twin pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2019 **53**:166–174.
10. Di Mascio D, Acharya G, Khalil A, Odibo A, Prefumo F, Liberati M, Buca D, Manzoli L, Flacco ME, Brunelli R, Benedetti Panici P, D'Antonio F. Birthweight discordance and neonatal morbidity in twin pregnancies: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2019; **98**:1245–1257.
11. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med* 2004; **351**: 136–144.
12. D'Antonio F, Herrera M, Oronzii L, Khalil A. Solomon technique *vs* selective fetoscopic laser photocoagulation for twin–twin transfusion syndrome: systematic review and meta-analysis of maternal and perinatal outcomes. *Ultrasound Obstet Gynecol* 2022; **60**: 731–738.
13. Murgano D, Khalil A, Prefumo F, Mieghem TV, Rizzo G, Heyborne KD, Melchiorre K, Peeters S, Lewi L, Familiari A, Lopriore E, Oepkes D, Murata M, Anselem O, Buca D, Liberati M, Hack K, Nappi L, Baxi LV, Scambia G, Acharya G, D'antonio F. Outcome of twin-to-twin transfusion syndrome in monochorionic monoamniotic twin pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2020; **55**: 310–317.
14. Di Mascio D, Khalil A, D'Amico A, Buca D, Benedetti Panici P, Flacco ME, Manzoli L, Liberati M, Nappi L, Berghella V, D'Antonio F. Outcome of twin–twin transfusion syndrome according to Quintero stage of disease: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2020; **56**: 811–820.
15. D'Antonio F, Thilaganathan B, Toms J, Manzoli L, Bhide A, Papageorghiou A, Khalil A. Perinatal outcome after fetoscopic laser surgery for twin-to-twin transfusion syndrome in triplet pregnancies. *BJOG* 2016; **123**: 328–336.
16. Van Winden KR, Quintero RA, Kontopoulos EV, Korst LM, Llanes A, Chmait RH. Perinatal survival in cases of twin-twin transfusion syndrome complicated by selective intrauterine growth restriction. *J Matern Fetal Neonatal Med* 2015; **28**: 1549–1553.
17. Groene SG, Tollenaar LSA, van Klink JMM, Haak MC, Klumper FJCM, Middeldorp JM, Oepkes D, Slaghekke F, Lopriore E. Twin–twin transfusion syndrome with and without selective fetal growth restriction prior to fetoscopic laser surgery: short and long-term outcome. *J Clin Med* 2019; **8**: 969.
18. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, Kilby MD, Lewi L, Nicolaides KH, Oepkes D, Raine-Fenning N, Reed K, Salomon LJ, Sotiriadis A, Thilaganathan B, Ville Y. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. *Ultrasound Obstet Gynecol* 2016; **47**: 247–263.
19. Gratacós E, Lewi L, Muñoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, Carreras E, Deprest J. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. *Ultrasound Obstet Gynecol* 2007; **30**: 28–34.
20. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. *Nephrology (Carlton)* 2010; **15**: 617–624.
21. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York Publishing Services Ltd: York, 2009. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf.
22. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62**: 1006–1012.
23. Khalil A, Beune I, Hecher K, Wynia K, Ganzevoort W, Reed K, Lewi L, Oepkes D, Gratacos E, Thilaganathan B, Gordijn SJ. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. *Ultrasound Obstet Gynecol* 2019; **53**: 47–54.
24. D'Antonio F, Khalil A, Dias T, Thilaganathan B; Southwest Thames Obstetric Research Collaborative (STORK). Weight discordance and perinatal mortality in twins: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2013; **41**: 643–648.
25. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016 **12**; 355: i4919.
26. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol* 2014; **67**: 897–903.
27. Manzoli L, De Vito C, Salanti G, D'Addario M, Villari P, Ioannidis JP. Meta-analysis of the immunogenicity and tolerability of pandemic influenza A 2009 (H1N1) vaccines. *PLoS One* 2011; **6**: e24384.
28. Gibbone E, Campos RV, Calero AJ, Lucena PC, Molina Garcia FS. Perinatal and long-term outcome of endoscopic laser surgery for twin–twin transfusion syndrome with and without selective fetal growth restriction: a retrospective cohort study. *Prenat Diagn* 2022; **42**: 1438–1447.
29. Kim R, Lee MY, Won HS, Kim JM, Lee YJ, Jeong BD, Kim HJ. Perinatal outcomes and factors affecting the survival rate of fetuses with twin-to-twin transfusion syndrome treated with fetoscopic laser coagulation: a single-center seven-year experience. *J Matern Fetal Neonatal Med* 2022; **35**: 5595–5606.
30. Donepudi R, Espinoza J, Nassr AA, Belfort MA, Shamshirsaz AA, Sanz Cortes M. Prediction of post-laser fetal death in selective growth restriction complicating twin–twin transfusion syndrome using standardized definitions. *Ultrasound Obstet Gynecol* 2021; **58**: 738–743.
31. Groene SG, Tollenaar LSA, van Klink JMM, Haak MC, Klumper FJCM, Middeldorp JM, Oepkes D, Slaghekke F, Lopriore E. Twin–Twin Transfusion Syndrome with and without Selective Fetal Growth Restriction Prior to Fetoscopic Laser Surgery: Short and Long-Term Outcome. *J Clin Med* 2019; **8**: 969.
32. Van Winden KR, Quintero RA, Kontopoulos EV, Korst LM, Llanes A, Chmait RH. Perinatal survival in cases of twin–twin transfusion syndrome complicated by selective intrauterine growth restriction. *J Matern Fetal Neonatal Med* 2015; **28**: 1549–1553.
33. Sileo FG, Curado J, D'Antonio F, Benlioglu C, Khalil A. Incidence and outcome of prenatal brain abnormality in twin-to-twin transfusion syndrome: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2022; **60**: 176–184.
34. Society for Maternal–Fetal Medicine; Simpson LL. Twin–twin transfusion syndrome. *Am J Obstet Gynecol* 2013; **208**: 3–18.
35. Leombroni M, Liberati M, Fanfani F, Pagani G, Familiari A, Buca D, Manzoli L, Scambia G, Rizzo G, D'Antonio F. Diagnostic accuracy of ultrasound in predicting birth-weight discordance in twin pregnancies: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017; **50**: 442–450.
36. Groene SG, Stegmeijer KJJ, Tan RNGB, Steggerda SJ, Haak MC, Slaghekke F, Roest AAW, Heijmans BT, Lopriore E, van Klink JMM. Long-term effects of selective fetal growth restriction (LEMON): a cohort study of neurodevelopmental outcome in growth discordant identical twins in the Netherlands. *Lancet Child Adolesc Health* 2022; **6**: 624–632.
37. Akkermans J, de Vries SM, Zhao D, Peeters SHP, Klumper FJ, Middeldorp JM, Oepkes D, Slaghekke F, Lopriore E. What is the impact of placental tissue damage after laser surgery for twin–twin transfusion syndrome? A secondary analysis of the Solomon trial. *Placenta* 2017; **52**: 71–76.

SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Search strategy

Table S2 Excluded studies and reason for exclusion

Table S3 Pooled odd ratios for pregnancy characteristics of monochorionic diamniotic twin pregnancies with twin–twin transfusion syndrome (TTTS) complicated by selective fetal growth restriction (sFGR) compared to those not complicated by sFGR

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Resultado tras la cirugía láser del síndrome de transfusión feto-fetal complicado por restricción selectiva del crecimiento fetal: revisión sistemática y metaanálisis

RESUMEN

Objetivo. La literatura publicada informa principalmente sobre el resultado de los embarazos de gemelos complicados por el síndrome de transfusión feto-fetal (STFF) sin tener en cuenta si el embarazo también estaba complicado por otra patología, como la restricción selectiva del crecimiento fetal (RSCF). El objetivo de esta revisión sistemática fue informar sobre el resultado de los embarazos de gemelos monocoriales biamnióticos (MCBA) sometidos a cirugía láser para el STFF complicados con RSCF y los no complicados con RSCF.

Métodos. Se buscó en las bases de datos MEDLINE, EMBASE y Cochrane. Los criterios de inclusión fueron los estudios que informaban sobre embarazos de gemelos MCBA con STFF sometidos a terapia láser complicados adicionalmente con RSCF y los no complicados con RCFG. El resultado primario fue la pérdida fetal total tras la cirugía láser, definida como aborto y muerte intrauterina. Los resultados secundarios fueron la pérdida fetal en las 24 h siguientes a la cirugía láser, la supervivencia al nacimiento, el parto pretérmino (PPT) antes de las 32 semanas de gestación, el PPT antes de las 28 semanas, la morbilidad neonatal compuesta, la morbilidad neurológica y respiratoria, y la supervivencia libre de trastornos neurológicos. Todos los resultados se estudiaron en la población global de embarazos de gemelos complicados por RSCF frente a los no complicados por RSCF en el contexto del STFF y en los gemelos donantes y receptores por separado. Se utilizó un metaanálisis de efectos aleatorios para combinar los datos y los resultados se presentan como razones de momios (RM) agrupadas con un IC del 95%.

