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Predicting Adverse Outcomes in Monochorionic-Diamniotic Twins: The Role of Intertwin Discrepancy in Middle Cerebral Artery Doppler Measurements and the Cerebroplacental Ratio

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Abstract

Objective This study was aimed to evaluate the role of intertwin discrepancy in middle cerebral artery peak systolic velocity (MCA-PSV) and cerebroplacental ratio (CPR) for the prediction of adverse outcomes in monochorionic-diamniotic (MCDA) twin pregnancies.

Study Design A retrospective cohort study of MCDA pregnancies that underwent ultrasound surveillance at a perinatal referral center from 2007 to 2017. Intertwin MCA-PSV discrepancy (MCA-$\Delta_{PSV\text{-}MoM}$) was defined as the absolute difference of MCA-PSV multiple of the median (MoM) for gestational age between twins. Intertwin CPR discrepancy (CPR-Δ) was defined as the absolute difference of CPR between twins. The maximum MCA-$\Delta_{PSV\text{-}MoM}$ and CPR-Δ before and after 26 weeks of gestation were assessed as predictors of pregnancy and neonatal outcomes through simple logistic regression models and Pearson's correlation coefficients. Receiver operating characteristic (ROC) curves were generated to determine the predictive value of maximum MCA-$\Delta_{PSV\text{-}MoM}$ and CPR-Δ.

Results A total of 143 MCDA pregnancies met inclusion criteria. There was a significant association between MCA-$\Delta_{PSV\text{-}MoM}$ at <26 weeks and the development of twin anemia-polycythemia sequence (TAPS; $p = 0.007$), intrauterine fetal demise (IUFD; $p = 0.009$), and neonatal intensive care unit (NICU) admission ($p < 0.05$). MCA-$\Delta_{PSV\text{-}MoM}$ at ≥26 weeks was associated with the development of TAPS ($p < 0.001$). CPR-Δ at <26 weeks was associated with the development of twin-twin transfusion syndrome (TTTS; $p = 0.03$) and NICU admission ($p = 0.02$). MCA-$\Delta_{PSV\text{-}MoM}$ at ≥26 weeks was highly predictive of TAPS (area under curve [AUC] = 0.92). A cut-off of 0.44 would identify TAPS with 100% sensitivity and 73% specificity.

Keywords
- intertwin discrepancy
- monochorionic-diamniotic twins
- middle cerebral artery
- cerebroplacental ratio
- Doppler

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Conclusion In MCDA pregnancies, intertwin MCA and CPR discrepancies are associated with adverse pregnancy and neonatal outcomes, including TAPS, TTTS, IUFD, and NICU admission. Evaluation of intertwin MCA and CPR differences demonstrated the potential for clinical predictive utility in the surveillance of MCDA twin pregnancies.

Key Points

- Intertwin discrepancy of MCA-PSV and CPR is associated with adverse pregnancy outcomes.
- Intertwin differences in Doppler ultrasound may occur prior to meeting diagnostic criteria for TTTS or TAPS.
- There is potential clinical predictive utility in MCA and CPR surveillance of MCDA twin pregnancies.

Monochorionic-diamniotic (MCDA) twin pregnancies are at a three to five times higher risk of perinatal morbidity and mortality than dichorionic twins.[1] This increase in risk is attributed to a shared placenta and characterized by intertwin vascular anastomoses which, when unbalanced, leads to complications specific to MCDA twins.[2,3] These risks include twin-twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence (TAPS), and selective intrauterine growth restriction (sIUGR).[4]

Due to the increased risk of complications, these pregnancies require close surveillance. However, the evidence for timing and components of monitoring is limited and the recommendations for surveillance vary between governing bodies.[4–7] The Society for Maternal-Fetal Medicine recommends serial ultrasound surveillance at every 2 weeks, starting at 16 weeks, to monitor amniotic fluid levels and bladder filling per guidance from the North American Fetal Therapy Network, but there continues to be no consensus on the inclusion of umbilical artery (UA) and middle cerebral artery (MCA) Doppler measurements in the surveillance of MCDA pregnancies.[7] Doppler interrogation of the UA and MCA have been shown to play an important role in antenatal assessment of high-risk pregnancies, decreasing perinatal morbidity and mortality.[8–11] In addition, the cerebroplacental ratio (CPR) may have value in the assessment of fetal wellbeing and prediction of adverse neonatal outcomes.[12–16] CPR is a combined measurement of fetal response and placental status and theorized to be a more sensitive Doppler index for predicting perinatal outcomes.[17,18]

The data on the utility of Doppler measurements in MCDA twins and prediction of adverse pregnancy outcomes are limited with variable conclusions. Some have demonstrated an association between abnormal Doppler measurements in monochorionic twins with neonatal morbidity, preterm delivery, and low birth weight (BW), while others demonstrated that isolated Doppler abnormalities are commonly observed in monochorionic twins and are not associated with adverse outcomes.[19,20] Gaziano et al was the first study to evaluate CPR in both monochorionic and dichorionic twin pregnancies and demonstrated that CPR was superior to the UA and MCA in prediction of adverse neonatal events.[21] Lastly, two retrospective studies have explored the novel utility of intertwin discrepancy of CPR and MCA-PSV and demonstrated an association with perinatal loss and sIUGR, respectively.[22,23]

Doppler ultrasonography, specifically intertwin differences of Doppler indices, in MCDA twin pregnancies requires further exploration to identify optimal methods of surveillance and subsequent timely interventions for these high-risk pregnancies. Here, we report our evaluation of the role of intertwin differences in MCA-PSV and CPR in the surveillance of MCDA pregnancies and association with MCDA-specific complications.

