Artery-to-vein anastomoses in unequally divided placentas and their association with birthweight discordance

Noll, A.T.R.; Lof, F.C.; Groene, S.G.; Haak, M.C.; Lopriore, E.; Russo, F.M.; ... ; Lewic, L.

Placenta 146 (2024) 58–63

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Artery-to-vein anastomoses in unequally divided placentas and their association with birthweight discordance

A.T.R. Noll [a,c], F.C. Lof [a], S.G. Groene [b], M.C. Haak [a], E. Lopriore [b], F.M. Russo [c], F. Slaghekke [a], L.S.A. Tollenaar [b], J. Van der Merwe [c], E.J.T. Verweij [a], L. Lewi [c,d,1,*]

[a] Division of Fetal Medicine, Department of Obstetrics, Leiden University Medical Center, the Netherlands
[b] Division of Neonatology, Department of Pediatrics, Leiden University Medical Center, the Netherlands
[c] Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium
[d] Department of Development and Regeneration, Biomedical Sciences, KU Leuven, Leuven, Belgium

ARTICLE INFO

Keywords:
Anastomoses
Monochorionic twins
Birthweight discordance
Artery-to-vein
Selective fetal growth restriction
Placenta

ABSTRACT

Introduction: This study investigated the impact of the shared intertwin circulation in unequally divided monochorionic (MC) placentas on fetal growth.
Methods: This retrospective analysis included color-dyed, unequally shared placentas from two tertiary centers. Exclusions included twin-twin transfusion syndrome, twin anemia polycythemia sequence, and lethal anomalies. Measurement of the external diameters and areas of the artery-to-artery (AA), artery-to-vein (AV), and vein-to-vein (VV) anastomoses was performed. The ratio of the shared circulation (AV ratio) was determined by comparing the areas of the summed venous components of shared AV anastomoses to those in the individual AV anastomoses of the smaller placental part. The birth weight ratio/placental ratio (BWR/PR), total AV size areas and net AV transfusion were calculated. Univariable and multivariable linear regressions were performed to assess the relationship between BWR/PR, the AV ratio, the areas of the different anastomoses and cord insertion discordance.
Results: Among 352 placentas, 97 % (340) had intertwin AV anastomoses, and 50 % (176) were from pregnancies with selective growth restriction. The AV ratio, AA, VV, total AV areas, and cord insertion discordance negatively correlated with BWR/PR. Multivariable linear regression confirmed the independent negative association between BWR/PR and the AV ratio, suggesting that a larger shared circulation benefits the twin with the smaller placental part. Type III sFGR placentas exhibited the highest AV ratio, resulting in the lowest BWR/PR.
Discussion: A larger shared circulation mitigates the impact of an unequally divided placenta on fetal growth. This effect surpasses the influence of AA and VV diameters and is most prominent in Type III sFGR placentas.

1. Introduction

The monochorionic (MC) placenta typically consists of three parts: two parts that are perfused by each twin individually and a third shared part supplied by indirect artery-to-vein (AV) anastomoses [1,2]. This shared part was described by Friedrich Schatz as the 'third circulation' in his comprehensive late 19th-century work [3].

AV anastomoses are often referred to as 'deep and unidirectional' due to their capillary-level occurrence, enabling blood flow in only one direction [1,4]. In contrast, direct surface anastomoses (artery-to-artery; AA or vein-to-vein; VV) permit bidirectional blood flow, depending on intertwin vascular pressure gradients. Unidirectional AV anastomoses may lead to imbalanced net blood flow, potentially causing twin-twin transfusion syndrome (TTTS) and twin anemia-polycythemia sequence (TAPS) [5–7].

Intertwin blood exchange via the different anastomoses may benefit the growth of a twin with a smaller part of the placenta if unequally divided, which is the primary cause of selective fetal growth restriction (sFGR) [8–10]. Through intertwin blood exchange, the twin with the smaller placental part may recruit additional nutrients and oxygen from its co-twin on the larger part [9,11]. As such, the presence and size of AA- and VV anastomoses have a positive impact, reducing birthweight

* Corresponding author. Fetal Medicine Unit, Dept. Obstetrics and Gynecology, University Hospitals Leuven, Herestraat 49, 3000, Leuven, Belgium.
E-mail address: liesbeth.lewi@uzleuven.be (L. Lewi).
[1] L Lewi is the recipient of a grant by the FWO Fonds Wetenschappelijk Onderzoek 1804723N.

https://doi.org/10.1016/j.placenta.2023.12.023
Received 13 October 2023; Received in revised form 20 December 2023; Accepted 27 December 2023
Available online 30 December 2023

discordance (BWD) relative to placental discordance [10,12].

The significance of the shared 'third' circulation has not been thoroughly assessed in relation to the growth of the twin with the smaller part. Insight into the angioarchitecture and its role in unequally divided placentas will enhance our understanding of the pathophysiology of sFGR and may lead to improved clinical management in the future. This study aims to examine whether a more elaborate intertwin blood exchange through AV anastomoses, and thus more extensive shared circulation, benefits the twin with the smaller part in unequally divided placentas. Second, we compare the size of the shared circulation between the different sFGR types.

