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Percent Absent End-Diastolic Velocity in the Umbilical Artery and Donor Twin Demise after Laser Surgery for Twin-Twin Transfusion Syndrome

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Keywords
Umbilical artery absent end-diastolic velocity · Donor demise · Twin-twin transfusion syndrome · Estimated fetal weight discordance

Abstract
Introduction: To examine the association of preoperative absent end-diastolic velocity (AEDV) and percent AEDV (%AEDV) in the umbilical artery (UA) with donor twin intrauterine fetal demise (IUFD) after laser surgery for twin-twin transfusion syndrome (TTTS). ***Methods:*** We performed a retrospective study of stage III/IV TTTS patients who underwent laser surgery from 2006 to 2016. Donors were classified as having preoperative persistent AEDV (yes/no). %AEDV was calculated for those with AEDV as 100× the proportion of the total cardiac cycle in AEDV. Using multiple logistic regression, we tested for an association between the outcome donor IUFD and AEDV risk factors (part 1) and %AEDV (part 2). We stratified these analyses by estimated fetal weight (EFW) discordance ≥20 versus <20%. ***Results:*** Of 344 cases, 153 (44.5%) donors had AEDV. Part 1 did not confirm an independent association between AEDV and donor IUFD. In the part 2 analysis of the 153 patients with AEDV, %AEDV was a positive risk factor for donor IUFD only in those with discordance ($n = 129$) (OR 1.04, 95% CI 1.01–1.08, $p = 0.0278$) when adjusting for %EFW discordance, presence of arterioarterial anastomoses, and multiparity. ***Discussion:*** Among stage III/IV TTTS patients with AEDV, %AEDV was a risk factor for donor IUFD only in the presence of EFW discordance.

Introduction

The twin-twin transfusion syndrome (TTTS) affects approximately 8–15% of all monochorionic diamniotic gestations [1–3]. TTTS is attributed to an underlying imbalance in blood flow from the donor to the recipient twin through vascular anastomoses of the monochorionic placenta. This results in oligohydramnios in the donor and polyhydramnios in the recipient. Selective laser photocoagulation of communicating vessels (SLPCV) is the preferred method of TTTS treatment [4], leading to the survival of at least 1 twin approximately 90% of the time and dual survivorship of approximately 70% [5]. Thus, the risk of intrauterine fetal demise (IUFD) in this vulnerable population remains high.

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Previous studies have shown that estimated fetal weight (EFW) discordance [6–9], hydrops fetalis [10], reverse blood flow in the ductus venosus [9–11], the presence of arterioarterial (AA) anastomoses [9], and abnormal umbilical artery (UA) Doppler waveforms [6–10, 12–14] are preoperative risk factors for IUFD. Abnormal UA Doppler waveforms, defined as persistently absent (AEDV) or reversed end-diastolic velocity (REDV), are typically seen in the donor twin [11–13, 15]. Previous studies have demonstrated that 41–67% of donors with preoperative AEDV undergo IUFD after SLPCV [7, 12, 16]. In an earlier study, we found that, among patients with persistent AEDV, patients who had at least 30% of the donor's cardiac cycle spent in AEDV were more likely to undergo IUFD of the donor after laser surgery for TTTS [16]. The purpose of the current study was to repeat the initial study in a separate patient population, controlling for multiple covariates that may be associated with IUFD.

Methods

This was a retrospective cohort study that included all consecutive monochorionic diamniotic twin pregnancies with TTTS Quintero stage III and IV with a gestational age (GA) of 16–26 weeks who underwent laser surgery at Los Angeles Fetal Surgery between 2006 and 2016. TTTS was diagnosed if the maximum vertical pocket of the amniotic sac was ≥8 cm for the recipient and ≤2 cm for the donor. Patients diagnosed with TTTS were staged according to the Quintero staging system [15]. Stage I and II patients who, by definition, did not have critically abnormal fetal Doppler ultrasound were excluded from the analysis. No patients were upstaged on the basis of echocardiographic findings. A detailed preoperative ultrasound examination which included maximum vertical pocket of amniotic fluid for each fetus, fetal anatomy, Doppler measurements (UA/umbilical vein, ductus venosus, and middle cerebral artery), and endovaginal cervical length was performed. SLPCV with or without sequential technique was performed as previously described [5, 17]. Starting in 2010, eligible patients were randomized to either SLPCV with or without sequential technique as part of an ongoing open-labeled randomized trial (NCT02122328) [18, 19]. Type and number of placental anastomoses, including AA anastomoses, were noted intraoperatively. A detailed postoperative ultrasound examination was performed on postoperative day 1. Patient information was gathered and prospectively recorded in a database, which included: maternal demographics, perioperative ultrasound findings, surgical findings, and delivery outcomes.

