Retrospective validation of ultrasound characteristics at 19–24 weeks as predictive tools for selective intrauterine growth restriction in monochorionic diamniotic twin pregnancies: a diagnostic study

Yin-Di Zhu[1#], Ming-Yue Wang[1#], Mei-Fang Pan[2#], Jin-Yan Bian[1], You-Guo Chen[1], Xin-Xian Gu[1,3]

[1]Department of Gynecology and Obstetrics, The First Affiliated Hospital of Soochow University, Suzhou, China; [2]Department of Ultrasound, Suzhou Xiangcheng People's Hospital, Suzhou, China; [3]Department of Ultrasound, Dushu Lake Hospital Affiliated to Soochow University, Suzhou, China

Contributions: (I) Conception and design: YD Zhu, MY Wang; (II) Administrative support: XX Gu, YG Chen; (III) Provision of study materials or patients: MY Wang, MF Pan; (IV) Collection and assembly of data: MY Wang, YG Chen; (V) Data analysis and interpretation: MY Wang, JY Bian; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Xin-Xian Gu. Department of Ultrasound, Dushu Lake Hospital Affiliated to Soochow University, Suzhou 215124, China. Email: guxinxian@suda.edu.cn; You-Guo Chen. Department of Gynecology and Obstetrics, The First Affiliated Hospital of Soochow University, Suzhou 215006, China. Email: chenyouguo@suda.edu.cn.

Background: Seeking an optimal time point for ultrasound examination is important for the diagnosis of late selective intrauterine growth restriction (sIUGR) at birth in monochorionic diamniotic (MCDA) twin pregnancies. We aimed to assess the role of ultrasound characteristics at 19–24 weeks as predictive tools for late sIUGR at birth in MCDA twin pregnancies.

Methods: We retrospectively recruited 32 sIUGR and 56 normal patients with MCDA twin pregnancies. Ultrasound indexes of these included subjects at 19–24 weeks, including the middle cerebral artery peak systolic velocity (MCA-PSV), umbilical artery pulsatility index (UA-PI), middle cerebral artery pulsatility index (MCA-PI), and cerebroplacental ratio (CPR) were assessed. Receiver operating characteristic (ROC) curves were used to ascertain the predictive value of ultrasound characteristics discrepancy for such complications, and the relationship between the ultrasound characteristics and sIUGR was assessed by a logistic regression analysis.

Results: Differences were found in the MCA-PI, UA-PI, and CPR discordances between the normal MCDA and sIUGR subjects. CPR discordance was the most effective characteristic for predicting sIUGR [area under the ROC curve (AUC) =0.883; 95% CI: 0.795–0.948], followed by UA-PI discordance (AUC =0.772; 95% CI: 0.685–0.829), and MCA-PI discordance (AUC =0.746; 95% CI: 0.681–0.823), respectively. Additionally, the optimal cutoff value of CPR discordance was 21.65, and the corresponding sensitivity and specificity were 0.750 and 0.929, respectively. The correlation analysis revealed that gestational age (GA) at ultrasound scan but not at delivery was significantly correlated with the MCA-PSV ($r=0.55$, $P<0.01$), UA-PI ($r=0.55$, $P<0.01$), MCA-PI ($r=0.49$, $P<0.01$), and CPR ($r=0.55$, $P<0.01$) in sIUGR, while GA at both ultrasound scan and birth was significantly correlated with MCA-PSV ($r=0.65$, $P<0.01$), UA-PI ($r=0.49$, $P<0.01$), MCA-PI ($r=0.48$, $P<0.01$), and CPR ($r=0.63$, $P<0.01$) in normal MCDA.

Conclusions: Increased MCA-PI, UA-PI, and CPR discordances were found in fetuses with sIUGR. CPR discordance could serve as a predictive index for sIUGR. An early ultrasound examination may be more accurate than biochemical modality for sIUGR prediction.

