Selective fetal growth restriction in identical twins: from womb to adolescence

Groene, S.G.

Chapter 2

Impact of placental sharing and large bidirectional anastomoses on birth weight discordance in monochorionic twins: a retrospective cohort study in 449 cases.

American Journal of Obstetrics and Gynecology. 2022 Nov 1; 227(5):755.E1-755.E10.

Sophie G. Groene

Kristine M. Openshaw*

Laura R. Jansén-Storbacka*

Femke Slaghekke

Monique C. Haak

Bastiaan T. Heijmans

Jeanine M.M. van Klink

Arno A.W. Roest

Lotte E. van der Meeren

Enrico Lopriore

*Both authors contributed equally to this paper

Abstract

Background. In monochorionic twin pregnancies the fetuses share a single placenta. When this placenta is unequally shared, a discordant antenatal growth pattern ensues resulting in high rates of perinatal morbidity and mortality. Understanding of placental pathophysiology is paramount in devising feasible antenatal management strategies. Unequal placental sharing is not the sole determinant of a birth weight discordance as there is no one-to-one relationship with placental share discordance. Placental angioarchitecture, especially the presence of large bidirectional anastomoses, is thought to affect this relationship by allowing for a compensatory intertwin blood flow.

Objective(s). To assess whether placental angioarchitecture can affect birth weight discordance in live-born monochorionic twins, the aim of our study is twofold: 1) to assess the relationship between birth weight discordance and placental share discordance and 2) to examine to what extent large bidirectional anastomoses can compensate for the effect of unequal placental sharing on birth weight discordance, with a subgroup analysis for umbilical artery Doppler flow patterns in cases with a birth weight discordance ≥ 20%.

Study design. Retrospective cohort study including monochorionic twin pregnancies followed in our center between March 2002-June 2021, in which twins with a birth weight discordance ≥ 20% were classified according to umbilical artery Doppler flow patterns of the smaller twin. We excluded cases with twin-twin transfusion syndrome and twin anemia polycythemia sequence. Monochorionic placentas of live-born twins were injected with dye and images were saved for computer measurements of placental sharing and diameter of anastomoses. Univariate linear regression of the relationship between placental share discordance and birth weight discordance (both calculated as larger weight or share – smaller weight or share / larger weight or share x 100%), and the relationship between arterio-arterial and veno-venous diameter and birth weight ratio/placental territory ratio were performed.

Results. A total of 449 placentas were included in the analysis. Placental share discordance was positively correlated with birth weight discordance (β-coefficient 0.325; 95% CI; 0.254-0.397, $p < 0.0001$). Arterio-arterial diameter was negatively correlated with birth weight ratio/placental territory ratio (β-coefficient -0.041; 95% CI -0.059--0.023, $p < 0.0001$), meaning that an increase in arterio-arterial diameter leads to less birth weight discordance than expected for the amount of placental share

discordance. There was no relationship between veno-venous diameter and birth weight ratio/placental territory ratio (β-coefficient -0.007; 95% CI -0.027-0.012, p = 0.473).

Conclusions. Birth weight discordance in monochorionic twins is strongly associated with placental share discordance. Large arterio-arterial anastomoses can mitigate the effect of unequal placental sharing.

Funding: The Dutch Heart Foundation (grant number 2017T075)

Introduction

In monochorionic (MC) twin pregnancies the fetuses share a single placenta[1]. This shared placenta can give rise to different complications due to vascular anastomoses on its surface[2]. The most prevalent complication is a discordant antenatal growth pattern resulting in a birth weight discordance (BWD)[3,4]. A large BWD is associated with increased rates of neonatal morbidity as well as impaired long-term neurodevelopment[5-7]. The antenatal classification of the severity of discordant antenatal growth (generally termed selective fetal growth restriction (sFGR)) proposed by Gratacós et al. in 2007 is based on umbilical artery (UA) end-diastolic flow patterns of the smaller twin and allows clinicians to estimate the prognosis[8]. Type I is characterized by positive end-diastolic flow (pEDF), type II by persistent absent or reversed end-diastolic flow (A/REDF) and type III by intermittent A/REDF (iA/REDF). Type II and type III have the most unpredictable clinical course and thereby still exhibit the highest rates of perinatal morbidity and mortality.

Understanding of placental pathophysiology is paramount in devising feasible antenatal management strategies for pregnancies with discordant growth. The primary cause of a BWD in MC twins is generally considered to be unequal placental sharing[9]. However, it is not the sole determinant as there is no one-to-one relationship between placental share discordance and BWD[10]. Placental angioarchitecture, especially the presence of large bidirectional anastomoses, is thought to affect this relationship by allowing for a compensatory intertwin blood flow. This hypothesis was put forward by the previous finding that type III sFGR placentas have a relatively lower degree of BWD than expected for the amount of placental share discordance whilst also having a large arterio-arterial (AA) anastomosis[11]. Yet, this large AA anastomosis also increases the risk of acute feto-fetal transfusion after demise of either twin. Hence, intensive fetal surveillance in type III is advised. This illustrates that each UA Doppler flow pattern as described by Gratacós is an expression of a distinct placental mechanism that affects clinical decision making, particularly in type II and type III. By further studying placental sharing and angioarchitecture we can gain more etiological knowledge on the origin of discordant antenatal growth that allows us to enhance our risk assessment and subsequent management approach in the future.