Patients were categorized based on whether the donor twin did or did not have umbilical artery persistent AEDV documented at the time of the preoperative ultrasound examination. In cases with persistent AEDV, the percent AEDV (%AEDV) in the umbilical artery was prospectively calculated. A representative cardiac cycle during a typical 6-s window of observation was chosen to measure %AEDV, which was calculated as 100 × length of time during the cardiac cycle spent in AEDV/duration of the total cardiac cycle. Patients with %AEDV >0 (persistently absent end-diastolic velocity) were subcategorized based on the presence or absence of REDV. %AEDV in patients with REDV was calculated as 100 × (length of cardiac cycle spent in [AEDV + REDV]/duration of the total cardiac cycle). Patients with donor twin intermittent AEDV who, by definition, did not have persistent AEDV, were categorized as donors without AEDV and therefore had a %AEDV of zero. Patients with persistently and intermittently absent REDV were classified as donors with AEDV as the REDV was not persistent.

Patients who did not have %AEDV measurements documented at the time of the preoperative examination were excluded. Additional exclusion criteria included preoperative septostomy, prior incomplete laser surgery at an outside facility, delivery prior to the postoperative ultrasound examination, umbilical cord occlusion of either fetus, and pregnancy termination. Umbilical cord occlusion is not routinely performed at our center for TTTS, and selection is on a case-by-case basis.

In part 1 of the analysis, patient demographics and outcome data were analyzed bivariately for the entire population, comparing patient characteristics and outcomes (including donor IUFD) for those with and without AEDV. The statistical significance of categorical variables was evaluated by χ^2 or Fisher's exact testing, as appropriate. Continuous variables were expressed as means ± SD, and statistical significance was determined using Kruskal-Wallis testing. Bivariate analyses were also carried out comparing patient characteristics associated with donor IUFD. Those characteristics associated with donor IUFD that had a value of $p < 0.15$ were considered candidates for inclusion in a multiple logistic regression model to determine if AEDV (yes/no) was associated with donor IUFD.

Because of the documented association between percent EFW (%EFW) discordance and AEDV [7, 9], we performed a similar but stratified set of analyses for those with and without fetal weight discordance, defined as preoperative %EFW discordance ≥20 versus <20%. %EFW discordance was calculated as 100 × (EFW of larger twin – EFW of smaller twin)/EFW of larger twin.

In part 2 of the analysis, the denominator was limited to those with persistent AEDV, and the predictor of IUFD was hypothesized to be the %AEDV. Bivariate analyses were carried out between patient characteristics, including %AEDV, and donor IUFD. In this reduced denominator, those characteristics associated with donor IUFD that had a value of $p < 0.15$ were considered candidates for inclusion in a multiple logistic regression model to determine if %AEDV was associated with donor IUFD. In deriving this model, AEDV was considered both as a continuous variable and as a dichotomized variable at >30%. This categorization was based on an earlier paper published by our group that found that %AEDV >30 was associated with a 4.3-fold increase in risk of donor IUFD [16].

We performed a similar but stratified set of analyses by those with and without fetal weight discordance, defined as preoperative %EFW discordance ≥20 versus <20%. Odds ratios (OR) followed by 95% confidence intervals (CI) are presented. Receiver-operating characteristic (ROC) curves were constructed to determine the optimal cutoff for %AEDV to identify patients at risk for donor IUFD.