2. Materials and methods

2.1. Study population

Both the Leiden University Medical Centre (LUMC) and University Hospital Leuven (UZ Leuven) have consistently injected color dye into MC placentas over several years, resulting in an extensive data collection [10,12]. The methods employed for placenta dye injection remained consistent across both centers over time [1,5]. Both centers serve as referral centers for complex MC twin pregnancies, resulting in a diverse case mix representative of unique MC twin complications. This retrospective study focused solely on unequally divided MC placentas, defined by a placental ratio of ≥1.5, signifying that the twin with the larger part received ≥60 % of the placental blood flow [8]. Placentas of the UZ Leuven were obtained from two previous prospective studies: the EuroTwin2Twin- and TWINSHARE studies (#QLG1-CT-2002-01632 and ClinicalTrials.gov Identifier: NCT03024918), conducted between February 2004–October 2008 and August 2016 and January 2023, respectively. Placentas from the LUMC between January 2010 and December 2022 were eligible for inclusion.

Placentas involving a birth before 24 weeks, double or single fetal demise were excluded. Cases with lethal congenital malformations, TTTS, and TAPS were excluded because of their influence on fetal growth and distinct placental angioarchitecture [13]. TTTS and TAPS were characterized based on criteria previously outlined [14,15]. Lastly, placentas that were too damaged for the vasculature to be visible or photos that did not meet the required quality standards for precise measurement and alignment of placental anastomoses were excluded. The ATTACHED study (ArTery-To-vein Anastomoses in unequally divided plaCentas and tHEir association with birthweight Discordance) was approved, and written informed consent was waived by the ethics committees of LUMC (22–028/MK) and UZ Leuven (S67535). The cohorts are part of previous publications [10,12,16–20].

