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Predictors of fetal death, neonatal survival and neurological outcomes in severe twin-twin transfusion syndrome treated by laser ablation of placental vessels

Cleisson Fábio Andrioli Peralta[1,2,3] | Karina Jorge Rodrigues da Costa[1,2,3] | Ana Clara Peneluppi Horak[3] | Samara Pinheiro do Carmo Gomes[3] | Elton Sousa Santos[3] | Letícia Galvão Barbante[3] | Renato Hideo Nakagawa Santos[3]

[1]Fetal Medicine Unit, Heart Hospital (HCor), São Paulo, São Paulo, Brazil

[2]Fetal Medicine and Surgery Center (Gestar), São Paulo, São Paulo, Brazil

[3]Research Institute (HCor), São Paulo, São Paulo, Brazil

Correspondence
Cleisson Fábio Andrioli Peralta, Fetal Medicine and Surgery Center (Gestar), Alameda Santos, 211, cj 1305, Cerqueira César, São Paulo, São Paulo 01419-000, Brazil.
Email: cfaperalta@gmail.com

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Abstract

Objectives: To identify predictors of outcomes in severe twin oligo-polyhydramnios sequence (TOPS) with or without twin anemia-polycythemia sequence (TAPS) and/or selective fetal growth restriction (SFGR) treated by laser ablation of placental vessels (LAPV).

Methods: Analysis of cases treated from 2011 to 2022. Variables evaluated Prenatal predictors: stages of TOPS, presence of TAPS and/or SFGR; pre-LAPV fetal ultrasound parameters; peri-LAPV variables. Perinatal predictors: GA at birth; birthweight; Apgar scores; transfontanellar ultrasonography (TFUS). Outcome variables: fetal death, neonatal survival, infant's neurodevelopment. Binary logistic regression analyses were performed to detect predictors of outcomes.

Results: 265 cases were included. Predictors of post-LAPV donor fetus' death were delta EFW (p:0.045) and absent/reverse end-diastolic flow in the umbilical artery (AREDF-UA) ($p < 0.001$). The predictor of post-LAPV recipient fetus' death was hydrops (p:0.009). Predictors of neonatal survival were GA at birth and Apgar scores. Predictors of infant's neurodevelopment were TFUS and pre-LAPV middle cerebral artery Doppler (MCAD) for the donor twin; and pre-LAPV ductus venosus' flow and MCAD for the recipient twin.

Conclusions: Prediction of fetal death, neonatal survival and infant's neurodevelopment is possible in cases of TOPS associated or not with SFGR and/or TAPS that were treated by LAPV.

Key points

What is already known about this topic?

- The treatment of choice for severe twin-twin transfusion syndrome is laser ablation of placental vessels.
- Severe twin-twin transfusion syndrome is often associated with several degrees of selective fetal growth restriction and/or twin anemia-polycythemia sequence, which may challenge the prediction of prognosis when laser ablation of placental vessels must be performed.

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What does this study add?

- For severe twin-twin transfusion syndrome cases (associated or not with signs of selective fetal growth restriction and/or twin anemia-polycythemia sequence) treated by laser ablation of placental vessels, the prediction of fetal death, neonatal survival and infants' neurological compromise is possible by a combination of prenatal and neonatal variables.

1 | INTRODUCTION

Twin-twin transfusion syndrome (TTTS) results from unbalanced arterio-venous anastomosis between fetuses in monochorionic multiple gestations. It complicates spontaneously about 10%–15% of monochorionic-diamniotic (MCDA) twin pregnancies in its oligo-polyhydramnios phenotype (TOPS – twin oligo-polyhydramnios sequence) and about 1.5%–4% in its anemia-polycythemia presentation (TAPS – twin anemia-polycythemia sequence).[1–8] Both clinical forms are categorized into five degrees of severity. Another complication of MCDA twin pregnancies is the selective fetal growth restriction (SFGR),[9] which results from unequal sharing of the placenta. This condition occurs in 12%–25% of MCDA twin pregnancies and is divided into three types according to the pattern of the umbilical artery (UA) Doppler flow of the smaller fetus.

The treatment of choice for severe TOPS (stages II-IV by the classification of Quintero et al.[1]) is the laser ablation of placental vessels (LAPV) and recent studies demonstrated that some cases of TAPS and SFGR may also benefit from this approach.[10–21] Despite these conditions often occur independently, several degrees of overlapping among them may happen, depending on the characteristics of the anastomosing vessels between the twins and the severity of the discrepancies in placental sharing.[19–21] This may challenge the prediction of perinatal and neurological outcomes, especially when the LAPV is offered as one of the management options.[19–21] The aim of this study is to identify predictors of perinatal and neurological outcomes in cases of severe TOPS (associated or not with TAPS and/or SFGR) treated by LAPV.

2 | MATERIALS AND METHODS

This was a retrospective cohort study of severe TOPS cases associated or not with TAPS and/or SFGR and treated by LAPV at The Heart Hospital, São Paulo, from January 2011 to February 2022. The study was approved by the institutional review board of this institution (CAAE: 52159721.3.0000.0060) and followed the recommendations of the STROBE initiative[22] for reporting observational data.