Materials and Methods

We conducted a retrospective cohort study reviewing all MCDA twin pregnancies that underwent antenatal surveillance over a 10-year period between January 1, 2007, and February 1, 2017, at a single, high-volume metropolitan perinatal referral center associated with the Department of Obstetrics and Gynecology at the David Geffen School of Medicine at the University of California Los Angeles (UCLA). This study was approved by the UCLA Institutional Review Board (IRB no.: 17–000486) and a waiver of informed consent was obtained. Women with MCDA twin pregnancies who were scheduled for biweekly ultrasounds, or as clinically indicated, between 16 and 34 weeks were included. All ultrasound studies were performed by registered diagnostic sonographers, followed by a confirmatory scan by a board-certified maternal-fetal medicine specialist. During each biweekly ultrasound, patients underwent Doppler evaluation of UA and MCA parameters, along with amniotic fluid and growth assessments per our center's protocol. Patients were identified through a search function within the clinical ultrasound database. We performed a multilayer search using dropdown values for number of gestation ("2"), chorionicity ("monochorionic-diamniotic"), and report comments for appropriate terms ("twin," "twins," and "monochorionic"). Each chart was reviewed individually to ensure accuracy of chorionicity, and clinical information and ultrasound variables were extracted from the review of medical records by one obstetrician (T.M.) to ensure uniformity in coding. Only deidentified information was used.

Pregnancies were dated by measurement of crown-rump length (CRL) of the larger twin in the first trimester, dates of

embryo transfer in in vitro fertilization (IVF) patients, or by the date of a certain last menstrual period (LMP) in women with regular cycles, unless there was a discrepancy of more than 5 to 7 days between dating by LMP and the CRL of the larger twin.[6] Chorionicity was determined by the presence of lambda or T signs and number of placentas at the first ultrasound.[24] Exclusion criteria included pregnancies complicated by chromosomal abnormalities or major structural anomalies and patients who presented after intrauterine fetal demise (IUFD) before 16 weeks of either twin or after the development of MCDA-twin-specific complications, including TTTS, TAPS, and sIUGR. Patients with incomplete ultrasound records or without MCA Doppler measurements were also excluded.

Variables collected included maximum vertical pockets of amniotic fluid in each sac, estimated fetal weight, UA, and MCA Doppler measurements. The head circumference, biparietal diameter, abdominal circumference, and femur length were used to calculate estimated fetal weight via Hadlock's formula.[25] UA Doppler measurements were categorized as normal, elevated systolic-to-diastolic ratio defined as greater than 95th percentile for gestational age, absent-end diastolic flow, or reverse-end diastolic flow. MCA Doppler measurements were defined as elevated if peak systolic velocity (PSV) was greater than 1.5 multiples of the median (MoM) for gestational age.[26]

Intertwin MCA-PSV discrepancy (MCA-$\Delta_{PSV\text{-}MoM}$) was defined as the absolute difference of MCA-PSV MoM between the twins. CPR was calculated as the ratio of MCA PI to UA PI, and intertwin CPR discrepancy (CPR-Δ) was defined as the absolute difference of CPR between the twins. Measurements were performed between 14 to 37 weeks. For this study, the MCA-$\Delta_{PSV\text{-}MoM}$ and CPR-Δ measurements were divided evenly into two groups defined as the $<$26 weeks group (14–25 completed weeks) and the $\geq$26 weeks group (26–37 completed weeks) and assessed as predictors of adverse pregnancy outcomes. If multiple measurements were performed, the maximum intertwin discrepancy for MCA and CPR were used for analysis.

