Placental characteristics and complications in monochorionic twin pregnancies

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Chapter 6

Placental share and hemoglobin level in relation to birth weight in twin anemia-polycythemia sequence

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Abstract

Introduction: Twin anemia-polycythemia sequence (TAPS) is a newly described form of chronic twin transfusion. Previous observational studies noted a discordance between birth weight and individual placental share in TAPS. The purpose of this study was to investigate if fetal growth in monochorionic (MC) twins with TAPS is determined by placental share or by the net inter-twin blood transfusion.

Methods: All consecutive MC twin placentas of live-born twin pairs with and without TAPS examined at our center between June 2002 and February 2014 were included in this study. Hemoglobin (Hb) levels and individual placental share were evaluated at birth and correlated with birth weight share. We excluded MC twin pregnancies with twin-twin transfusion syndrome.

Results: A total of 270 MC twin pregnancies (TAPS group, n=20; control group without TAPS, n=250) were included in this study. Donors with TAPS had a lower birth weight than recipients in 90% (18/20) of cases, but a larger placental share in 65% (13/20) of cases. In the TAPS group, birth weight share was positively correlated with Hb share at birth ($P<0.01$) but not with placental share ($P=0.54$). In the control group without TAPS, birth weight share was strongly correlated with placental share ($P<0.01$) but not with Hb share ($P=0.14$).

Discussion: A relatively larger placental share may enable survival of anemic twin in TAPS.

Conclusion: In contrast with uncomplicated MC twins, fetal growth in MC twins with TAPS is determined primarily by the net inter-twin blood transfusion instead of placental share.

Keywords: monochorionic twins, twin anemia-polycythemia sequence, placental share, hemoglobin level, fetal growth

Introduction

Twin anemia-polycythemia sequence (TAPS) is a rare condition of monochorionic (MC) twin pregnancies and is characterized by large inter-twin difference in hemoglobin (Hb) level without large differences in amniotic fluid such as in twin-twin transfusion syndrome (TTTS) [1]. The pathogenesis of TAPS is associated with the presence of few tiny arterio-venous (AV) anastomoses, leading to chronic blood loss from the anemic twin (donor) to the polycythemic twin (recipient).[2, 3] TAPS can occur spontaneously or after laser for TTTS (post-laser TAPS)[1].

Fetal growth in MC twins has been demonstrated to be primarily determined by placental share[4-6]. A larger placental share usually leads to a larger birth weight, while a smaller placental share results in a smaller birth weight. In TAPS cases, however, several authors reported contrasting findings. The donor twin in TAPS cases is most often the smaller twin but seems to have a larger placental territory compared to its recipient co-twin[7, 8]. These observations suggest that fetal growth in TAPS twins could be determined by other factors besides placental share. We hypothesized that the net inter-twin blood transfusion in TAPS twins could have a greater contribution to fetal growth than relative placental share.

The aim of this study was to investigate the correlation between birth weight share and placental share and Hb level in MC twin pregnancies with TAPS compared to a control group of MC twin pregnancies without TAPS.

Materials and Methods

All consecutive MC placentas examined at our center, the Leiden University Medical Center, between June 2002 and February 2014 were eligible for this study. We included all MC twin

pregnancies with spontaneous TAPS (study group) and uncomplicated MC twin pregnancies without TAPS (control group). The management protocol for MC twins implies a routine bi-weekly Doppler-ultrasound examination, including middle cerebral artery peak systolic velocity (MCA-PSV) measurements. For the purpose of this study, only MC twin pregnancies resulting in two live-born twins were included. We excluded cases with TTTS, twin reversed arterial perfusion sequence and/or MC pregnancies treated with fetoscopic laser surgery. Fetoscopic laser surgery affects the trajectory of fetal growth in TTTS by iatrogenically destroying the placental angio-architecture, suggesting the inter-twin growth pattern may be different between spontaneous TAPS and post-laser TAPS[9]. Thus, cases with post-laser TAPS were excluded. Cases with incomplete placental injection due to severe damage or fixation in formalin were also excluded. TAPS was diagnosed prenatally or postnatally based on previously published international criteria.[1] Briefly, prenatal diagnosis of TAPS is reached when Doppler ultrasound examinations show an increased MCA-PSV(> 1·5 multiples of the median (MoM)) in one fetus and a decreased MCA-PSV (<1 MoM) in the co-twin; postnatal criteria include an inter-twin Hb difference > 8.0g/dL at birth, inter-twin reticulocyte count ratio > 1.7 and/or placental injection showing only few small anastomoses. Part of the placental data in the present study was reported previously to map the localization of vascular anastomoses on placental plate[10] and to determine the placental characteristics of TAPS placentas[3, 11].

