ORIGINAL ARTICLE

Comparison of renal artery Doppler parameters of monochorionic diamniotic twin pregnancies with and without twin-to-twin transfusion syndrome

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Background: Monochorionic diamniotic (MCDA) twin pregnancies are considered high-risk for several reasons, especially the risk of twin-to-twin transfusion syndrome (TTTS). Renal artery Doppler (RAD) is reported as a useful tool for predicting oligohydramnios in singleton pregnancies. We aimed to compare the RAD indices between MCDA twins with and without TTTS. **Materials and Methods:** In this case–control study, all pregnant women aged 18–38 years, with gestational age ≥ 18 weeks, who were referred to two Prenatal Clinics, Alzahra and Beheshti Educational Hospitals, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, October 2020–March 2022 were enrolled; the women with MCDA twin pregnancies complicated by TTTS (case group, $n = 12$) and without TTTS (control group, $n = 24$). For each twin, biometric analysis, fetal weight, and Doppler study of fetal arteries, including RAD, middle cerebral artery (MCA), umbilical artery, and ductus venosus were performed. Peak systolic velocity, Pulsatility index (PI), resistance index (RI), and systole/diastole (S/D) were measured for all arteries. **Results:** The donors of the case group had a lower mean MCA S/D (4.48 ± 1.89) than the control group (6.48 ± 1.97) ($P = 0.01$) and higher mean umbilical parameters, including PI, RI, and S/D ($P < 0.05$). The recipients of the case group had a lower mean renal PI than the control ($P = 0.008$) and lower mean MCA PI, RI, and S/D ($P < 0.05$). The donor group had a higher mean umbilical RI and S/D than the recipient twin, while the mean fetal weight of the recipient group was higher ($P < 0.05$). **Conclusion:** Comparing the RAD parameters between the twins with and without TTTS in the present study did not identify significant results, which rejected the primary hypothesis. Among all RAD parameters, the only significant difference observed in the present study was the lower RAD PI in RT, which cannot suggest this measurement as a valuable tool for the prediction of TTTS in MCDA twins. Therefore, the results of the present study failed to show the additional value of RAD, compared with the conventional Doppler examination of fetal arteries. Further studies are required to prove this conclusion.

Key words: Doppler, monochorionic diamniotic twin, pregnancy, renal artery, twin, twin-twin transfusion, ultrasonography

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INTRODUCTION

Twin pregnancies are considered high risk with a high maternal, fetal, and neonatal mortality and morbidity.[1] The risk is even higher when fetuses have share chorion and/or amnion. Fetus with a shared chorion but separate amnion, known as monochorionic diamniotic (MCDA), may have several abnormalities,[2] considering the abnormal vascular anastomosis in the placenta and blood circulation between the two fetuses, known as twin-to-twin transfusion syndrome (TTTS). The prenatal diagnosis and staging of TTTS are based on the evidence of MCDA pregnancy, markedly discordant amniotic

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fluid volume between twin sacs, and presence (stage I) or absence (stage II) of bladder filling in the donor, Doppler abnormalities in one or both fetuses (stage III), and the development of hydrops (stage IV).[3]

Volume imbalance in TTTS involves, in part, uncompensated unidirectional blood flow from one twin to another through vascular anastomosis within the shared placenta. Nonetheless, TTTS is not the result of simply a shift of blood from the donor to the recipient; more importantly, it is the exposure of the twins to the endocrine environment and vasoactive mediators of the other twin.[4] Then, natriuretic peptides are secreted from the recipient's cardiomyocytes in response to cardiac stretch, which results in increasing glomerular filtration rate and decreasing tubular reabsorption, fostering polyuria and polyhydramnios. In the donor's kidney, hypoperfusion results in oliguria and oligohydramnios, which lead to the upregulation of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II increases peripheral vascular resistance and might initially be protective by maintaining the donor's blood pressure. Moreover, it provokes aldosterone secretion from the adrenal cortex, which increases tubular reabsorption of sodium and fluid to regulate against hypovolemia; renin mRNA is upregulated in the donor's kidneys and down-regulated in the recipient's kidneys equally; yet, elevated cord blood renin levels have been observed in both twins. This supports the role of placental anastomosis in the transfer of RAAS components from donor to recipient. The chronic volume shift to the recipient fetus and the activation of RAAS in the donor aggravates renal hypoperfusion, resulting in persistent activation of RAAS and maintaining a vicious circle.[4] Elevated resistance in renal artery Doppler (RAD) indices in stage I predicts the risk of progression in TTTS staging. Therefore, we aimed to investigate renal artery indices in TTTS and without TTTS MCDA for early diagnosis and staging of TTTS to enhancement the fetus and neonatal survival.