Therefore, the aim of this study is twofold: 1) to assess the relationship between BWD and placental share discordance (a measure for unequal placental sharing) and 2) to examine to what extent large bidirectional anastomoses (AA and VV anastomoses) can compensate for the effect of unequal placental sharing on BWD, with a subgroup analysis for each UA Doppler flow pattern as diagnosed prenatally in twin pairs with a BWD ≥ 20%.

Materials and methods

All MC twin placentas of live-born twins injected with colored dye in our center between March 2002 and June 2021 were eligible for inclusion. Placentas of monoamniotic (MA) twins, twins with twin-twin transfusion syndrome (TTTS) or twin anemia polycythemia sequence (TAPS) were excluded due to their distinct pathophysiology and corresponding placental characteristics[2,12]. We also excluded MC triplet pregnancies, cases with twin reversed arterial perfusion (TRAP) and/or other congenital abnormalities. Cases in which placental measurements were impossible due to maceration after fetal death (either single/double intrauterine fetal demise (IUFD), selective reduction or termination of pregnancy (TOP)) or damage to the placenta due to manual removal were further excluded, as well as cases with unknown birth weights.

The following maternal and neonatal baseline characteristics were collected: maternal age, gravidity, parity, UA Doppler flow pattern (for cases with a BWD ≥ 20% as this can be considered a postnatal expression of discordant antenatal growth), gestational age at birth, sex, delivery mode, birth weight, BWD (calculated as (birth weight larger twin – birth weight smaller twin)/birth weight larger twin x 100[13]), birth weight ratio (calculated as birth weight larger twin / birth weight smaller twin), proportion of neonates born small for gestational age (SGA) (defined as birth weight < 10th centile on a singleton chart)[14,15] and the incidence of neonatal mortality (defined as death within 28 days after birth). The UA Doppler flow pattern was established in line with the Gratacós classification based on antenatal ultrasound with routine UA Doppler evaluations for MC twin pregnancies, distinguishing between pEDF, persistent A/REDF and iA/REDF. As the UA Doppler flow pattern can change during the course of a pregnancy, the most prevalent type was chosen[16]. In our center, pregnancies with discordant antenatal growth are managed expectantly. In severe cases, a selective reduction is considered. Fetoscopic laser coagulation is not performed.

MC placentas are routinely injected with dye in our center as previously described[17]. After dye injection, placentas are photographed and the images are digitally saved for computer analysis using Image J version 1.57. The total number of anastomoses and the number of arterio-venous (AV) and veno-arterial (VA) anastomoses were recorded from the firstborn twin to the second-born twin, as well as the presence, number and total diameter of arterio-arterial (AA) and veno-venous (VV) anastomoses. The proportion of fetuses with a velamentous or marginal (< 1 centimeter from the margin of the placenta) cord insertion was documented for the smaller and larger twin. Fetal

territories were demarcated by the margins of the twin-specific colored dyes and expressed by a percentage of the total placental surface. Placental share discordance was calculated as (larger placental share – smaller placental share)/larger placental share x 100. Placental territory ratio was calculated in a similar manner as birth weight ratio: larger placental share / smaller placental share. Part of this data was previously published in 2018[11]. Birth weight ratio/placental territory ratio was calculated. A value below 1 suggests a lower BWD for the given placental share discordance (i.e., equal birth weights with an unequally shared placenta). A value above 1 suggest a higher BWD for the given placental share discordance (i.e., discordant birth weights with an equally shared placenta)[18]. We have chosen to report on both BWD and birth weight ratio as well as placental share discordance and placental territory ratio for comparability to other available studies reporting on similar parameters.

Statistical data was analyzed using IBM Statistics Version 25.0 (SPSS, Inc., an IBM company, Chicago, IL, USA). Data are presented as median (interquartile range), n/N (%) or n (%). To assess the first aim of our study, multivariate linear regression was performed to examine the relationship between placental share discordance, total AA diameter, total VV diameter and BWD. To assess the second aim of our study, univariate linear regression was performed to examine the relationship between both total AA and total VV diameter and birth weight ratio/placental territory ratio. We chose a different outcome measure than in the first aim, as the strong effect of placental share discordance on BWD can cloud the compensatory effect of AA and VV diameter we want to research. Birth weight ratio/placental territory ratio eliminates this strong effect from the analysis by looking at BWD relative to placental share discordance and is an outcome parameter that is consistent with previous literature[8,10,18]. When a significant association was found for both AA and VV diameter in univariate analysis, they were included in a multivariate linear regression model. A subgroup analysis per UA Doppler flow pattern in twin pairs with a BWD ≥ 20% was performed for both aims. As VV anastomoses are rare, we did not include total VV diameter in this subgroup analysis due to probable insufficient power. A *p*-value of < 0.05 was considered statistically significant. The relationship between placental share discordance, BWD, total AA and VV diameter and birth weight ratio/placental territory ratio for the total population and per UA Doppler flow pattern were plotted using RStudio Version 2021.9.2.382 (RStudio, PBC, Boston, MA, USA).

This retrospective study was approved and waived of the requirement for written informed consent by the ethics committee of the Leiden University Medical Center (LUMC) (protocol number G21.184) and funded by The Dutch Heart Foundation (grant number 2017T075). The funding source had no role in conducting the research or writing the research paper.