The primary outcome of interest for this study was the development of MCDA-specific complications, including TTTS, TAPS, and sIUGR. TTTS was diagnosed according to Quintero staging criteria.[27] TAPS was defined as MCA-PSV higher than 1.5 MoM for gestational age in one twin and lower than 0.8 MoM in the other twin.[28] This definition is based on our regional fetal surgeon's diagnostic criteria for TAPS which is required before fetal interventions will be offered. sIUGR was diagnosed when the estimated fetal weight of one twin was below 10th percentile for the assigned gestational age.[29] Secondary outcomes that were collected included pregnancy and neonatal outcomes. Pregnancy outcomes included IUFD(s), gestational age at delivery, and mode of delivery. Neonatal outcomes included average birth weight (BW), BW difference, and NICU admission. BW difference was calculated as (larger twin BW – smaller twin BW) / larger twin BW $\times$ 100%.[30]

Fisher's exact test or Chi-square test was used to examine the association between categorical variables and complication groups, presented as frequency count (%). Continuous variables were presented as median (interquartile range [IQR]) and compared using the Wilcoxon's rank-sum test. The association between maximum MCA-$\Delta_{PSV\text{-}MoM}$ or CPR-Δ at $<$26 weeks and $\geq$26 weeks and development of MCDA-specific complications and other adverse pregnancy or neonatal outcomes were evaluated through simple logistic regression models and calculation of Pearson's correlation coefficients. Receiver operating characteristic (ROC) curves were generated to assess the predictive value of maximum MCA-$\Delta_{PSV\text{-}MoM}$ and CPR-Δ at $<$26 weeks and $\geq$26 weeks, and Youden's index was used to identify their best cut-off values in the prediction of respective outcomes. p-Values of <0.05 were considered statistically significant. All analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC).

Results

Two hundred and twenty MCDA twin pregnancies were identified. Seventy pregnancies were excluded due to incomplete clinical data (e.g., single, second-opinion ultrasound or lack of MCA data prior to development of a standardized protocol), one was excluded due to unclear chorionicity, three were excluded due to referral after development of TTTS, and three were excluded because of major fetal structural anomalies. As a result, 143 MCDA twin pregnancies met inclusion criteria and were included in the analysis. A total of 1,763 ultrasounds were reviewed with a median of 11 (IQR: 8–14) ultrasounds performed per patient throughout the gestation. A total of 1,187 MCA and 834 CPR measurements were collected for analysis.

Baseline maternal demographics and clinical characteristics of all MCDA twin pregnancies and those that developed TTTS, TAPS, or sIUGR are depicted in ►Table 1. Maternal age, body mass index (BMI), race, parity, and the presence of maternal comorbidity did not differ significantly between pregnancies complicated by MCDA-twin-specific complications. Pregnancies complicated by sIUGR were more likely to have a history of a prior preterm delivery ($p = 0.02$) and had a higher proportion of Hispanic ethnicity ($p = 0.04$). Pregnancies conceived by assisted reproductive technology did not differ in development of TTTS, TAPS, or sIUGR when compared with those that conceived spontaneously ($p > 0.10$).

Sixteen (11.2%) pregnancies were complicated by TTTS, 7 (4.9%) by TAPS, and 41 (28.7%) by sIUGR (►Fig. 1). The median gestational age at diagnosis was 22.7 weeks (range: 15.4–30.0), 30.1 weeks (range: 17.9–35.0), and 26.3 weeks (range: 14.9–25.9) for TTTS, TAPS, and sIUGR, respectively. Of those with TTTS, four (25%) were stage I, six (37.5%) were stage II, four (25%) were stage III, one (6.3%) was stage IV, and one (6.3%) was stage V. Nine (56.3%) pregnancies complicated by TTTS underwent laser ablation, and the remaining seven pregnancies underwent expectant management due to being ineligible for intervention. Five pregnancies were greater than 26 weeks of gestation at the time of diagnosis and two were complicated by IUFD of both twins. Of the seven pregnancies complicated by TAPS, six (85.7%) were spontaneous TAPS and one (14.3%) developed following laser

Table 1 Maternal demographics and characteristics of all MCDA twin pregnancies and those with MCDA-twin-specific complications