The cases were selected among all complicated MCDA twin pregnancies (TOPS and/or SFGR and/or TAPS) without fetal major anatomical defects (twin reverse arterial perfusion sequence or any other major fetal abnormality) who underwent LAPV at the above-mentioned institute and period. The inclusion criteria for this study were MCDA twin pregnancies with severe TOPS (stages II-IV in the classification by Quintero et al.[1]), associated or not with signs compatible with TAPS and/or SFGR, and a cervical length greater than 15 mm (the 5th percentile according to To et al.[23]) before the procedure. Patients who had isolated TAPS and/or SFGR were not included (Supplementary Table).

The association of TOPS with SFGR was defined when the estimated fetal weight (EFW) of the smaller twin was below the 3rd centile of normative ranges,[24] or when a difference between the EFWs of the twins was greater than 25% and the EFW of the smaller twin was below the 10th centile. The concurrence of TAPS was defined when a discrepancy in the middle cerebral artery peak systolic velocity (MCA-PSV) was greater than 0.5 multiples of the median (MoM).[6]

All interventions were performed by the same surgeon (CFAP) according to a previously published technique.[25] Briefly, the procedure was conducted as follows: the placental chorionic plate vessels through the amniotic cavity of the recipient fetus were initially mapped endoscopically; the vascular equator (where the majority of arterio-venous anastomoses are expected to be) was identified; a line of ablation of the chorionic plate was created from one edge of the placenta to the other, including the arterio-venous anastomoses and vessels with unknown courses (those crossing the inter-twin membrane from the recipient to the donor side and concealed behind the fixed twin). Caution was taken to preserve the vessels originating from and returning to the same fetus, which were surrounded by this line of ablation. At the end of LAPV, the excess amniotic fluid causing the polyhydramnios was drained through the fetoscopy sheath to ensure that the deepest amniotic fluid pocket measured less than 8 cm.

Maternal characteristics evaluated in this study were age, parity (nulliparous or not) and type of conception (natural or assisted reproduction).

Pre-laser and laser variables evaluated in this study were the stage of TOPS according to Quintero's classification; association or not with TAPS and/or SFGR; the discrepancy between the EFWs [(larger twin EFW – smaller twin EFW/larger EFW) × 100]; umbilical artery Doppler pulsatility index (UA-PI); the presence of absent/reverse end-diastolic flow in the umbilical artery (AREDF-UA); ductus venosus pulsatility index (DV-PI); the presence of absent/reverse A wave in the DV flow (ARAW-DV); middle cerebral artery peak systolic velocity (MCA-PSV); difference between the MCA-PSVs expressed as multiple of the medians (MoM); the presence of fetal hydrops; gestational age (GA), placental position (anterior or not) and cervical length at LAPV; total time of LAPV. Post-laser variables were the rates of intrauterine death of the donor and recipient twins until delivery and the rates of premature preterm rupture of membranes (PPTRM). Perinatal variables included GA at birth, birthweight (BW),

Apgar scores, the presence of severe alterations in the transfontanellar ultrasonography (TFUS) and survival rates of the neonates until hospital discharge. Infant's variables evaluated after hospital discharge were the age at the application of the third edition ages and stages questionnaire (ASQ-3)[26] and the results of this test.

Pre-laser ultrasound variables were recorded less than 2 days before the LAPV.

Severe alterations shown on TFUS were the presence of ventriculomegaly and/or porencephaly and/or peri-intraventricular hemorrhage stages III or IV according to the classification by Papile et al.[27] Infant ventriculomegaly was defined using different TFUS measurements, such as the ventricular index, the anterior horn width and thalamo-occipital distance.[28]

For LAPV performed from April 2015 onwards, the parents or caregivers of the surviving twins were regularly asked to complete the ASQ-3, after proper instruction by one of the participants in this study (KJRC). The ASQ-3 covers five domains of the infant's neurological development: communication, gross motor control, fine motor control, problem solving, and personal-social behavior. In each of these areas, the infant reaches a score, which is interpreted according to a specific preestablished cutoff for that domain. Depending on the score in each area, the development of the infant is classified as follows: a. above the cutoff (the infant's development appears to be on schedule); b. close to the cutoff (provide learning activities and monitor); c. below the cutoff (further assessment with a professional may be needed). For the binary logistic regression analysis in this study, we categorized these outcomes as normal (a) or abnormal (b and c).

Averages (standard deviations – SD) and medians (ranges) were used to describe normally and non-normally distributed continuous variables, respectively. Absolute and relative frequencies were calculated to describe categorical data. Comparisons of categorical variables were performed using the Chi-square or Fisher's exact tests. Univariate and multivariate binary logistic regression analysis were performed to identify significant maternal, pre-laser and perioperative variables that influenced the occurrence of fetal death (at any time from laser to delivery) of the donor and the recipient twins, separately. Among the liveborns, the same analyzes were performed to detect pre-laser, perioperative and perinatal variables that influenced the chance of survival until hospital discharge. In the subset of cases that responded to ASQ-3, univariate and multivariate binary logistic regression analysis was performed to identify significant maternal, prenatal and perinatal variables that influenced infants' neurological outcomes. A *p*-value of less than 5% was considered statistically significant. The Statistical Package for the Social Sciences (SPSS) version 29.0 was used for the analyses.

3 | RESULTS

In the study period, there were 344 MCDA twin pregnancies complicated by TOPS and/or SFGR and/or TAPS, without any fetal major anatomical defect, who were treated by LAPV in the participating center. Seventy-nine cases (79/344: 23.0%) were not included in the final analysis because the main diagnoses were TOPS stage I and/or SFGR and/or TAPS (58/79: 73.4%) and/or the cervical length was less than 15 mm (22/79: 27.8%). Two-hundred-sixty-five patients (265/344: 77.0%) with severe TOPS met the entry criteria (Supplementary Figure S1).

