Cardiovascular compromise in monochorionic twins

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CHAPTER 4

THE VALUE OF ECHOCARDIOGRAPHY AND DOPPLER IN THE PREDICTION OF FETAL DEMISE AFTER LASER COAGULATION FOR TTTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

This study aimed to investigate the value of echocardiography and Doppler before fetoscopic laser coagulation for twin-twin transfusion syndrome (TTTS) in the prediction of intrauterine fetal demise (IUFD). We performed a systematic review and meta-analysis to compare preoperative parameters between fetuses with and without demise after laser surgery. Eighteen studies were included. Recipient twins have an increased risk of demise in case of preoperative absent/reversed flow (A/REDF) in the umbilical artery (odds ratio [OR] 2.76, 95% confidence interval [CI] 1.78-4 28), absent or reversed a-wave in the ductus venosus (OR 2.32, 95% CI 1.70-3.16) or a middle cerebral artery peak systolic velocity > 1.5 multiples of the median (MoM) (OR 7.59, 95% CI 2.56-22.46). In donors, only A/REDF in the umbilical artery (OR 3 40, 95% CI 2.68-4.32) and absent or reversed a-wave in the ductus venosus (OR 1.66, 95% CI 1.12-2 47) were associated with IUFD. No association was found between donor-IUFD and preoperative myocardial performance index (MPI). Two studies found an association between abnormal MPI and recipient demise. With this study, we have identified a set of preoperative Doppler parameters predictive of fetal demise after laser surgery. More research is needed to assess the utility of preoperative echocardiographic parameters such as the MPI in predicting IUFD.

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) complicates approximately 10-15% of monochorionic twin pregnancies and results from unbalanced intertwin transfusion through placental vascular anastomoses, which impacts cardiovascular loading conditions.[1, 2] If left untreated, the overall perinatal mortality can be as high as 90% to 100%.[3, 4] Fetoscopic laser coagulation of placental anastomoses significantly improves the dual twin survival rate to 64% to 70% and the survival rate of at least one survivor to 85% to 92%.[5, 6] Survival after surgery is determined by a combination of post-laser intrauterine fetal demise (IUFD) and non-viable delivery. Compromised cardiac function is thought to contribute significantly to the mortality rates after TTTS.[7] Cardiac (functional) abnormalities, most commonly observed in recipients[8-10] are, however, not taken into account in the disease severity classification by Quintero.[11] The diagnosis of TTTS is made by ultrasound and encompasses the presence of concurrent polyhydramnios in the recipient and oligohydramnios in the donor twin.[12] Since fetuses with cardiac compromise are more likely to die in utero, assessment of fetal cardiac function prior to laser surgery might help in staging disease severity.

Several studies have focused on fetal circulation and cardiac involvement in TTTS and the prognostic value of these measurements. The objective of this systematic review and meta-analysis was to determine the capability to predict IUFD after fetoscopic laser coagulation with echocardiography and Doppler before surgery.

METHODS

Search strategy

This systematic review was performed using the PRISMA methodology.[13] Relevant articles were identified using electronic databases (Pubmed, Embase, Web of Science and Cochrane). Publications from January 1990 to July 2018, written in English and containing the search terms related to twin-twin transfusion syndrome, fetoscopic laser coagulation, prediction of fetal demise and ultrasonography were included. The final search was performed on 1 October 2018. Two reviewers (M.G. and S.E.) screened titles and abstracts independently for relevance. If a title or abstract seemed relevant, full text was retrieved and assessed for inclusion. Selected articles were cross-referenced. Disagreement was resolved by consensus between the two reviewers. Studies were excluded from the analysis if no ultrasound had been performed prior to laser surgery or IUFD was not an endpoint of the study. IUFD was defined as fetal demise at any time after laser surgery and before onset of labor.

Quality assessment

Study quality and risk of bias was assessed by the two reviewers using the Hayden bias rating tool,[14] as suggested by the Cochrane Collaboration. With this tool the risk of bias was assessed in 6 domains (study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting). Each of the 6 potential bias domains was rated as having high, moderate, or low risk of bias. Low methodological quality was not an exclusion criterion.