All patients provided informed consent for clinical data to be collected and secured in a database for research purposes. This study was approved by the Institutional Review Board at the Health Sciences Campus of the University of Southern California and complied with all patient protection criteria stipulated therein.

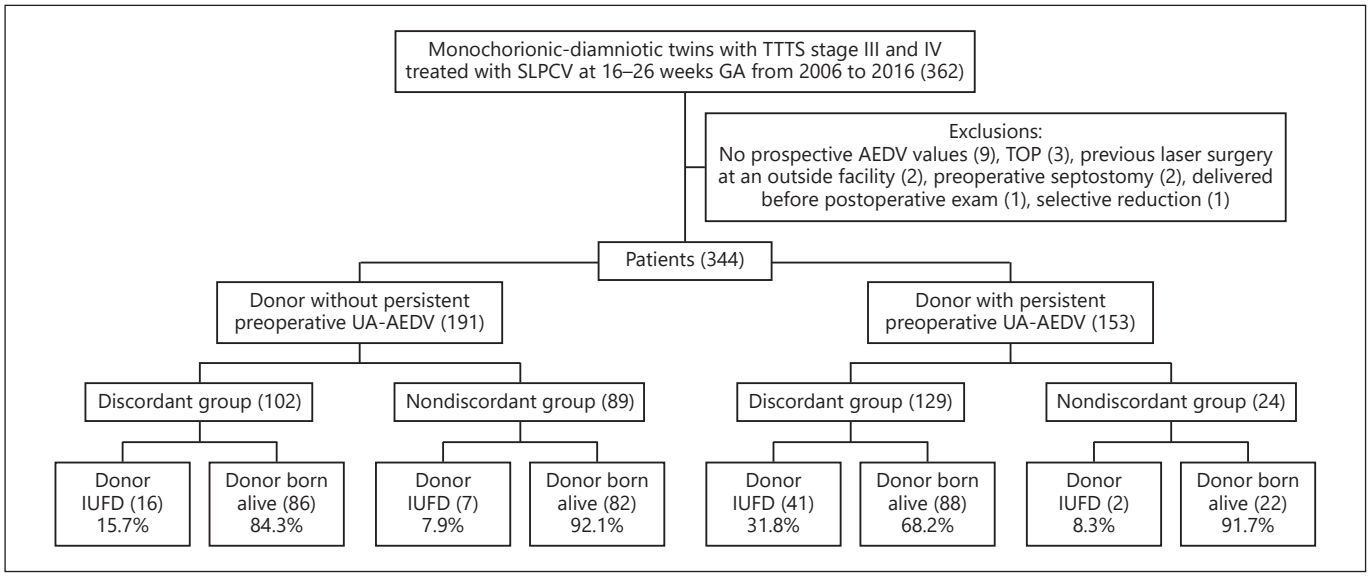

Fig. 1. Natural history of monochorionic diamniotic twin gestations with stage III and IV twin-twin transfusion syndrome (TTTS) treated with selective laser photocoagulation of communicating vessels (SLPCV). The patient population was first dichotomized into patients with donor twin persistent preoperative umbilical artery (UA) absent end-diastolic velocity (AEDV) (yes/no). Next, the population was stratified by percent estimated fetal weight discordance of ≥20% (yes/no) with intrauterine fetal demise (IUFD) of the outcome donor. GA, gestational age; TOP, termination of pregnancy.

Results

Of 362 stage III or IV TTTS patients who underwent SLPCV during the study period, 9 (2.5%) patients were excluded (Fig. 1). Of the remaining 353 patients, 162 (45.9%) donors had preoperative AEDV. Nine (5.6%) patients with AEDV were excluded from the analysis for lacking prospectively measured and recorded cardiac cycle time and time of cycle spent in AEDV. The final study population included 344 patients. Of these 344 patients, 1 patient (0.3%) had incomplete laser surgery at our center, resulting in persistent TTTS. This patient had preoperative AEDV, the %AEDV was 36.6%, and the donor twin suffered an IUFD on postoperative day 35 (27 gestational weeks). This patient also had an EFW discordance of 50%.

