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

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KEYWORDS: diagnostic accuracy; MCA-PSV; monochorionic twins; TAPS; twin–twin transfusion syndrome

ABSTRACT

Objectives *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 MCA-PSV cut-off values of > 1.5 MoM in the donor and < 1.0 MoM in the recipient, for the diagnosis of twin anemia–polycythemia sequence (TAPS) in monochorionic twin pregnancy.*

Methods *This was a retrospective consecutive cohort study comprising all uncomplicated monochorionic twin pregnancies and twin pregnancies with a postnatal diagnosis of TAPS managed 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 intertwin 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 intertwin difference in MCA-PSV > 0.5 MoM for prediction of TAPS.*

Results *In total, 45 uncomplicated and 35 TAPS monochorionic twin pregnancies were analyzed. The sensitivity and specificity of the cut-off MCA-PSV values (donor > 1.5 MoM, recipient < 1.0 MoM) to predict 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 and negative predictive values 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 intertwin 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. © 2018 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Twin anemia–polycythemia sequence (TAPS) is a fetofetal transfusion syndrome in monochorionic twins, in which chronic net intertwin blood transfusion through minuscule placental anastomoses leads to large hemoglobin differences between donor and recipient, without signs

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of twin oligohydramnios–polyhydramnios sequence[1]. TAPS occurs spontaneously in 2–5% of the 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 (MCA) peak systolic velocity (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 was questioned in a study by Fishel-Bartal *et al.*[8], which revealed that monochorionic twins diagnosed with polycythemia at birth often showed MCA-PSV values > 1.0 MoM prior to delivery. In the same study, the delta MCA-PSV correlated strongly with the intertwin hematocrit difference and was thus proposed as a better indicator for the antenatal detection of TAPS[8]. 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 for 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 prior to delivery were considered eligible for analysis. The postnatal diagnosis of TAPS was based on an intertwin 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 obstetric records. MCA-PSV was measured according to the technique described by Mari *et al.*[10]. The reference ranges for monochorionic diamniotic twin pregnancy published by Klaritsch *et al.*[11] were used to convert MCA-PSV values (cm/s) to MoM. When twins exceeded both cut-off values for TAPS, i.e. > 1.5 MoM in one twin and < 1.0 MoM in the cotwin, this was named a cut-off MCA-PSV diagnosis. When there was an intertwin 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 or polycythemia requiring blood transfusion or partial exchange transfusion (PET), respectively, within 24 h after birth.

Statistical analysis was performed using SPSS version 23.0 (IBM, Armonk, NY, USA). Data are reported as median and interquartile range (IQR). Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were calculated using 2 × 2 tables and standard formulae for binominal proportions. Wilson's interval method was used to calculate the 95% CI[12]. Group differences of continuous variables were compared using the Mann–Whitney *U*-test. The chi-square test was used to calculate differences in proportions. Spearman's correlation coefficient was used to measure the correlation between delta MCA-PSV and intertwin 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 twin pregnancies and 35 twin pairs diagnosed postnatally with TAPS were included in this study. Figure 1 shows the derivation of the study population. In total, 183 uncomplicated monochorionic twin pregnancies and 38 twin pregnancies with TAPS were excluded due to missing or incomplete MCA-PSV records within 1 week prior to delivery. Baseline characteristics of 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

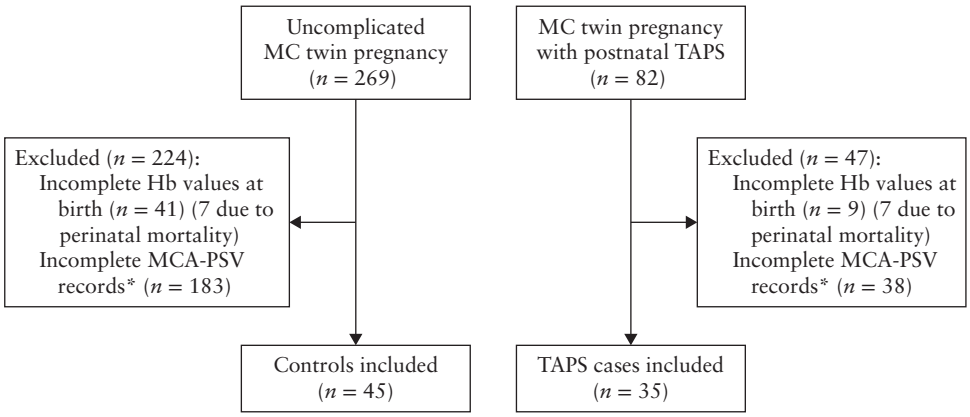

Figure 1 Flowchart showing derivation of study population consisting of uncomplicated monochorionic (MC) twin pregnancies (controls) and twins diagnosed postnatally with twin anemia–polycythemia sequence (TAPS). *Within 1 week prior to delivery. Hb, hemoglobin; MCA-PSV, middle cerebral artery peak systolic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

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
Intertwin 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.

larger intertwin difference in hemoglobin level and birth weight.