If TTTS misdiagnosed or diagnosed late, it can cause 70%–100% perinatal loss in the advanced stages, occurring before 26 weeks of gestation. Poor outcomes prevented in 70%–85% of cases after laser ablation and 85% after selective reduction.[5,6] Considering the significance of TTTS, it is important to monitor twins with MCDA pregnancy with serial sonographies because TTTS usually presents in the second trimester and is a dynamic condition that can remain stable throughout gestation. The progression rate can be quick or slow; it may occasionally regress spontaneously. Early detection of evolving TTTS is critical, as it can be successfully treated by fetoscopy laser ablation of interconnecting vessels in the placenta.[7]

The predictive power of oligohydramnios for a poor perinatal outcome is reported with a sensitivity, specificity, and accuracy of 100%, 0%, and 50%, respectively. The fetal renal circulation can also be assessed using ultrasound. Intermittent assessment of renal artery flow velocity waveforms has been shown to be predictive of changes in amniotic fluid dynamics; renal artery pulsatility index (PI) increases in oligohydramnios and decreases in polyhydramnios in singleton pregnancies.[8,9] RAD differences between TTTS and non-TTTS MCDA twin pregnancies may explain the decreased renal perfusion, secondary to the hypovolemic state of the donor twin (DT). However, little is known about the value of renal artery Doppler in the prediction of TTTS.[10] Therefore, in the present study, we aimed to investigate arteries, especially the renal artery, in MCDA twins with and without TTTS.

MATERIALS AND METHODS

Study design

We conducted a case–control study on women with MCDA pregnancies complicated by TTTS and those without this complication. The inclusion criteria for this study consisted of all women aged 18–38 years old, with gestational age (GA) ≥18 weeks, who were referred to the Prenatal Clinics of Alzahra and Beheshti Educational Hospitals, affiliated with Isfahan University of Medical Sciences, Isfahan, Iran, from October 2020 to March 2022, were diagnosed with MCDA with or without TTTS. The participants were enrolled in the study after they were informed about the study objectives and enrolled in the study after they read and signed the written informed consent. This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Code: IR. MUI. MED. REC.1400.328). A calculation of the GA was based on the nuchal translucency scan in the first trimester. A feto-maternal specialist performed the ultrasound examination using a GE Ultrasound Voluson™ E6-2020 device at GA of 18 weeks for all participants and recorded the type of twin pregnancy and the presence or absence of TTTS. A diagnosis of TTTS was made based on MCDA pregnancy with markedly discordant amniotic fluid volumes between twin sacs: polyhydramnios (defined as an MVP >8 cm in the amniotic sac) of the designated recipient twin (RT) and oligohydramnios (defined as a MVP <2 cm) in the DT.[6] The ultrasound exam was done every 2 weeks. The women with fetal TTTS were enrolled in the case group, and for each woman in the case group, two pregnant women with the same inclusion criteria and similar GA (maximum 1 week difference), but without TTTS, were considered in the control group.