Keywords: Monochorionic diamniotic (MCDA); selective intrauterine growth restriction (sIUGR); ultrasound characteristics

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Introduction

Monochorionic diamniotic (MCDA) twins represent 70% of monozygotic twins that split between 4 and 8 days after fertilization (1-3). Increased perinatal mortality and morbidity are found in MCDA twins due to shared placentation (4-6) and the presence of inter-twin placental vascular anastomoses (7). Selective intrauterine growth restriction (sIUGR) is one of the main risks in MCDA twins, and has a prevalence of 15–20% (3,8). Due to the high prevalence of sIUGR, early prediction is necessary to ensure effective surveillance.

Ultrasound examination serves as a routine method for predicting sIUGR. Previous studies have shown that the evaluation of utero-placental perfusion indices, including umbilical artery and middle cerebral artery velocimetry using Doppler ultrasound, have good efficacy for sIUGR prediction (9-14). Additionally, magnetic resonance imaging (MRI) of placental invasion has recently become part of clinical practice (15); however, the major disadvantages of MRI include expensive devices and relatively complex techniques. Biochemical serum markers (16), invasion tissue (17), and hair (18) gene expression examinations are hindered by lower specificity than imaging based examinations and can result in late diagnoses.

Most previous routine ultrasound studies have focused on ultrasound data from 11–13 weeks. We previously found significant differences in nuchal translucency (NT) discordance between normal, sIUGR, and twin-to-twin transfusion syndrome (TTTS) groups, and NT difference and NT discordance were identified as predictive markers for sIUGR and TTTS, respectively (19). Compared with 11–13 weeks, ultrasound characteristics at 19–24 weeks were most important fetal systematic screening during the whole pregnancy, with more detectable indicators and more mature data. Ultrasound characteristics at 19–24 weeks' gestation have not yet been determined.

The present study sought to validate the ultrasound characteristics at 19–24 weeks' gestation and examine their use as predictive tools for sIUGR in MCDA twin pregnancies using the discordance data between the middle cerebral artery peak systolic velocity (MCA-PSV), umbilical artery pulsatility index (UA-PI), middle cerebral artery pulsatility index (MCA-PI), and cerebroplacental ratio (CPR). We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3089/rc).

Methods

Study design

This retrospective cohort diagnostic study was carried out using data from The First Affiliated Hospital of Soochow University between January 2015 and December 2020. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University (No. 21-012). Because of the retrospective nature of the research, the requirement for informed consent was waived.

Population

Women with MCDA twin pregnancies at 18–38 weeks' gestation were included in this study. The diagnostic criteria were based on the existence of a single placental mass and the absence of a bimodal sign, as described previously (20).

The sIUGR patients had to meet the following inclusion criteria: have been diagnosed with (I) a MCDA twin pregnancy; and (II) sIUGR. In this study, sIUGR was defined as either the birth weight of the smaller neonate being below the 10th percentile for gestational age (GA), or as the birth weight discordance being >25% between a pair of twins (4). Birthweight discordance was calculated according to the following equation: (larger weight – small weight)/larger weight. Normal MCDA twins were defined as with the normal birth weight, whose mother are with a normal maternal age. The GA matched normal MCDA twins were served as the control group.

Participants were excluded from the study for the following reasons: (I) co-twin demise; (II) pregnancy with a fetal abnormality, aneuploidy, or a genetic syndrome; (III) pregnancy complicated by TTTS or twin-anemia polycythemia sequence; and (IV) an inability to detect the placenta by ultrasound.

All the selected patients with MCDA twin pregnancies had known pregnancy outcomes.