A 2 × 2 cross table of the cut-off MCA-PSV diagnostic accuracy for TAPS is presented in Table 2. Of the 35 pregnancies with a postnatal diagnosis of TAPS, 16 fulfilled the cut-off MCA-PSV diagnosis antenatally, reflected by a sensitivity of 46% (95% CI, 30–62%). The specificity of this antenatal diagnostic criterion was 100% (95% CI, 92–100%), positive predictive value was 100% (95% CI, 81–100%), negative predictive value was 70% (95% CI, 58–80%) and negative likelihood ratio was 0.54. The cross table of the diagnostic accuracy of delta MCA-PSV > 0.5 MoM for TAPS is shown in Table 3. Of the 35 TAPS cases diagnosed postnatally, 29 were characterized by a delta MCA-PSV > 0.5 MoM ultrasound measurement prior to delivery; thus, the sensitivity of this antenatal diagnostic criterion was 83% (95% CI, 67–92%). In the control group, there was no case which fulfilled the delta MCA-PSV > 0.5 MoM criterion, reflected by a specificity of 100% (95% CI, 92–100%). The positive and negative predictive values of this criterion were 100% (95% CI, 88–100%) and 88% (95% CI, 77–94%), respectively, and the negative likelihood ratio was 0.17. Due to a specificity of 100% for both antenatal MCA-PSV criteria, the positive likelihood ratios could not be calculated.

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 the recipient ($n = 4$), but showed delta MCA-PSV > 0.5 MoM. Table 4 shows

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 intertwin 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

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% (95% CI, 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.

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)

Characteristic	*Met cut-off MCA-PSV criteria (n = 16)*	*Normal MCA-PSV but delta MCA-PSV > 0.5 MoM (n = 13)*	P
Male sex	6/16 (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)	0/9 (0)	
Antenatal therapy			0.087
None	8/16 (50)	11/13 (85)	
IUT	4/16 (25)	2/13 (15)	
IUT and PET	4/16 (25)	0/13 (0)	
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
Intertwin 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	8/16 (50)	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.

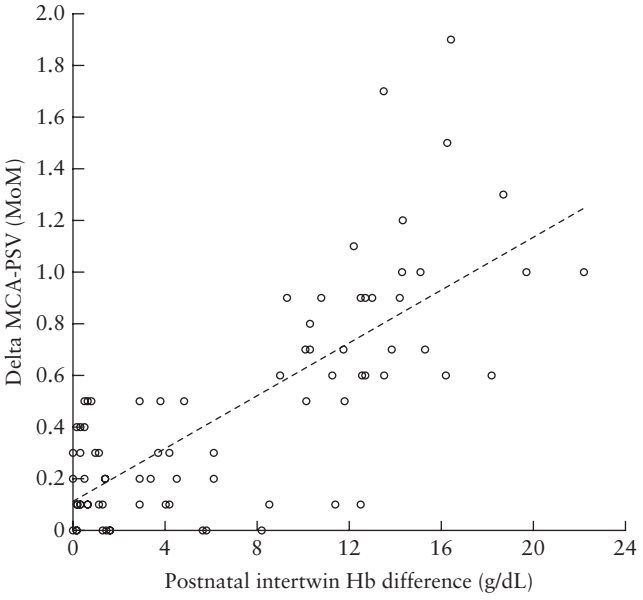

Figure 2 Correlation between delta middle cerebral artery peak systolic velocity (MCA-PSV) and intertwin difference in hemoglobin (Hb) levels in 45 uncomplicated monochorionic twin pregnancies and 35 with twin anemia–polycythemia sequence. Strong correlation was observed ($R = 0.725$; $P < 0.01$). MoM,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

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.

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

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 compared

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, recipient < 1.0 MoM; without signs of fetal compromise	Delta MCA-PSV > 0.5 MoM; without signs of fetal compromise
Stage 2	MCA-PSV donor > 1.7 MoM, recipient < 0.8 MoM; without signs of fetal compromise	Delta MCA-PSV > 0.7 MoM; without signs of fetal compromise
Stage 3	As Stage 1 or 2; with cardiac compromise of donor*	As Stage 1 or 2; with cardiac compromise of donor*
Stage 4	Hydrops of donor	Hydrops of donor
Stage 5	Intrauterine demise of one or both fetuses preceded by TAPS	Intrauterine 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.

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 the recipient) were comparable with respect to perinatal mortality and neonatal morbidity to the TAPS twins that met MCA-PSV cut-off criteria. Based on these findings, we propose a new antenatal classification system for TAPS (Table 5).

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 > 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 intrauterine transfusion 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 MCA-PSV > 0.7 MoM for Stage 2 TAPS[13].

Our findings show that TAPS twins with delta MCA-PSV > 0.5 MoM but with normal MCA-PSV values in either the donor or the recipient have a similar perinatal outcome to that of the 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 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 cut-off MCA-PSV criteria, but this difference may be a result of the 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 but normal MCA-PSV compared with 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 intertwin difference in hemoglobin level.

Although TAPS derives its acronym from the presence of anemia and coexisting polycythemia, our results show that the interfetal 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 intertwin hemoglobin difference, because it was a more logical approach to describe this form of fetofetal 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 intertwin hemoglobin difference, 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 pregnancy 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 based primarily on an intertwin 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 diagnosed only 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 intertwin 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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