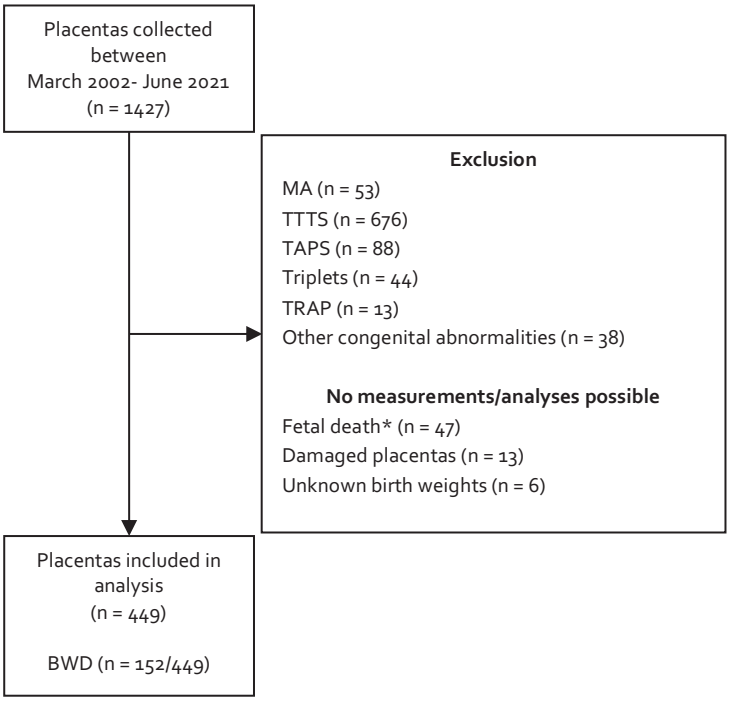

Figure 1. Flowchart of study inclusion. Of the fetal death cases, 26 were diagnosed with sFGR antenatally (estimated fetal weight (EFW) < 10th centile and EFW discordance ≥ 25%) of which 4 were type I, 10 type II and 9 type III (unknown in two cases). MA: monoamniotic, TTTS: twin-twin transfusion syndrome, TAPS: twin anemia polycythemia sequence, TRAP: twin reversed arterial perfusion, BWD: birth weight discordance. *Either single/double IUFD or selective reduction/TOP.

Results

Between March 2002 and June 2021, 1427 placentas were injected with colored dye. After applying the aforementioned exclusion criteria, 449 placentas were included for analysis (Figure 1). Of these 449 placentas, 152 (34%) had a BWD ≥ 20%.

Baseline characteristics

Baseline characteristics for the total population and the subgroup of MC twins with a BWD ≥ 20% are summarized in Table 1. Median gestational age at birth was 35.3 (IQR 32.1-36.3) weeks for the total population. Median birth weight in the smaller twin was 1956 (IQR 1415-2350) grams as opposed to 2350 (IQR 1792-2670) grams in the larger twin. BWD was 13.3% (IQR 6.3-25.2), with a birth weight ratio of 1.2 (IQR 1.1-1.3) meaning the larger twin had a 1.2 times higher birth weight than the smaller twin. Neonatal mortality occurred in 3% (11/423) of smaller twins and 1% (4/282) of larger twins.

In the subgroup of MC twins with a BWD ≥ 20% (n = 152), 71 pairs (50%) presented with pEDF, 28 pairs (20%) with A/REDF and 44 pairs (33%) with iA/REDF. The UA Doppler flow patterns was unknown in nine twin pairs as no antenatal ultrasound was available. The median gestational age at birth for the subgroup was 33.5 (IQR 31.0-35.8) weeks and 70% (212/304) were delivered by way of caesarean section. The smaller twin had a median birth weight of 1381 (IQR 996-1796) grams and the larger twin of 2566 (IQR 1540-2010) grams. Of the smaller twins, 95% (144/152) were born SGA compared to 16% (25/152) of the larger twins. Median BWD was 30.2% (IQR 25.1-36.9) and the birth weight ratio was 1.4 (IQR 1.3-1.6) implicating that the larger twin had a 1.4 times higher birth weight compared to the smaller twin. Neonatal mortality occurred in 5% (7/141) of smaller twins (of which 1/7 from a pregnancy with pEDF, 2/7 from a pregnancy with A/REDF and 4/7 from a pregnancy with iA/REDF) and 1% (2/140) of larger twins (of which 1/2 from a pregnancy with pEDF and 1/2 from a pregnancy with iA/REDF).

Placental characteristics

Placental characteristics of the 449 MC twin pregnancies and the subgroup of 152 MC twin pregnancies with a BWD ≥ 20% are presented in Table 2. AA anastomoses were present in the majority of placentas (92% (411/449)) and VV anastomoses in 24% (109/449) of the total population. Median AA diameter was 2.2 (IQR 1.3-3.0) mm and median VV diameter was 3.1 (IQR 1.8-4.3) mm. Of the smaller twins, 63% (282/449) had a

velamentous or marginal cord insertion, of which 62% (175/282) velamentous and 38% (107/282) marginal. This was the case for 23% (104/449) of the larger twins, with 33% (34/104) velamentous and 67% (70/104) marginal. Median placental share discordance was 35.1% (IQR 18.2-52.8) with 41% (IQR 33-50) of the placenta for the smaller twin and 59% (IQR 50-67) for the larger twin. Placental territory ratio was 1.5 (IQR 1.2-2.10), meaning that the larger twin had a 1.5 times larger placental share as opposed to the smaller twin. The birth weight ratio/placental territory ratio of 0.8 (IQR 0.6-0.9), implicating 0.2 times lower BWD than expected for the given placental share discordance.