Characteristic	All patients ($n = 143$)	TTTS ($n = 16$)	*p*-Value	TAPS ($n = 7$)	*p*-Value	sIUGR ($n = 41$)	*p*-Value
Maternal age (y) Median (IQR)	35.0 (31–38)	34.0 (31.5–37.5)	0.75	36 (33–39)	0.36	34.0 (30–36)	0.07
Body mass index (kg/m^2) Median (IQR)	26.1 (22.2–28.9, $n = 124$)	24.5 (21.8–29.4, $n = 14$)	0.63	28.0 (21.9–28.3, $n = 5$)	0.84	26.6 (21.9–29.3, $n = 34$)	0.58
Weight (kg) Median (IQR)	64.4 (56.7–75.2, $n = 131$)	60.6 (55.8–75.2, $n = 14$)	0.86	75.1 (69.9–77.1, $n = 6$)	0.12	62.8 (56.7–70.5, $n = 36$)	0.18
Ethnicity							
Hispanic/Latino	9 (6.3)	1 (6.3)	1.00	0 (0)	1.00	6 (14.6)	0.04
Not Hispanic/Latino	135 (94.4)	15 (93.7)		7 (100)		35 (85.4)	
Race							
White/more than one race	97 (67.8)	11 (68.8)	0.71	5 (71.4)	0.29	28 (68.3)	0.51
Black/African American	3 (2.1)	0 (0)		0 (0)		0 (0)	
Asian or Pacific Islander	28 (19.6)	3 (18.8)		0 (0)		7 (17.1)	
Other	12 (8.4)	1 (6.3)		2 (28.6)		4 (9.8)	
Unknown	4 (2.8)	1 (6.3)		0 (0)		2 (4.9)	
Nulliparous	59 (41.3)	7 (43.8)	1.00	1 (14.3)	0.24	19 (46.3)	0.46
History of preterm delivery							
No	140 (97.9)	16 (100)	1.00	7 (100)	1.00	38 (92.7)	0.02
Yes	3 (2.1)	0 (0)		0 (0)		3 (7.3)	
Maternal comorbidity							
None	122 (85.3)	14 (87.5)	0.69	6 (85.7)	0.41	31 (75.6)	0.11
Chronic hypertension	1 (0.7)	0 (0)		0 (0)		0 (0)	
Diabetes mellitus	3 (2.1)	0 (0)		1 (14.3)		2 (4.9)	
Asthma	3 (2.1)	1 (6.3)		0 (0)		1 (2.4)	
Thyroid disease	6 (4.2)	0 (0)		0 (0)		4 (9.8)	
Other	8 (5.6)	1 (6.3)		0 (0)		3 (7.3)	
Use of ART							
No	97 (67.8)	13 (81.3)	0.27	7 (100)	0.10	29 (70.7)	0.70
Yes	46 (32.2)	3 (18.8)		0 (0)		12 (29.3)	

Abbreviations: ART, assisted reproductive technology; IQR, interquartile range; MCDA, monochorionic-diamniotic; sIUGR, selective intrauterine growth restriction; TAPS, twin anemia-polycythemia sequences; TTTS, twin-to-twin transfusion syndrome.
Note: Values are presented as *n* (%) unless otherwise indicated. If values were missing for certain parameters, *n* is indicated.

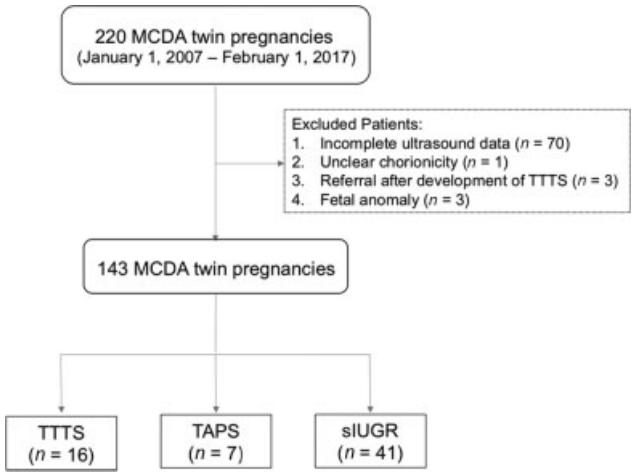

Fig. 1 Flow diagram of monochorionic-diamniotic twin pregnancies and development of primary outcomes. MCDA, monochorionic-diamniotic; sIUGR, selective intrauterine growth restriction; TAPS, twin anemia-polycythemia sequence; TTTS, twin-twin transfusion syndrome.

ablation treatment of TTTS. All but one of the pregnancies complicated by sIUGR was diagnosed with type-1 sIUGR, and all underwent expectant management with close surveillance.

Pregnancy and neonatal outcomes are summarized in ►**Table 2**. Fourteen patients did not have delivery outcomes available for review due to delivery outside the system, and two pregnancies were complicated by TTTS resulting in fetal demise of both twins. As a result, a total of 127 patients with pregnancy and neonatal outcomes were available for review. Gestational age of delivery was significantly lower for pregnancies complicated by TTTS ($p < 0.01$) and sIUGR ($p = 0.01$) but not for TAPS ($p = 0.23$). Indication for delivery was also significantly different for pregnancies complicated by TTTS ($p < 0.01$) and sIUGR ($p < 0.01$) but not TAPS ($p = 0.46$). There was not an increased risk of cesarean delivery for pregnancies with MCDA-specific complications. The average BW was significantly lower in pregnancies that were complicated by TTTS ($p < 0.01$) and sIUGR ($p < 0.01$) but not for pregnancies complicated by TAPS ($p = 0.53$). As expected, BW discordance was higher in pregnancies complicated by sIUGR at 17.7% (IQR: 12.1–24.0, $p < 0.01$). Pregnancies that developed MCDA-specific complications had more than twice the NICU admissions of one or both twins compared with respective uncomplicated MCDA pregnancies. There were a total of four neonatal deaths, three of which were pregnancies complicated by TTTS.