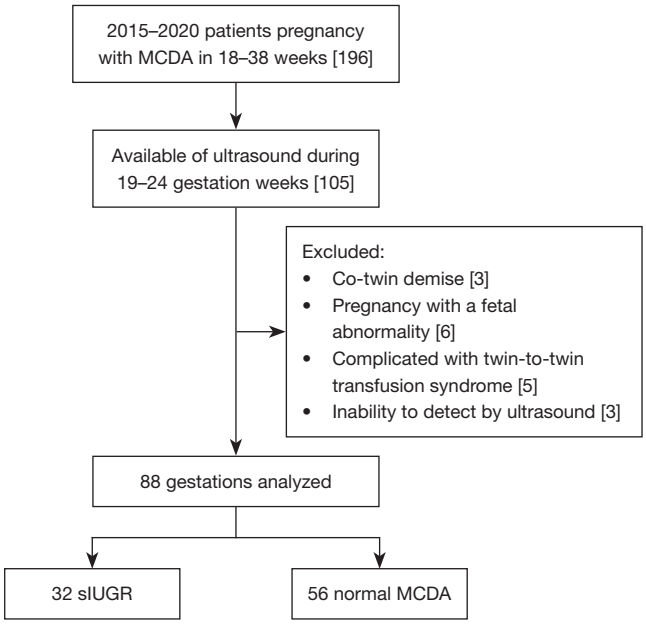

Figure 1 Patient selection process. MCDA, monochorionic diamniotic; sIUGR, selective intrauterine growth restriction.

Procedure

The clinical information of the pregnant women and the pregnancy outcome data were obtained from obstetric electronic medical records or follow-up telephone calls. The ultrasound examination data were obtained using the ultrasound information system. Voluson E10 ultrasound instruments (GE Healthcare, Austria) were used together with C1-5-D (1.0–5.0 MHz) transducers. Complete ultrasound measurements were performed by a well-experienced observer at 19–24 weeks of gestation.

The following 4 potential characteristics of MCDA complications were evaluated: discordances in the MCA-PSV, UA-PI, MCA-PI, and CPR. The MCA-PSV, UA-PI, and MCA-PI were measured by ultrasound at 19–23+6 weeks of gestation in accordance with the standard techniques (21). The CPR was calculated as the ratio of MCA-PI to UA-PI. Discordances of MCA-PSV, UA-PI, MCA-PI, and CPR twin pairs were calculated according to the following equation: (twin with larger weight – twin with small weight)/twin with larger weight.

Statistical analysis

The statistical analysis and figure construction were performed using R software (version 4.03). The between-group comparison of the discordances in the twin-pair characteristics (MCA-PSV, UA-PI, MCA-PI, and CPR) in groups with different pregnancy outcomes was performed using the Wilcoxon and Kruskal-Wallis tests, respectively. The diagnostic value of the above markers in the identification of high-risk cohort pregnancies at risk of adverse pregnancy outcomes was evaluated using receiver operating characteristic (ROC), and the area under the curve and corresponding specificity and sensitivity are calculated using pROC package. The optimal cutoff value was calculated using the Youden index. Sample size calculations were performed as previously described (22). The correlation analysis between GA and ultrasonic characteristics was performed using Spearman's rank correlation. Statistical significance was set at two side $P<0.05$.

Results

Patient inclusion process

As *Figure 1* shows, pregnant patients between 2015 and 2020 with MCDA and available ultrasound images from 18–38 weeks were included in this study. After excluding those with co-twin demise, abnormal fetal pregnancy, and TTTS, and those for whom the placenta was unable to be detected on ultrasound, 88 pregnancies were included in the study, including 32 sIUGR patients and 56 normal MCDA patients.

Clinical characteristics comparison between the normal MCDA and sIUGR

The results revealed no difference in the characteristics, including maternal age, assisted conception ratio, body mass index (BMI), nulliparity, and GA at ultrasound scan (all $P>0.05$); however, a significant difference was found in GA at delivery ($P<0.05$) and birth weight discordance ($P<0.01$; see *Table 1*).

The discordance of ultrasound characteristics between the normal MCDA and sIUGR groups

We further compared the discordance of ultrasound characteristics between the normal MCDA and sIUGR groups and found no difference in MCA-PSV between these groups; however, we found significant increases in the UA-PI, MCA-PI, and CPR in the sIUGR group compared to the normal MCDA group (all $P<0.01$; see *Figure 2A-2D*).

