Next steps towards improved care for twin anemia polycythemia sequence

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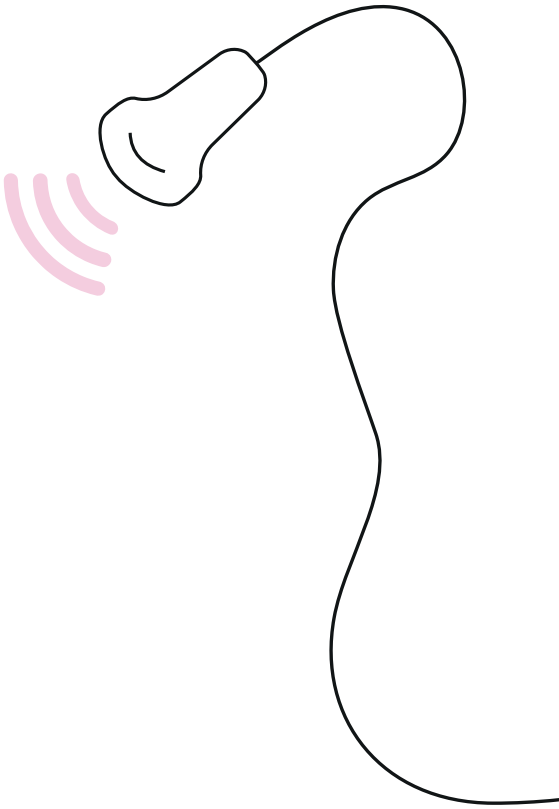
PART 5

antenatal diagnosis



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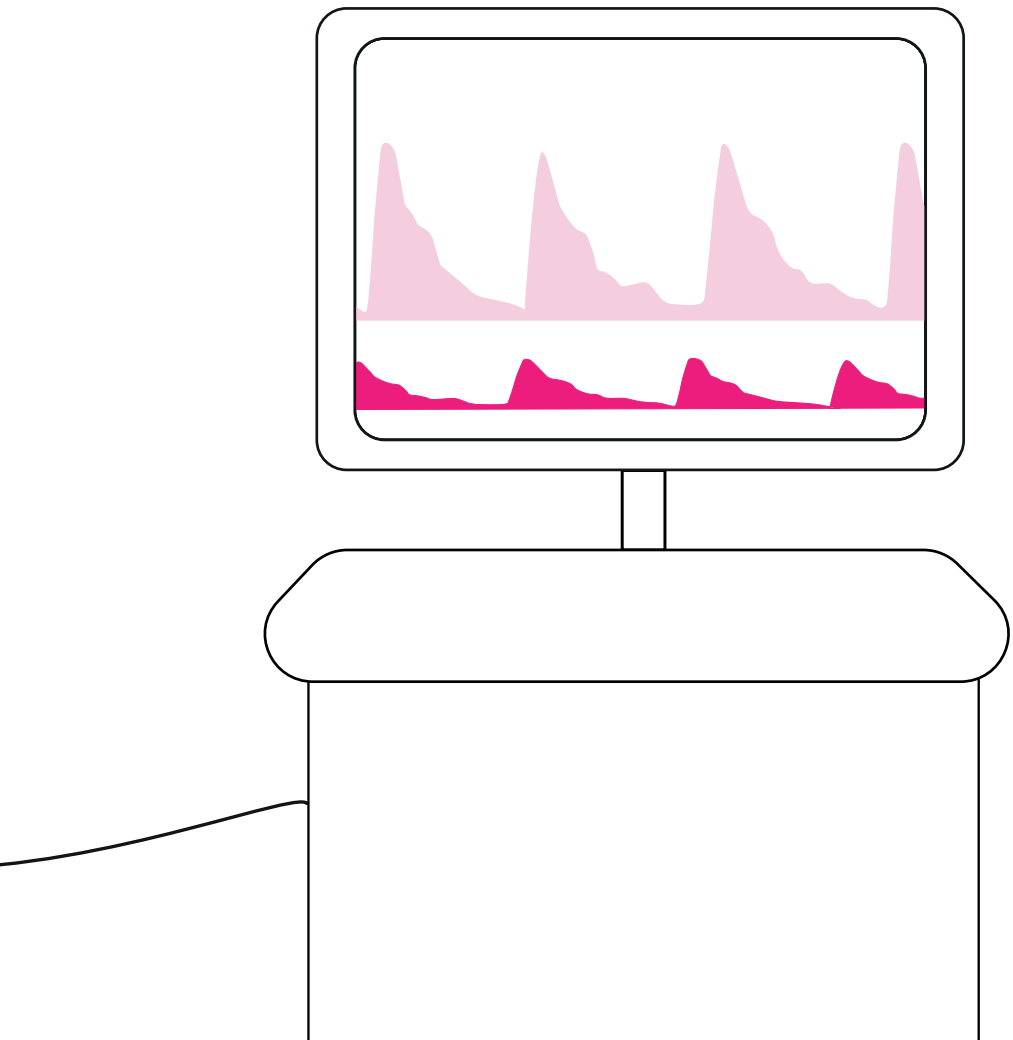
Chapter 3