The average maternal age at surgery was 32.1 years (SD: 5.8; range: 17.9–48.1), 56.6% (150/265) of the women were multiparous and 95.1% (252/265) of them conceived naturally. None of the maternal variables significantly interfered with fetal, neonatal and infants' outcomes.

The average pre-laser cervical length was 32.1 mm (SD: 6.9; range: 15.0–52.0). Averages of GA at LAPV, total time of the procedure (from maternal anesthesia to the end of the amnio drainage) and amount of drained amniotic fluid were 21.2 weeks (SD: 2.4; range: 17.0–26.6), 50 min (SD: 16.2; range: 15.0–90.0) and 2081 mL (SD: 1092; range: 400–6600) respectively. In 41.10% (109/265) of the cases, the placenta was predominantly anterior.

One-hundred-twenty-four cases (124/265%–46.79%) were treated in TOPS stage II (Quintero et al.[1]), 119 (1119/265%–44.90%) in stage III and 22 (22/265%–8.30%) in stage IV. The associations of TOPS with SFGR, TAPS and at least one of the last two conditions were 69.81% (185/265), 10.56% (28/265) and 74.34% (197/265), respectively (Supplementary Figure S1).

There were 82 (82/530%–15.47%) fetal deaths from LAPV until delivery, 63.41% of them (52/82) among the ex-donor twins and 36.59% of them (30/82) among the ex-recipient twins ($p < 0.001$) (Supplementary Figure S1).

In the univariate binary logistic regression analyses, significant predictors of the ex-donor's death from LAPV to delivery were the Quintero's stages II and III, the discrepancy between EFW, UA-PI and the presence of AREDF-UA. Using backward multivariate binary logistic regression analyses, only the discrepancy between EFW and the presence of AREDF-UA remained significant predictors of the ex-donor fetus' demise (Table 1 and Supplementary Table S1). The probability of occurrence of this event increased with the discrepancy between EFW and the presence of AREDF-UA and can be calculated as follows: Probability = Odds/1 + Odds, where the Odds is the $e^{\ln(\text{Odds})}$ and the ln(Odds) = −2.669 + 0.026 (discrepancy between EFW) + 1.151 (0: absence of AREDF-UA; 1: presence of AREDF-UA).

In the univariate binary logistic regression analyses, significant predictors of the ex-recipient's death from LAPV to delivery were the Quintero's stages IV, DV-PI, the presence of ARAW-DV and the presence of hydrops. Using backward multivariate binary logistic regression analyses, only the presence of hydrops remained a significant predictor of the ex-recipient fetus' demise (Table 1 and Supplementary Table S1). The probability of occurrence of this event increased with the presence of hydrops and can be calculated as follows: Probability = Odds/1 + Odds, where the Odds is the $e^{\ln(\text{Odds})}$ and the ln(Odds) = −2.244 + 1.300 (0: absence of hydrops; 1: presence of hydrops). This means a probability of ex-recipient death of 9.60% in the absence of hydrops and 28.00% in the presence of this finding.

TABLE 1 Significant pre-laser, perioperative variables and fetal demise from laser ablation of placental vessels until delivery in cases of severe twin oligo-polyhydramnios sequence – Uni and multivariate analysis.

Pre-laser and perioperative variables		Fetal demise from laser until delivery							
		Ex-donor twin (265)				Ex-recipient twin (265)			
				p-value; OR (CI 95%)				*p*-value; OR (CI 95%)	
		No (*n*: 213)	Yes (*n*: 52)	Univariate	Multivariate	No (*n*: 235)	Yes (*n*: 30)	Univariate	Multivariate
Quintero's stage of TOPS: *n*/total (%)	II	108/124 (87.0)	16/124 (12.9)	**0.026; –**	0.621	113/124 (91.1)	11/124 (8.5)	0.057; –	0.981; –
	III	87/119 (73.1)	32/119 (26.9)	**0.007; 2.48 (1.28 – 4.82)**	0.331; 0.55 (0.17–1.84)	105/118 (88.9)	13/118 (11.0)	0.592; 1.26 (0.54–2.94)	0.924; 0.95 (0.35–2.59)
	IV	18/22 (81.8)	4/22 (18.2)	0.509; 1.50 (0.45–5.00)	0.600; 0.70 (0.18–2.71)	17/23 (73.9)	6/23 (26.1)	**0.019; 3.85 (1.25–11.86)**	0.849; 0.77 (0.05–11.87)
	Yes	156/197 (79.2)	41/197 (20.8)			174/197 (88.3)	23/197 (11.7)		
Discrepancy between EFW, %: Average (SD)		24.5 (14.27)	31.68 (12.46)	**0.001; 1.04 (1.02 – 1.06)**	**0.045; 1.03 (1.01 – 1.05)**	26.16 (14.11)	23.77 (15.00)	0.386; 0.99 (0.96–1.02)	-
UA-PI: Average (SD)		1.61 (0.51)	1.90 (0.68)	**0.001; 2.43 (1.42 – 4.15)**	0.877; 0.94 (0.40–2.21)	1.23 (0.34)	1.29 (0.48)	0.424; 1.50 (0.56–4.03)	-
AREDF-UA: *n*/total (%)	No	148/167 (88.6)	19/167 (11.4)	**0.001; 3.96 (2.10 – 7.47)**	**<0.001; 3.16 (1.62 – 6.15)**	227/255 (89.0)	28/255 (11.0)	0.386; 2.03 (0.41–10.02)	-
	Yes	65/98 (66.3)	33/98 (33.7)			8/10 (80.0)	2/10 (20.0)		
DV-PI: Average (SD)		0.84 (0.41)	0.91 (0.43)	0.260; 1.48 (0.75–2.91)	-	1.06 (0.49)	1.28 (0.63)	**0.031; 2.09 (1.07 – 4.07)**	0.485; 1.41 (0.54–3.70)
ARAW-DV: *n*/total (%)	No	198/244 (81.1)	46/244 (18.9)	0.287; 1.72 (0.63–4.68)	-	181/199 (91.0)	18/199 (9.0)	**0.046; 2.24 (1.01 – 4.93)**	0.710; 1.27 (0.37–4.38)
	Yes	15/21 (71.4)	6/21 (28.6)			54/66 (81.8)	12/66 (18.2)		
Hydrops: *n*/total (%)	No	213/265 (80.4)	52/265 (19.6)	-	-	217/240 (90.4)	23/240 (9.6)	**0.009; 3.67 (1.39 – 9.71)**	**0.009; 3.67 (1.39 – 9.71)**
	Yes	-	-			18/25 (72.0)	7/25 (28.0)		