We excluded subjects with high-order multiple gestations and grand multiparity (≥5 parity) or those with gestational diabetes mellitus, hypertension, or other vascular disorders (which may affect amniotic fluid levels), those with pregnancy induced by assistive reproductive technology (ART), and those with any known genetic and structural anomalies and selective fetal growth restriction. All eligible women were enrolled in the study using a convenient sampling method based on the calculated sample size. The total sample size was considered at 30 mothers, based on a similar study[10] with a 2:1 ratio of the control versus case group: at least 10 with MCDA with TTTS and 20 without TTTS. For calculating the sample size, type I error was considered at 1%, type II error at 10%, minimum significant difference at 0.59, and standard deviation (SD) at 0.37 (for the main variable of the study: Peak systolic velocity [PSV] ratio) using standard statistical equations for calculating sample size.

$$n = \frac{2\times(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2(s^2)}{(d)^2}$$

The mother's age, weight, and height values before pregnancy, and GA at the time of study were recorded in the study's checklist, and body mass index (BMI) value was calculated based on the weight and height values of each mother. All mothers underwent ultrasound examination by one perinatologist at 18 weeks of gestation, and the following information was recorded for each twin: Biometric analysis, fetal weight (measured using Hadlock equation), MVP, and the Doppler study of fetal arteries, including umbilical artery (UA), middle cerebral artery (MCA), ductus venosus, and renal artery. The biometric analysis includes the measurement of head circumference, abdominal circumference, biparietal diameter, and femur length for each fetus. PSV, PI, resistive index (RI), and systole/diastole index (S/D) were measured in all four arteries. The same indices were measured for renal arteries, i.e., RI, PI, and PSV using intertwine ratio by calculating the values of donor to receiver fetus in the case group and that of the bigger fetus to the smaller one in the control group; the case and control groups were also compared. The Doppler ultrasound was performed according to the method described by the International Society of Ultrasound in Obstetrics and Gynecology standard guideline.[9,11-13] Then DT and RT were compared with the control group pairwise. Furthermore, any participant who refused to continue the study was excluded from the study. If the fetuses in the case group required laser therapy, they were referred to another center for treatment but were not excluded from this study.

Statistical analysis

For the statistical analysis, the collected data were input into the statistical software IBM SPSS Statistics for Windows version 24.0 (IBM Corp. 2015. Armonk, NY, USA: IBM Corp), by which all the statistical analyses were performed. First, the normal distribution of the numeric variables was tested using the Shapiro–Wilk test. As the results showed that all data had normal distribution, mean ± SD was used for describing the results and independent samples *t*-test for comparison between the study groups. Pairwise comparisons were performed between the fetuses, i.e., RT versus control group, DT versus control group, and RT versus DT. As the control group also had two fetuses (as they were twins), for comparing each of the fetuses in the case group (RT or DT) with the control group, we considered quantitative indices of both fetuses in the control group. PSV and PI ratios had an abnormal distribution, for which we used the Mann–Whitney *U*-test. In all tests, $P < 0.05$ were considered statistically significant.

RESULTS

A total of 12 women were enrolled in the case group and 24 in the control group. The groups were not different in terms of mean age, BMI (before start of pregnancy), and GA [$P > 0.05$; Table 1].

The mean values of all Doppler parameters were compared between DT of the case group and the control group [Table 2], between RT in the case group and the control group [Table 3], and between the DT and RT of the case group [Table 4]. As shown in Table 2, the mean

Table 1: Comparison of baseline characteristics between the two study groups

Variable	Total (*n*=36)	Case group (*n*=12)	Control group (*n*=24)	*P**
Age (years)	29.36±4.98	27.67±5.86	30.21±4.37	0.152
BMI (kg/m^2)	28.06±5.23	28.17±4.36	28.00±5.70	0.930
GA (weeks)	22.36±3.75	20.83±3.88	23.13±3.51	0.084

*The result of independent samples *t*-test, all values reported are mean±SD. BMI=Body mass index; SD=Standard deviation; GA=Gestational age

Table 2: Comparison of Doppler parameters of the four fetal arteries between the donor fetus of the case group and the control group