Prenatal and postnatal clinical variables were prospectively recorded for all twins in a dedicated MC twins database, including antenatal and postnatal TAPS stage, antenatal management of TAPS, gestational age at birth, birth weight, gender, mode of delivery, and albumin levels at birth. Hematological investigations including Hb levels and reticulocyte

counts were routinely determined at birth in all MC twins. The inter-twin reticulocyte count ratio was calculated by dividing the reticulocyte count of the twin with lower hemoglobin level by the reticulocyte count of the co-twin. Individual birth weight share was calculated by dividing the birth weight of each infant by the sum of the birth weights of both infants. Individual Hb share was calculated by dividing the Hb level of each neonate by the sum of the Hb levels of both neonates. Individual reticulocyte count share was calculated by dividing the reticulocyte count of each neonate by the sum of the reticulocyte count of both neonates. The inter-twin birth weight discordance was calculated by the following formula: ((birth weight of larger twin – birth weight of smaller twin)/birth weight of larger twin) × 100%.

All MC placentas were routinely examined and injected with colored dye according to a previously reported protocol[12]. High-resolution digital pictures were taken for computer analysis. The number and type of vascular anastomoses and type of cord insertion was recorded after each injection. Umbilical cord insertion site was recorded as central, marginal and velamentous. Velamentous cord insertion was referred as to direct insertion of the umbilical cord into amniotic membrane instead of placental plate. Marginal cord insertion was defined as insertion within 1 cm of the margin Individual placental territory was measured on the digital picture as the area of venous return using Image J 1.45s (Image J, National Institute of Health, USA). Individual placental share was calculated by dividing the placental territory of each infant by the total placental plate surface area. The placental share difference was calculated by subtracting the lower placental share to the larger placental share. We calculated individual birth weight share/placental share (BWS/PS) ratio according to a report from Lewi et al[4]. Briefly, BWS/PS ratio was calculated by dividing the

birth weight share by the corresponding placental share. A BWS/PS ratio close to 1.0 indicates the birth weight share matches the placental share. A BWS/PS ratio of <1.0 means the birth weight is smaller in relation to its placental share. A BWS/PS ratio of >1.0 indicates the birth weight is larger in relation to its placental share.

Statistics

Fisher's exact test and Mann-Whitney U test was applied to analyze categorical variables and continuous variables, respectively. For comparison within twins, the paired *t* test was used for continuous variables and the Mc Nemar test was employed to analyze paired nominal variables. The nonparametric correlation coefficients (Spearman r) was calculated to evaluate the correlation between bi-variables. The straight lines fitting the bivariate diagrams were yielded to determine the slope and intercept using linear regression. Differences with a *P* value <0.05 were regarded as statistical significance. Statistical analysis was performed using GraphPad Prism v6.0 (GraphPad Software Inc. La Jolla, CA 92037 USA).

Results

A total of 704 MC placentas were examined at our center during this study period. We excluded 328 TTTS cases and three spontaneous TAPS managed with fetoscopic laser surgery. Fifty-four TTTS cases managed conservatively or with amniodrainage were also excluded. Forty-nine placentas were excluded due to severe placental damage (n=10), intrauterine fetal demise (n=24), fixation in formalin (n=6) and placenta lost (n=9). Finally, a total of 270 cases with double live-born twins were analyzed in the study, including 20 (7%) MC twin pregnancies with TAPS and 250 (93%) MC twin pregnancies without TAPS.