Part 1: Full Patient Denominator

In part 1, the full patient denominator was used to determine if preoperative AEDV (yes/no) was predictive of donor IUFD. All 344 patients were initially stratified into those with (n = 153) and without (n = 191) donor preoperative AEDV (Table 1). IUFD within 24 h of surgery occurred in 7.8% (12/153) of donors with preoperative AEDV, and 2.6% (5/191) of those without AEDV (p = 0.0424). The overall prevalence of IUFD of the donor was 28.1% (43/153) versus 12.0% (23/191) in those with and without AEDV (OR = 2.86, 95% CI 1.58–5.20, p = 0.0002).

Patients with and without postoperative donor IUFD were compared with bivariate analysis (Table 2). EFW discordance (≥20% [n = 231] vs. <20% [n = 113]) was associated with both AEDV (129/231 [55.8%] vs. 24/113 [21.2%], p < 0.0001) and donor IUFD (57/231 [24.7%] vs. 9/113 [7.8%], p = 0.0001). The final multiple logistic regression model of donor IUFD for the full, unstratified denominator included the following covariates with OR (95% CI) p value: %EFW discordance 1.05 (1.02–1.08) p = 0.0003, AA anastomoses 2.37 (1.27–4.41), p = 0.0066, GA at surgery 0.84 (0.73–0.97), p = 0.0190, and multiparity 1.82 (1.00–3.29), p = 0.0498. After adjusting for the aforementioned covariates, the presence of AEDV was not associated with donor IUFD (OR 1.38 [0.72–2.67], p = 0.3312). Interaction terms between AEDV (yes/no) and EFW discordance (≥20 vs. <20%) and between AEDV and presence of AA anastomoses were noncontributory.

In a bivariate analysis stratified by EFW discordance, among those with discordance (≥20%), there was a positive relationship between persistent AEDV and donor

Table 1. Clinical characteristics of the patients with and without donor preoperative umbilical artery (UA) absent end-diastolic flow (AEDV)

Characteristics	Donors with preoperative UA-AEDV (n = 153)	Donors without preoperative UA-AEDV (n = 191)	p value
Twin-twin transfusion syndrome			<0.0001
Quintero stage III	144 (94.1%)	145 (75.9%)	
Quintero stage IV	9 (5.9%)	46 (24.1%)	
EFW discordance ≥20%	129 (84.3%)	102 (53.4%)	<0.0001
%EFW discordance	32.6±12.3	22.3±12.4	<0.0001
Median (range)	33.0 (0–60.0)	21.0 (0–61.0)	
Preoperative donor IUGR	131 (85.6%)	115 (60.2%)	<0.0001
GA at surgery, weeks	19.7±2.2	20.4±2.3	0.0076
Median (range)	19.3 (16.4–26.0)	20.1 (16.3–26.0)	
AA anastomoses	63 (41.2%)	23 (12.0%)	<0.0001
SQLPCV	89 (58.2%)	99 (51.8%)	0.2760
GA at delivery, weeks	32.9±4.2	33.0±4.2	0.7513
Median (range)	33.6 (19.3–40.4)	34.0 (18.3–39.9)	
30-day survivorship donor	103 (67.3%)	162 (84.8%)	0.0002
30-day survivorship recipient	139 (91.8%)	166 (86.9%)	0.3055
30-day total survivors			0.0010
0	9 (5.9%)	14 (7.3%)	
1	46 (30.1%)	26 (13.6%)	
2	98 (64.1%)	151 (79.1%)	

Values are given as n (%) or means ± SD, unless indicated otherwise. %EFW, percent estimated fetal weight; IUGR, intrauterine growth restriction; GA, gestational age; AA, arterioarterial; SQLPCV, sequential selective laser photocoagulation of communicating vessels.

IUFD (41/129 [31.8%] vs. 16/102 [15.7%], p = 0.0056, and OR 2.50, 95% CI 1.30–4.80); among those without discordance (<20%) there was no such relationship (2/24 [8.3%] vs. 7/89 [7.9%], OR = 1.06, 95% CI 0.21–5.49, p = 1.0000).