Table 1 Clinical characteristic comparison between the normal MCDA and sIUGR

Characteristics	sIUGR (n=32)	Normal MCDA (n=56)	P value
Maternal age (years)	34 (28.7–37.1)	32 (28.6–35.2)	0.32
Assisted conception, n (%)	3 (9.4)	4 (6.7)	–
BMI (kg/m^2)	23 (20.1–25.8)	22 (19.8–25.1)	0.82
Nulliparous, n (%)	19 (59.4)	34 (56.7)	0.91
GA at ultrasound scan (weeks + days)	22+1 (19+2 to 24+2)	22+3 (20+1 to 23+5)	0.86
GA at delivery (weeks + days)	34+3 (32+5 to 36+3)	36+2 (33+4 to 37+5)	<0.05
Birthweight discordance (%)	35.68 (28.16–42.53)	16.86 (10.21–21.29)	<0.01

MCDA, monochorionic diamniotic; sIUGR, selective intrauterine growth restriction; BMI, body mass index; GA, gestation age.

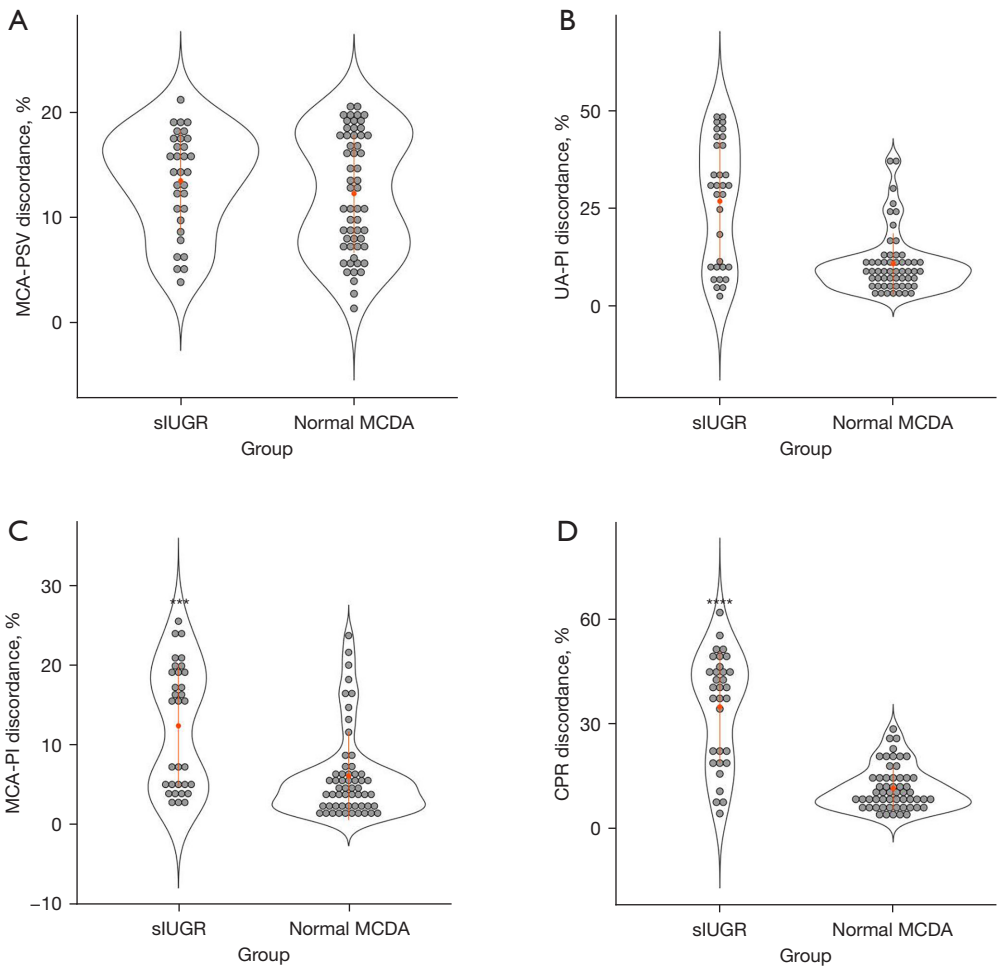

Figure 2 The discordance of ultrasound characteristics between the normal MCDA and sIUGR groups. No difference was found in the MCA-PSV (A) between the normal MCDA and sIUGR groups, while a significantly higher UA-PI (B), MCA-PI (C), and CPR (D) were found in the sIUGR group compared to the normal MCDA group (all P<0.01). ***, P<0.01, ****, P<0.001. MCDA, monochorionic diamniotic; sIUGR, selective intrauterine growth restriction; MCA-PSV, middle cerebral artery peak systolic velocity; UA-PI, umbilical artery pulsatility index; MCA-PI, middle cerebral artery pulsatility index; CPR, cerebroplacental ratio.

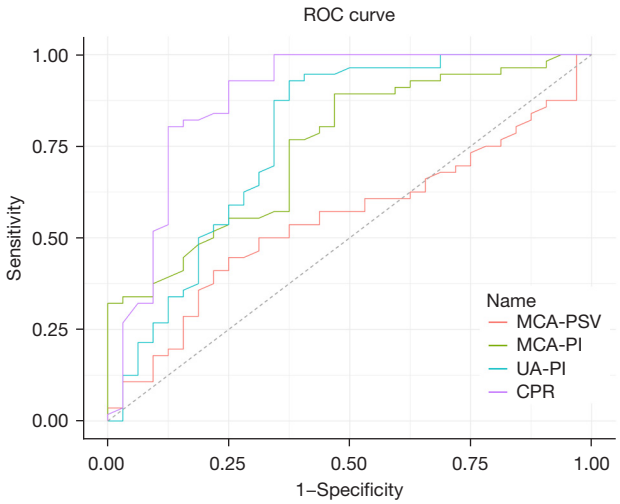