TAPS was detected antenatally in 40% (8/20) of cases and all TAPS cases met the postnatal diagnostic criteria. Four TAPS cases (20%, 4/20) were managed with intrauterine transfusion and were excluded when relating Hb and reticulocyte count at birth to birth weight. Hb levels and reticulocyte count at birth were measured in all twin pairs with TAPS but were missing in 16% (40/250) of MC twin pairs in the control group without TAPS. The baseline characteristics of MC twins with and without TAPS are displayed in Table 1.

Table 1 Baseline characteristics in MC twin pregnancies with and without TAPS

	TAPS (n=20)	no TAPS (n=250)	P value
Female – n (%)	9 (45)	127 (51)	.40
Caesarean – n (%)	10 (50)	94 (38)	.20
GA at birth – weeks[a]	33 ± 2	34 ± 3	<.01
BW – grams[a]	1771 ± 445	2094 ± 647	<.01
BWD - %[b]	17.8 (8.6-27.4)	13.4 (5.7-25.0)	.29
BWD ≥ 25% - n (%)	6 (30)	67 (27)	.80
HB difference – g/dL[b]	13.8 (12.0-18.1)	1.6 (0.6-3.5)[c]	<.01
Reticulocyte count ratio[d]	3.6 (1.7-10.0)	1.0 (1.0-2.0)[c]	<.01

Table 1 [a] Data displayed as mean ± SD. [b] Data given as median (IQR).[c] The hemoglobin (Hb) values of 40 pairs were not available. GA: gestational age; BW: birth weight; BWD: birth

The placental characteristics of MC twin gestations with and without TAPS are shown in Table 2. The number of vascular anastomoses in TAPS placentas was significantly lower compared to placentas from MC twin pregnancies without TAPS. The majority of donor twins (90%, 18/20) in the TAPS group had a smaller birth weight, but a larger placenta share in 65% (13/20) of cases whereas in the control group twins with smaller birth weight usually had a smaller placental share in 60% cases (151/250) (P=0.03).

In MC twin pairs with TAPS, the anemic twins always had a lower level of albumin and increased reticulocytosis compared to their polycythemic counterparts, 28g/L (IQR:24 g/L-30g/L) vs 35g/L (IQR: 34g/L -36g/L)(P=0.02) and 142‰ (IQR: 114‰-212‰) vs 39‰ (IQR: 36‰-51‰)(P<0.01), respectively. We did not detect these discrepancies between twins with lower Hb and the co-twins with higher Hb in the control group.

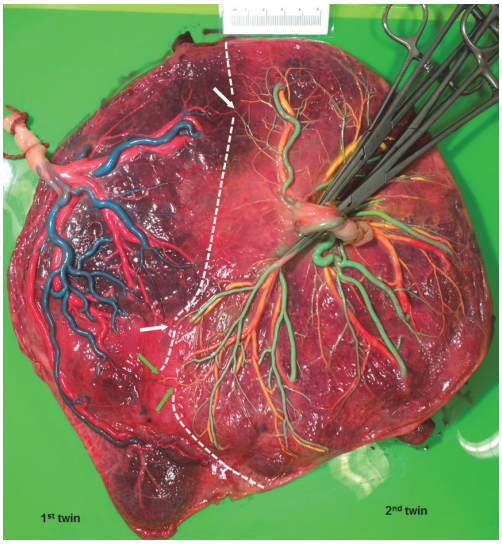

Figure 1 A typical TAPS placenta.

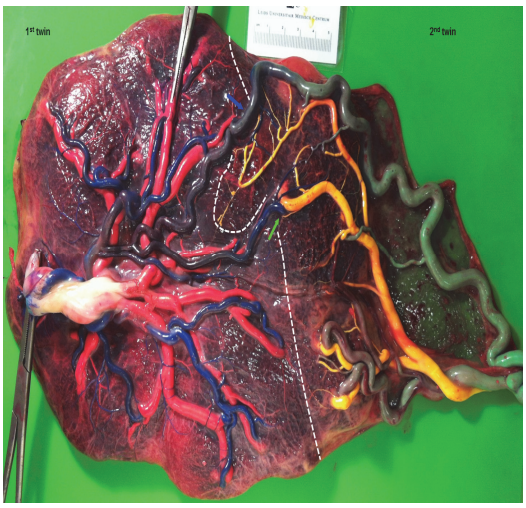

Figure 2 A typical MC placenta with selective intrauterine growth restriction.