Results of the univariate logistic regression model analysis of MCA-$\Delta_{PSV\text{-}MoM}$ and CPR-Δ are presented in ►**Table 3**. MCA-$\Delta_{PSV\text{-}MoM}$ at <26 weeks was associated with IUFD (odds ratio [OR] = 18.91, 95% confidence interval [CI]: 2.11–169.13, $p = 0.01$,), NICU admission (OR = 91.46, 95% CI: 1.26–301.74, $p = 0.03$), and TAPS (OR = 21.39, 2.33–196.80, $p = 0.01$). MCA-$\Delta_{PSV\text{-}MoM}$ at ≥26 weeks was also associated with TAPS (OR = 769.79, 95% CI: 15.98–999.99, $p < 0.01$). Intertwin CPR discrepancy at <26 weeks was significantly associated with the development of TTTS (OR = 2.23, 95% CI: 1.10–4.76, $p = 0.03$). The average time before TTTS developed and intertwin CPR discordance first noted was 2 weeks and 1 day, and 80% of the measurements demonstrated a lower CPR value in the donor and a higher CPR value in the recipient. CPR-Δ at <26 weeks was also significantly associated with NICU admission of at least one twin (OR = 3.94, 95% CI: 1.31–11.85, $p = 0.02$).

Pearson's correlation coefficient demonstrated a significant correlation between CPR-Δ at <26 weeks to gestational age at delivery ($r = -0.30$, $p = 0.002$) and average BW ($r = -0.38$, $p < 0.001$). Increasing CPR-Δ at <26 weeks was correlated with earlier gestational age at delivery and lower average BW, respectively. There was also a moderate association of increasing CPR-Δ at <26 weeks with nonreassuring fetal testing requiring delivery ($r = 0.39$). In contrast, CPR-Δ at ≥26 weeks was not associated with the development of complications or adverse perinatal outcomes.

ROC curves were developed to assess the predictive performance of MCA-$\Delta_{PSV\text{-}MoM}$ and CPR-Δ for MCDA-twin-specific complications and other adverse pregnancy and neonatal outcomes. ►**Fig. 2** presents the ROC curves for MCA-$\Delta_{PSV\text{-}MoM}$ at <26 weeks for TAPS (area under curve [AUC] = 0.62), IUFD (AUC = 0.61), and NICU admission (AUC = 0.61) and MCA-$\Delta_{PSV\text{-}MoM}$ at ≥26 weeks for TAPS (AUC = 0.92). An intertwin MCA PSV MoM discrepancy of 0.61 at <26 weeks would identify TAPS with a sensitivity of 57% and specificity of 98%. A MCA-$\Delta_{PSV\text{-}MoM}$ cut-off of 0.27 at <26 weeks would identify pregnancies complicated by IUFD with sensitivity of 71% and specificity of 61%, and an intertwin MCA PSV MoM discrepancy of 0.36 at <26 weeks would predict the requirement of NICU admission with a sensitivity of 34% and specificity of 89%. With an MCA-$\Delta_{PSV\text{-}MoM}$ cut-off of 0.44 at ≥26 weeks, we would identify pregnancies complicated by TAPS with a sensitivity of 100% and specificity of 73%.

ROC curves for the development of TTTS (AUC = 0.68) and NICU admissions (AUC = 0.67) by CPR-Δ at <26 weeks are shown in ►**Fig. 3**. With a CPR-Δ cut-off of 0.73 at <26 weeks, we would identify pregnancies complicated by TTTS with a sensitivity of 67% and a specificity of 73%. Using a CPR-Δ cut-off of 0.39 at <26 weeks, we would identify pregnancies requiring NICU admission following delivery with 78 and 55% of sensitivity and specificity, respectively.

Discussion

This study evaluates the utility of intertwin discrepancy of MCA-PSV MoM and CPR in the surveillance of MCDA twin pregnancies and its association with the development of MCDA-twin-specific complications and adverse pregnancy outcomes. We identified that increased intertwin differences in these parameters at various times in gestation can be associated with the development of complications of MCDA twin gestations and adverse pregnancy outcomes.

Confirmation that MCA-$\Delta_{PSV\text{-}MoM}$ at ≥26 weeks is a strong predictor of TAPS is consistent with the current diagnostic criteria of TAPS.[28] A recent study by Tollenaar et al demonstrated that delta MCA PSV > 0.5 MoM had a greater diagnostic accuracy for predicting TAPS than the traditional

Table 2 Pregnancy and neonatal outcomes of all MCDA twin pregnancies and those with MCDA-twin-specific complications