Resultados. Se incluyeron cinco estudios (1710 embarazos de gemelos MCBA) en la síntesis cualitativa y cuatro en el metaanálisis. El riesgo global de pérdida fetal tras la cirugía láser fue significativamente mayor en los embarazos de gemelos MCBA con STFF complicados por RSCF (20,90% frente a 14,42%), con una RM combinada de 1,6 (IC 95%, 1,3–1,9) (P<0,001). El riesgo de pérdida del feto fue significativamente mayor en los embarazos de gemelos MCBA con STFF y RSCF para el donante, pero no para el gemelo receptor. La tasa de gemelos vivos fue del 79,1% (IC 95%, 72,6–84,9%) en los embarazos STFF con RSCF y del 85,6% (IC 95%, 81,0–89,6%) en aquellos sin RSCF (RM combinada, 0,6 [IC 95%, 0,5–0,8]) (P<0,001). No hubo diferencias significativas en el riesgo de parto prematuro antes de las 32 semanas de gestación (P=0,308) o antes de las 28 semanas (P=0,310). La evaluación de la morbilidad a corto y largo plazo se vio afectada por el reducido número de casos. No hubo diferencias significativas en el riesgo de morbilidad compuesta (P=0,506) o respiratoria (P=0,531) entre gemelos complicados por STFF frente a aquellos sin RSCF, mientras que el riesgo de morbilidad neurológica fue significativamente mayor en los gemelos con STFF y RSCF (RM combinada, 1,8 [IC 95%, 1,1–2,9]) (P=0,034). El riesgo de morbilidad neurológica fue significativamente mayor para el gemelo donante (RM combinada, 2,4 [IC 95%, 1,1–5,2]) (P=0,029), pero no para el gemelo receptor (P=0,361). Se observó una supervivencia libre de trastornos neurológicos en el 70,8% (IC 95%, 45,0–91,0%) de los embarazos de gemelos con STFF complicados por RSCF y en el 75,8% (IC 95%, 51,9–93,3%) de los no complicados por RSCF, sin diferencias entre ambos grupos.

Conclusiones. La RSCF en embarazos MCBA con STFF representa un factor de riesgo adicional para la pérdida fetal tras la cirugía láser. Los resultados de este metaanálisis pueden ser útiles para la evaluación individual del riesgo de embarazo de gemelos complicado por STFF y el asesoramiento personalizado a los padres antes de la cirugía láser.

双胎输血综合征并发选择性胎儿生长受限的激光手术结局：系统回顾和荟萃分析

摘要

目的 已发表的文献大多报道了并发双胎输血综合征（TTTS）的双胎妊娠的结局，而未考虑妊娠是否还合并有其他病理因素，如选择性胎儿生长受限（sFGR）。本系统综述旨在报告因并发 sFGR 的 TTTS 和未并发 sFGR 的 TTTS 而接受激光手术 的单绒毛膜双羊膜腔（MCDA）双胎妊娠的结局。

方法 检索MEDLINE、EMBASE和Cochrane数据库。纳入标准为 报告 TTTS 并发 sFGR 和未并发 sFGR 的 MCDA 双胎妊娠 接受激光治疗的研究。主要结果是激光手术后的总体妊娠丢失，即流产和宫内死亡。次要结果包括激光手术后24小时内的妊娠丢失、出生存活率、妊娠32周前早产（PTB）、妊娠28周前早产、新生儿综合发病率、神经系统和呼吸系统发病率以及无神经系统损伤的存活率。所有结果都在并发 sFGR 的 TTTS 双胎妊娠与未并发 sFGR 的 TTTS 双胎妊娠的总体人群中以及在供体和受体双胎中分别进行探讨。随机效应荟萃分析用于合并数据，结果以汇总比值比（OR）和 95% CI 的形式报告。

结果 五项研究（1710 例 MCDA 双胎妊娠）被纳入定性合成，四项被纳入荟萃分析。激光手术后妊娠丢失的总体风险在 TTTS 并发 sFGR 的 MCDA 双胎妊娠中明显较高（20.90% vs 14.42%），汇总比值比 1.6（95% CI，1.3-1.9）（P<0.001）。在TTTS 并发 sFGR 的 MCDA 双胎妊娠中，供体双胎的妊娠丢失风险明显高于受体双胎。有并发 sFGR 的 TTTS 妊娠的活双胎率为 79.1%（95% CI，72.6-84.9%），未并发 sFGR 的 TTTS 妊娠的活双胎率为 85.6%（95% CI，81.0-89.6%）（汇总比值比 0.6（95% CI， 0.5-0.8））（P<0.001）。妊娠32周前早产（P=0.308）或28周前早产（P=0.310）风险无明显差异。由于病例数量较少，短期和长期发病率的评估受到影响。TTTS 并发 sFGR 的双胎与未并发 sFGR 的双胎的综合发病风险（P=0.506）或呼吸系统发病风险（P=0.531）无明显差异，而 TTTS 并发 sFGR 的双胎妊娠的神经系统发病风险明显更高（汇总比值比 1.8（95% CI，1.1-2.9））（P=0.034）。供体双胎的神经系统发病风险明显更高（汇总比值比，2.4（95% CI，1.1-5.2））（P=0.029），但受体双胎的神经系统发病风险不高（P=0.361）。在 TTTS 并发 sFGR 的双胎妊娠中，70.8%（95% CI，45.0-91.0%）的胎儿存活且无神经损伤，而在 TTTS 未并发 sFGR 的双胎妊娠中，75.8%（95% CI，51.9-93.3%）的胎儿存活且无神经损伤，两组间无差异。

结论 在患有 TTTS 的 MCDA 妊娠中，sFGR 是激光手术后妊娠丢失的额外风险因素。这项荟萃分析的结果可能有助于对并发 TTTS 的双胎妊娠进行个体化风险评估，也有助于在激光手术前对父母进行有针对性的咨询指导。