Data extraction

One reviewer (M.G) extracted relevant information from the selected articles. The following data were extracted from the selected articles and tabulated: first author, year of publication, study design, country of origin, number of patients, type of fetoscopic laser surgery (selective laser photocoagulation of communicating vessels [SLPCV] or the Solomon technique)[5], operationalization of primary outcome and outcome measurement and the incidence of IUFD in cases and controls (2 x 2 tables). If possible, deaths attributable to pregnancy loss before 24 weeks gestation or termination of pregnancy were excluded from the analyses.

Statistical analysis

Statistical analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Odds ratios (ORs) and their 95% confidence intervals (CIs) were used as effect sizes for meta-analysis of dichotomous data. Heterogeneity between studies was examined with the inconsistency square

(I^2) statistics, with between-study heterogeneity at $I^2 \geq 50\%$ and $p \geq 0.05$.[15] In case of heterogeneity, a random effects model was used.[16] Otherwise, or in case of limited studies to reliably estimate between study variability, a fixed effect model was used. We performed meta-analyses and constructed forest plots to examine the effect of abnormal Doppler flow velocity waveforms (FVWs) on IUFD with separate analyses for recipients and donors. Absent and reversed end-diastolic flow (A/REDF) in the umbilical artery (UA) were combined in one group. Likewise, absent or reversed a-wave in the ductus venosus (DV) were combined in one group. Parameters measured in the same twin were used for the analyses (i.e. umbilical artery Doppler in the recipient twin in relation to recipient IUFD).

RESULTS

The search resulted in 473 articles, of which 18 were included in this study (Figure 1). The study characteristics are summarized in Table 1. Quality assessment is summarized in Table 2.

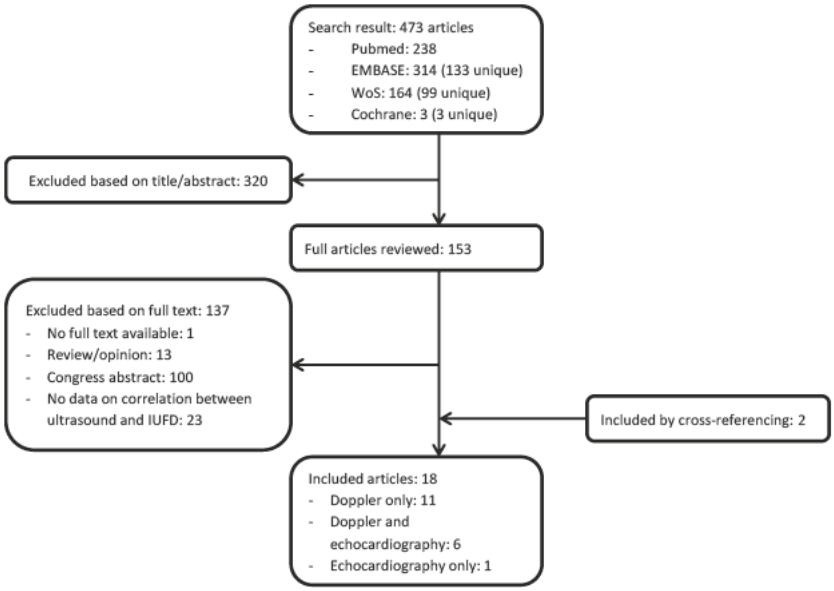

Figure 1. Flow chart demonstrating results of systematic review

Overall IUFD

Five studies report on fetal demise in the first 24 hours after surgery. An IUFD rate of 12% for donors and 8% for recipients was reported.[17-21] If the period was extended to the first week after laser surgery the mortality rates increased to 17% and 15%, respectively.[19, 20, 22] In studies including all fetal deaths before onset of labor, 23% of donor twins and 17% of recipient twins died in utero.[19, 21, 23-33] In the early years of fetoscopic laser coagulation (1998-2008) these rates were 29% and 21%. These rates improved to 19% and 13%, respectively, in the following decade (2008-2018).