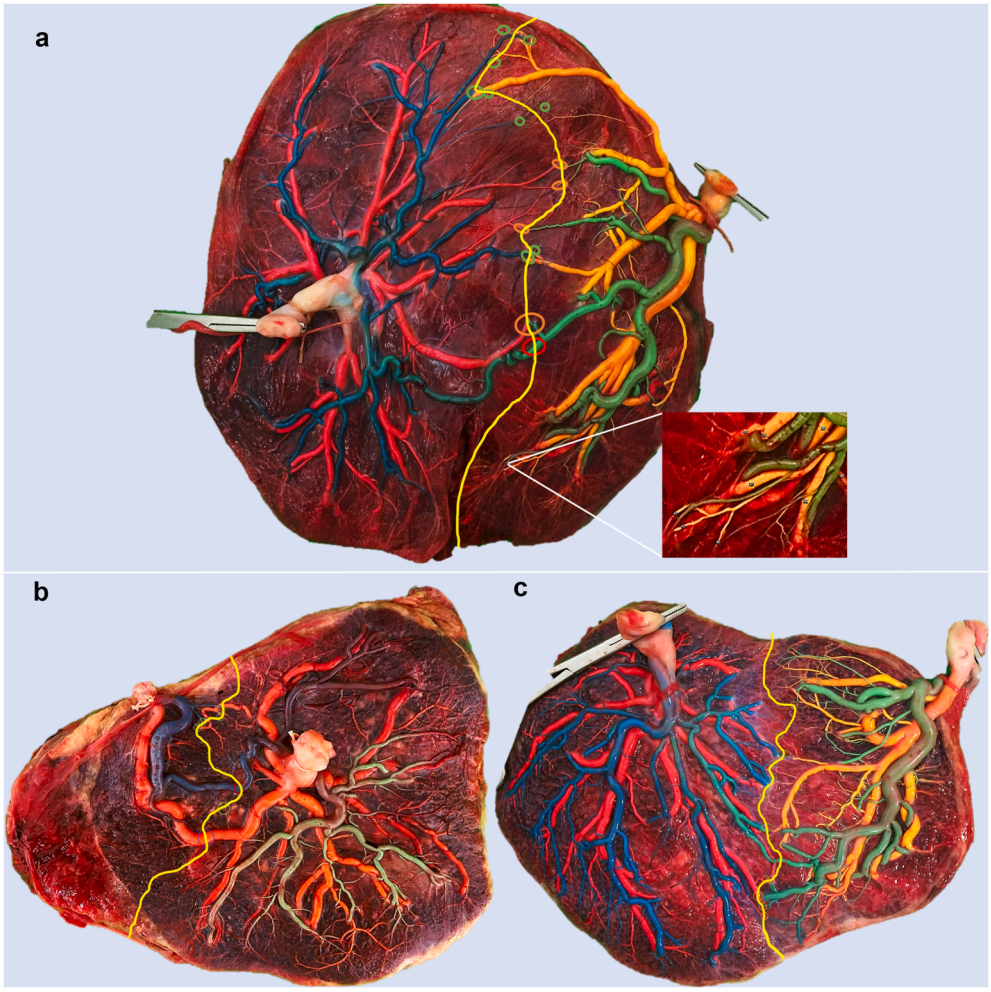

Fig. 1. 1.a. (top) Measuring the vascular anastomoses. The shared anastomoses are circled (green: AV anastomoses from the larger to the smaller part, orange: AV anastomoses from the smaller to the larger part, red: AA anastomosis). Close up: measuring the AV connections of the smaller placental part. 1.b. (bottom left) Placenta with a relatively large shared part (high AV ratio) (1.19) and low BWR/PR (0.37). 1.c. (bottom right) Placenta with a relatively small shared part (low AV ratio) (0.23) and high BWR/PR (0.99). *AV: artery-to-vein, AA: artery-to-artery, BWR: birthweight ratio, PR: placental ratio Dye colors: blue and green mark the arteries, red and yellow the veins. The vascular equator is represented by the yellow line.*

2.2. Placental studies

Placental dye injection methods have been previously outlined [1,5]. Post-dye injection, photographs were taken perpendicular to the placental surface. These images were saved for computer analysis using ImageJ (version 1.54b; National Institutes of Health, USA). Twin-specific colored dyes delineated individual fetal territories. The intertwin anastomoses (AA, VV, and AV anastomoses) as well as the individual AV connections within the smaller placental part were quantified and their external diameters were measured. AV anastomoses were identified when an unpaired artery from one twin entered the chorionic plate within 1.0 mm of an unpaired vein from the other twin [21]. Measurement of each AA, VV, and vein of an AV anastomosis was performed at the level of the vascular equator where the vessels would be coagulated in case of selective laser ablation [22]. The venous component of each individual AV connection was measured in the smaller part (Fig. 1). If more than one AA or VV anastomosis was present, the diameters and areas were summed. Cord insertion sites were categorized as concordant (identical insertions), intermediate (central – marginal or marginal – velamentous), or discordant (central – velamentous) [23].

2.3. Data collection

Maternal and pregnancy characteristics were collected, including maternal age, parity, conception mode, the presence of sFGR, umbilical artery (UA) Doppler flow pattern in the smaller twin in sFGR, mode of delivery, gestational age (GA) at birth, and birthweight (BW) of each twin. SFGR was defined by a BWD of ≥20 % [24]. SFGR cases were categorized by Gratacós classification based on the UA Doppler flow pattern in the smaller twin, distinguishing among positive end-diastolic flow (pEDF; Type I), persistent absent or reversed end-diastolic flow (A/REDF; Type II) and intermittent absent or reversed end-diastolic flow (iA/REDF; Type III) [25]. The UA flow pattern most prevalent throughout gestation was reported.

2.4. Data analysis

We chose to measure the diameter of the AV anastomoses and individual AV connections as a measure of the shared and individual part on the placental surface. To account more accurately for the impact on blood flow, we have calculated the cross-sectional areas of all the vessels using the following formula: $area\ (A) = \pi \left(\frac{D}{2}\right)^2$. The third shared part (total area of the AV anastomoses) was determined by summing the areas of all veins involved in AV anastomoses between the twins. The individual small part was calculated similarly, by summing the areas of all veins involved in individual AV connections within the small placental part (total areas of individual AV connections).

The AV ratio represents the size of the third shared part relative to the individual smaller part. It was calculated as the third shared part (total area of the AV anastomoses) divided by the individual small part (total area of the individual AV connections). The AV ratio measures the extent of shared circulation in comparison to the individual circulation within the small placental share. A higher AV ratio indicates a larger shared circulation relative to the individual circulation.

Net AV flow was calculated as the difference between the area of AV anastomoses towards the larger placental part and those towards the smaller part. A positive value indicated net AV flow towards the larger part, while a negative value indicated net AV flow towards the smaller part.

BWD was calculated as the difference between the larger BW and the smaller BW, divided by the larger BW. The placental ratio (PR) was calculated by dividing the larger placental part by the smaller part [10,12]. Finally, the BW ratio (BWR) was calculated as the BW of the twin with the smaller placental part divided by the BW of the twin with the larger part. A BWR/PR < 1 indicated a lower BWD relative to placental discordance, e.g., twins with comparable BW despite an unequally divided placenta [12].

To address the primary study aim, uni- and multivariable linear regression was conducted to examine the association between the BWR/PR and the AV ratio, the area size of the AA and VV anastomoses, the total AV area, the net AV flow and the cord insertion discordance. Statistically significant associations ($p < 0.05$) were incorporated into a multivariable linear regression model. Given the high correlation between the AV ratio and total AV anastomotic area, only the AV ratio was included in the multivariable regression analysis.

For our second aim, we compared placental angioarchitecture among different sFGR types. The Kruskal-Wallis H test for numerical data and the Pearson's Chi-squared test for categorical data were used, as appropriate.

Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.) was used for all analyses. Data are presented as median (interquartile range (IQR)) or number/total number (percentage). A 2-sided p-value <0.05 was considered statistically significant.