Figure 3 The diagnostic efficacy of the ultrasound characteristics in differentiating between normal MCDA and sIUGR. The results indicated that CPR discordance was the most effective characteristic for predicting sIUGR (ROC AUC =0.883; 95% CI: 0.795–0.948), while the other markers from the most to least effective were as follows: UA-PI discordance (AUC =0.772; 95% CI: 0.685–0.829), MCA-PI discordance (AUC =0.746; 95% CI: 0.681–0.823), and MCA-PSV discordance (AUC =0.548; 95% CI: 0.446–0.650). MCDA, monochorionic diamniotic; sIUGR, selective intrauterine growth restriction; CPR, cerebroplacental ratio; ROC, receiver operating characteristic; AUC, area under the ROC curve; UA-PI, umbilical artery pulsatility index; MCA-PI, middle cerebral artery pulsatility index; MCA-PSV, middle cerebral artery peak systolic velocity.

The diagnostic efficacy of ultrasound characteristics in differentiating between normal MCDA and sIUGR

The diagnostic efficacy of the ultrasound characteristics in differentiating between normal MCDA and sIUGR was also calculated, and the results indicated that CPR discordance was the most effective characteristic for predicting sIUGR [area under the ROC curve (AUC) =0.883; 95% CI, 0.795–0.948], while the other markers from the most to least effective were as follows UA-PI discordance (AUC =0.772; 95% CI: 0.685–0.829), MCA-PI discordance (AUC =0.746; 95% CI: 0.681–0.823), and MCA-PSV discordance (AUC =0.548; 95% CI: 0.446–0.650) (see *Figure 3*). Additionally, the optimal cutoff value of CPR discordance was 21.65, and the corresponding sensitivity and specificity were 0.750 and 0.929, respectively. These results indicate that CPR discordance can serve as a predictive marker for sIUGR.