Doppler ultrasonography

Three studies were excluded from the meta-analysis[19, 33, 34] because abnormal Doppler FVWs were not analyzed in relation to IUFD,[19, 33] or only time-interval variables of the DV FVW were analyzed.[34] Since the number of included studies was too small for reliable assessment of between-study variance, a fixed effect model was used throughout.

We estimated the prevalence of abnormal Doppler FVWs in both donors and recipients prior to laser surgery. Of all fetuses, both alive and demised, 25.3% of donors and 6.2% of recipients had A/REDF in the UA prior to laser surgery. Abnormal DV FVW was found in 9.7% of donors and 28.3% of recipients. In 6.9% of donors and 35.6% of recipients pulsations in the umbilical vein were present. An elevated middle cerebral artery peak systolic velocity (MCA-PSV) prior to surgery was reported in 7.9% of donor twins and 2.4% in recipient twins.

Variables associated with fetal demise in recipient twins were: A/REDF in the UA, absent or reversed a-wave in the DV and MCA-PSV > 1.5 multiples of the median (MoM; Figure 2). Pulsatile flow in the umbilical vein was seen in over one-third of recipients but this did not increase the risk of recipient IUFD (OR 1.50, 95% CI 0.98-2.29). In donors, only A/REDF in the umbilical artery and absent or reversed a-wave in the DV were associated with IUFD (Figure 3). An elevated MCA-PSV in the donor almost doubled the risk of demise, but this finding did not reach significance (OR 1.91, 95% CI 0.97-3.76). Three studies reported the odds of donor demise for AEDF and REDF in the UA separately.[28-30] All three studies concluded that REDF in the UA was the strongest predictor of donor demise. Many studies included in this review were underpowered to detect a difference in IUFD rate of donors and recipients with abnormal DV FVW. No study except for the study by Ishii *et al.*[26] found a significant association between preoperative abnormal DV FVW and donor demise. By pooling the data in this meta-analysis, we were able to find an association between abnormal DV FVW and an increased risk of IUFD of both donors and recipients.

In the included studies, additional variables were also investigated. Kontopoulos *et al.*[27] showed that the proportion of time in the cardiac cycle spent in AEDF (%AEDF) was significantly higher in patients with IUFD of the donor as compared to surviving donors (36.5% vs. 29.6%, p = 0.01). In a recent study by Delabaere *et al.*[20] with 111 patients, donors with early fetal demise (less than 7 days after laser surgery) had a lower MCA-pulsatility index (PI) (1.43 vs 1.65, p = 0.02), a higher UA-PI (2.03 vs 1.59, p = 0.05) and a lower cerebroplacental ratio (0.81 vs 1.11, p = 0.01) as compared to donors who survived the first week after surgery. Two other studies were not able to confirm these findings.[21, 29]

Table 1. Article characteristics

	Author (year) Country	Design	Multi-/ singlecenter	Patients	Type of FLS
1	Ville (1998) UK	P	M	132	SLPCV
2	Zilulnig (1999) Germany	P	S	121	SLPCV
3	Martinez (2003) USA	P	S	110	SLPCV
4	Cavicchioni (2006) France	R	S	120	SLPCV
5	Ishii (2007) Japan	P	M	55	SLPCV
6	Kontopoulos (2007) USA	P	S	401	SLPCV
7	Kontopoulos (2009) USA	P	S	189	SLPCV
8	Skupski (2010) USA	R	M	466	SLPCV
9	Trieu (2012) France	R	S	86	N/A
10	Eixarch (2013) Spain	P	S	215	SLPCV
11	Gapp-Born (2014) France	P	S	105	Both
12	Tachibana (2015) Germany	R	S	107	SLPCV
13	Snowise (2015) USA	P	S	166	Solomon
14	Patel (2015) USA	R	S	369	SLPCV
15	Eschbach (2016) Netherlands	R	S	288	Both
16	Finneran (2016) USA	R	S	53	SLPCV
17	Leduc (2017) Canada	R	S	105	Both
18	Delabaere (2018) Canada	R	S	111	Both

FLS, fetoscopic laser surgery; IUFD, intrauterine fetal demise; P, prospective; M, multicenter; SLPCV, selective laser photocoagulation of communicating vessels; UA, umbilical artery;