Note: Bold values are statistically significant results.

Abbreviations: ARAW-DW, Absent or Reversed A-Wave in the Ductos Vesosus Doppler; AREDF-UA, Absent or Reversed End-Diastolic Flow in the Umbilical Artery Doppler; CI, Confidence Interval; DV-PI, Ductus Venosus Doppler Pulsatility Index; OR, Odds-Ratio; SD, Standard Deviation; SFGR, selective fetal growth restriction; TAPS, EFW: Estimated Fetal Weight; TOPS, Twin Oligo-Polyhydramnios Sequence; UA-PI, Umbilical Artery Doppler Pusatility Index.

The rate of PPTRM was 32.1% (85/265) at an average GA of 29.2 weeks (SD: 4.3; range: 19.0–36.0). The average GA at delivery was 31.2 weeks (SD: 4.2; range: 17.9–39.1).

Among the ex-donor liveborn twins, the survival rate until hospital discharge was 79.34% (169/213). In the univariate binary logistic regression analysis, significant predictors of survival in this subgroup were pre-laser discrepancy between EFW, GA at birth, BW, and 1st and 5th minutes Apgar scores. Using backward multivariate binary logistic regression, only the GA at birth and 1st minute Apgar score remained as significant predictors of the ex-donor twins' survival until hospital discharge (Table 2 and Supplementary Table S2). The probability of this event happening increased with GA at birth and 1st minute Apgar score and can be calculated as follows: Probability = Odds/1 + Odds, where the Odds is the $e^{\ln(\text{Odds})}$ and the ln(Odds) = −22.665 + 0.557 (1st minute Apgar score) + 0.715 (GA at birth).

Among the ex-recipient liveborn twins, the survival rate until hospital discharge was 85.53% (201/235). In the univariate binary logistic regression analysis, significant predictors of survival in this subgroup were pre-laser cervical length, total time of LAPV, GA at birth, BW, 1st and 5th minutes Apgar scores, and the presence of severe alterations in the TFUS. Using backward multivariate binary logistic regression, only the GA at birth and 1st minute Apgar score remained as significant predictors of the ex-recipient twins' survival until hospital discharge (Table 2 and Supplementary Table S2). The probability of this event happening increased with GA at birth and 1st minute Apgar score and can be calculated as follows: Probability = Odds/1 + Odds, where the Odds is the $e^{\ln(\text{Odds})}$ and the ln(Odds) = −15.729 + 0.432 (1st minute Apgar score) + 0.510 (GA at birth).

From LAPV until hospital discharge, the overall survival rate, survival of both twins and at least one twin were 69.62% (369/530), 56.60% (150/265) and 83.00% (220/265), respectively.

ASQ-3 was completed by the parents or caregivers of 60 ex-donor and 63 ex-recipient infants at a median age of 36 months (2–60). As most of them were co-twins, there was no significant difference between the ages of ex-donors and ex-recipients at the time of application of the test (p: 0.463). Moreover, there were no differences between these groups in the frequency of alterations detected in all ASQ-3 domains (Table 3).

Among the ex-donor infants, 58.3% (35/60) had abnormal results in at least one of the five ASQ-3 domains, 20.0% (12/60) had abnormal communication results, 35.0% (21/60) had abnormal gross motor control, 28.3% (17/60) had abnormal fine motor control, 28.3% (17/60) had abnormal problem-solving results and 40.0% (24/60) had abnormal personal-social behavior. In the univariate binary logistic regression analysis, altered neonatal TFUS was the single predictor of altered communication and gross motor control results, and pre-laser MCA-PSV expressed in MoM was the single predictor of altered personal-social behavior. Using backward multivariate binary logistic regression, altered neonatal TFUS also remained as the single predictor of altered fine motor and problem-solving skills (Table 4, Figure 1 and Supplementary Table S3).

Among the ex-recipient infants, 52.3% (33/63) had abnormal results in at least one of the five ASQ-3 domains, 15.9% (10/63) had abnormal communication results, 30.2% (19/63) had abnormal gross motor control, 27.0% (17/63) had abnormal fine motor control, 17.4% (11/63) had abnormal problem-solving results and 30.2% (19/63) had abnormal personal-social behavior. In the univariate binary logistic regression analysis, pre-laser UA-PI was the single predictor of altered personal-social behavior, pre-laser ARAW-DW was the single predictor of altered fine motor skills and pre-laser delta MCA-PSV expressed in MoM was the single predictor of altered personal-social behavior (Table 5, Figure 1 and Supplementary Table S4).