3. Results

A total of 369 eligible unequally placentas were identified in our databases. After applying the exclusion criteria, 352 placentas were included for further analysis (Fig. 2).

Maternal and obstetric characteristics are summarized in Table 1. Notably, half of the twin pairs had sFGR. Most sFGR cases presented with either pEDF (43 %) or iA/REDF (37 %). Placental characteristics are summarized in Table 2. In 16/352 (5 %) pairs, the smaller twin had the larger placental part. In 12/352 placentas (3 %), there were no anastomoses. The median AV ratio was 0.21 (IQR 0.07–0.47), indicating that the shared part was about one-fifth the size of the smaller part. The median BWR/PR was 0.6, indicating a 40 % lower BW difference relative to placental discordance. The maximum PR associated with two live births in our series was 9.1, indicating that the twin with the larger share received ≥90 % of the placental blood flow. This placenta also had the largest AV ratio of 2.7, implying a third shared part that is almost three times larger than the smaller individual part.

The results of the linear regression analysis examining the association of the AV ratio and angioarchitecture with the BWR/PR are presented in Table 3 and illustrated in Fig. S1. Univariable linear regression indicated that the AV ratio, the AA, VV, total AV areas, and the cord insertion discordance were all negatively associated with the BWR/PR.

Multivariable linear regression confirmed a negative association between the BWR/PR and the AV ratio, after adjusting for the AA and VV areas, as well as the cord insertion discordance. Examples of sFGR placentas with high and low AV ratios are displayed in Fig. 1.

Within the sFGR subgroups, significant variations in placental angioarchitecture were observed among the different types of sFGR. Twin pairs with iA/REDF (Type III) exhibited the highest PR, AV ratio, AA, VV and total AV anastomotic areas, along with cord insertion discordance, while the BWR/PR was lowest compared to those with pEDF (Type I) or A/REDF (Type II) (Table 4).

4. Discussion

This study reveals that in MC twins with an unevenly divided placenta, a larger shared circulation, relative to the individual circulation of the smaller placental part, is associated with a reduced discordance in BW relative to placental discordance. This negative association remains significant after accounting for the AA and VV areas. In other words, a larger shared circulation appears to lessen the impact of an unequally divided placenta. While larger AA and VV anastomoses also mitigate the impact of an unequally divided placenta, their effect is somewhat less pronounced than that of the shared circulation. When

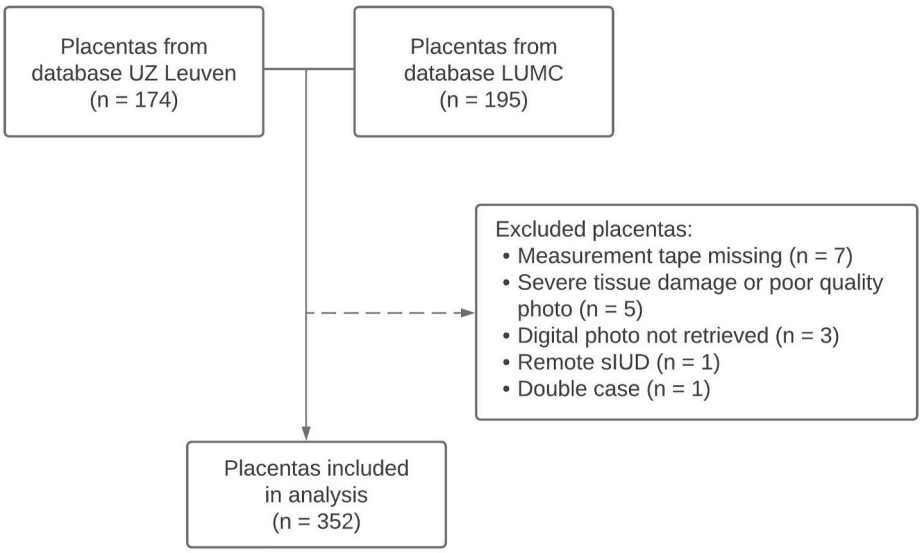

Fig. 2. Placenta flowchart.

Table 1
Maternal and obstetric characteristics.

Characteristics	352 pregnancies
Maternal age (years)[a]	31 (28–34)
Nulliparous[b]	174 (50)
Mode of conception[c]	237 (84)
Spontaneous	42 (15)
Assisted conception	
Selective fetal growth restriction (sFGR)	176 (50)
sFGR type[d]	75 (43)
pEDF (Type I)	17 (10)
A/REDF (Type II)	66 (37)
iA/REDF (Type III)	
Mode of delivery[e]	104 (35)
Vaginal	196 (65)
Caesarean section	
Gestational age birth (weeks)	34 + 3 (32 + 0–36 + 1)
Birthweight twin on smaller part (g)	1810 (1255–2235)
Birthweight win on larger part (g)	2260 (1762–2620)
Birthweight ratio[f]	1.25 (1.11–1.43)
Birthweight discordance	19.8 (9.9–30.0)

Data presented as median (interquartile range) or number/total (percentage).
[a] Missing in 20.
[b] Missing in 4.
[c] Missing in 69.
[d] Missing in 18.
[e] Missing in 52.
[f] Calculated as BW twin small part/BW twin large part; pEDF, positive end diastolic flow in smaller twin's umbilical artery; A/REDF, absent or reversed end diastolic flow; iA/REDF, intermittent absent or reversed end diastolic flow.