Time of IUFD	Doppler measurements	Echocardiography	Included in meta-analysis
Before onset of labor	UA	No	UA
Before onset of labor	UA, DV	No	UA
Unspecified	UA, DV, UV, MCA	Yes	UA, DV, UV
Before onset of labor	UA, DV	No	UA, DV
Before onset of labor	UA, DV, UV	No	UA, DV, UV
Unspecified (donor)	UA, %UA	No	UA
<24 h after FLS	MCA	No	MCA-PSV
Before onset of labor	UA, DV, UV	Yes	UA, DV, UV
<7 d after FLS	MCA	No	MCA-PSV
<7 d after FLS	UA, DV, MCA	Yes	UA, MCA-PSV, DV
Unspecified (recipient)	-	Yes	-
<2 d after FLS	DV (time intervals)	No	-
Before onset of labor (donor)	UA, DV, MCA	No	UA, DV
<24 h after FLS (recipient)	UA	No	UA
SFD before onset of labor	UA, DV, UV	No	UA, DV, VU
<7 d after FLS	-	Yes	-
Unspecified	UA	Yes	UA
<7 d after FLS	UA, DV, MCA	Yes	UA, DV, MCA-PSV

S, single center; DV, ductus venosus; MCA, middle cerebral artery; UV, umbilical vein; R, retrospective; h, hours; PSV, peak systolic velocity; N/A, not applicable; d, days; SFD, single fetal demise.

Table 2. Risk of bias in six domains based on the Hayden bias rating tool

	Variable	Study participation	Study attrition
1	Ville (1998)	Moderate	Low
2	Zilulnig (1999)	Moderate	Low
3	Martinez (2003)	Low	Low
4	Cavicchioni (2006)	Moderate	Low
5	Ishii (2007)	High	Low
6	Kontopoulos (2007)	Moderate	Low
7	Kontopoulos (2009)	Moderate	Low
8	Skupski (2010)	Low	Low
9	Trieu (2012)	Low	Low
10	Eixarch (2013)	Low	Low
11	Gapp-Born (2014)	Low	Low
12	Tachibana (2015)	Low	Low
13	Snowise (2015)	Low	Low
14	Patel (2015)	Moderate	Low
15	Eschbach (2016)	Low	Low
16	Finneran (2016)	Moderate	Low
17	Leduc (2017)	Moderate	Low
18	Delabaere (2018)	Low	Low

	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
	Low	Moderate	Moderate	Low
	Low	Moderate	Moderate	Low
	Low	Moderate	High	Low
	Moderate	Low	Low	Low
	Low	Low	Moderate	Low
	Low	Moderate	High	Moderate
	Low	Low	Low	Low
	Moderate	Low	Low	Low
	Low	Moderate	Low	Low
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	Moderate	Low	Low	Low
	Moderate	Low	High	Low
	Low	Low	Moderate	Low