Table 1. Baseline maternal and neonatal characteristics for the analyzed placentas, with the subgroup of MC twins with a BWD ≥ 20%.

Characteristics	**MC twins (n=898; 449 pregnancies)**	**BWD ≥ 20% (n=304; 152 pregnancies)**
Maternal age – *years*	32 (28-34)	31 (28-34)
Gravidity	2 (1-3)	1 (1-3)
Parity	1 (0-1)	0 (0-1)
UA Doppler flow pattern*		
pEDF		71 (50)
A/REDF		28 (20)
iA/REDF		44 (31)
Gestational age at birth – *weeks*	35.3 (32.1-36.3)	33.5 (31.0-35.8)
Female	448/894 (50)	150/304 (49)
Caesarean	415/890 (46)	212/304 (70)
Birth weight – *grams*		
Smaller twin	1956 (1415-2350)	1381 (996-1796)
Larger twin	2350 (1792-2670)	2566 (1540-2010)
Small for gestational age		
Smaller twin	273/447 (61)	144/152 (95)
Larger twin	67/447 (15)	25/152 (16)
Birth weight discordance – *%*	13.3 (6.3-25.2)	30.2 (25.1-36.9)
Birth weight ratio	1.2 (1.1-1.3)	1.4 (1.3-1.6)
Neonatal mortality		
Smaller twin	11/423 (3)	7/141 (5)
Larger twin	4/282 (1)	2/140 (1)

MC: monochorionic, UA: umbilical artery, pEDF: positive end-diastolic flow, A/REDF: persistent absent/reversed end-diastolic flow, iA/REDF: intermittent absent/reversed end-diastolic flow, BWD: birth weight discordance. Outcomes are presented as median (interquartile range (IQR)) or n (%).
*Unknown in nine twin pairs.

Similarly, nearly all placentas of MC twins with a BWD ≥ 20% had AA anastomoses (97% (147/152). VV anastomoses were present in 22% (33/152) of these placentas. Median AA diameter was 2.2 (IQR 1.3-3.1) and median VV diameter was 3.3 (IQR 1.9-3.9). The majority of the smaller twins had a velamentous or marginal cord insertion (82% (124/152), of which 69% (85/124) velamentous and 31% (39/124) marginal. Of the larger twins, 11% (17/152) had a velamentous or marginal cord insertion, of which 29% (5/17) velamentous and 75% (12/16) marginal. Median placental share discordance was 55.4% (IQR 36.8-66.4), with 31% (IQR 25-40) of the placenta for the smaller twin and 69 (IQR 60-75) for the larger twin. Placental territory ratio was 2.2 (IQR 1.6-3.0), meaning that the larger twin had a 2.2 times larger placental share compared to the smaller twin. Birth weight ratio/placental territory ratio was 0.7 (IQR 0.5-0.9), implicating a 0.3 times lower BWD than expected for the given placental share discordance.

Table 2. Placental characteristics of the analyzed placentas, including the subgroup of MC twins with a BWD ≥ 20%.

Characteristics	**MC twins (n=898; 449 pregnancies)**	**BWD ≥ 20% (n=304; 152 pregnancies)**
Total anastomoses – *n*	10 (6-16)	10 (6-16)
AV anastomoses – *n*	4 (2-7)	4 (2-8)
VA anastomoses – *n*	4 (1-7)	4 (2-7)
Presence of AA anastomoses	411 (92)	147 (97)
> 1 AA anastomoses	22 (5)	8 (6)
Total AA diameter – *mm*	2.2 (1.3-3.0)	2.2 (1.3-3.1)
Presence of VV anastomoses	109 (24)	33 (22)
> 1 VV anastomoses	17 (4)	4 (3)
Total VV diameter – *mm*	3.1 (1.8-4.3)	3.3 (1.9-3.9)
Velamentous or marginal cord insertion		
Smaller twin	282 (63)	124 (82)
Larger twin	104 (23)	17 (11)
Placental share – *%*		
Smaller twin	41 (33-50)	31 (25-40)
Larger twin	59 (50-67)	69 (60-75)
Placental share discordance – *%*	35.1 (18.2-52.8)	55.4 (36.8-66.4)
Placental territory ratio	1.5 (1.2-2.1)	2.2 (1.6-3.0)
Birth weight ratio/Placental territory ratio	0.8 (0.6-0.9)	0.7 (0.5-0.9)

MC: monochorionic, BWD: birth weight discordance, AV: arterio-venous, VA: veno-arterial, AA: arterio-arterial, VV: veno-venous.

Outcomes are presented as median (interquartile range (IQR)) or n (%).

Relationship placental sharing, AA and VV diameter and BWD

Results from the multivariate linear regression of placental share discordance, total AA diameter and total VV diameter and BWD (aim 1) for the total population and the subgroup with a BWD ≥ 20% and available UA Doppler flow patterns (n = 143) are shown in Table 3 and depicted in Figure 2. An increase in placental share discordance was associated with an increase in BWD (β coefficient 0.325; 95% CI; 0.254-0.397, p < 0.0001) in the total population. Cases with pEDF demonstrated a similar positive correlation for placental share discordance and BWD (β coefficient 0.214; 95% CI 0.102-0.326, p = 0.001). In cases with A/REDF and iA/REDF, there was no significant association between placental share discordance and BWD, but for cases with A/REDF there was a significant negative correlation between total AA diameter and BWD (β coefficient -4.143; 95% CI -7.103--1.182, p = 0.006).