Table 2
Placental characteristics.

Characteristics	352 placentas
Placental territory ratio (PR)[a]	2.0 (1.7–2.7)
Birthweight ratio[b]/placental territory ratio (BWR/PR)	0.6 (0.5–0.7)
AV anastomosis present	340 (97)
Number of AV anastomoses	9 (6–14)
Total diameter AV anastomoses (mm)	9.04 (5.03–14.99)
Total area AV anastomoses (mm2)	11.55 (4.73–23.80)
Total diameter AV anastomosis small-to-large part (mm)	4.59 (1.78–8.48)
Total area[c] AV anastomosis small-to-large part (mm^2)	5.05 (1.09–13.41)
Total diameter AV anastomosis large-to-small part (mm)	3.37 (1.22–6.87)
Total area[c] AV anastomosis large-to-small part (mm^2)	3.26 (0.68–8.90)
Total diameter individual AV connections small part (mm)	34.31 (23.28–47.57)
Total area[c] individual AV connections small part (mm^2)	60.91 (36.33–85.69)
AV ratio[d]	0.21 (0.07–0.47)
AA anastomosis present	326 (93)
More than one	27 (8)
Total diameter AA anastomoses (mm)[e]	2.69 (1.66–3.92)
Total area[c] AA anastomoses (mm^2)[e]	5.64 (2.04–11.34)
VV anastomosis present	96 (27)
More than one	17 (18)
Total diameter VV anastomoses (mm)[f]	3.99 (2.68–5.35)
Total area[c] VV anastomoses (mm^2)[f]	12.25 (5.51–19.40)
Net AV flow (mm)[g]	1.41 (−1.95 – 8.17)
Concordant cord insertion	74 (21)
Intermediate cord insertion	149 (42)
Discordant cord insertion	129 (37)

Data presented as median (interquartile range) or number/total (percentage). AV,artery-to-vein; AA, artery-to-artery; VV, vein-to-vein.
[a] Calculated as large placental part/small part.
[b] Calculated as BW twin small part/BW twin large part.
[c] Areas (A) calculated as: $A = \pi \left(\frac{D}{2}\right)^2$.
[d] Calculated as total area AV anastomoses/total area individual AV connections small part, only calculated in placentas with AV anastomoses (n = 340).
[e] In placentas that have an AA present.
[f] In placentas that have a VV present.
[g] Calculated as total area of the AV anastomoses to the larger part minus those towards the smaller part; only calculated in placentas with AV anastomoses (n = 340).

compared to placentas of sFGR pregnancies with pEDF (Type I) and A/REDF (Type II), iA/REDF (Type III) placentas exhibit the largest shared circulation relative to the small individual part. Simultaneously, they also display the lowest BWD to placental discordance, which highlights the importance of the shared circulation in Type III sFGR.

Our study is the first to quantify the extent of the shared circulation in relation to the individual circulation of the smaller placental part. We believe this approach provides a more nuanced understanding of the interplay between shared and individual circulations, as these two should be considered in relation to each other. Our results also validate the previously established association between AA and VV anastomoses and BW discordance relative to placental discordance [10,12,26,27]. We did not observe an impact of any net AV transfusion on BWD relative to placental discordance. Furthermore, while cord insertion type showed an association with birth weight discordance relative to placental discordance in the univariable analysis, this association became

Table 3
Uni-and multivariable regression analyses for the association of the angioarchitecture with the birthweight relative to placental discordance.

Characteristics	Univariable linear regression			Multivariable linear regression		
	β-coefficient (95 % CI)	p-value	aR^2	β-coefficient (95 % CI)	P-value	aR^2
AV ratio[a]	**−0.09 (-0.12–-0.07)**	**<.001**	**0.12**	**−0.06 (-0.09–-0.03)**	**<.001**	0.21
Total area[b] **AA (mm^2)**	**−0.008 (-0.01–-0.006)**	**<.001**	**0.15**	**−0.005 (-0.008–-0.003)**	**<.001**	
Total area[b] **VV (mm^2)**	**−0.004 (-0.006–-0.002)**	**<.001**	**0.05**	**−0.002 (-0.004–-0.00002)**	**.048**	
Total area[b] **AV (mm^2)**	**0.002 (-0.003–-0.0009)**	**<.001**	**0.04**	–	–	
Net AV flow (mm^2)[c]	−0.0005 (-0.002 – 0.0006)	.377	−0.0006	–	–	
Concordant cord	Reference	.267	0.02	−0.01 (−0.05 – 0.03)	.576	
Intermediate cord	−0.026 (−0.072–-0.020)	.008		−0.04 (−0.08 – 0.006)	.094	
Discordant cord	−0.063 (−0.111–-0.016)					

Data presented as median (interquartile range). AV, artery-to-vein; AA, artery-to-artery; VV, vein-to-vein.