4 | DISCUSSION

4.1 | Summary of key findings

This study demonstrated that in cases of severe TOPS associated or not with TAPS and/or SFGR, significant predictors of the ex-donor's death from LAPV to delivery were pre-laser discrepancy between EFW and the presence of AREDF-UA, and a significant predictor of the ex-recipient fetus' demise was the presence of hydrops. It was also demonstrated that among the liveborn twins, GA at birth and 1st minute Apgar scores were the only predictors of survival until hospital discharge for both the ex-donor and ex-recipient twins. Furthermore, in a subset of twins who underwent neurological follow-up using ASQ-3, the occurrence of severe alterations in the neonatal TFUS was the most important predictor of altered ASQ-3 results, while different pre-laser fetal Doppler parameters seemed to interfere with postnatal neurological outcomes in the ex-recipient twins.

4.2 | Interpretation in the context of what is known on the topic

Endoscopic LAPV is the treatment of choice for severe TOPS (Quintero stages 2–4) and can be offered as one of the management options to select cases of TOPS stage 1, TAPS and SFGR.[4,6,10–21] When combinations of these conditions occur and LAPV is proposed as the main treatment option, it may be difficult to predict fetal, perinatal and neurological outcomes while taking into consideration the stages and types of each disease. In fact, the present study did not show a correlation between Quintero TOPS stages and the presence or absence of SFGR or TAPS with fetal, perinatal, neonatal and infants' neurological outcomes.

In the present study, discrepancy in the EFWs and the presence of AREDF-UA were significant predictors of the ex-donor twin demise in the period from LAPV to delivery, which probably reflects the coexistence of SFGR, although SFGR was not a significant predictor of this outcome when considered a categorical variable. Similarly, the presence of hydrops, which is used to define stage IV of TOPS, was more important than Quintero's classification in the

TABLE 2 Significant pre-laser, perioperative and perinatal variables and liveborn survival until hospital discharge in cases of severe twin oligo-polyhydramnios sequence – Uni and multivariate analysis.

Pre-laser, perioperative and perinatal variables		Liveborn survival until hospital discharge							
		Ex-donor twin (213)				Ex-recipient twin (235)			
		No (*n*: 44; 20.66%)	Yes (*n*: 169; 79.34%)	*p*-value; OR (CI 95%)		No (*n*: 34; 14.46)	Yes (*n*: 201; 85.53)	*p*-value; OR (CI 95%)	
				Univariate	Multivariate			Univariate	Multivariate
Discrepancy between EFW, %: Average (SD)		29.03 (14.51)	23.29 (14.01)	**0.019; 0.97 (0.95 – 0.99)**	0.284; 0.96 (0.89–1.04)	28.35 (15.64)	25.78 (13.84)	0.325; 0.99 (0.96–1.01)	-
Cervical length, mm: Average (SD)		28.70 (8.80)	30.93 (7.65)	0.117; 1.035 (0.991–1.080)	-	25.71 (9.72)	31.31 (7.47)	**<0.001; 1.08 (1.03 – 1.13)**	0.996; 4.025 (0.000–2.166)
Total time LAPV, min.: Average (SD)		53.51 (28.83)	54.08 (22.41)	0.891; 1.001 (0.986–1.016)	-	45.13 (15.77)	56.45 (26.14)	**0.023; 1.027 (1.004 – 1.052)**	0.999; 1.247 (0.000–8.05)
GA at birth, weeks: Average (SD)		27.23 (3.16)	32.60 (2.81)	**<0.001; 1.90 (1.54 – 2.34)**	**0.001; 2.15 (1.35 – 3.41)**	26.45 (3.09)	32.55 (3.00)	**<0.001; 2.10 (1.63 – 2.70)**	**0.002; 1.707 (1.210 – 2.408)**
Birthweight, grams: Average (SD)		812.78 (388.75)	1564.99 (511.60)	**<0.001; 1.004 (1.003 – 1.005)**	0.657; 0.999 (0.996–1.003)	942.72 (357.95)	1794.25 (553.34)	**<0.001; 1.004 (1.003 – 1.005)**	0.999; 1.019 (0.000–1.729)
Apgar score 1: Median (limits)		1 (0–8)	8 (1–10)	**<0.001; 2.08 (1.57 – 2.75)**	**0.002; 1.76 (1.23 – 2.53)**	3 (0–8)	8 (0–10)	**<0.001; 1.89 (1.46 – 2.44)**	**0.009; 1.585 (1.119 – 2.243)**
Apgar score 5: Median (limits)		1 (0–9)	9 (5–10)	**<0.001; 2.16 (1.48 – 3.15)**	0.36; 1.39 (0.68–2.82)	3 (0–9)	9 (5–10)	**<0.001; 2.35 (1.56 – 3.52)**	0.971; 8.084 (0.000 -.)
Altered TFUS: n/ total (%)	No	6/104 (5.77)	98/104 (94.23)	0.664; 0.61 (0.07–5.61)	-	1/126 (0.79)	125/126 (99.20)	**0.005; 0.028 (0.002 – 0.347)**	0.995; 0.000 (0.000 -.)
	Yes	1/11 (9.10)	10/11 (91.01)			2/9 (22.22)	7/9 (77.78)		

Note: Bold values are statistically significant results.