Relationship birth weight ratio/placental territory ratio, AA and VV diameter

Results from the univariate linear regression of total AA and VV diameter and birth weight ratio/placental territory ratio (aim 2) are shown in Table 4 and depicted in Figure 3. AA diameter, but not VV diameter, was correlated with birth weight ratio/placental territory ratio (β coefficient -0.041; 95% CI -0.059—0.023, p < 0.0001) for the total population, meaning that an increase in total AA diameter leads to less BWD than expected for the amount of placental share discordance. This was similar for cases with pEDF (β coefficient -0.055; 95% CI -0.098--0.011, p = 0.013) and cases with A/REDF (β coefficient -0.180; 95% CI -0.297--0.063, p = 0.002). The association between total AA diameter and birth weight ratio/placental territory ratio in cases with iA/REDF approached statistical significance (β coefficient -0.053, 95% CI -0.111-0.004, p = 0.070).

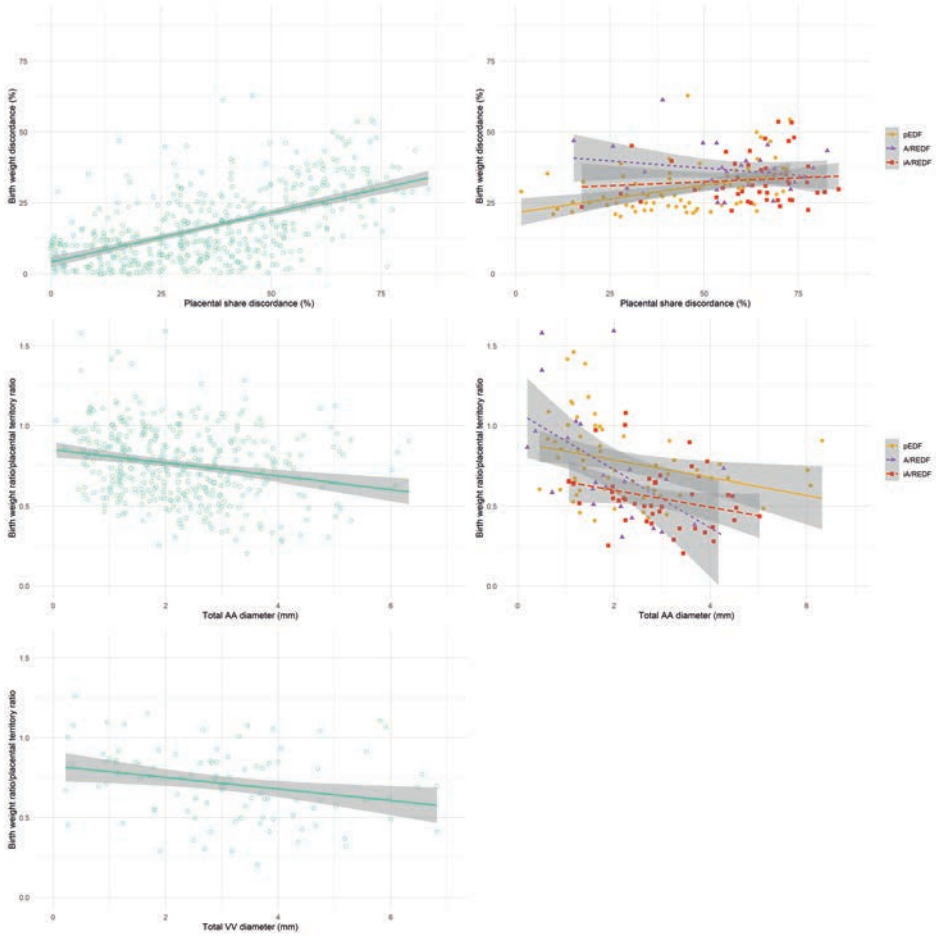

Figure 2. Scatterplots depicting the relationship between placental share discordance and BWD with 95% confidence interval bands; total AA diameter and birth weight ratio/placental territory ratio; and total VV diameter and birth weight ratio/placental territory ratio for the total population and per UA Doppler flow pattern.

Table 3. Multivariate linear regression to evaluate the association between birth weight discordance and placental share discordance for the total population and per antenatal UA Doppler flow pattern for the twin pairs with a BWD ≥ 20%.

	Total population			pEDF			A/REDF			iA/REDF		
Characteristics		β coefficient (95% CI)	*p*-value		β coefficient (95% CI)	*p*-value		β coefficient (95% CI)	*p*-value		β coefficient (95% CI)	*p*-value
Placental share discordance – *%*	35 (18-53)	0.325 (0.254-0.397)	**<0.0001**	45 (30-60)	0.214 (0.102-0.326)	**0.001**	56 (50-68))	0.018 (-0.157-0.193)	0.840	66 (58-72)	0.136 (-0.037-0.310)	0.124
Total AA diameter – *mm*	2.2 (1.3-3.0)	0.470 (-1.106-2.047)	0.559	1.7 (1.2-2.9)	-1.039 (-2.515-0.326)	0.167	1.8 (1.1-2.4)	-4.143 (-7.103--1.182)	**0.006**	2.8 (2.2-3.6)	-1.726 (-4.191-0.740)	0.170
Total VV diameter – *mm*	3.1 (1.8-4.3)	-0.180 (-1.071-0.712)	0.693									

pEDF: positive end-diastolic flow, A/REDF: persistent absent/reversed end-diastolic flow, iA/REDF: intermittent absent/reversed end-diastolic flow, AA: arterio-arterial, VV: veno-venous. Outcomes are presented as median (interquartile range (IQR)).