[a] Calculated as total area AV anastomoses/total area individual AV connections small part.

[b] Areas (A) calculated as: $A = \pi \left(\frac{D}{2}\right)^2$.

[c] Calculated as total area of the AV anastomoses to the larger part minus those towards the smaller part.

Table 4
Placental characteristics according to the type of selective fetal growth restriction.

Characteristics	pEDF-Type I (n = 75)	A/REDF-Type II (n = 17)	iA/REDF-Type III (n = 66)	p-value
Gestational age birth (weeks)	**34 + 2 (32 + 4–36 + 0)**	**31 + 1 (29 + 0–31 + 4)**	**31 + 5 (29 + 4–32 + 4)**	**<.001**
BW discordance (%)	**29.07 (25–35.1)**	**36.96 (31.6–46.1)**	**31.55 (26.1–38.3)**	**<.005**
BW ratio (BWR)[a]	**1.41 (1.33–1.54)**	**1.59 (1.46–1.85)**	**1.46 (1.35–1.62)**	**<.008**
Placental territory ratio (PR)[b]	**2.07 (1.78–2.64)**	**2.26 (2.08–3.17)**	**3.00 (2.51–3.67)**	**<.001**
BWR/PR ratio	**0.67 (0.57–0.79)**	**0.67 (0.5–0.86)**	**0.50 (0.39–0.59)**	**<.001**
AV ratio[c,d]	**0.16 (0.05–0.32)**	**0.26 (0.06–0.63)**	**0.49 (0.26–0.87)**	**<.001**
Total diameter AA (mm)[e]	**2.62 (1.43–3.79)**	**2.15 (1.36–2.84)**	**3.28 (2.39–5.12)**	**<.001**
Total area[d] **AA (mm^2)**[e]	**5.39 (1.61–8.76)**	**3.36 (1.45–5.63)**	**8.07 (4.49–18.63)**	**<.001**
Total diameter VV (mm)[f]	3.81 (2.65–4.85)	2.87 (1.02–3.44)	4.36 (3.27–5.65)	0.099
Total area[d] **VV (mm^2)**[f]	8.62 (4.40–17.87)	6.47 (0.82–9.29)	13.50 (8.58–19.80)	0.066
Total diameter AV (mm)[g]	**6.99 (3.86–11.82)**	**6.71 (5.26–14.26)**	**13.38 (7.79–17.89)**	**<.001**
Total area[d] **AV (mm^2)**[g]	**11.12 (3.76–18.15)**	**8.15 (3.55–21.03)**	**19.05 (8.91–29.37)**	**0.005**
Net AV flow[h]	1.34 (−0.77 – 4.56)	1.20 (−0.63 – 3.55)	1.63 (−3.93 – 6.35)	.949
Discordant cord insertion	**26 (35)**	**6 (35)**	**41 (62)**	**.003**

Data presented as median (interquartile range) or number/total (percentage). GA, gestational age; BW, birthweight, AV, artery-to-vein; AA, artery-to-artery; VV, vein-to-vein.

[a] Calculated as BW twin small part/BW twin large part.

[b] Calculated as large part/small part.

[c] Calculated as total area AV anastomoses/total area individual AV connections small part.

[d] Area (A) calculated as: $A = \pi \left(\frac{D}{2}\right)^2$.

[e] In placentas that have an AA present.

[f] In placentas that have an VV present.

[g] Only calculated in sFGR placentas with AV anastomoses (n = 170).

[h] Calculated as total area of the AV anastomoses to the larger part minus those towards the smaller part.

non-significant when adjusting for the AA, VV, and AV ratio.

Denbow et al. initially coined the term ‘rescue transfusion’ to describe the phenomenon in which a twin with a smaller placental part harnesses oxygen and nutrients from its co-twin through AV anastomoses, resulting in an increased BW [7]. However, Denbow’s study encompassed a substantial proportion of TTTS placentas (30 %), whereas TTTS and TAPS were excluded from our series. Transfusion imbalances such as TTTS or TAPS affect twin growth [28,29]. Additionally, their analysis primarily focused on the number of AV anastomoses without considering their diameters. In a recent series from UZ Leuven on 247 placentas, including equally divided placentas [12], net AV flow did not impact fetal growth either. It is probably the intertwin blood exchange that benefits the twin on the smaller part rather than a net AV transfusion, which, in the absence of TTTS and TAPS, must be balanced by a bidirectional AA or VV anastomosis. The term ‘rescue exchange’ rather than ‘rescue transfusion’ would more accurately describe the beneficial effect of the shared circulation on BWD. Furthermore, our subgroup analysis of sFGR cases showed that pregnancies with iA/RAEDF (Type III) have the most elaborate intertwin blood exchange, which appears to benefit the twin on the smaller part, aligning with previously documented findings [10,17,25–27].