Improved prediction of twin anemia polycythemia sequence by delta middle cerebral artery peak systolic velocity: a new antenatal classification system



Abstract

Objective

To investigate the diagnostic accuracy of delta middle cerebral artery peak systolic velocity (MCA-PSV) > 0.5 multiples of the median (MoM) and compare its predictive value with that of the current cut-off MCA-PSV values of >1.5 MoM in the donor and < 1.0 MoM in the recipient, for the diagnosis of twin anemia polycythemia sequence (TAPS).

Methods

This was a retrospective consecutive cohort study comprising all uncomplicated monochorionic twin pregnancies and twin pregnancies with a postnatal diagnosis of TAPS between 2003 and 2017 in the Dutch national referral center for fetal therapy. Cases with incomplete MCA-PSV Doppler measurements 1 week prior to delivery or with incomplete hemoglobin measurements within 1 day after birth were excluded. The postnatal diagnosis of TAPS was based on an inter-twin hemoglobin difference > 8 g/dL and at least one of the following: reticulocyte count ratio > 1.7 or presence of minuscule anastomoses on the placental surface. We compared the predictive accuracy of the current diagnostic method using MCA-PSV cut-off values of > 1.5 MoM in the donor and < 1.0 MoM in the recipient with that of a new method based on inter-twin difference in MCA-PSV > 0.5 MoM for prediction of TAPS.

Results

In total, 45 uncomplicated monochorionic and 35 TAPS twins were analyzed. The sensitivity and specificity of the cut-off MCA-PSV values (donor >1.5 MoM, recipient <1.0 MoM) to predict postnatal TAPS was 46% (95%CI 30-62%) and 100% (95%CI 92-100%), respectively; positive predictive value was 100% (95%CI 81-100%) and negative predictive value 70% (95%CI 58-80%). Delta MCA-PSV showed a sensitivity of 83% (95%CI 67-92%) and a specificity of 100% (95%CI 92-100%); the positive predictive value and negative predictive value were 100% (95%CI 88-100%) and 88% (95%CI 77-94%), respectively. Of the 35 cases with TAPS diagnosed postnatally, 13 twin pairs showed a delta MCA-PSV > 0.5 MoM, but did not fulfill the cut-off MCA-PSV criteria. Of these 13 TAPS twins, nine donors and four recipients had normal MCA-PSV values. There was a high

correlation between delta MCA-PSV and inter-twin difference in hemoglobin level (R= 0.725, $p < 0.01$).

Conclusion

Delta MCA-PSV > 0.5 MoM has a greater diagnostic accuracy for predicting TAPS compared to the current MCA-PSV cut-off criteria. We therefore propose a new antenatal classification system for TAPS. In monochorionic twin pregnancies with delta MCA-PSV > 0.5 MoM on Doppler ultrasound, but normal MCA-PSV values in the donor or recipient, obstetricians should be aware of the therapeutic implications and neonatal morbidities associated with TAPS.