Table 2 Placental characteristics in MC twin pregnancies with and without TAPS

	TAPS (n=20)	no TAPS (n=250)	P value
Number of anastomoses – n[a]	4 (3-6)	8 (5-12)	<.01
VCI – n (%)[b]	4 (10)	114 (23)	.06
Placental share difference - %[a]	18.1 (4.0-28.8)	20.1 (9.8-34.4)	.19

Table 2 [a] Data shown as median (IQR). [b] Values given per umbilical cord. VCI: velamentous cord insertion

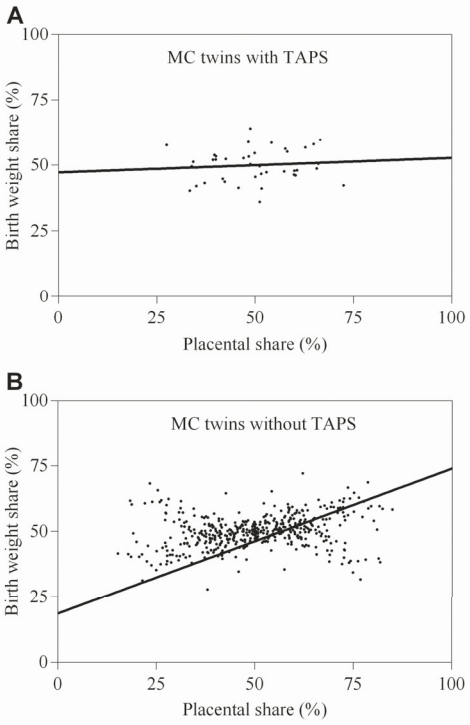

Figure 3 Correlation between placental share and birth weight share in MC twin pregnancies with TAPS (Spearman r=0.14; 95% confidence interval (CI): -0.18 to 0.45; P=0.36; Figure 3A) and without TAPS (Spearman r=0.28; 95% CI: 0.20 to 0.36; P<0.0001; Figure 3B).

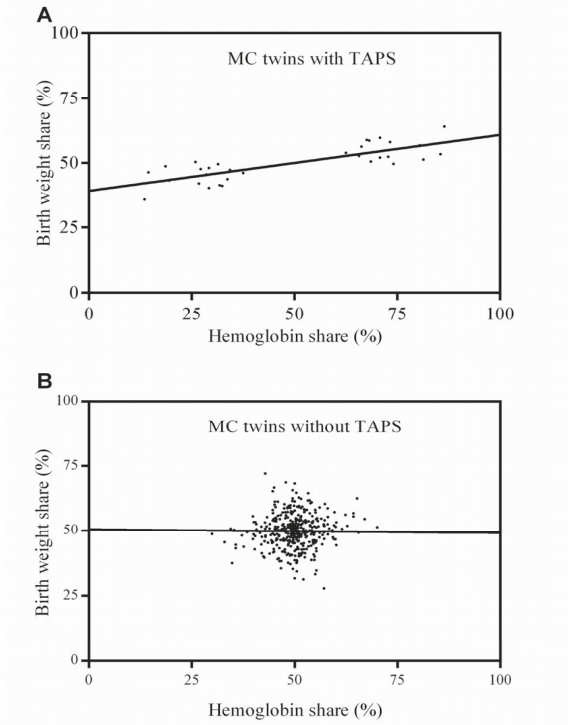

Figure 4 Correlation between Hb share and birth weight share in MC twin pregnancies with TAPS (Spearman r=0.74; 95% CI: 0.51 to 0.87; P<0.0001; Figure 4A) and without TAPS (Spearman r=0.07; 95% CI: -0.03 to 0.17; P=0.14; Figure 4B).