Subsequent multiple logistic regression analyses were then conducted on separate discordance strata. Among those with EFW discordance, there was a nonsignificant relationship for persistent AEDV and donor IUFD (OR 1.57 [0.75–3.26], p = 0.2304), and a positive relationship for the presence of AA anastomoses (OR 2.60 [1.31–5.14], p = 0.0062), multiparity (OR 2.49 [1.25–4.94], p = 0.0092), and %EFW discordance (OR 1.05 [1.02–1.09], p = 0.0056); there was a negative relationship for GA (weeks) at surgery (OR 0.84 [0.70–0.99], p = 0.0376). For those without discordance, no variables contributed to the equation, and the final OR for AEDV as a risk factor for donor IUFD remained unchanged (OR = 1.06, 95% CI 0.21–5.49).

Part 2: Patients with AEDV

In part 2, the subpopulation of patients with AEDV (n = 153) was used to analyze the association of %AEDV and IUFD. In bivariate analysis, the %AEDV did not differ significantly between those with and without donor IUFD (32.6 ± 12.3 vs. 28.7 ± 10.5%, p = 0.1172). This was also true for each of the discordance strata (discordant group: 32.8 ± 12.6 vs. 29.0 ± 10.6%, p = 0.2634, and the nondiscordant group: 28.7 ± 4.3 vs. 27.7 ± 10.6%, p = 0.7146).

Preoperative donor persistent REDV was present in only 9 patients and was associated with donor IUFD (6/43 [14.0%] vs. 3/110 [2.7%], p = 0.0153). It was present only in those with donor AEDV and was not included in the model for this population denominator.

In the unstratified subpopulation of patients with preoperative donor AEDV, 129 patients (84.3%) had discordance (%EFW ≥20%). Multiple logistic regression models were derived for the outcome donor IUFD using %AEDV as a continuous predictor variable. %AEDV was found to be positively associated with donor IUFD (OR 1.04 [1.00–1.08], p = 0.0280). Covariates that also contributed to the model were: presence of AA anastomoses (yes/no) (OR 4.74 [2.04–11.03], p = 0.0003), %EFW discordance (OR 1.07 [1.03–1.11], p = 0.0013), and multiparity (OR 2.63 [1.17–5.95], p = 0.0197).

Table 2. Clinical characteristics of the patient subset with donor preoperative umbilical artery (UA) absent end-diastolic flow (AEDV) with and without donor intrauterine fetal demise (IUFD)

Characteristics	Patients with donor IUFD (n = 43)	Patients without donor IUFD (n = 110)	p value
Multiparity	28 (65.1%)	49 (44.5%)	0.0305
%EFW discordance	37.9±10.5	30.6±12.4	0.0009
Median (range)	40.0 (10–59)	30.5 (0–60)	
%AEDV donor	32.6±12.3	28.7±10.5	0.1172
Median (range)	31.0 (11.4–68.8)	29.9 (6.6–52.2)	
%AEDV donor >30%	24 (55.8%)	53 (48.2%)	0.4727
Donor preoperative MCA MoM	(n = 43)	(n = 109)	0.0272
Means ± SD	1.16±0.37	1.03±0.27	
Median (range)	1.14 (0.56–2.16)	1.03 (0.47–2.38)	
Preoperative membrane detachment	1 (2.3%)	16 (14.5%)	0.0419
GA at surgery, weeks	19.3±1.7	19.9±2.3	0.2209
Median (range)	19.1 (17.0–24.6)	19.4 (16.4–26.0)	
Any AA anastomoses	27 (62.8%)	36 (32.7%)	0.0009
Total AVRD anastomoses	3.58±2.84	5.02±3.74	0.0401
Median (range)	3.00 (0–11)	5.00 (0–17)	
GA delivery, weeks	33.1±5.9	32.9±3.4	0.1125
Median (range)	34.9 (19.3–40.4)	33.1 (24.1–39.3)	

Values are given as n (%) or means ± SD, unless indicated otherwise. %EFW, estimated fetal weight; AA, arterioarterial; AVRD, recipient to donor arteriovenous; MCA MoM, middle cerebral artery multiples of the median.