The clinical relevance of our findings is that the shared circulation may be critical for the growth of the twin with the smaller part. If the AV anastomoses are targeted for coagulation through laser ablation in the context of sFGR, a reduced supply of oxygen and nutrients can potentially be lethal for the twin on the smaller placental part. This ominous scenario was recently confirmed in a systematic review by Buskmiller et al. [30].

In interpreting our findings, we must acknowledge the limitations of color-dye research involving placentas. Accurate dye injection was only possible for dual survivors, potentially introducing a selection bias that favors milder degrees of unequal placental sharing. Moreover, the visibility of small anastomoses could be compromised because of incomplete injection; however, we were able to identify and quantify anastomoses as minute as 0.2 mm. Additionally, the assessment of anastomoses is founded upon two-dimensional measurements on photographic records. However, the dynamics of intertwin blood exchange involve multiple other factors, including total vessel length, external and internal pressure, viscosity, and branching patterns [2]. Hence, our study methodology did not allow for the precise estimation of absolute blood flow. Moreover, due to the nature of our study design, the inclusion of placental weight in our analysis was not feasible, although we acknowledge its potential value in correlation with birthweight [31,32]. Furthermore, placental examination is inherently static, capturing a singular time point in a dynamic process. Placental growth may influence the development of anastomoses, potentially leading to their persistence or atrophy, contingent on the flow volume and

velocity, a complex interplay recognized already by Friedrich Schatz [2, 3]. Data regarding the natural progression of anastomotic dimensions relative to GA are currently unavailable. Consequently, the normalization of diameters between the different sFGR subtypes is impossible, and differences in GA at birth between Type I and Type II-III may have influenced the difference in anastomotic diameter. However, Type II and III delivered at comparable GA, and the observation that Type III has larger AA anastomoses seems valid, as confirmed also by other series [10,12,16,25,26]. Although our study provides insights into the relationships between placental characteristics and BWD, implications for long-term infant health remain areas that warrant further investigation. Lastly, the role of placental pathology in relation to the development of growth discordance should be investigated in future studies.

As a strength, our study benefits from a substantial placental series obtained from two expert centers with a long-standing experience in placental injection studies. The systematic approach employed for placental injection and subsequent photographic analysis enhances the robustness and reliability of our data collection process. Another notable strength is our consideration of vessel areas; in addition to measuring diameter, we have calculated cross-sectional areas. We contend that this approach more accurately represents the actual impact of the shared circulation and flow, providing a more comprehensive understanding compared to calculations based solely on one-dimensional vessel diameters.

In summary, our study represents the first quantitative assessment of the overall extent of AV anastomoses. An extensive shared circulation, relative to the smaller placental part, diminishes the impact of an unequally divided placenta. This effect surpasses that of any AA and VV anastomoses and is particularly pronounced in placentas of sFGR pregnancies with iA/REDF (Type III). These insights enhance our understanding of the intricate interplay between placental angioarchitecture and twin growth, particularly when the placenta is unequally divided.

CRediT authorship contribution statement

A.T.R. Noll: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **F.C. Lof:** Data curation, Formal analysis, Investigation, Methodology. **S. G. Groene:** Data curation, Methodology. **M.C. Haak:** Data curation. **E. Lopriore:** Data curation, Writing – review & editing. **F.M. Russo:** Data curation, Writing – review & editing. **F. Slaghekke:** Writing – review & editing. **L.S.A. Tollenaar:** Data curation. **J. Van der Merwe:** Data curation, Writing – review & editing. **E.J.T. Verweij:** Data curation, Writing – review & editing. **L. Lewi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2023.12.023.