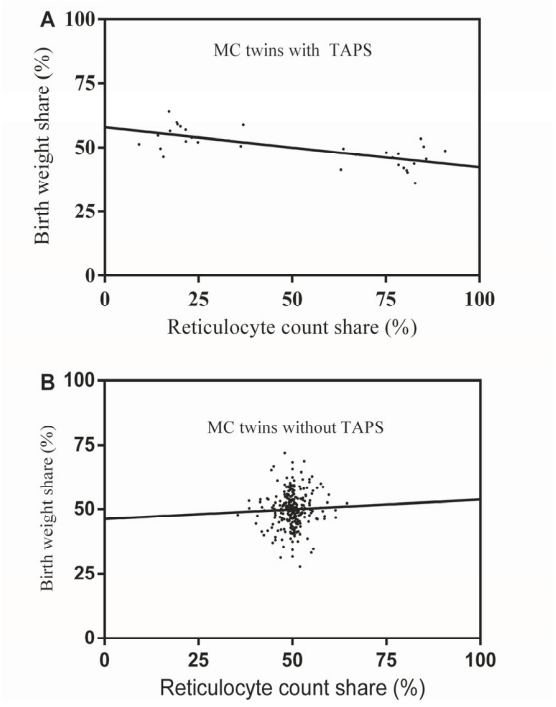

Figure 5 Correlation between reticulocyte count share and birth weight share in MC twin pregnancies with TAPS (Spearman r= -0.62; 95% CI: -0.80 to -0.34; *P*<0.001; Figure 5A) and without TAPS (Spearman r= 0.01; 95% CI: -0.11 to 0.12; *P*=0.92; Figure 5B).

In the TAPS group, the median BWS/PS ratio in the smaller twin and/or anemic twins was < 1.0 and significantly lower than in larger and/or recipient twins (P <0.01), indicating that birth weight share in donors was lower than their corresponding placental share. In contrast, this mismatch between placental share and birth weight share was not detected in the control group of MC twins without TAPS. In the control group the median BWS/PS ratio was 1.0 indicating that birth weight was well reflected in the corresponding placental share. Table 3 shows the comparison within twin pairs with and without TAPS. Examples of placentas originated from MC twins with and without TAPS are shown in Fig 1 and Fig 2, respectively.

Correlation between birth weight share and placental share in MC twins with and without TAPS

Birth weight share was not associated with placental share in MC twins with prenatal TAPS (Spearman r= -0.13; 95% confidence interval (CI): -0.60 to 0.41; *P*=0.63) or TAPS detected prenatally or postnatally (Spearman r=0.10; 95% confidence interval (CI): -0.23 to 0.41; *P*=0.54; Figure 3A). Conversely, in MC twins without TAPS, birth weight share increased linearly with placental share (Spearman r=0.28; 95% CI: 0.20 to 0.36; *P*<0.0001; Figure 3B).

Correlation between birth weight share and Hb share in MC twins with and without TAPS

Birth weight share increased linearly with Hb share in MC twins with TAPS (Spearman r=0.74; 95% CI: 0.51 to 0.87; *P*<0.0001; Figure 4A). In contrast, in MC twins without TAPS, birth weight share was not related to Hb share (Spearman r=0.07; 95% CI: -0.03 to 0.17; *P*=0.14; Figure 4B).

Correlation between birth weight share and reticulocyte count share in MC twins with and without TAPS

Birth weight share was inversely related to the reticulocyte count share in MC twins with TAPS (Spearman r= -0.62; 95% CI: -0.80 to -0.34; *P*<0.001; Figure 5A) whereas this relation between reticulocyte count share and birth weight share was not found in the control group (Spearman r= 0.01; 95% CI: -0.11 to 0.12; *P*=0.92; Figure 5B).

Discussion

This is the first study to investigate the various factors contributing to fetal growth in MC twins with TAPS. Our findings confirm that in uncomplicated MC twins, individual placental share contributes fundamentally to the fetal growth. As shown in this and other studies in uncomplicated MC twins the fetus with the larger placental share has usually also the larger birth weight share[4, 5]. However, this rule does not seem to apply to the category of MC twins with spontaneous TAPS. This study demonstrates that fetal growth in TAPS twins is not determined by the placental share. Donors in TAPS twins have mostly (90% of cases) a smaller birth weight share but the majority (65%) have a larger placental share. Conversely, the recipient twins have a larger birth weight but a smaller placental share. This inverse correlation between placental share and birth weight was recently noted by several authors in recent reports[7, 8]. Our results suggest that the placental share is not the primary contributor to fetal growth in MC twins with TAPS regardless of the timing at diagnosis (prenatal or postnatal). Instead, fetal growth in TAPS twins seems to be predominantly determined by the net inter-twin blood flow. The chronic blood loss from the donor twin through the vascular anastomoses into the circulation of the recipient twin causes anemia and a decreased red cell mass in the donor, whereas the recipient presents polycythemia and an increased red cell mass. These differences in red cell mass may have an important effect on fetal growth and birth weight. In addition, as shown in a previous study