An alternative model was derived replacing %AEDV with %AEDV dichotomized at >30% (yes/no). Multiple logistic regression models found no association between %AEDV >30 as a categorical variable and donor IUFD (OR 1.36 [0.61–3.01], p = 0.4529).

Stratified models based on EFW discordance were also constructed for this subpopulation with donor AEDV. In the final model, multiple logistic regression for the discordant stratum identified a positive association between the %AEDV and donor IUFD (OR = 1.04 [1.01–1.08], p = 0.0278) in the presence of the following covariates: the presence of AA anastomoses (OR = 5.15 [2.06–12.89], p = 0.0005), multiparity (OR = 3.43 [1.44–8.19], p = 0.0054), and %EFW discordance (OR = 1.07 [1.02–1.13], p = 0.0054). For the nondiscordant stratum, no model could be constructed because the outcome consisted of only 2 IUFD.

No association between %AEDV >30 as a categorical variable and donor IUFD was found for the discordant stratum (OR = 1.25 [0.54–2.88], p = 0.6013).

An ROC curve was constructed in an attempt to identify an optimal cutoff value for %AEDV in those with EFW discordance. A cutoff of 28.8% had the highest YJ value (where YJ = specificity + sensitivity – 1) of 0.4526, which was associated with a sensitivity of 80.5% and a specificity of 64.8% (Fig. 2). In bivariate analysis, this cutoff value for %AEDV was not associated with donor IUFD.

Discussion

For patients with TTTS who underwent SLPCV, our results suggest that preoperative UA-AEDV in the donor twin was strongly associated with EFW discordance. In gestations with EFW discordance, where analyses were controlled for the %EFW discordance, AEDV was not associated with donor IUFD. However, in the subpopulation of patients with AEDV present, the %AEDV was positively associated with donor IUFD (OR 1.04) as a continuous variable, but no specific threshold, e.g., %AEDV >30, that accurately predicted donor IUFD was identified.

The reported rate of donor demise after SLPCV in all TTTS stages ranges from 11 to 28% [5, 8–10]. Previous studies have found Quintero stage III [5], UA-AEDV [7, 9, 12, 14], UA-REDV [6–9, 12, 14], low EFW [10], fetal growth restriction [5], EFW discordance [6–9], early

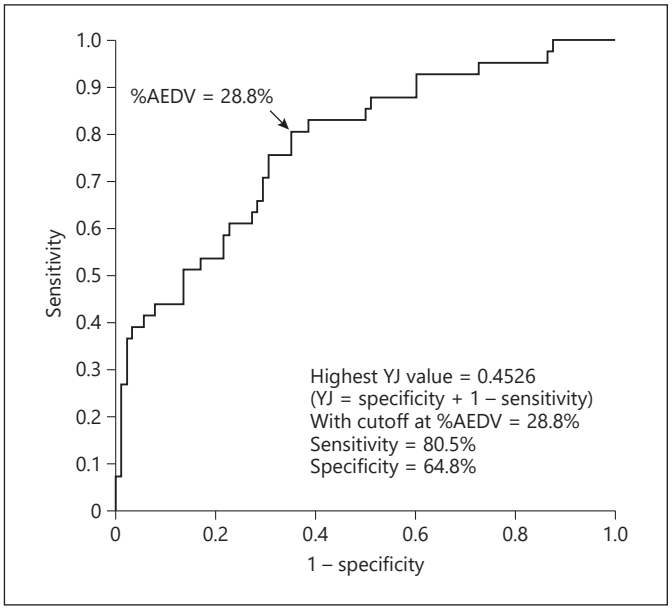

Fig. 2. ROC curve to determine the optimal cutoff point of donor preoperative %AEDV in twins with EFW discordance of ≥20% as a preoperative predictor of donor IUFD in patients with TTTS treated with SLPCV. See legend to Figure 1 or text for abbreviations.