Introduction

Twin anemia polycythemia sequence (TAPS) is a feto-fetal transfusion syndrome in monochorionic twins, in which chronic net inter-twin blood transfusion through minuscule placental anastomoses leads to large hemoglobin differences between donor and recipient, without signs of twin oligohydramnios polyhydramnios sequence (TOPS).[1] TAPS occurs spontaneously in 2-5% of monochorionic twin pregnancies, and develops in 3-16% of twins with twin-twin transfusion syndrome (TTTS) after fetoscopic laser surgery, as a result of the presence of small residual anastomoses.[2-5]

Antenatal diagnosis of TAPS is currently based on discordant middle cerebral artery peak systolic velocity (MCA-PSV) Doppler measurements. To identify TAPS before birth, the following MCA-PSV cut-off values have been proposed: > 1.5 multiples of the median (MoM) in the donor twin, suggestive of fetal anemia, and MCA-PSV < 1.0 MoM in the recipient, indicating fetal polycythemia.[6, 7] Recently, the predictive value and clinical usefulness of the lower cut-off level for polycythemia has been questioned in a recent study by Fishel-Bartel et al., which revealed that monochorionic twins diagnosed with polycythemia at birth often showed MCA-PSV values > 1.0 MoM prior to delivery.[8] In the same study, the delta MCA-PSV correlated strongly with the inter-twin hematocrit difference and was thus proposed a better indicator for the antenatal detection of TAPS. However, the study consisted of only nine TAPS cases, highlighting the need for additional studies with a larger population to investigate the potential value of this alternative antenatal diagnostic criterion in TAPS.

This study sets out to evaluate the diagnostic accuracy of delta MCA-PSV > 0.5 MoM and to compare its predictive value to that of the fixed cut-off values of MCA-PSV (< 1.0 MoM in the recipient and > 1.5 MoM in the donor) used currently for the detection of TAPS in monochorionic twin pregnancy.

Methods

This was a retrospective study of all consecutive uncomplicated monochorionic diamniotic twin pairs and monochorionic twins with TAPS diagnosed postnatally, managed between 2003 and 2017 in the Dutch national referral center for fetal therapy. Cases in which MCA-PSV ultrasound Doppler measurements were performed in both fetuses within 1 week before delivery were considered

eligible for analysis. The postnatal diagnosis of TAPS was based on an inter-twin hemoglobin difference > 8 g/dL and at least one of the following: reticulocyte count ratio > 1.7 or the presence of minuscule anastomoses (diameter < 1.0 mm) on the placental surface, detected through placental color dye injection.[9] Since a large difference in hemoglobin levels is essential for the postnatal diagnosis of TAPS, all cases with incomplete postnatal hemoglobin values were excluded from this study.

MCA-PSV values were obtained retrospectively from obstetrical records. MCA-PSV was measured according to the technique described by Mari et al.[10] The reference ranges for monochorionic diamniotic twin pregnancies published by Klaritsch et al. were used to convert MCA-PSV (cm/s) values to MoM.[11] When twins exceeded both cut-off values, i.e. > 1.5 MoM in one twin *and* < 1.0 MoM in the co-twin, this was named a cut-off MCA-PSV diagnosis. When there was an inter-twin difference in MCA-PSV > 0.5 MoM, the term delta MCA-PSV > 0.5 MoM diagnosis was used.

The following obstetric, fetal and neonatal data were collected from our database: gestational age at birth, antenatal fetal intervention, indication of TAPS on ultrasound, type of TAPS (spontaneous or post-laser), Quintero stage of TTTS preceding post-laser TAPS, mode of delivery, birth weight, postnatal hemoglobin values, postnatal intervention, severe neonatal morbidities and neonatal mortality. Adverse outcome was defined as either neonatal mortality or severe neonatal morbidity. Severe neonatal morbidity included at least one of the following: respiratory distress syndrome requiring mechanical ventilation or surfactant, necrotizing enterocolitis stage 2 or higher, patent ductus arteriosus requiring medical therapy or surgical closure, severe cerebral injury (at least one of the following: intraventricular hemorrhage grade 3 or higher, cystic periventricular leukomalacia grade 2 or higher, ventricular dilation > 97th percentile or porencephalic or parenchymal cysts) or severe anemia/polycythemia requiring blood transfusion or partial exchange transfusion respectively, within 24h after birth.