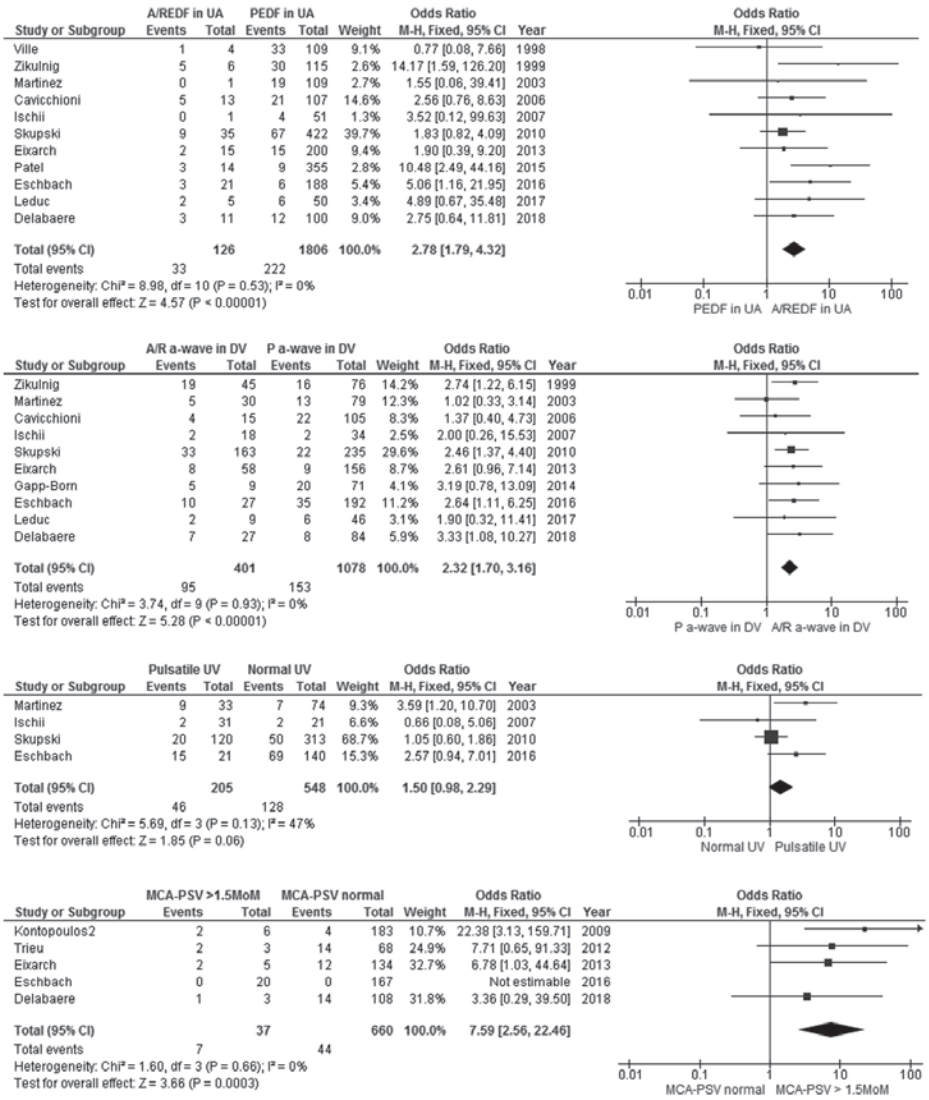

Figure 2. Doppler flows in the recipient twin. PEDF or A/REDF in UA, positive or absent/reversed end-diastolic flow in the umbilical artery; P or A/E a-wave in DV, positive or absent/reversed a-wave in the ductus venosus; UV, umbilical vein; MCA-PSV, middle cerebral artery-peak systolic velocity