References

[1] L. Lewi, J. Deprest, K. Hecher, The vascular anastomoses in monochorionic twin pregnancies and their clinical consequences, Am. J. Obstet. Gynecol. 208 (1) (2013) 19–30.
[2] V.J. Baldwin, Pathology of Multiple Pregnancy, XV, Springer New York, New York, 1994, p. 409.
[3] F. Schatz, Die Gefässverbindungen der Placentakreisläufe eineiiger Zwillinge, ihre Entwickelung und ihre Folgen, Archiv für Gynäkologie (1898).
[4] L.Y. Wee, et al., Characterisation of deep arterio-venous anastomoses within monochorionic placentae by vascular casting, Placenta 26 (1) (2005) 19–24.
[5] E. Lopriore, et al., Accurate and simple evaluation of vascular anastomoses in monochorionic placenta using coloured dye, J. Vis. Exp. (55) (2011) e3208.
[6] E. Lopriore, et al., Placental characteristics in growth-discordant monochorionic twins: a matched case-control study, Placenta 33 (3) (2012) 171–174.
[7] M.L. Denbow, et al., Placental angioarchitecture in monochorionic twin pregnancies: relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome, Am. J. Obstet. Gynecol. 182 (2) (2000) 417–426.
[8] A.L. Fick, et al., Unequal placental sharing and birth weight discordance in monochorionic diamniotic twins, Am. J. Obstet. Gynecol. 195 (1) (2006) 178–183.
[9] L. Lewi, et al., Placental sharing, birthweight discordance, and vascular anastomoses in monochorionic diamniotic twin placentas, Am. J. Obstet. Gynecol. 197 (6) (2007) 587.e1–587.e8.
[10] S.G. Groene, et al., Impact of placental sharing and large bidirectional anastomoses on birth weight discordance in monochorionic twins: a retrospective cohort study in 449 cases, Am. J. Obstet. Gynecol. 227 (5) (2022) 755.e1–755.e10.
[11] G. Machin, K. Still, T. Lalani, Correlations of placental vascular anatomy and clinical outcomes in 69 monochorionic twin pregnancies, Am. J. Med. Genet. 61 (3) (1996) 229–236.
[12] I. Couck, et al., The association between vein-to-vein anastomoses and birth weight discordance in relation to placental sharing in monochorionic twin placentas, Placenta 118 (2022) 16–19.
[13] M.E. De Paepe, et al., Placental markers of twin-to-twin transfusion syndrome in diamniotic-monochorionic twins: a morphometric analysis of deep artery-to-vein anastomoses, Placenta 31 (4) (2010) 269–276.
[14] R.A. Quintero, et al., Staging of twin-twin transfusion syndrome, J. Perinatol. 19 (8 Pt 1) (1999) 550–555.
[15] A. Khalil, et al., Consensus diagnostic criteria and monitoring of twin anemia-polycythemia sequence: delphi procedure, Ultrasound Obstet. Gynecol. 56 (3) (2020) 388–394.
[16] L. Lewi, et al., Placental sharing, birthweight discordance, and vascular anastomoses in monochorionic diamniotic twin placentas, Am. J. Obstet. Gynecol. 197 (6) (2007), 587 e1-e8.
[17] L. Lewi, et al., Clinical outcome and placental characteristics of monochorionic diamniotic twin pairs with early- and late-onset discordant growth, Am. J. Obstet. Gynecol. 199 (5) (2008), 511 e1-e7.
[18] I. Couck, et al., The assessment of placental sharing using X-ray angiogram versus digital photograph: a prospective study, Placenta 83 (2019) 1–4.
[19] I. Couck, et al., The vascular equator in monochorionic twin placentas, Placenta 99 (2020) 193–196.
[20] S.G. Groene, et al., Placental characteristics in monochorionic twins with selective intrauterine growth restriction in relation to the umbilical artery Doppler classification, Placenta 71 (2018) 1–5.
[21] G.J.B. Kurt Benirschke, N. Rebecca, Baergen Pathology of the Human Placenta, sixth ed., Springer-Verlag Berlin, Heidelberg GmbH & Co. KG, 2016, p. 941.
[22] R.A. Quintero, et al., Selective photocoagulation of communicating vessels in the treatment of monochorionic twins with selective growth retardation, Am. J. Obstet. Gynecol. 185 (3) (2001) 689–696.
[23] I. Couck, et al., Does site of cord insertion increase risk of adverse outcome, twin-to-twin transfusion syndrome and discordant growth in monochorionic twin pregnancy? Ultrasound Obstet. Gynecol. 52 (3) (2018) 385–389.
[24] S.G. Groene, et al., Neonatal management and outcome in complicated monochorionic twins: what have we learned in the past decade and what should you know? Best Pract. Res. Clin. Obstet. Gynaecol. 84 (2022) 218–228.
[25] E. Gratacós, et al., A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin, Ultrasound Obstet. Gynecol. 30 (1) (2007) 28–34.
[26] X. Wang, et al., The relationship between placental characteristics and birthweight discordance in different types of selective intrauterine growth restriction in monochorionic diamniotic twins: a single-center 7 year cohort study, Prenat. Diagn. 41 (12) (2021) 1518–1523.
[27] X. Wang, et al., Comparison of pregnancy outcomes and placental characteristics between selective fetal growth restriction with and without thick arterio-arterial anastomosis in monochorionic diamniotic twins, BMC Pregnancy Childbirth 22 (1) (2022) 15.
[28] R.H. Chmait, et al., Fetal growth after laser therapy for twin-twin transfusion syndrome, Am. J. Obstet. Gynecol. 199 (1) (2008), 47 e1-e6.
[29] E. Lopriore, et al., Placental characteristics in monochorionic twins with and without twin anemia-polycythemia sequence, Obstet. Gynecol. 112 (4) (2008) 753–758.
[30] C. Buskmiller, et al., Laser Therapy versus Expectant Management for Selective Fetal Growth Restriction in Monochorionic Twins: A Systematic Review, Prenat Diagn, 2023.
[31] Y.L. Chang, et al., The individual fetal weight/estimated placental weight ratios in monochorionic twins with selective intrauterine growth restriction, Prenat. Diagn. 28 (3) (2008) 217–221.
[32] M.E. De Paepe, et al., Placental weight, birth weight and fetal:placental weight ratio in dichorionic and monochorionic twin gestations in function of gestational age, cord insertion type and placental partition, Placenta 36 (2) (2015) 213–220.