GA at surgery [6], and presence of marginal or velamentous donor cord insertion [8] to be preoperative risk factors for donor IUFD. Additional risk factors of donor IUFD include presence of AA anastomoses [9] and increased number of anastomoses [8]. Previous studies have shown that TTTS patients have significantly fewer AA anastomoses than unaffected monochorionic pregnancies, suggesting that AA anastomoses may play a protective role [20, 21]. Given the association of AA anastomoses with donor IUFD, our study suggests otherwise. In fact, our group previously showed that patients with AEDV or REDV were more likely to have AA anastomoses (p = 0.002) [22]. Eschbach et al. [9] also showed an association between AA anastomoses and donor IUFD. They hypothesized that AA anastomoses may also behave as functional donor-to-recipient arteriovenous anastomoses which further contribute to TTTS, hypotension, and, therefore, AEDV [9]. The role of AA anastomoses in the pathophysiology of TTTS development as well as the subsequent hemodynamic effects from laser photocoagulation remains speculative and largely undetermined.

In bivariate analyses, Kontopoulos et al. [16] described a positive relationship between AEDV and donor IUFD (52/127 [40.9%] vs. 39/274 [14.2%], $p < 0.0001$). This included Quintero stage I and II patients who, by definition, did not have persistent AEDV. We, therefore, began our analysis with bivariate analysis confirming the association in the current study population of stage III and IV patients (OR 2.86 [1.58–5.20]). However, we found the relationship between presence of AEDV and donor IUFD was attenuated (OR 1.38 [0.72–2.67]) in a multiple logistic regression model when controlling for %EFW discordance, the presence of AA anastomoses, GA at surgery, and multiparity.

Our analyses, stratified by EFW discordance, demonstrated that donor preoperative AEDV was not associated with IUFD when controlling for the %EFW discordance. Even in the stratified subpopulation in part 2, in which we found that %AEDV was positively associated with donor IUFD, we were unable to confirm the %AEDV cutoff value of 30% as a predictor of donor IUFD identified by Kontopolous et al. [16] (Fig. 1).

Cavicchioni et al. [14] found that preoperative donor AEDV or REDV was associated with IUFD, and Martinez et al. [12] found AEDV or REDV were preoperative Doppler predictors of donor IUFD. However, the studies used simple univariate and bivariate analyses, respectively, included all TTTS stages, and did not control for other potential IUFD risk factors [12, 14]. Other studies have shown an association between only REDV and donor IUFD [6, 8]. Zikulnig et al. [11] did not find donor IUFD to be associated with either AEDV or REDV.

In regard to our data, strong associations between AEDV and EFW discordance suggest that analyses between donor AEDV and IUFD should be stratified by EFW discordance. In one such stratified analysis, Finneran et al. [7] examined the risk of donor demise with AEDV or REDV by discordance (yes/no), defined as ≥20% difference in EFW between the donor and recipient, and found that, in patients with discordance, AEDV or REDV was a high risk factor of donor IUFD (RR 5.2, 95% CI 1.7–16.3), and in those without discordance there was a lower risk (RR 3.6, 95% CI 1.1–12.1) [7]. However, contrary to our study findings, they found that EFW discordance alone did not significantly increase the risk of IUFD (RR 3.2, 95% CI 0.8–13.2) [7]. Snowise et al. [8] noted the presence of EFW discordance >30% and REDV, together, was highly predictive of donor IUFD. Finally, in a case-control study attempting to identify predictors of donor IUFD in all TTTS stages, Eschbach et al. [9] found, in a multivariate analysis, that the presence of AEDV or REDV was a predictor of donor IUFD (OR 3.0, 95% CI 1.1–8.0) when control-

ling for the presence of AA anastomoses and %EFW discordance [9].

Our analysis showed that in patients with EFW discordance the higher the %AEDV, the higher the likelihood of donor IUFD. Such a relationship was not found in patients without EFW discordance. In our analyses, EFW discordance was a consistent predictor of postoperative donor demise. It may be more clinically concerning than AEDV because it results from both high placental insufficiency and low individual placental territory (IPT), whereas AEDV serves as a sonographic marker of placental insufficiency. As demonstrated in in vitro and animal models, forces increasing downstream opposition to pulsatile flow in the UA or placental unit result in expected increases in the Doppler indices (systolic/diastolic ratio, pulsatility index, and resistance index) [23, 24].