Abbreviations: CI, Confidence Interval; EFW, Estimated Fetal Weight; GA, Gestational Age; LAPV, Laser Ablation of Placental Vessels; OR, Odds-Ratio; SD, Standard Deviation; TFUS, Transfontanellar ultrasound.

TABLE 3 Frequency of normal and abnormal results of the Ages and Stages Questionnaire in 60 ex-donor and 63 ex-recipient twins in cases of severe twin oligo-polyhydramnios sequence treated by laser ablation of placental vessels.

ASQ-3 domains of the infant's neurological development															
	Communication		*p*	Gross motor control		*p*	Fine motor control		*p*	Problem solving		*p*	Personal-social behavior		*p*
Category	D (60)	R (63)		D (60)	R (63)		D (60)	R (63)		D (60)	R (63)		D (60)	R (63)	
Above cutoff: *n* (%)	48 (80.0)	54 (85.7)	0.259	38 (63.3)	44 (69.8)	0.713	42 (70.0)	46 (73.0)	0.832	43 (71.7)	52 (82.5)	0.345	36 (60.0)	44 (69.8)	0.517
Close to cutoff: *n* (%)	9 (15.0)	4 (6.3)		6 (10.0)	6 (9.5)		6 (6.0)	7 (11.1)		7 (11.7)	4 (6.3)		11 (18.3)	9 (14.3)	
Bellow cutoff: *n* (%)	3 (5.0)	5 (7.9)		16 (26.7)	13 (20.6)		12 (20.0)	10 (15.9)		10 (16.7)	7 (11.1)		13 (21.7)	10 (15.9)	

Note: Normal result: Above cutoff; Abnormal results: Close to cutoff and bellow cutoff.

TABLE 4 Significant pre-laser, perioperative and perinatal variables and results of the Ages and Stages Questionnaire of the ex-donor twins in cases of severe twin oligo-polyhydramnios sequence – univariate analysis.

Ex-donor twin (60)																
Pre-laser, perioperative and perinatal variables		Com		*p*; OR (95% CI)	GM		*p*; OR (95% CI)	FM		*p*; OR (95% CI)	PSolv		*p*; OR (95% CI)	PSoc		*p*; OR (95% CI)
		NI (48)	Alt (12)	Univ	NI (39)	Alt (21)	Univ	NI (43)	Alt (17)	Univ	NI (43)	Alt (17)	Univ	NI (36)	Alt (24)	Univ
DV-PI: Average (SD)		0.86 (0.49)	1.01 (0.59)	0.357; 1.66 (0.57–4.87)	0.80 (0.31)	1.04 (0.73)	0.131; 2.66 (0.75–9.43)	0.77 (0.27)	1.18 (0.80)	**0.031; 7.30 (1.20 – 44.51)**	0.88 (0.50)	0.92 (0.56)	0.772; 1.17 (0.41–3.37)	0.89 (0.55)	0.88 (0.46)	0.953; 0.97 (0.35–2.70)
MCA-PSV, MoM: Average (SD)		1.05 (0.28)	0.94 (0.25	0.190; 0.15 (0.01–2.57)	1.03 (0.23)	1.04 (0.34)	0.889; 1.15 (0.17–7.78)	1.02 (0.24)	1.07 (0.36)	0.490; 2.03 (0.27–15.13)	1.05 (0.23)	1.00 (0.38)	0.584; 0.55 (0.06–4.78)	1.09 (0.21)	0.95 (0.33)	**0.049; 0.08 (0.01 – 0.99)**
Anterior placenta: *n*/total (%)	N	25/35 (71.4)	10/35 (28.6)	0.065; 0.22 (0.04–1.10)	20/35 (57.1)	15/35 (42.9)	0.242; 0.52 (0.17–1.56)	21/35 (60.0)	14/35 (40.0)	**0.025; 0.21 (0.05 – 0.82)**	21/35 (60.0)	14/35 (40.0)	**0.025; 0.21 (0.05 – 0.82)**	19/35 (54.3)	16/35 (45.7)	0.287; 0.56 (0.19–0.63)
	Y	23/25 (92.0)	2/25 (8.0)		18/25 (72.0)	7/25 (28.0)		22/25 (88.0)	3/25 (12.0)		22/25 (88.0)	3/25 (12.0)		17/25 (68.0)	8/25 (32.0)	
Altered TFUS: *n*/total (%)	N	46/54	8/54	**0.010; 11.50 (1.80 – 73.58)**	38/54	16/54	**0.017; 16.43 (1.63 – 165.13)**	42/54	12/54	**0.012; 17.50 (1.86 – 164.52)**	41/54	13/54	**0.046; 6.31 (1.03 – 38.48)**	35/54	19/54	0.05; 9.21 (1.00–84.68)
	Y	2/6	4/6		1/6	0/6		1/6	5/6		2/6	4/6		1/6	5/6	

Note: Bold values are statistically significant results.

Abbreviations: Alt, Altered; CI: Confidence Interval; Com, Communication; DV-PI, Ductus Venosus Doppler Pulsatility Index; FM, Fine motor skills; GM, Gross motor skills; MCA-PSV, Middle Cerebral Artery – Peak Systolic Velocity; MoM, Multiple of the Median; N, No; NI, Normal; OR, Odds-Ratio; PSoc, Personal-social; PSol, Problem-solving; SD, Standard Deviation; TFUS, Transfontanellar ultrasound; Univ, Univatiate analysis; Y, Yes.