Variable	Total (*n*=36)	Case group (donor, *n*=12)	Control group (*n*=24)	*P**
Renal PI	2.02±0.55	1.86±0.79	2.10±0.38	0.336
Renal RI	0.79±0.08	0.77±0.12	0.80±0.05	0.313
Renal PSV	26.69±7.84	24.58±8.09	27.74±7.67	0.273
Renal S/D	6.03±3.45	6.15±5.44	5.97±1.99	0.914
MCA PI	2.04±0.45	1.88±0.55	2.12±0.39	0.182
MCA RI	0.82±0.07	0.78±0.11	0.83±0.04	0.135
MCA PSV	30.86±8.91	27.01±6.89	32.63±9.30	0.057
MCA S/D	5.85±2.14	4.48±1.89	6.48±1.97	0.010
Umbilical PI	1.45±0.37	1.74±0.46	1.32±0.24	0.016
Umbilical RI	0.75±0.10	0.84±0.12	0.71±0.06	0.006
Umbilical S/D	6.10±5.59	10.53±8.10	3.88±0.96	0.016
Ductus PI	0.87±0.36	0.96±0.26	0.82±0.40	0.234
Ductus RI	0.61±0.11	0.65±0.13	0.58±0.10	0.163
Ductus S/D	2.26±1.04	2.15±1.14	2.31±1	0.686

*The result of independent samples *t*-test, all values reported are mean±SD. PI=Pulsatility index; RI=Resistance index; PSV=Peak systolic velocity; S/D=Systolic/diastolic; MCA=Middle cerebral artery; SD=Standard deviation

Table 3: Comparison of Doppler parameters of the four fetal arteries between the receiver fetus of the case group and the control group

Variable	Total (*n*=36)	Case group (*n*=12)	Control group (*n*=24)	*P**
Renal PI	1.97±0.42	1.70±0.38	2.10±0.38	0.008
Renal RI	0.79±0.07	0.77±0.10	0.80±0.05	0.259
Renal PSV	28.86±11.51	29.98±13.08	27.74±9.95	0.563
Renal S/D	5.53±2.09	4.65±2.10	5.97±1.99	0.087
MCA PI	1.99±0.40	1.72±0.27	2.12±0.39	0.001
MCA RI	0.80±0.06	0.74±0.06	0.83±0.04	0.001
MCA PSV	31.81±8.54	30.16±6.82	32.63±9.30	0.375
MCA S/D	5.72±2.02	1.08±4.21	1.97±6.48	0.001
Umbilical PI	1.37±0.33	1.48±0.47	1.32±0.24	0.273
Umbilical RI	0.72±0.06	0.75±0.07	0.71±0.06	0.229
Umbilical S/D	3.98±1.18	4.19±1.59	3.88±0.96	0.569
Ductus PI	0.86±0.38	0.93±0.32	0.82±0.40	0.396
Ductus RI	0.61±0.12	0.67±0.15	0.58±0.10	0.089
Ductus S/D	2.41±1.73	2.59±2.71	2.31±1.00	0.737

*The result of independent samples *t*-test, all values reported are mean±SD. PI=Pulsatility index; RI=Resistance index; PSV=Peak systolic velocity; S/D=Systolic/diastolic; MCA=Middle cerebral artery; SD=Standard deviation

Table 4: Comparison of Doppler parameters of the four fetal arteries between the donor fetus and the recipient twin of the case group

Variable	DT	RT	*P**
Renal PI	1.86±0.79	1.70±0.38	0.564
Renal RI	0.77±0.12	0.77±0.10	0.984
Renal PSV	24.58±8.09	29.98±13.08	0.232
Renal S/D	6.15±5.44	4.65±2.10	0.356
MCA PI	1.88±0.55	1.72±0.27	0.357
MCA RI	0.78±0.11	0.74±0.06	0.257
MCA PSV	27.01±6.89	29.82±7.04	0.206
MCA S/D	4.48±1.89	4.05±0.99	0.436
Umbilical PI	1.74±0.46	1.48±0.49	0.228
Umbilical RI	0.84±0.12	0.75±0.07	0.019
Umbilical S/D	11.08±8.26	4.19±1.59	0.014
Ductus PI	0.96±0.26	0.93±0.32	0.614
Ductus RI	0.65±0.13	0.67±0.15	0.517
Ductus S/D	2.15±1.14	2.59±2.71	0.477
Fetal weight (g)	342.50±246.36	489.33±333.23	0.007