Statistical analysis was performed using SPSS version 23.0 (IBM, Armonk, NY, USA). Data are reported as medians and interquartile ranges (IQR). Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were calculated using 2 x 2 tables and standard formulas for binominal proportions. Wilson's interval method

was used to calculate the 95% confidence interval (CI).[12] Group differences of continuous variables were compared using the Mann-Whitney U-test. The Chi square test was applied when calculating differences in proportions. Spearman's correlation coefficient was used to measure the correlation between delta MCA-PSV and inter-twin hemoglobin difference. All analyses per fetus or neonate were performed using the generalized estimated equation module to account for the fact that observations between cotwins are not independent. A p-value < 0.05 was considered statistically significant.

Results

A total of 45 uncomplicated monochorionic twins and 35 twin pairs diagnosed postnatally with TAPS were included in this study. Figure 1 shows the derivation of the study population.

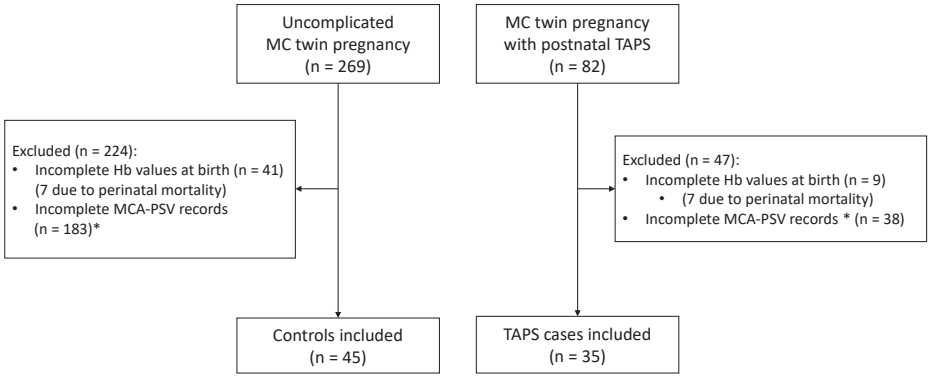


Figure 1 Flowchart showing derivation of study population consisting of uncomplicated monochorionic (MC) twin pregnancies (controls) and twins diagnosed postnatally with twin anemia polycythemia sequence (TAPS). *Within 1 week prior to delivery. Hb, hemoglobin; MCA-PSV, middle cerebral artery peak systolic velocity.

In total, 183 uncomplicated monochorionic twins and 38 TAPS twins were excluded due to lacking or incomplete MCA-PSV records 1 week prior to delivery. Baseline characteristics for both groups are presented in Table 1. Compared with uncomplicated monochorionic twins, TAPS twins were delivered more frequently via Cesarean section, showed a lower gestational age at birth, and were characterized by a larger inter-twin difference in hemoglobin and birth weight.

Table 1. Baseline characteristics of uncomplicated monochorionic twin pregnancies (controls) and pregnancies diagnosed postnatally with twin anemia polycythemia sequence (TAPS)

Characteristic	Controls (N=45)	TAPS (N=35)	P
Female sex	23/45 (51)	14/35 (40)	0.163
Cesarean section	39/90 (43)	52/70 (74)	<0.0001
Gestational age at birth (weeks)	35 (33-36)	32 (29-34)	<0.0001
Birth-weight discordance (%)	11.6 (5.9-17.3)	14.5 (7.9-20.8)	0.114
Birth-weight discordance ≥ 20%	4/45 (9)	12/35 (34)	0.005
Inter-twin Hb difference (g/dL)	1.2 (0.3-3.6)	12.7 (10.8-15.1)	<0.0001