Table 3 Comparison within MC twin pairs with and without TAPS

	MC twin pregnancies with TAPS (n=20)		P value	MC twin pregnancies without TAPS (n=250)		P value
	Smaller twin (n=20)	Larger twin (n=20)		Smaller twin (n=250)	Larger twin (n=250)	
Birth weight - grams[a]	1592 ± 399	1949 ± 424	<0.01	1916 ± 623	2273 ± 624	<0.01
Placental share - %[b]	51.4 (41.9-60.0)	48.6 (40.0-58.1)	0.77	45.1 (37.6-54.6)	54.9 (45.5-62.4)	<0.01
BWS/PS ratio[c]	0.90 (0.78-1.03)	1.11 (0.98-1.31)	0.02	1.00 (0.98-1.07)	1.00 (0.95-1.02)	0.15
	Anemic twin (n=20)	Polycythemic twin (n=20)	P value	Twin with lower Hb level (n=210)[d]	Twin with higher Hb level (n=210)[d]	P value
Birth weight - grams[a]	1705 ± 401	1980 ± 424	<0.01	2055 ± 614	2133 ± 674	0.62
Placental share - %[b]	51.7 (43.2-60.2)	48.3 (39.8-56.8)	0.37	47.4 (38.8-58.9)	52.6 (41.1-61.2)	0.18
BWS/PS ratio[c]	0.86 (0.77-1.03)	1.17 (0.98-1.32)	<0.01	1.02 (0.98-1.08)	0.98 (0.94-1.02)	0.15

Table 3 BWS/PS ratio: birth weight share/placental share ratio. a Data displayed as mean ± SD. b Data given as median (IQR). c Data given as median (95%CI). d The values of 40 pairs were not available.

by Verbeek et al., donor twins in TAPS have not only a significantly lower Hb level but also lower albumin and total protein levels[8]. Furthermore, blood loss-causing chronic hypoxia represented by increased reticulocyte count may also affect the growth of the anemic donor twin. We speculate that chronic loss of blood, nutritional elements and associated chronic hypoxia may contribute to the impaired fetal growth and lower birth weight in donor twins with TAPS.

It is not clear, however, why donor twins with TAPS often have larger placental shares than the recipient twins. Chronic blood loss may lead to chronic hypoxia and depletion of nutrition in the placental share of the donor twin with TAPS. This could theoretically stimulate compensatory placental expansion to transport more oxygen and nutrition to the fetus, consequently leading to a relative larger placental share in relation to the fetal size[13-15]. The increased reticulocyte count in anemic twin with TAPS indicates its exposure to intrauterine environment of chronic hypoxia. Another, most plausible explanation, could be that the larger placental share found in donor twins is a result of selection bias in this study due to the inclusion of only TAPS cases with two live-born infants. We speculate that donor twins with TAPS with a significantly smaller placental share may be at increased risk of fetal demise due to the accumulation of potential risks (chronic blood loss and smaller placental share). As shown by several authors, MC twin pregnancies are at increased risk of unexplained fetal demise, which could in part be related to severe placental share discordances[16, 17]. Underreporting of donor twins with smaller placental shares may have occurred due to our study design.

The main limitation of this study, besides its retrospective nature, is related to the introduction of a selection bias attributed to the exclusion of cases with fetal demise. Since

fetal demise consequently leads to placental maceration, these cases had to be excluded from the study due to the impossibility of measuring the individual placental share or Hb levels. Our date should therefore be interpreted with care as they only relate MC pregnancies resulting in double survivals.

In conclusion, our study shows that fetal growth in MC twins with TAPS is determined primarily by the net inter-twin transfusion rather than the placental share. Our data may help elucidate the various factors determining fetal growth in MC twins pregnancies with and without TAPS.

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