Increased placental resistance due to fewer small muscular arteries in the placental tertiary stem villi [25], maldevelopment of terminal villi [26], and increased fetal blood viscosity [27] are known to be associated with AEDV in singleton pregnancies. In TTTS patients, umbilical artery AEDV may be due to hypotension [12, 22] and hypovolemia [28]. Chang et al. [22] suggest that AEDV in TTTS appears to be associated with low IPT, showing that abnormal UA Doppler findings may be detected at 37% IPT [22]. It can be hypothesized that EFW discordance is also associated with IPT discordance. Unfortunately, due to post demise placental atrophy, the placenta of TTTS patients with IUFD, and therefore IPT, cannot be reliably evaluated.

A strength of this study was the prospective measurement of %AEDF in 94.4% of TTTS patients. Although the %AEDF measurement was not used for clinical decision making, its prospective collection for research purposes did allow for a large cohort. Second, the stratified analysis provided an opportunity to further evaluate the association between AEDV and EFW discordance. This stratification is especially important considering EFW discordance is not included in TTTS staging, while AEDV is. These results are consistent with other recent studies in the literature that have used similar analyses [7, 9], but these studies measured only the presence or absence of AEDV. In our study, calculating %AEDV, a quantitative variable, allows for more detailed preoperative prediction of donor IUFD. Furthermore, the large cohort size allowed for multiple logistic regression analysis of other predictors of IUFD.

There are several limitations to this study. First, although the %AEDV was prospectively collected, this was a retrospective study. Second, patients with intermittent AEDV could not be included in our analysis. Although these patients are on a continuum between normal UA Doppler findings and persistent AEDV, intermittent AEDV alone is not a qualifier for Quintero stages III and IV. Third, while there was variation in %AEDV in each donor, we measured only 1 representative cardiac cycle to calculate %AEDV. Fourth, 1 patient had incomplete laser surgery at our institution, resulting in persistent TTTS. All other patients had successful surgery, and this patient accounted for <1% of the denominators for both part 1 and part 2 of the analyses. Fifth, the use of %AEDF is not widely accepted and remains an investigational method to assess placental vascular impedance. The UA pulsatility index is commonly used when end-diastolic flow is absent [29]. The measurement of %AEDF may prove to be more time consuming and less reproducible than the pulsatility index, which can be obtained automatically from ultrasound machine software. The utility of either %AEDF or the pulsatility index should be investigated in future studies.

This study can provide patients with data regarding post-SLPCV fetal outcomes based on preoperative information. Patients with preoperative donor AEDV with significant EFW discordance can be advised of the relatively high risk of donor IUFD. More specifically, in patients with EFW discordance, the higher the %AEDV, the higher the risk of donor demise. Finally, this study illustrates one example in which the percentage of UA-AEDV may be a useful semiquantitative measure to describe the degree of AEDV in the umbilical artery. This tool may be useful in other clinical scenarios as well.

Statement of Ethics

This study was approved by the Institutional Review Board of the University of Southern California.

Disclosure Statement

Lisa M. Korst assists with research studies as an independent contractor. The other authors have nothing to disclose. No external financial support was received for this work.

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Author Contributions

M.E.P. and A.H.C.: contributed to the design of the work, the acquisition, management, and interpretation of data, and manuscript writing and revisioning; L.M.K.: contributed to the design of the work, performed statistical analysis, interpretation of data, and manuscript writing and revisioning; A.L.: contributed to the design of the work, the acquisition and management of data, and manuscript revisioning; B.H.G.: contributed to the acquisition of data and manuscript revisioning; R.H.C.: contributed by conceiving of and designing the study, acquisition and interpretation of data, and manuscript revisioning. All authors approved the final version of the manuscript and ensure the accuracy and integrity of this work.

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