Data are given as n/N (%) or median (interquartile range). Hb, hemoglobin

In Table 2 a 2x2 cross table on the diagnostic accuracy of the cut-off MCA-PSV diagnosis for postnatal TAPS is presented. Out of the 35 cases with a postnatal TAPS diagnosis, 16 pregnancies fulfilled the cut-off MCA-PSV diagnosis antenatally, reflected by a sensitivity rate of 46% (95%CI 30-62%). The specificity for this antenatal diagnostic criterion was 100% (95%CI 92-100%): out of the 45 control cases none showed a cut-off MCA-PSV diagnosis. Positive predictive value was 100% (95%CI 81-100%) and negative predictive value 70% (95%CI 58-80%). The negative likelihood ratio was 0.54. The cross table on de diagnostic accuracy of delta MCA-PSV > 0.5 MoM for postnatal TAPS is shown in Table 3. The sensitivity for this second antenatal diagnostic criterion was 83% (95%CI 67-92%): 29 out of the 35 postnatally diagnosed TAPS cases were characterized by a delta MCA-PSV > 0.5 MoM ultrasound measurement prior to delivery. In the control group there was no case which fulfilled the delta MCA-PSV > 0.5 MoM criterion, reflected by a specificity rate of 100% (95%CI 92-100%). The positive predictive value and negative predictive value were 100% (95%CI 88-100%) and 88% (95%CI 77-94%), respectively. The negative likelihood ratio was 0.17. Due to a specificity rate of 100% for both antenatal MCA-PSV criteria, the positive likelihood ratio could not be calculated.

Table 2. Prediction of twin anemia polycythemia sequence (TAPS) using fixed cut-off values of middle cerebral artery peak systolic velocity (MCA-PSV) < 1.0 multiples of the median (MoM) and > 1.5 MoM in recipient and in donor twin, respectively, in monochorionic twin pregnancy diagnosed postnatally with TAPS

Met MCA-PSV cut-off criteria	**Postnatal diagnosis of TAPS**		
	Yes	No	Total
Yes	16	0	16
No	19	45	64
Total	35	45	80

Sensitivity = 46% (95%CI 30-62%), specificity = 100% (95%CI 92-100%), positive predictive value = 100% (95%CI 81-100%) negative predictive value = 70% (95%CI 58%-80%), positive likelihood ratio not calculable, negative likelihood ratio = 0.54

Table 3. Prediction of twin anemia polycythemia sequence (TAPS) based on inter-twin difference in middle cerebral artery peak systolic velocity (MCA-PSV) > 0.5 multiples of the median (MoM), in monochorionic twin pregnancy diagnosed postnatally with TAPS

Met Delta MCA-PSV > 0.5 MoM	**Postnatal diagnosis of TAPS**		
	Yes	No	Total
Yes	29	0	29
No	6	45	51
Total	35	45	80

Sensitivity = 83% (95% CI 67-92%), specificity = 100% (CI95%, 92-100%), positive predictive value =100% (95%CI 88-100%), negative predictive value = 88% (95% CI 77%-94%), positive likelihood ratio not calculable, negative likelihood ratio = 0.17

In total, 13 TAPS cases did not fulfill the cut-off MCA-PSV criteria, having normal MCA-PSV values in either the donor (n = 9) or recipient (n = 4), but showed a delta MCA-PSV > 0.5 MoM. Table 4 shows fetal and neonatal characteristics of these 13 cases in comparison with the TAPS cases that met the cut-off MCA-PSV criteria (n=16). TAPS pregnancies that did not reach both MCA-PSV cut-off levels but had delta MCA-PSV > 0.5 MoM were non-significantly less likely to be treated antenatally with intrauterine transfusion and/or PET, were delivered at a later gestational age and were characterized by a larger birth-weight discordance compared with twin pregnancies that fulfilled the cut-off MCA-PSV criteria. There were no noteworthy differences with respect to postnatal treatment and neonatal outcome between the two groups.