Table 4. Univariate linear regression to evaluate the association between birth weight ratio/placental territory ratio and total AA and VV diameter per antenatal UA Doppler flow pattern in twin pairs with a BWD ≥ 20%.

	Total population			pEDF			A/REDF			iA/REDF		
Characteristics		β coefficient (95% CI)	*p*-value		β coefficient (95% CI)	*p*-value		β coefficient (95% CI)	*p*-value		β coefficient (95% CI)	*p*-value
Total AA diameter – *mm*	2.2 (1.3-3.0)	-0.041 (-0.059--0.023)	**<0.0001**	1.7 (1.2-2.9)	-0.055 (-0.098--0.011)	**0.013**	1.8 (1.1-2.4)	-0.180 (-0.297--0.063)	**0.002**	2.8 (2.2-3.6)	-0.053 (-0.111-0.004)	0.070
Total VV diameter – *mm*	3.1 (1.8-4.3)	-0.007 (-0.027-0.012)	0.473									

pEDF: positive end-diastolic flow, A/REDF: persistent absent/reversed end-diastolic flow, iA/REDF: intermittent absent/reversed end-diastolic flow, AA: arterio-arterial, VV: veno-venous. Outcomes are presented as median (interquartile range (IQR)).

Comment

Principal findings

This study shows that there was a strong association between placental share discordance and BWD in live-born MC twins. Yet, the amount of BWD was smaller than the amount of placental share discordance. A larger AA diameter was shown to mitigate the effect of unequal placental sharing on BWD as reflected by a lower birth weight ratio/placental territory ratio with increasing diameter. With regard to the different UA Doppler flow patterns in twin pairs with a BWD ≥ 20%, cases with pEDF demonstrated similar associations as the total population in line with type I sFGR pregnancies also having a relatively uncomplicated course. As expected, cases with A/REDF and iA/REDF showed a distinct placental pathophysiology in which both did not show a significant association between placental share discordance and BWD, while compensation through a larger AA diameter (approaching statistical significance for iA/REDF) was present. This suggests an increased importance of placental angioarchitecture.

Results in the context of what is known

Our results are in line with previous studies performed by Lewi et al. and Couck et al. including 100 and 247 MC placentas respectively[10,18]. We confirmed the strong linear relationship between placental share discordance and BWD as well as the effect of a larger AA diameter in reducing the birth weight ratio/placental territory ratio in a substantially larger study population with a subgroup analysis per antenatal UA Doppler flow pattern. Couck et al. found that a larger VV diameter also decreases the amount of BWD for any given placental share discordance, independent of the AA diameter[18]. We did not find this effect in our population, potentially due to the nearly double amount of placentas with VV anastomoses we were able to include. In a study performed by Wang et al., the presence of VV anastomoses was found to be negatively correlated with BWD in type III sFGR when corrected for gestational age at diagnosis and delivery[19]. We were unable to draw conclusions about the effect of VV diameter in the subgroup analysis of the UA Doppler flow patterns, as only nine pEDF, six A/REDF and twelve iA/REDF placentas had a VV anastomosis. More research is necessary, preferably in a multicenter setting, to study the role of VV anastomoses.

In previous literature on the placental characteristics of the Gratacós types in sFGR, the large AA diameter was considered to be the compensation mechanism for unequal placental sharing primarily in type III placentas, as type III had both the largest AA diameter and the lowest birth weight ratio/placental territory ratio in comparison

with type I and type II[8,11]. Our study now demonstrates that in type I (pEDF) and II (A/REDF), there is also compensation through the AA anastomoses. However, as the AA diameter is smaller in these types, they still demonstrate a higher birth weight ratio/placental territory ratio than reported in type III (iA/REDF).

The hazard in comparing studies using the Gratacós classification is the different scoring methods that are widely used. Some studies classify a pregnancy as type II or type III when abnormal UA Doppler flow patterns were observed on a single occasion[20], others use the final classification prior to delivery[19], and others use the most prevalent type of flows as we have done now and in the past[11]. UA Doppler flow patterns are dynamic in nature and can change over time, presenting difficulty in determining the 'definitive' Gratacós type[16]. International consensus is urgently needed to minimize this variation in diagnosis, as this currently clouds the exploration of pathophysiological mechanisms and hampers comparisons between studies.

Clinical implications

These findings support the hypothesis that large bidirectional anastomoses, AA anastomoses in particular, allow for an increased feto-fetal blood flow and can thereby compensate for unequal placental sharing by way of a rescue transfusion from the larger to the smaller twin. Whilst being beneficial for the growth of the smaller twin during pregnancy, large anastomoses can also pose a threat to either twin due to the risk of acute feto-fetal transfusion potentially leading to fetal demise or neurological damage[8,21,22]. This is especially thought to be the cause of the unpredictable clinical course of type III sFGR, which is reported to have the largest AA diameter[8,11]. At present, this also determines the current management protocol in which fetal surveillance is advised. The knowledge from our current study can now lead to a more accurate risk assessment, especially if antenatal visualization of large, bidirectional anastomoses is further improved in the future.