Pregnancy/neonatal outcome	All patients ($n = 127$)	TTTS ($n = 14$)	*p*-Value	TAPS ($n = 6$)	*p*-Value	sIUGR ($n = 36$)	*p*-Value
Mode of delivery							
Cesarean section	105 (82.7)	12 (85.7)	1.00	4 (66.7)	0.30	32 (88.9)	0.59
Vaginal delivery	21 (16.5)	2 (14.3)		2 (33.3)		4 (11.1)	
Assisted vaginal delivery	1 (0.01)	0 (0)		0 (0)		0 (0)	
Gestational age at birth Median (IQR)	35.9 (34.0–36.4)	30.7 (28–35)	<0.01	34.7 (34.1–35.7)	0.23	34.9 (33.9–35.9)	0.01
Indication for delivery							
Spontaneous labor	38 (29.9)	6 (42.9)	<0.01	2 (33.3)	0.46	8 (22.2)	<0.01
Uncomplicated MCDA twins	36 (28.3)	0 (0)		0 (0)		0 (0)	
Complicated MCDA twins	31 (24.4)	4 (28.6)		3 (50.0)		24 (66.7)	
NRFHT	8 (6.3)	4 (28.6)		1 (16.7)		3 (8.3)	
HTN disease of pregnancy	8 (6.3)	0 (0)		0 (0)		1 (2.8)	
Other	6 (4.7)	0 (0)		0 (0)		0 (0)	
Birth weight difference (%) Median (IQR)	9.2 (4.2–16.9), $n = 122$	10.6 (7.2–13.0), $n = 11$	0.62	5.3 (3.4–8.0), $n = 5$	0.14	17.7 (12.3–24.0), $n = 35$	<0.01
Average birth weight (g) Median (IQR)	2,237.5 (1,925.1–2,494.8), $n = 122$	1,675.0 (917.5–1,927.8), $n = 11$	<0.01	2,092.5 (2,077.5–2,205.0), $n = 5$	0.53	1,990 (1,692.5–2,193.8), $n = 35$	<0.01
NICU admission							
None	53 (42.7)	3 (21.4)	0.02	2 (33.3)	0.08	6 (17.1)	<0.01
One twin	20 (16.1)	3 (21.4)		1 (16.7)		9 (25.7)	
Both twins	51 (41.1)	8 (61.5)		3 (50.0)		20 (57.1)	
Length of NICU stay (d)	6 (0–20), $n = 124$	46 (15–75)	<0.01	13.5 (7–19)	0.21	15 (6–24), $n = 35$	<0.01

Abbreviations: HTN, hypertensive; IQR, interquartile range; MCDA, monochorionic-diamniotic; NICU, neonatal intensive care unit; NRFHT, nonreassuring fetal heart rate tracing; sIUGR, selective intrauterine growth restriction; TAPS, twin anemia-polycythemia sequences; TTTS, twin-to-twin transfusion syndrome.
Note: Values are presented as *n* (%) unless otherwise indicated. If values were missing for certain parameters, *n* is indicated.

Table 3 Logistic regression model analysis of intertwin MCA-PSV MoM and CPR difference at <26 and ≥26 weeks as predictors of complications in MCDA twin pregnancies

Outcome	Intertwin difference with outcome	Intertwin difference without outcome	Odds ratio	95% CI	*p*-Value
<26 weeks intertwin MCA-PSV MoM difference					
TTTS	0.35 ± 0.32	0.28 ± 0.20	3.20	0.48–21.33	0.23
TAPS	0.60 ± 0.55	0.27 ± 0.17	21.39	2.33–196.80	0.01
sIUGR	0.31 ± 0.24	0.28 ± 0.21	1.79	0.34–9.42	0.49
IUFD	0.59 ± 0.63	0.28 ± 0.16	18.91	2.11–169.13	0.01
NICU admission	0.33 ± 0.26	0.23 ± 0.11	19.46	1.26–301.74	0.03
≥26 weeks intertwin MCA-PSV MoM difference					
TTTS	0.35 ± 0.18	0.37 ± 0.19	0.88	0.03–24.99	0.94
TAPS	0.72 ± 0.25	0.35 ± 0.17	769.79	15.98–>999.99	<0.01
sIUGR	0.36 ± 0.19	0.37 ± 0.19	0.78	0.09–6.68	0.82
IUFD	0.18	0.37 ± 0.19	0.002	<0.001–314.35	0.31
NICU admission	0.40 ± 0.22	0.33 ± 0.15	6.86	0.70–66.89	0.10
<26 weeks intertwin CPR difference					
TTTS	1.21 ± 1.48	0.60 ± 0.50	2.23	1.10–4.76	0.03
TAPS	0.56 ± 0.30	0.68 ± 0.72	1.09	0.39–3.04	0.87
sIUGR	0.76 ± 0.53	0.65 ± 0.77	1.23	0.73–2.05	0.44
IUFD	0.95 ± 1.09	0.64 ± 0.67	0.92	0.30–2.82	0.80
NICU admission	0.81 ± 0.82	0.50 ± 0.40	3.94	1.31–11.85	0.02
≥26 weeks intertwin CPR difference					
TTTS	0.78 ± 0.53	1.05 ± 1.01	0.58	0.16–2.14	0.42
TAPS	0.96 ± 0.46	1.03 ± 1.01	1.21	0.66–2.23	0.55
sIUGR	0.94 ± 0.57	1.06 ± 1.09	0.84	0.48–1.46	0.53
IUFD	0.58 ± 0.37	1.04 ± 0.99	0.11	<0.001–32.94	0.44
NICU admission	0.86 ± 0.54	1.20 ± 1.44	0.61	0.34–1.11	0.11