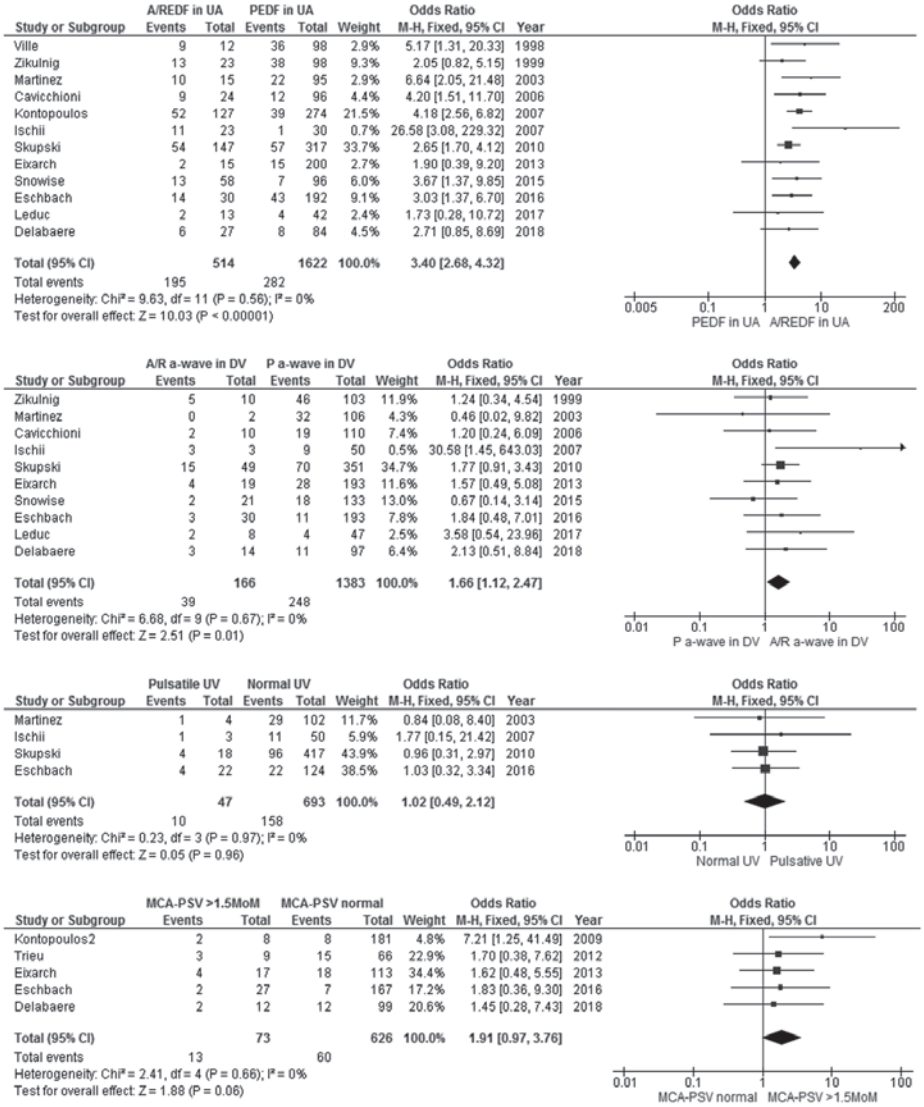

Figure 3. Doppler flows in the donor twin. PEDF or A/REDF in UA, positive or absent/reversed end-diastolic flow in the umbilical artery; P or A/E a-wave in DV, positive or absent/reversed a-wave in the ductus venosus; UV, umbilical vein; MCA-PSV, middle cerebral artery-peak systolic velocity

Results of individual studies on echocardiography in relation to IUFD

In seven studies echocardiographic findings were analyzed in relation to IUFD.[19-21, 28, 29, 32, 33] We could only perform a meta-analysis on atrioventricular regurgitation. The presence of this finding was not associated with a higher risk of either donor (OR 1.34, 95% CI 0.39-4.62) or recipient demise (OR 1.20, 95% CI 0.79-1.83).[20, 21, 28]

The substantial methodical heterogeneity prevented the construction of other forest plots, we therefore present a summary of outcomes for other echocardiographic parameters. Five studies assessed the preoperative myocardial performance index (MPI) as a separate parameter,[19, 20, 29, 32, 33] of which two report an increased risk of recipient demise.[20, 33] In a study of 105 recipients,[33] the risk of recipient demise was four times higher if the MPI *z* score was above a cut-off *z* score of 1.645, which corresponds to the 95th percentile ($p < 0.01$). After adjustment for gestational age and placental localization, there was no increased risk (OR 3.09, 95% CI 0.94-9.30, $p = 0.06$). In the most recent study by Delabaere *et al.*,[20] demised recipients had a higher mean MPI of the right ventricle (RV-MPI) as compared with survivors after adjustment for gestational age at laser surgery (unadjusted $p = 0.07$, adjusted $p = 0.02$). The three remaining studies did not find an association between preoperative MPI and postoperative recipient demise.[19, 29, 32] The results are therefore conflicting. An association between preoperative MPI and donor-IUFD was absent in all studies.