Table 4. Fetal and neonatal characteristics of 16 pregnancies with twin anemia polycythemia sequence (TAPS) that fulfilled cut-off middle cerebral artery peak systolic velocity (MCA-PSV) criteria and 13 TAPS pregnancies that did not reach MCA-PSV cut-off levels in both twins but had delta MCA-PSV > 0.5 multiples of the median (MoM)

	Met Cut-off MCA-PSV criteria (N=16)	**Normal MCA-PSV but delta MCA-PSV > 0.5 MoM (N=13)**	**P**
Male sex	6/10 (37)	11/13 (85)	0.007
Type of TAPS			0.452
Spontaneous	3/16 (19)	4/13 (31)	
Post-laser	13/16 (81)	9/13 (69)	
Quintero stage			0.646
I	1/13 (8)	2/9 (22)	
II	4/13 (31)	2/9 (22)	
III	7/13 (54)	5/9 (56)	
IV	1/13 (8)	-	
Antenatal Therapy			0.087
None	8/16 (50)	11/13 (85)	
IUT	4/16 (25)	2/13 (15)	
IUT and PET	4/16 (25)	-	
Difference in placental echogenicity on ultrasound	6/16 (38)	6/13 (46)	0.716
Starry-sky liver in recipient	8/16 (50)	3/13 (23)	0.135
Gestational age at birth (weeks)	31 (28-32)	34 (31-35)	0.430
Inter-twin Hb difference (g/dL)	13.9 (12.3-16.0)	12.7 (10.2-15.8)	0.350
Reticulocyte count ratio	3.9 (2.7-4.6)	4.5 (2.5-5.8)	0.384
Postnatal therapy on day 1			
BT	11/16 (68)	9/13 (69)	0.978
PET	11/16 (68)	6/13 (46)	0.219
BT and PET	7/15 (47)	4/13 (31)	0.296
Birth-weight discordance (%)	11.5 (5.8-20.3)	19.7 (13.4-38.2)	0.070
Birth-weight discordance > 20%	4/16 (25)	7/13 (54)	0.111
Severe neonatal morbidity*	14/32 (44)	7/26 (27)	0.227
Neonatal mortality	2/32 (6)	1/26 (4)	0.665

Data are given as n/N (%) or median (interquartile range). *Severe neonatal morbidity defined as at least one of: respiratory distress syndrome, patent ductus arteriosus requiring medical or surgical intervention, necrotizing enterocolitis and severe cerebral injury. BT, blood transfusion; Hb, hemoglobin; IUT, intrauterine transfusion; PET, partial exchange transfusion.

The correlation between delta MCA-PSV and inter-twin hemoglobin level difference is displayed in Figure 2. There was a strong correlation between delta MCA-PSV and inter-twin difference in hemoglobin level (R = 0.725, P < 0.01)