*The result of independent samples *t*-test, all values reported are mean±SD. PI=Pulsatility index; RI=Resistance index; PSV=Peak systolic velocity; S/D=Systolic/diastolic; MCA=Middle cerebral artery; SD=Standard deviation; RT=Recipient twin; DT=Donor twin

MCA S/D was significantly lower in the DT of the case group compared with the control group ($P = 0.01$), while UA parameters, including PI, RI, and S/D were higher in the DT of the case group, compared with the control group [$P < 0.05$; Table 2]. Other Doppler parameters were not different between DT in the case group and the control group [$P > 0.05$; Table 2].

As shown in Table 3, the comparison of the mean values between RT in the case group and the control group showed different mean RAD PI between the groups, significantly lower in the case group ($P = 0.008$). Furthermore, MCA PI, RI, and S/D were different between the groups; significantly lower in the case group compared with the control group [$P < 0.05$; Table 3]. The primary outcome of the study, RAD PI, RI, and PSV, differed neither between DT nor RT and the control group [Tables 2 and 3].

The comparing the two fetuses in the case group between DT and RT showed that they were similar in most of the Doppler parameters, except in mean values of UA RI and S/D, which were significantly higher in the DT, while the mean fetal weight of the RT was higher [$P < 0.05$; Table 4]. The RAD PI, RI, and PSV inter-twin ratio (recipient-to-donor) did not differ between the TTTS group and the control group [Table 5].

Of the 12 pregnancies complicated by TTTS, four patients were with TTTS stage I (33.3%), four patients with TTTS stage II (33.3%), and four patients with TTTS stage III (33.3%). The four patients with TTTS stage I did not undergo laser photocoagulation because of pregnancy termination: one patient at 24 weeks because of the intrauterine fetal death of one fetus, and three patients at 29, 30, and 34 weeks, because of preterm labor. Of the eight subjects who underwent laser photocoagulation (with TTTS stage II and III), four resulted in double survivors, one resulted in a post-procedural RT demise, and another resulted in a ruptured amniotic membrane and termination 10 weeks after the procedure because of the deterioration of heart failure in RT, two resulted in no survivors after the procedure.

DISCUSSION

In the present study, we compared each twin separately in the case group with the control group. The results of this comparison showed that most indices of the renal artery were not different between the two groups except for a lower mean RA PI in RTs, compared with the control group. There are few studies on the value of RAD parameters for the prediction of TTTS in MCDA twins. In a recent study, Jain *et al.* compared the Doppler results of 12 cases and 12 controls and showed no difference in PI and RI of the groups (neither with the donor nor the recipient fetus), while they found a lower PSV in DT of the cases group and higher PSV ratio, compared with the controls.[10] Nevertheless, we did not find any significant difference in RAD PSV values between DT and the control group. Instead, we found a lower RDA PI in DT, compared with the control, which can be attributed to the decreased renal perfusion and changes in cardiac velocity related to the reduced left ventricular output.[14] To eliminate the effect of GA on Doppler parameters, we matched the two groups in terms of GA. Investigation of singleton pregnancies has also shown lower RAD PI in cases with polyhydramnios,[11,15,16]

Table 5: Comparison of renal Doppler parameters between the case and control groups

Variable	Case group (recipient-to-DT) (n=12)	Control group (larger-to-smaller twin) (n=24)	P
Renal RI ratio	1.024±0.219	1.019±0.107	0.917*
Renal PSV ratio	1.142 (1.14)	0.996 (0.45)	0.562†
Renal PI ratio	0.831 (0.81)	1.025 (0.49)	0.585†

*The result of independent samples *t*-test: Values reported are mean±SD; †The result of Mann-Whitney *U*-test; values reported are median (IQR). RI=Resistance index; PSV=Peak systolic velocity; PI=Pulsatility index; SD=Standard deviation; IQR=Interquartile range; DT=Donor twin

which confirms the results of the present study, although RAD PI was not different.