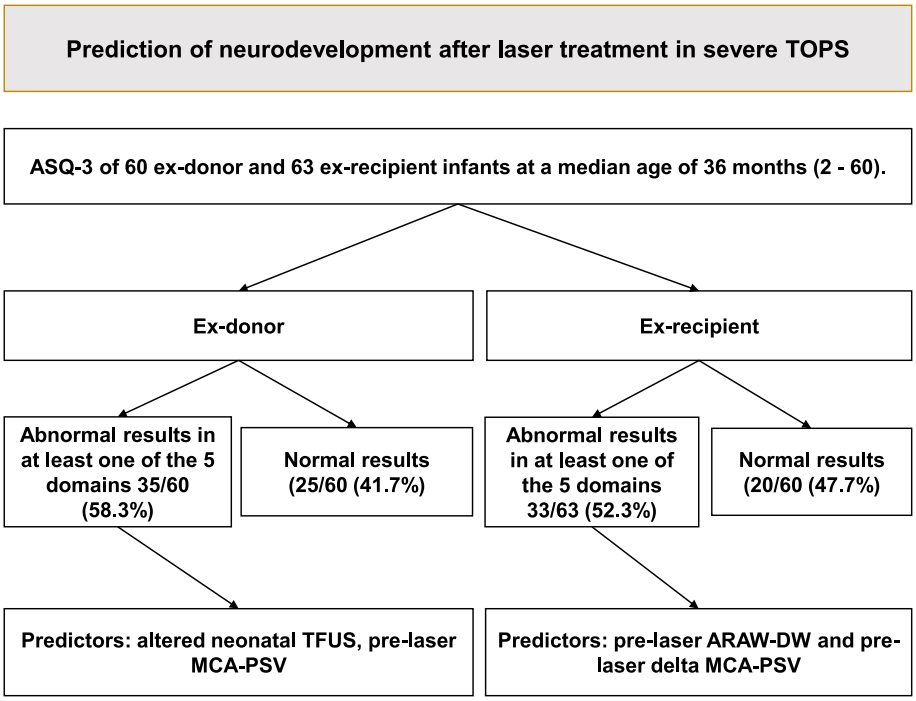

FIGURE 1 Prediction of neurodevelopment after laser treatment in severe twin oligo-polyhydramnios sequence.

prediction of the ex-recipient twin demise in the period from LAPV until delivery. The assumption that using specific ultrasound and/or clinical parameters to predict outcomes may be better than classifying types or stages of diseases is in accordance with other authors,[21,29] although there is no consensus. As in our study, Krispin et al.[29] developed a predictive model for dual survival after LAPV for TOPS, which included variables obtained at the time of TOPS diagnosis, such as a donor twin EFW <10th centile, an intertwin EFW discordance >25%, the position of the placenta, and Doppler parameters of the donor twin. In contrast to our study, in a systematic review, Nassr et al.[30] demonstrated that the risk of post-LAPV ex-donor twin demise was significantly increased for higher Quintero stages (III and IV) compared with lower stages (I and II). These results may be biased by the inclusion of patients with Quintero stage I in the meta-analysis. A recent randomized trial performed by Stirnemann et al.[31] demonstrated that LAPV does not improve the outcomes of TOPS stage I in asymptomatic pregnant women with a long cervix. This is one of the reasons why we did not include patients with TOPS stage I in our cohort, which may also explain the differences between our results and those presented in the above-mentioned systematic review. Also different from our approach was a meta-analysis by D'Antonio et al.[32] demonstrated that the overall risk of fetal loss after LAPV was significantly higher in patients with TOPS complicated by SFGR, especially due to the death of the donor twin. Carmant et al.[33] also showed that SFGR, especially types II and III, is independently associated with decreased dual survivorship in TOPS patients undergoing LAPV.

Previous studies[29,30] have also demonstrated the importance of anterior placentas and a lower GA at the time of LAPV as predictors of fetal demise, but this relation was not observed in our study. These differences may be due to variations in technical approaches, equipment and medical skills.

In the present study, it was expected that other parameters, rather than prenatal ultrasound signs, would interfere with the probability of hospital discharge among the liveborn twins. In fact, GA at birth and 1st minute Apgar scores obviously influenced the chance of survival.

Regarding the infants' neurological follow-up in our cohort, it seems clear that the relationship between severe alterations shown on TFUS for the ex-donor twin and a higher risk of compromise in almost all domains covered by the ASQ-3 seems clear. However, it is not straightforward to understand the relation between the pre-LAPV UA-PI, ARAW-DV and delta MCA-PSV (MoM) and a higher risk of compromise in specific domains of the ASQ-3 in the ex-recipient twins. The association of prenatal ultrasound findings in cases of TOPS with or without TAPS and/or SFGR and neurodevelopmental compromise is still a controversial issue in the literature. In a recent study, Tollenaar et al.[6] demonstrated that surviving donor twins of pregnancies complicated by spontaneous TAPS have fourfold higher odds of neurodevelopmental impairment than recipient wins. Furthermore, in cases of TOPS, D'Antonio et al.[32] demonstrated that pre-LAPV discrepancies in EFWs significantly affected the neurodevelopment of the ex-donor twins. In previous studies by our group, we could not find a relationship between prenatal fetal ultrasound parameters and the results of magnetic resonance imaging (MRI) performed before and after LAPV in cases of severe TOPS with infant neurological outcomes evaluated with the Bayley's scale.[34–36] It could be speculated that some Doppler findings in cases of TOPS and/or TAPS could be associated with a certain degree of brain hypoxia, however, this needs to be further evaluated

TABLE 5 Significant pre-laser, perioperative and perinatal variables and results of the Ages and Stages Questionnaire of the ex-recipient twins in cases of severe twin oligo-polyhydramnios sequence – univariate analysis.