In three studies, the Children's Hospital of Philadelphia (CHOP) score[35] (a sum of 12 cardiovascular parameters, including the MPI) was analyzed in relation to IUFD.[20, 28, 33] A CHOP score above 5 is generally considered as abnormal. Interestingly, only a CHOP score ≥ 3 was associated with recipient demise (40% with a score ≥ 3 vs 13% with a score < 3, $p < 0.01$)[33] and a score > 5 was not.[20] In the study of 466 TTTS cases, 'global cardiac dysfunction' was included in the analysis, a factor defined as an abnormal MPI, ventricular dyskinesia, abnormal ejection fraction, abnormal CHOP score (or other measure of cardiac dysfunction; exact cut-off values for separate parameters were not stated). The presence of "global cardiac dysfunction" prior to surgery did not increase the risk of either donor or recipient demise.[28]

In a small study by Leduc *et al.*[32] of 55 treated pregnancies the aortic isthmus flow velocity patterns were assessed. The isthmic systolic index,[36] which reflects the relative performances of the right and left ventricle, measured in recipients before laser, was associated with recipient IUFD ($p = 0.04$).

DISCUSSION

In this systematic review and meta-analysis we found an association between preoperative Doppler FVWs and IUFD after fetoscopic laser coagulation. Fetal echocardiographic parameters such as the MPI appear not to be associated with fetal demise after laser coagulation. Results from studies investigating echocardiographic parameters do almost reach significance however, possibly indicating lack of power in these studies. The conflicting results regarding the use of echocardiography in the prediction of demise prevented us from building a prediction model including both Doppler and echocardiographic parameters.

We have shown an IUFD rate of 19% for donors and 13% for recipients in the last decade. Improved survival after laser surgery may reflect a learning-curve effect of the operators,[6, 37] who gain more experience with this procedure globally. Furthermore, evolution of the technique[38] and developments and improvements in ultrasonographic monitoring may play a role. The investigation of these factors on fetal survival rates fell outside of the scope of this article.

We found that A/REDF in the UA, absent or reversed a-wave in the DV and MCA-PSV > 1.5 MoM increases the risk of recipient-IUFD. Abnormal UA FVW, present in only 6% of recipients, may result from placental compression by increased intra-amniotic pressure due to massive polyhydramnios or, alternatively, from poor cardiac function. A suggested theory is that poor myocardial contractility as a result of recipient hypervolemia and cardiac overload, result in an insufficient generated blood pressure to propel the blood forward in the UA throughout diastole.[20] The theory that poor cardiac function causes A/REDF flow in the umbilical artery in recipient twins is further supported by the finding that recipient twins with abnormal UA FVW always have abnormal venous FVW of the umbilical vein, ductus venosus, or both.[18] More than one-third of recipients had a pulsatile umbilical vein preoperative, which could also indicate cardiac overload. This parameter was however not statistically significant associated with recipient demise. The mechanism underlying the association between increased MCA-PSV and IUFD in recipients is not entirely clear. Increased cardiac output resulting from the hypervolemic status of these fetuses, which is responsible for cardiomegaly and hypertrophy in some TTTS cases, could also elevate the blood velocity in the cerebral arteries. These changes have also been shown in fetuses with congenital heart disease[39] or intrauterine growth restriction.[40] Another suggested explanation is decreased fetal oxygenation due to placental interstitial edema which increases MCA blood velocity through autoregulation in the absence of low hemoglobin.[29, 41]

In donors, only A/REDF in the UA and absent or reversed a-wave in the DV were found to be associated with donor-IUFD. In these twins, the mechanism leading to hemodynamic changes appears to differ from the pathophysiology in recipient twins. Abnormal UA FVW occurs in a quarter of donors prior to laser surgery. If present, the odds of demise are 3.4 times higher as compared to fetuses who have a normal UA FVW. It reflects both placental insufficiency (maldevelopment and unequal sharing) and fetal hypotension secondary to the hemodynamic imbalance in TTTS. Three studies showed that REDF in the UA is a stronger predictor of donor-IUFD than AEDF.[28-30] It is suggested that reversed UA flow reflects placental insufficiency in a greater degree and that it is not amenable to improvement following restoration of volume status.[29] Abnormal venous FVW in donor twins may be explained by either cardiac decompensation due to severe placental insufficiency or hypovolemia as a result of the TTTS. The relative hypervolemia after occlusion of vascular anastomoses may increase the afterload and cause acute transient impaired cardiac function which attributes to a higher chance of donor demise after surgery. Elevated MCA-PSV prior to surgery is reported in 8% of donor twins. In monochorionic twins, unbalanced net intertwin blood transfusion may lead to TTTS, but also to twin anemia polycythemia sequence (TAPS). In TAPS, there is a chronic and slow transfusion of blood from the donor to the recipient twin through extremely small anastomoses.[42] This process leads to an anemic donor and polycythemic recipient. Two to eight percent of TTTS cases may have preoperative signs of TAPS,[43] which may explain the increased MCA-PSV in donors prior to laser surgery. Although there was a tendency for donor twins with an elevated MCA-PSV to die more frequently in utero after surgery this finding did not reach statistical significance.