Fetoscopic laser coagulation has been suggested for sFGR pregnancies with abnormal UA Doppler flow patterns to eliminate the risk of acute feto-fetal transfusion by coagulating the large anastomoses[23]. However, our study further substantiates that the smaller twin also relies on these anastomoses for an additional blood supply from its co-twin. This rescue transfusion is lost when anastomoses are coagulated, resulting in high rates of fetal demise in the smaller twin (60-77%)[24-27]. This phenomenon was also observed in TTTS pregnancies where sFGR prior to laser was identified as a risk factor for fetal demise of the smaller twin[28]. In addition, fetoscopic laser coagulation

in sFGR pregnancies comes with more technical challenges than in TTTS due to the absence of an amniotic fluid discordance.

Research implications

This study provides us a glimpse in the black box that is the MC placenta. However, its exact internal mechanisms are not yet fully understood. Future research should focus on volumetric measurements to quantify placental sharing more accurately. By early antenatal visualization of placental sharing and angioarchitecture (e.g., with placental mapping by three-dimensional color Doppler ultrasound or MRI[29-32]), the knowledge from this study can be applied to formulate an individualized risk assessment and adapt the management strategy accordingly in the future. Moreover, pathological examination of placental tissue including placental weight can provide more information on other potential causes of a BWD, such as antenatal placental insufficiency or maternal disease as reported in singletons with fetal growth restriction[33].

Strengths and limitations

Our study has limitations that should be considered when interpreting the data. Firstly, its retrospective nature can introduce bias in the results. Moreover, as we are a specialized center there might be an overrepresentation of severe cases with a large BWD. Importantly, reliable dye injection is only possible in cases with double survivors, automatically resulting in a selected population with relatively favorable outcome as cases in which fetal demise or selective reduction occurred are generally the most severe cases. Lastly, it should be noted that we solely look at the placental surface in determining the sharing and not placental volume. Nevertheless, our study is strengthened by its large study population, inclusion of placentas from twins with a broad range of BWD to explore, and the subgroup analyses per UA Doppler flow pattern in twins with a BWD ≥ 20% allowing for in depth investigation of the distinct placental mechanisms for each type. As dye injection of placentas has been part of standard care in our center for nearly twenty years, we have a large dataset of placentas available including digitally saved pictures that can be reviewed.

Conclusions

This study shows that BWD in MC twins is strongly associated to placental share discordance but that large bidirectional anastomoses, particularly AA anastomoses, can mitigate the effect of unequal placental sharing. Placentas from pregnancies with

UA Doppler abnormalities show a distinct mechanism with a greater importance of placental angioarchitecture.

References

1. Lee KA, Oh KJ, Lee SM, Kim A, Jun JK. The frequency and clinical significance of twin gestations according to zygosity and chorionicity. *Twin Res Hum Genet*. Dec 2010;13(6):609-19.

2. Lewi L, Deprest J, Hecher K. The vascular anastomoses in monochorionic twin pregnancies and their clinical consequences. *Am J Obstet Gynecol*. Jan 2013;208(1):19-30.

3. Bennasar M, Eixarch E, Martinez JM, Gratacos E. Selective intrauterine growth restriction in monochorionic diamniotic twin pregnancies. *Semin Fetal Neonatal Med*. Dec 2017;22(6):376-382.

4. Lewi L, Gucciardo L, Huber A, et al. Clinical outcome and placental characteristics of monochorionic diamniotic twin pairs with early- and late-onset discordant growth. *Am J Obstet Gynecol*. Nov 2008;199(5):511 e1-7.

5. Groene SG, de Vries LS, Slaghekke F, et al. Changes in structural brain development after selective fetal growth restriction in monochorionic twins. *Ultrasound Obst Gyn*. 2021;

6. Groene SG, Spekman JA, Te Pas AB, et al. Respiratory distress syndrome and bronchopulmonary dysplasia after fetal growth restriction: Lessons from a natural experiment in identical twins. *Eclinicalmedicine*. Feb 2021;32

7. Groene SG, Tollenaar LSA, Oepkes D, Lopriore E, van Klink JMM. The impact of selective fetal growth restriction or birth weight discordance on long-term neurodevelopment in monochorionic twins: a systematic literature review. Systematic literature review. *Journal of Clinical Medicine*. 2019;

8. Gratacos E, Lewi L, Munoz B, 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*. Jul 2007;30(1):28-34.

9. Fick AL, Feldstein VA, Norton ME, Wassel Fyr C, Caughey AB, Machin GA. Unequal placental sharing and birth weight discordance in monochorionic diamniotic twins. *Am J Obstet Gynecol*. Jul 2006;195(1):178-83.

10. Lewi L, Cannie M, Blickstein I, et al. Placental sharing, birthweight discordance, and vascular anastomoses in monochorionic diamniotic twin placentas. *Am J Obstet Gynecol*. Dec 2007;197(6):587 e1-8.

11. Groene SG, Tollenaar LSA, Slaghekke F, et al. Placental characteristics in monochorionic twins with selective intrauterine growth restriction in relation to the umbilical artery Doppler classification. *Placenta*. Nov 2018;71:1-5.

12. Tollenaar LSA, Zhao DP, Middeldorp JM, Oepkes D, Slaghekke F, Lopriore E. Can color difference on the maternal side of the placenta distinguish between acute peripartum twin-twin transfusion syndrome and twin anemia-polycythemia sequence? *Placenta*. Sep 2017;57:189-193.

13. Khalil A, Beune I, Hecher K, et al. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. *Ultrasound Obstet Gynecol*. Jan 2019;53(1):47-54.