Correlation analysis between GA and ultrasonic characteristics

For those in the sIUGR group, the results showed a positive correlation between GA at scan and 4 ultrasound characteristics; that is, MCA-PSV (r=0.55, P<0.01), UA-PI (r=0.55, P<0.01), MCA-PI (r=0.49, P<0.01), and CPR (r=0.55, P<0.01). However, no correlation was found between GA at delivery and any ultrasound characteristics (see *Figure 4*). For those in the normal MCDA group, the results showed a positive correlation between GA at scan and 4 ultrasound characteristics; that is, MCA-PSV (r=0.65, P<0.01), UA-PI (r=0.49, P<0.01), MCA-PI (r=0.48, P<0.01), and CPR (r=0.63, P<0.01). Additionally, a negative correlation was found between GA at delivery and the ultrasound characteristics of MCA-PSV (r=0.44, P<0.01), UA-PI (r=0.28, P=0.03), and CPR (r=0.4, P<0.01), but not MCA-PI (see *Figure 5*).

Discussion

In the present study, we found differences in MCA-PI, UA-PI, and CPR discordances between the normal MCDA and sIUGR subjects. CPR discordance was found to be the most effective predictor of sIUGR. Additionally, the correlation analysis revealed that GA at ultrasound scan but not at delivery was significantly correlated with MCA-PSV, MCA-PI, UA-PI, and CPR in the sIUGR group, while GA at both ultrasound scan and birth was significantly correlated with MCA-PSV, MCA-PI, UA-PI, and CPR in the normal MCDA group.

The use of the CPR for outcome prediction has been proposed in current clinical practice. Zhang *et al.* (23) used 3-dimensional Doppler ultrasound to assess the correlation between sIUGR and co-twin utero-placental perfusion discordance in 64 sIUGR and 64 normal MCDA subjects, and found that the UA-PI, MCA-PI, and CPR discordances were increased in the sIUGR cohort, which is consistent with our results. CPR is considered a higher sensitive Doppler index for predicting perinatal outcomes (24). Bano *et al.* reported that CPR hold 100% specificity and a high sensitivity for IUGR diagnosis and adverse perinatal outcomes prediction (25). Vergani *et al.* conducted a longitudinal study of 171 late-onset sIUGR fetuses and found minimal changes in the UA-PI after 30 weeks, but found a steady decrease in the CPR and MCA-PI from 30 weeks to delivery (26). Thus, it is necessary to identify a threshold value for the CPR to enable the efficacious