Abbreviations: CI, confidence interval; CPR, cerebroplacental ratio; IUFD, intrauterine fetal demise; MCA-PSV, middle cerebral artery-peak systolic velocity; MCDA, monochorionic-diamniotic; MoM, multiple of the median; NICU, neonatal intensive care unit; sIUGR, selective intrauterine growth restriction; TAPS, twin anemia-polycythemia sequences; TTTS, twin-to-twin transfusion syndrome.
Note: Values are presented as mean ± standard deviation.

individual MCA PSV cut-off criteria.[31] Our study supports their findings that increasing intertwin MCA-$\Delta_{PSV\text{-}MoM}$ may be predictive of the eventual development of TAPS. However, the MCA-$\Delta_{PSV\text{-}MoM}$ cut-off value shown to be most predictive of TAPS in our study was 0.44 MoM. This is lower than traditional diagnostic criteria for TAPS and the one suggested by Tollenaar et al. Based on our study findings, intertwin MCA-$\Delta_{PSV\text{-}MoM}$ may provide additional utility in identifying evidence of TAPS prior to meeting the classic diagnostic criteria and earlier in the process. In addition, the predictive

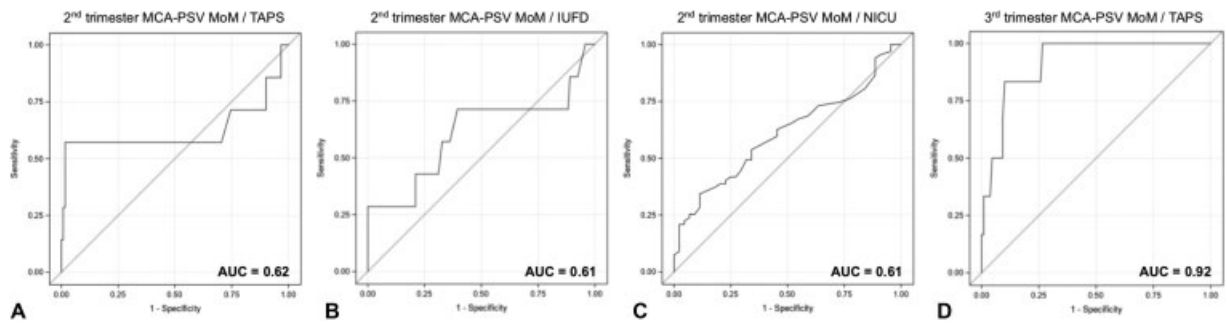

Fig. 2 Receiver operating characteristic curves for prediction of (**A**) TAPS, (**B**) IUFD, (**C**) NICU admission by intertwin MCA-PSV MoM difference at <26 weeks and (**D**) TAPS by intertwin MCA-PSV MoM difference at ≥26 weeks. AUC, area under curve; MCA-PSV; middle cerebral artery peak systolic velocity; MoM, multiple of the median; NICU, neonatal intensive care unit; IUFD, intrauterine fetal demise; TAPS, twin anemia-polycythemia sequence.

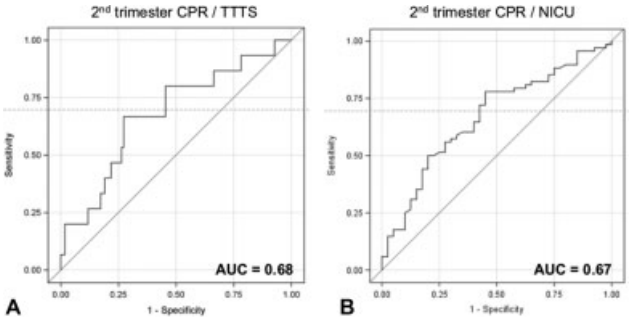

Fig. 3 Receiver operating characteristic curves for prediction of (**A**) TTTS and (**B**) NICU admission by intertwin CPR difference at < 26 weeks. CPR, cerebroplacental ratio; NICU, neonatal intensive care unit; TTTS, twin-twin transfusion syndrome.

value of MCA-$\Delta_{PSV\text{-}MoM}$ for TAPS was significantly higher at ≥26 weeks than at <26 weeks consistent with the majority of TAPS cases being diagnosed in the late second or third trimester.[32] The discrepancy in predictive value of MCA-$\Delta_{PSV\text{-}MoM}$ at <26 versus ≥26 weeks of TAPS argues for continued surveillance of the MCA throughout the entirety of the pregnancy.