14. Hoftiezer L, Hof MHP, Dijs-Elsinga J, Hogeveen M, Hukkelhoven CWPM, van Lingen RA. From population reference to national standard: new and improved birthweight charts. *American Journal of Obstetrics and Gynecology*. Apr 2019;220(4)

15. Hoftiezer L, Hukkelhoven CWPM, Hogeveen M, Straatman HMPM, van Lingen RA. Defining small-for-gestational-age: prescriptive versus descriptive birthweight standards. *European Journal of Pediatrics*. Aug 2016;175(8):1047-1057.

16. Rustico MA, Consonni D, Lanna M, et al. Selective intrauterine growth restriction in monochorionic twins: changing patterns in umbilical artery Doppler flow and outcomes. *Ultrasound Obstet Gynecol*. Mar 2017;49(3):387-393.

17. Lopriore E, Slaghekke F, Middeldorp JM, et al. Accurate and simple evaluation of vascular anastomoses in monochorionic placenta using colored dye. *J Vis Exp*. Sep 5 2011;(55):e3208.

18. Couck I, Cauwberghs B, Van Aelst M, Vivanti AJ, Deprest J, Lewi L. The association between vein-to-vein anastomoses and birth weight discordance in relation to placental sharing in monochorionic twin placentas. *Placenta*. Jan 2 2022;118:16-19.

19. Wang XJ, Shi HF, Li LY, Yuan PB, Zhao YY, Wei Y. 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. *Prenatal Diag*. Nov 2021;41(12):1518-1523.

20. Shinar S, Xing W, Pruthi V, et al. Outcome of monochorionic twin pregnancy complicated by Type-III selective intrauterine growth restriction. *Ultrasound Obst Gyn*. Jan 2021;57(1):126-133.

21. Inklaar MJ, van Klink JM, Stolk TT, van Zwet EW, Oepkes D, Lopriore E. Cerebral injury in monochorionic twins with selective intrauterine growth restriction: a systematic review. *Prenat Diagn*. Mar 2014;34(3):205-13.

22. Gratacos E, Carreras E, Becker J, et al. Prevalence of neurological damage in monochorionic twins with selective intrauterine growth restriction and intermittent absent or reversed end-diastolic umbilical artery flow. *Ultrasound Obstet Gynecol*. Aug 2004;24(2):159-63.

23. Townsend R, D'Antonio F, Sileo FG, Kumbay H, Thilaganathan B, Khalil A. Perinatal outcome of monochorionic twin pregnancy complicated by selective fetal growth restriction according to management: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. Jan 2019;53(1):36-46.

24. Gratacos E, Antolin E, Lewi L, et al. Monochorionic twins with selective intrauterine growth restriction and intermittent absent or reversed end-diastolic flow (Type III): feasibility and perinatal outcome of fetoscopic placental laser coagulation. *Ultrasound Obst Gyn*. Jun 2008;31(6):669-675.

25. Colmant C, Lapillonne A, Stirnemann J, et al. Impact of different prenatal management strategies in short- and long-term outcomes in monochorionic twin pregnancies with selective intrauterine growth restriction and abnormal flow velocity waveforms in the umbilical artery Doppler: a retrospective observational study of 108 cases. *Bjog-Int J Obstet Gy*. Jan 2021;128(2):401-409.

26. Koch A, Favre R, Viville B, et al. Expectant management and laser photocoagulation in isolated selective intra-uterine growth restriction: A single-center series. *J Gynecol Obstet Hum*. Dec 2017;46(10):731-736.

27. Ishii K, Nakata M, Wada S, Murakoshi T, Sago H. Feasibility and preliminary outcomes of fetoscopic laser photocoagulation for monochorionic twin gestation with selective intrauterine growth restriction accompanied by severe oligohydramnios. *J Obstet Gynaecol Re*. Nov 2015;41(11):1732-1737.

28. Groene SG, Tollenaar LSA, van Klink JMM, et al. Twin-Twin Transfusion Syndrome with and without Selective Fetal Growth Restriction Prior to Fetoscopic Laser Surgery: Short and Long-Term Outcome. *Journal of Clinical Medicine*. Jul 2019;8(7)

29. Sau A, Weber M, Shennan AH, Maxwell D. Antenatal detection of arteriovenous anastomoses in monochorionic twin pregnancy. *Int J Gynecol Obstet*. Jan 2008;100(1):56-59.

30. Welsh AW, Taylor MJO, Cosgrove D, Fisk NM. Freehand three-dimensional Doppler demonstration of monochorionic vascular anastomoses in vivo: a preliminary report. *Ultrasound Obst Gyn*. Oct 2001;18(4):317-324.

31. Pretorius DH, Nelson TR, Baergen RN, Pai E, Cantrell C. Imaging of placental vasculature using three-dimensional ultrasound and color power Doppler: a preliminary study. *Ultrasound Obst Gyn*. Jul 1998;12(1):45-49.

32. Joern H, Klein B, Schmid-Schoenbein H, Rath W. Antenatal visualization of vascular anastomoses in monochorionic twins using color Doppler sonography: the protective function of these anastomoses and the phenomenon of interference beating. *Ultrasound Obst Gyn*. Dec 1999;14(6):422-425.

33. Nardozza LMM, Caetano ACR, Zamarian ACP, et al. Fetal growth restriction: current knowledge. *Archives of Gynecology and Obstetrics*. May 2017;295(5):1061-1077.