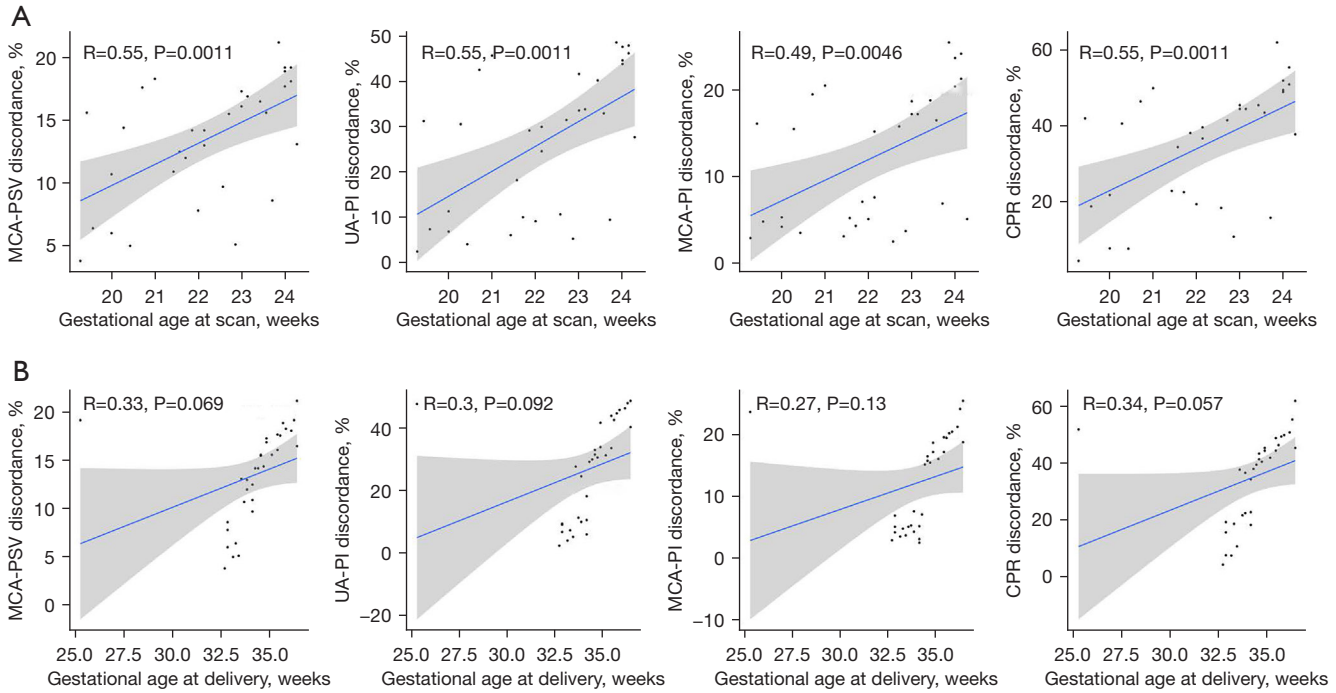

Figure 4 Correlation analysis between GAs at scan (A) or delivery (B) and ultrasound characteristics in patients with sIUGR. The results revealed a positive correlation between GA at scan and 4 ultrasound characteristics (i.e., MCA-PSV, UA-PI, MCA-PI, and CPR), while no correlation was found between GA at delivery and the ultrasound characteristics. sIUGR, selective intrauterine growth restriction; GA, gestational age; MCA-PSV, middle cerebral artery peak systolic velocity; UA-PI, umbilical artery pulsatility index; MCA-PI, middle cerebral artery pulsatility index; CPR, cerebroplacental ratio.

prediction of adverse perinatal outcomes. Odibo *et al.* (27) evaluated the screening efficacy of CPR for adverse perinatal outcome prediction in sIUGR fetuses and found that using either a categorical threshold of a CPR <1.08 or a GA-specific value of a CPR <10th percentile generated a similar test efficacy of 67%. Our results support the efficacy of using the CPR in sIUGR prediction as a combined reflection of fetal response and placental status. Thus, consideration should be given to adopting a combined approach when employing indexes based on different sensitivities and specificities for diagnosis.

A recent study showed placental vascular indices were strongly correlated with birth weight in normal MCDA and dichorionic-diamniotic twin pregnancies (28). In our study, we also found a significantly different birth weight discordance between sIUGR and normal MCDA twin pregnancies. These results indicate that birth weight is a critical phenotypic index due to abnormal development during pregnancy. We found no correlation between utero-placental perfusion and GA at delivery, but we did find a correlation with GA at scan, which suggests that the number of vessels and blood flow may increase proportionally to placental volume during early gestation; however, no significant correlation was found with increasing gestation time. These results are consistent with those of previous studies (29,30), but contradictory to other recent reports (31-33). A lack of uniform criteria on placental perfusion measurement, especially sample volume and sample numbers, may serve as an explanation for these contradictory results.

To the best of our knowledge, our study was the first to predict sIUGR using data at 19–24 weeks. The strengths of our study include our clear objective, which considered the properties of the retrospective study, our feasible research plan, the use of reasonable and effective observation indicators, the inclusion of detailed clinical data in accordance with the design requirements, and the strict control of the research quality.

The present study had some limitations. First, the retrospective nature of the study could have led to less reliable findings or produced a possible bias in the selection of the case and control subjects. Second, the relatively small number of sIUGR cases could have led to a conclusion bias.