Multiple studies have demonstrated the value of CPR in the evaluation of singleton pregnancies for the prediction of adverse perinatal outcomes, particularly in fetal growth restriction.[13–18] We did not see an association with intertwin CPR difference and development of sIUGR. A possible explanation for the lack of association with sIUGR is that we did not include an estimated fetal weight discordance of 25% in the diagnostic criteria for sIUGR and as a result, the average BW discordance in our cohort was 17.7% with no pair exceeding 24% discordance, likely demonstrating less-severe sIUGR. In addition, all of the pregnancies except one were complicated by type-1 sIUGR which is associated with a more favorable outcome. In contrast, we observed a significant association with CPR-Δ at <26 weeks with NICU admission. Increasing CPR-Δ at < 26 weeks was also correlated with earlier gestational age at delivery, lower average BW, and development of nonreassuring fetal status requiring delivery. It is possible that these were confounding factors, as they are interrelated and can influence the rate of NICU admission. However, prior studies on singleton gestations of both small for gestational age and appropriate for gestational age fetuses have also shown that CPR is an independent predictor for NICU admissions.[14,15] These studies along with our study findings of CPR-Δ at <26 weeks associated with NICU admission and nonreassuring fetal status requiring delivery may support the claim that CPR serves as a more sensitive marker for placental insufficiency.

Multiple second trimester ultrasound findings have been demonstrated to be associated with TTTS.[33–35] Our study is the first to demonstrate an association between intertwin CPR difference and the development of TTTS. On average, intertwin CPR discordance was identified 2 weeks and 1 day prior to the development of TTTS, and 62.5% (10/16) of pregnancies complicated by TTTS did not demonstrate an abnormal CPR value by the traditional criteria of <1. This temporal association of impending TTTS may prompt heightened surveillance. Although there was a significant association of CPR-Δ at <26 weeks with development of TTTS, our cohort did not demonstrate significant predictive ability of the measurement. The assessment in predictive value of CPR-Δ at <26 weeks may have been limited by the lower number of pregnancies complicated by TTTS and further studies are required to assess its clinical utility.

Limitations and Strengths

The primary limitation of this study is its retrospective design. Approximately one-third of the patients identified as MCDA twins for possible inclusion were one-time second-opinion evaluations without continued serial surveillance at our center or were evaluated prior to the inclusion of MCA evaluation into our center's surveillance protocol. As a result, the number of MCDA twins and specifically those with MCDA-specific complications that were included in the study for analysis was decreased. Additionally, delivery outcomes were unavailable for 14 patients due to delivery outside the system, but they were included in the analysis because both ultrasound and primary outcome data were available for review. Furthermore, neonatal hemoglobin and hematocrit data were not included in the analysis and antenatal diagnosis of TAPS could not be confirmed. Missing data are inherent to the retrospective nature of this study and may have resulted in a bias. Patients included in the study were identified through the search function of the clinical ultrasound database which may have led to ascertainment bias. There may also be a component of selection bias for a high-risk population, given that the patients selected for this study are from a perinatal referral center.

Overall, our study demonstrates that intertwin MCA-$\Delta_{PSV\text{-}MoM}$ is associated with TAPS, IUFD, and NICU admission, and intertwin CPR-Δ is associated with TTTS and NICU admission. We also demonstrate the strong predictive value of MCA-$\Delta_{PSV\text{-}MoM}$ at ≥26 weeks for TAPS with a cut-off value lower than the current diagnostic criteria for TAPS. Current recommendations from the Society for Maternal-Fetal Medicine on management of MCDA twin pregnancies do not include routine surveillance of UA or MCA Doppler during biweekly ultrasounds, but the findings from this study may suggest potential utility.[7] We recognize that the overall number of complicated MCDA-twin pregnancies is lower within the study and postnatal confirmation of TAPS was not performed, which makes it difficult to make robust clinical recommendations from our study. However, the associations identified in this study brings attention to an alternative method of assessing fetal status in MCDA twin gestations through intertwin discrepancy of measurements rather than isolated values.

Conclusion

Based on these study findings, an increase in intertwin MCA and CPR discrepancy may be associated with adverse pregnancy and neonatal outcomes, including TAPS, TTTS, IUFD, and NICU admission. This study highlights the utility of

assessing intertwin differences in Doppler indices in the surveillance of MCDA twin pregnancies and their role in potentially predicting the risk for development of perinatal complications. Earlier or more accurate identification of such complications may allow for earlier clinical interventions, including fetal therapy, evaluation for appropriate timing of delivery, allowing time for antenatal transfer to higher level of care, or ensuring delivery at a tertiary care center where adequate postnatal interventions are available. This in turn may improve neonatal outcomes. Prospective trials are required to evaluate the clinical utility of surveillance of intertwin MCA and CPR differences to identify pregnancies at risk for development of TTTS or TAPS, allowing for earlier detection and successful intervention.

Note

This work was previously presented as a poster presentation at the 28th World Congress on Ultrasound in Obstetrics and Gynecology, October 20–24, 2018, Singapore.

Conflict of Interest

L.D.P. serves on the medical advisory board of Nuvo, Jubel Health, Trice Imaging, and the Perinatal Quality Foundation. He is provided research support and is on the medical advisory board for GE Medical Systems. C.S.H. serves on the medical advisory board of Jubel Health. The remaining authors listed have no disclosures.

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