Ex-recipient twin (63)																
Pre-laser, perioperative and perinatal variables		Com.		p; OR (95% CI)	GM		p; OR (95% CI)	FM		p; OR (95% CI)	PSol		p; OR (95% CI)	PSoc		p; OR (95% CI)
		NI (53)	Alt (10)	Univ	NI (44)	Alt (19)	Univ	NI (46)	Alt (17)	Univ	NI (52)	Alt (11)	Univ	NI (44)	Alt (19)	Univ
UA-PI: Average (SD)		1.35 (0.47)	1.14 (0.33)	0.191; 0.25 (0.03 –2.02)	1.38 (0.50)	1.68 (0.27)	0.097; 0.26 (0.05–1.27)	1.34 (0.50)	1.24 (0.29)	0.403; 0.55 (0.14–2.22)	1.35 (0.46)	1.16 (0.36)	0.207; 0.28 (0.04–2.01)	1.39 (0.50)	1.13 (0.26)	**0.043; 0.16 (0.03 – 0.95)**
ARAW-DV: *n*/total (%)	N	41/49 (83.7)	8/49 ()	0.854; 0.85 (0.16 –4.57)	34/49 ()	15/49 ()	0.883; 0.91 (0.25–3.36)	39/49 ()	10/49 ()	**0.034; 3.90 (1.11 – 13.71)**	40/49 ()	9/49 ()	0.723; 0.74 (0.14–3.91)	35/49 ()	14/49 ()	0.608; 1.39 (0.34–4.88)
	Y	12/14 ()	2/14 ()		10/14 ()	4/14 ()		7/14 ()	7/14 ()		12/14 ()	2/14 ()		9/14 ()	5/14 ()	
Delta MCA-PSV, MoM: Average (SD)		0.01 (0.34)	0.03 (0.36)	0.853; 1.21 (0.16 –9.11)	0.04 (0.32)	–0.07 (0.38)	0.239; 0.36 (0.07–1.97)	0.05 (0.33)	0.09 (0.36)	0.168; 0.29 (0.05–1.70)	0.06 (0.31)	–0.21 (0.40)	**0.023; 0.07 (0.006 – 0.684)**	0.05 (0.35)	–0.07 (0.29)	0.223; 0.35 (0.06–1.90)

Note: Bold values are statistically significant results.

Abbreviations: Alt, Altered; ARAW-DW, Absent or Reversed A-Wave in the Ductos Vesosus Doppler; CI, Confidence Interval; Com, Communication; FM, Fine motor skills; GM, Gross motor skills; MCA-PSV, Middle Cerebral Artery – Peak Systolic Velocity; MoM, Multiple of the Median; NI, Normal; OR, Odds-Ratio; PSoc, Personal-social; PSol: Problem-solving; SD, Standard Deviation; UA-PI, Umbilical Artery Doppler Pusatility Index; Univ, Univatiate analysis.

in a greater number of patients. Our numbers in the present analysis show that both the ex-donor and ex-recipient twins carry a high risk of at least a mild neurological delay. This could help to orient the parents experiencing this situation so that a closer follow-up with a specialist could be ideal.

4.3 | Limitations and strengths

This study has some limitations. Firstly, neurological follow-up with the ASQ-3 was not performed in all cases. However, selection bias is unlikely, given that the test was introduced in our routine in 2016 and was offered to all consecutive cases. Secondly, the ASQ-3 has the disadvantage of not considering a presential neurological evaluation and is therefore dependent on the caregiver's subjective impression. Thirdly, we did not evaluate the importance of a cyclic flow in the umbilical artery of the twins, because this information was not regularly valorized in our database before the study of Gratacós et al.,[9] who used this aspect to categorize the SFGR in type III. Finally, the small number of patients with severe TAPS probably precludes us from drawing any conclusion about the influences of this condition on post-LAPV and/or postnatal outcomes.

Some strengths of this study could be highlighted. The sample size is significant, taking into account the incidence of severe TOPS. Moreover, it was a single center study, with a single operator using a homogeneous methodology for preoperative ultrasound assessment and surgical treatment. There was also a homogeneous postoperative and follow-up protocol. In addition, the possibility of performing multivariate logistic regression analysis, which is not often possible in smaller sample sizes, probably resulted in a better hierarchical assessment of predictors. Therefore, the knowledge arising from this study may help parental counseling in cases of TOPS associated or not with SFGR before LAPV is undertaken.

5 | CONCLUSIONS

This study may contribute to the prediction of outcomes in cases of severe TOPS associated or not with SFGR and/or TAPS treated by LAPV. Major predictors of fetal survival for the ex-donor twins were their size and umbilical artery Doppler pattern, and for the ex-recipient twins was the presence of hydrops. Additionally, predictors of neonatal survival after a livebirth were the gestational age at birth and early Apgar scores. Abnormal neurodevelopment at 36 months may be anticipated by abnormal TFUS at birth and pre-laser diagnosis of associated TAPS.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Cleisson Fábio Andrioli Peralta https://orcid.org/0000-0002-7279-5311

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