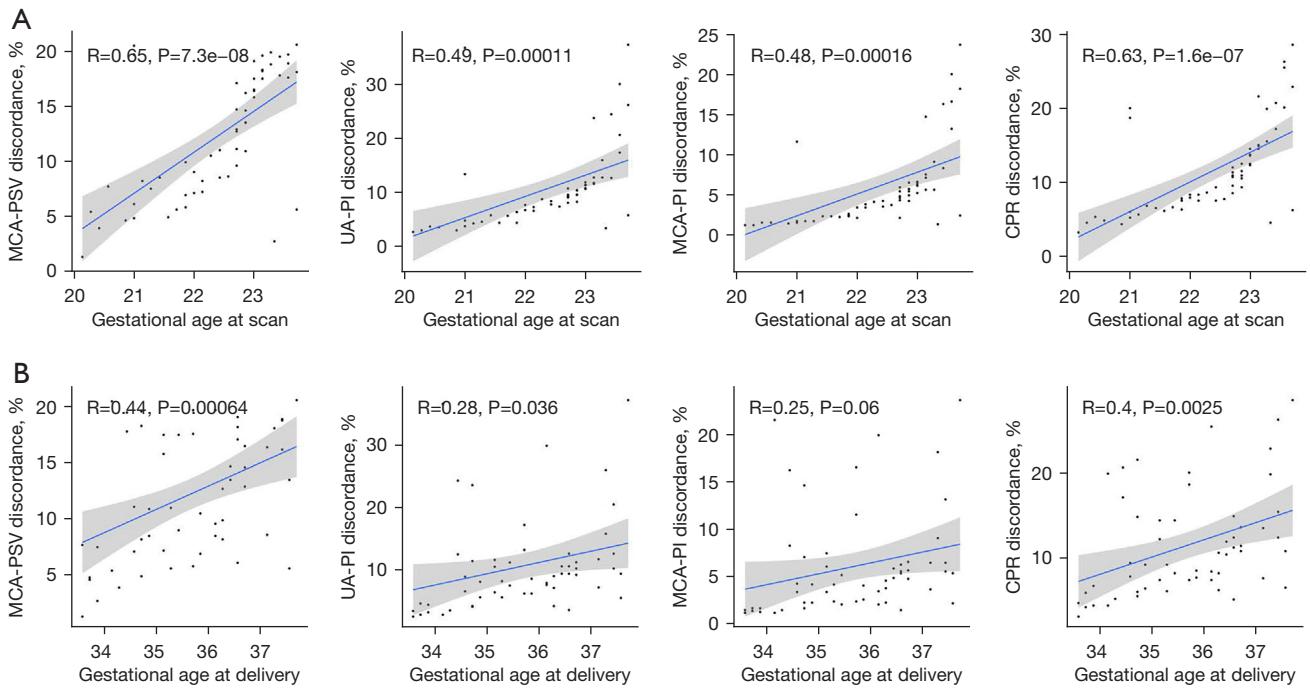

Figure 5 Correlation analysis between GA at scan (A) or delivery (B) and ultrasound characteristics in patients with normal MCDA. The results revealed a positive correlation between GA at scan and 4 ultrasound characteristics (i.e., MCA-PSV, UA-PI, MCA-PI, and CPR), and between GA at delivery and the ultrasound characteristics of MCA-PSV, UA-PI and CPR, but not MCA-PI. GA, gestational age; MCDA, monochorionic diamniotic; MCA-PSV, middle cerebral artery peak systolic velocity; UA-PI, umbilical artery pulsatility index; MCA-PI, middle cerebral artery pulsatility index; CPR, cerebroplacental ratio.

Thus, further prospective studies with larger numbers of sIUGR cases should be conducted to confirm the results of the present study.

In conclusion, the data at 19–24 weeks demonstrated that increased MCA-PI, UA-PI, and CPR discordances were found in patients with sIUGR. CPR discordance can serve as a predictive index for sIUGR. Early ultrasound examinations may be more accurate than biochemical modality for sIUGR prediction.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3089/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3089/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3089/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University (No. 21-012). Because of the retrospective nature of the research, the requirement for

informed consent was waived.

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