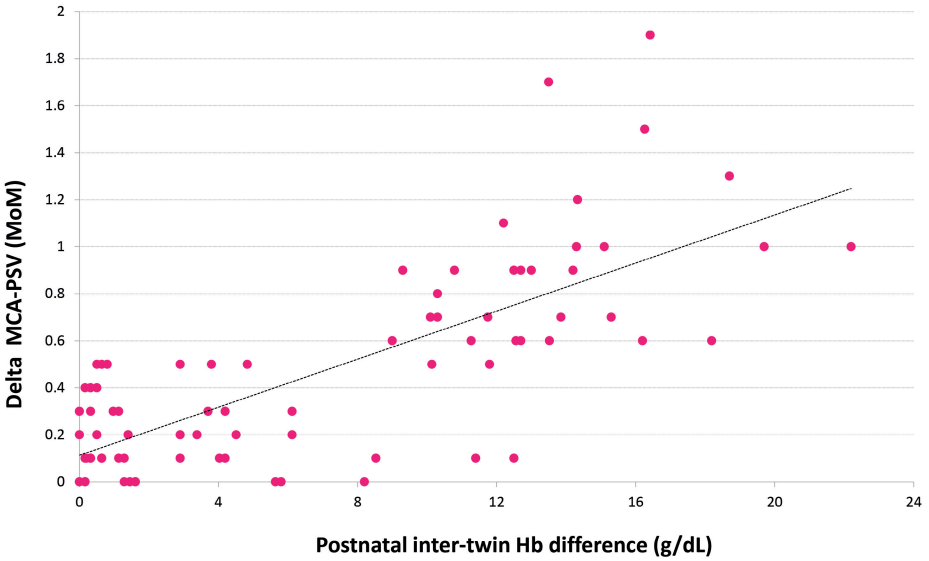


Figure 2 Correlation between delta middle cerebral artery peak systolic velocity (MCA-PSV) and inter-twin difference in hemoglobin (Hb) levels in 45 uncomplicated monochorionic twin pregnancies and 35 with twin anemia polycythemia sequence. Strong correlation was observed (R = 0.725; P < 0.01). MoM, multiples of the median.

Discussion

This is the first study evaluating the diagnostic accuracy of delta MCA-PSV for the prediction of TAPS. The criterion of delta MCA-PSV > 0.5 MoM showed high sensitivity and specificity for the prediction of TAPS and proved to be a superior predictor of postnatal TAPS compared with the current criteria of fixed MCA-PSV cut-off values. Moreover, we showed that TAPS twins with delta MCA-PSV > 0.5 MoM but with normal MCA-PSV values (in either the donor or recipient) were comparable with respect to perinatal mortality and neonatal morbidity to the TAPS twins that met the MCA-PSV cut-off criteria. Based on these findings, we propose a new antenatal classification system for TAPS (Table 5).

Table 5. Proposed antenatal classification system for twin anemia polycythemia sequence (TAPS)

Antenatal stage	Previous Criteria	Proposed criteria
Stage 1	MCA-PSV donor > 1.5 MoM and MCA-PSV recipient < 1.0 MoM without signs for fetal compromise	Delta MCA-PSV > 0.5 MoM without signs for fetal compromise
Stage 2	MCA-PSV donor > 1.7 MoM and MCA-PSV recipient < 0.8 MoM without signs for fetal compromise	Delta MCA-PSV > 0.7 MoM without signs for fetal compromise
Stage 3	As stage 1 or 2, with cardiac compromise of the donor, defined as critically abnormal flow*	As stage 1 or 2, with cardiac compromise of the donor, defined as critically abnormal flow*
Stage 4	Hydrops of donor	Hydrops of donor
Stage 5	Intra-uterine demise of one or both fetuses preceded by TAPS	Intra-uterine demise of one or both fetuses preceded by TAPS

*Defined as critically abnormal flow: Doppler shows absent or reversed end-diastolic flow in umbilical artery, pulsatile flow in umbilical vein and/or increased pulsatility index or reversed flow in ductus venosus. MCA-PSV, middle cerebral artery peak systolic velocity; MoM, multiples of the median.

In the new classification system, Stage 1 TAPS is changed from MCA-PSV > 1.5 MoM in the donor and <1.0 MoM in the recipient to delta MCA-PSV value > 0.5 MoM, while Stage 2 TAPS is changed from MCA-PSV > 1.7 MoM in the donor and < 0.8 MoM in the recipient to delta MCA-PSV > 0.7 MoM. We chose a lower delta MCA-PSV value (> 0.7 MoM) for TAPS Stage 2 than would be expected based on the previous criteria (MCA-PSV cut-off values > 1.7 MoM and < 0.8 MoM in the donor and recipient, respectively, would indicate delta MCA-PSV > 0.9 MoM) because our data show that using delta MCA-PSV > 0.9 MoM as the criterion, five of seven TAPS twins with delta MCA-PSV of 0.8 and 0.9 MoM would have adverse outcome. These twins could benefit from antenatal treatment with intra-uterine transfusions or laser surgery. Based on the proposed treatment flowchart for TAPS which indicates that antenatal intervention is recommended from Stage 2, we therefore accept delta > 0.7 MoM for Stage 2 TAPS.[13]

Our findings show that TAPS twins with a delta MCA-PSV > 0.5 but with normal MCA-PSV values in either the donor or recipient have a similar perinatal outcome as twins that fulfilled the MCA-PSV cut-off criteria. Notably, these TAPS twins were delivered at a later gestational age and were treated less often with an intrauterine intervention than the twins that fulfilled MCA-PSV cut-off diagnosis, although the differences were not statistically significant.