The question whether echocardiographic parameters should be included in the TTTS staging system remains unanswered. Most studies investigating the association between assessment of cardiac function and IUFD include neonatal demise instead of fetal demise as their endpoint.[44-49] A large amount of data reflecting cardiac function had therefore been excluded from this systematic review. Furthermore, the limited amount of available reports on the value of a detailed cardiovascular assessment in the prediction of fetal survival provide discordant results. Three out of five studies did not find any genuine correlation with IUFD.[19, 29, 32] The lack of correlation between severity of cardiac disease and intrauterine demise is not explained so far. The low reproducibility and repeatability indices of the MPI and a high degree of expertise needed to perform MPI or CHOP score measurements may be important factors. Very precise recordings and manual placement of calipers are needed for MPI calculations. For the left ventricle, the Doppler cursor is placed between the mitral valve and aortic valve, and both mitral inflow and aortic outflow can be visualized on the same trace. Measurement of the RV-MPI is further complicated because the right ventricular inflow

and outflow cannot be visualized in one plane and thus not in the same trace. Published normal ranges for different gestational ages demonstrate a wide variation,[50-54] probably because a standardized method has not been established. While automation of these measurements will remove the human factor on measurement error, experience is still required to be able to acquire the correct Doppler waveform successfully.[55, 56] The lack of correlation may also be explained by the effectiveness of laser surgery for improving recipient cardiac function. Other variables associated with laser surgery such as premature rupture of membranes, unequal placental share and preterm delivery become the predominant determinants of fetal mortality after correction of the hemodynamic imbalance.

To our knowledge, this is the first review and meta-analysis of pre-operative echocardiography and Doppler in the prediction of IUFD after fetoscopic laser surgery. To maximize our sample size, we included all studies which investigated fetal demise before birth, not only early-IUFD (< 7 days). Other causes of demise such as placental insufficiency or IUGR could therefore have influenced our results, even though the majority of IUFD after laser occurs in the first week after laser surgery.[7, 21, 26] There are also other limitations to this study. Most studies are single center reports. Half of the reports are retrospective studies. In all but one study[30] selective coagulation was used for all or for a proportion of cases. It is known that incomplete laser coagulation is a risk factor for recurrent TTTS or post-laser TAPS and therewith for possible subsequent fetal demise.[57] Finally, we did not include fetal growth discordance, selective fetal growth restriction (sFGR) or TAPS prior to laser surgery in this study. Future large-scale prospective studies could allow for multivariate analysis into the interference of sFGR and TAPS on fetal echocardiography and Doppler parameters for IUFD. Incorporating signs of sFGR or TAPS, but also factors such as Quintero stage, hydrops and gestational age at TTTS diagnosis, into a prediction model together with the beforementioned Doppler parameters could be useful in daily clinical care in cases where the risk of fetal demise turns out to be high, to spend additional counseling time on cord occlusion as a back-up plan if laser surgery seems technically challenging. A prediction model could also be useful in future clinical trials investigating innovations in treatment of TTTS.

In conclusion, we have identified a set of preoperative Doppler parameters predictive of fetal demise after fetoscopic laser coagulation. Recipient twins have an increased risk of demise in case of preoperative abnormal FWV of the UA, DV and MCA. In donor twins, only abnormal FVW of the UA and DV are associated with IUFD after surgery. The utility of preoperative parameters that reflect cardiac function such as the MPI in predicting IUFD remains unclear.

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