Besides RAD, the results of comparing other fetal arteries in the present study are also noteworthy. As shown, DTs had a lower mean MCA S/D, which reflects the increased diastolic flow by fetal hypoxia and cerebral vasodilation, which predict fetal distress and intrauterine growth retard (IUGR) in DT.[17,18] Furthermore, DTs had higher UA parameters, including PI, RI, and S/D, compared with the control group, which reflects the increased resistance and decreased blood flow, which results in hypoxia, reduced ATP, increased reactive oxygen species (oxidative stress), and fetal distress in the DT.[19] Both MCA PI and UA PI parameters (cerebro-placental ratio) are reproducible and confirmed as poor-valued predictors of adverse perinatal outcomes in singleton pregnancies,[20] although considered a valuable predictor for adverse perinatal outcomes in fetuses of women with preeclampsia, gestational hypertension, and IUGR. However, only a few studies have elucidated the value of MCA and UA in twins, especially MCDA twins.

Comparing the RT with the control group also showed a higher MCA PI, RI, and S/D in this group, which reflects the hypervolemia and cardiac abnormalities of the RT.[5] Delta MCA PSV Doppler parameters are considered valuable in MCDA twins, especially for the prediction of anemia in the DT and polycythemia in the RT;[21-23] but this predictive power is mainly attributed to MCA PSV, which was not different between any of the compared groups (DT vs. control, RT vs. control, or DT vs. RT) in the present study. The changes observed in Doppler parameters of fetal arteries reflect the effect of hypovolemia on RAAS, which increase angiotensin II and result in increased peripheral vascular resistance, while the persistent activation of RAAS aggravates renal hypoperfusion in a vicious cycle.[4,24]

The comparison of the two fetuses in the case group also showed higher mean values of UA RI and S/D in the donor fetus. These results showed that abnormal UA waveforms in MCDA twins may represent placental insufficiency but may also be secondary to the presence of inter-twin anastomosis and changes in vascular reactivity typical of TTTS. TTTS has serious complications not only in DT but also in RT. Cardiac complications are one of the most important ones, as they present at the early stages of TTTS with elevated left ventricular filling pressure and decreased systolic function in the RT.[25] Diastolic dysfunction is also observed in RTs at early stages.[26] Development of the cardiac abnormality in RT can cause concentric hypertrophy, associated with impaired ventricular relaxation and shortened filling time.[27] These changes are reflected in the Doppler examination of fetal arteries, especially UA and MCA,[28] as confirmed by the results of the present study. As the fetal kidneys receive about 2%–3% of the total cardiac output, it was anticipated that the peripheral circulation (renal arteries) respond to the neurohormonal stimuli induced by hypoxia; however, the study rejected the association of RAD parameters with adverse neonatal outcomes suggests that it has yet to be elucidated how the fetal cardiovascular system adapts to chronic hypoxia.[29]

Strengths and limitations

The main strength of the present study, the second to evaluate the predictive value of RAD for TTTS, was the comparison of the results between DT and control, RT and control, and DT and RT. Although, the current study had some limitations. One of the limitations worth noting includes the lack of subgroup analysis based on variables affecting the Doppler indices, such as the stages of TTTS in the case group, which was not performed, as it would have reduced the statistical power of the results, considering the small number of samples. The intraobserver reliability of Doppler parameters is also another limitation of our study.

CONCLUSION

The comparing the RAD parameters between the twins with and without TTTS in the present study did not identify significant results, which rejected the primary hypothesis. Among all RAD parameters, the only significant difference observed in the present study was the lower RAD PI in RT, which cannot suggest this measurement as a valuable tool for the prediction of TTTS in MCDA twins. Therefore, the results of the present study failed to show the additional value of RAD compared with the conventional Doppler examination of fetal arteries. Considering the scarce information in this regard in the literature and the limitations of the present study, definite conclusions can be made after examination of this issue in future studies. Further multicentric studies with a larger sample size are required to investigate the effect of other variables, such as pregnancy by ART, on the outcome.

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Conflicts of interest
There are no conflicts of interest.

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