Perhaps, this group was regarded as having mild or as atypical TAPS, resulting in a more reluctant attitude towards antenatal intervention. The group with delta MCA-PSV > 0.5 MoM but with normal MCA-PSV values in either the donor or the recipient comprised significantly more male twin pairs than the group that fulfilled the MCA-PSV cut-off criteria but this difference may be a result of small sample size and is not likely to be related to the pathophysiology of the disease. Interestingly, a higher rate of birth-weight discordance was found in TAPS twins with delta MCA-PSV > 0.5 MoM compared to the cut-off MCA-PSV group. It is possible that coexisting selective intrauterine growth restriction is of influence on the hemodynamic balance in this population. Between the two groups, no statistically significant differences were found with respect to the type of TAPS, placental anastomoses, and perinatal outcome, corroborating the fact that these two groups probably share the same elemental pathological mechanism responsible for the inter-twin difference in hemoglobin level.

Although TAPS derives its acronym from the presence of anemia and coexisting polycythemia, our results show that the inter-fetal net blood transfusion responsible for this condition does not necessarily lead to equally discordant MCA-PSV levels or an equally severe anemia or polycythemia. This idea has already been accepted when the primary postnatal criterion for TAPS was changed from presence of anemia and polycythemia based on fixed hemoglobin cut-off levels into an inter-twin hemoglobin difference, because it was a more logic approach to describe this form of feto-fetal transfusion.[14] To provide continuity between antenatal and postnatal diagnostic criteria, changing the fixed MCA-PSV cut-off values into delta MCA-PSV would be a suitable next step, and the greater diagnostic accuracy of this new criterion, combined with its correlation with postnatal inter-twin hemoglobin difference postnatally, shows its potential clinical benefits.

Our findings seem to contravene the previously published studies regarding the diagnostic accuracy of MCA-PSV cut-off values for the antenatal detection of TAPS, including one performed by our own research group in which we found high sensitivity rates for both MCA-PSV > 1.5 MoM for anemia and < 1.0 MoM for polycythemia.[6] It should, however, be stressed that this particular study was performed in TAPS pregnancies only, which might have resulted in an overestimation of these criteria. Moreover, in the current study, the MCA-PSV criteria were not tested for the presence of anemia and polycythemia at birth,

but for a postnatal TAPS diagnosis, which is primarily based on an inter-twin hemoglobin difference.

These results should be interpreted with caution due to the retrospective nature of this study and the limited sample size. Since TAPS was discovered only a decade ago, MCA-PSV measurements are not performed routinely in every monochorionic twin pregnancy. Therefore, many TAPS cases in our database were only diagnosed postnatally and were excluded due to missing MCA-PSV values. Furthermore, in this study, the diagnostic accuracy of delta MCA-PSV > 0.5 MoM is only assessed in a TAPS group and in a control group consisting of uncomplicated monochorionic twin pregnancies. MCA-PSV > 0.5 MoM as a diagnostic tool for TAPS may perform less well in a larger, more heterogeneous monochorionic twin population. To further evaluate the true potential of delta MCA-PSV > 0.5 MoM as an accurate and reliable screening tool to detect TAPS, a large prospective study of monochorionic twin pregnancies is needed. In addition, the effect of the new proposed classification on intervention protocols, perinatal survival and long-term neurodevelopmental outcome needs to be evaluated.

In conclusion, this study shows that delta MCA-PSV > 0.5 MoM has a greater accuracy for diagnosis of TAPS than the cut-off MCA-PSV criteria used currently; to improve antenatal detection of TAPS, we propose a new antenatal classification system. In monochorionic twin pregnancies with an inter-twin difference in MCA-PSV > 0.5 MoM, but with normal MCA-PSV values in either the donor or recipient, obstetricians should be aware of the pathogenesis, therapeutic implications and neonatal morbidities associated with TAPS.

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