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Prediction of late-onset fetal growth restriction by umbilical artery velocities at 37 weeks of gestation: a cross-sectional study

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ABSTRACT

Objective To explore the predictive capacity of umbilical artery (UA) velocities at 37 weeks of gestation in identifying fetal growth restriction (FGR).

Design Cross-sectional study.

Setting and participants We retrospectively recruited 569 fetuses in the study. Thirty-nine FGR infants and 57 small-for-gestational-age (SGA) infants with normal UA Doppler at 37 weeks, as the study groups and 473 adequate-for-gestational-age (AGA) infants as a control group in a tertiary referral centre.

Methods All the parameters of UA velocities, including the UA end-diastolic velocity (UA-EDV), UA peak systolic velocity (UA-PSV), UA mean diastolic velocity (UA-MDV) and UA time-averaged maximum velocity (UA-TAMXV), and UA Doppler were measured at approximately 37 weeks of gestation.

Results Among the FGR, SGA and AGA groups, the UA-MDV, UA-TAMXV, UA-PSV and UA-EDV decreased with the loss of fetal weight. Multivariate logistic regression analyses showed that the UA-TAMXV was an independent predicting factor of FGR. It had a moderate predictive value for FGR. The area under the receiver operating characteristic curve was 0.82 (95% CI: 0.79 to 0.85).

Conclusions The UA velocities decreased with the loss of fetal weight among the FGR, SGA and AGA groups and the UA-TAMXV was independently predictive of FGR. The results suggest that the UA-TAMXV might be a new parameter to predict FGR prior to delivery.

INTRODUCTION

Fetal growth restriction (FGR) accounts for approximately 5%–10% of singleton pregnancies.[1] This growth disorder is associated with an increased risk of adverse perinatal outcomes (APOs) and long-term impacts, including impaired neurological and cognitive development and cardiovascular or endocrine diseases in adulthood.[2 3] At present, the prenatal recognition of small size by ultrasound is the most commonly used method for identifying intrauterine growth disorders, which minimises the rates of APOs to some extent. However, ultrasound still fails

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The receiver operating characteristic curve and a decision curve analysis were performed in this study.
⇒ Our findings were independent of several potential confounders (ie, maternal age, gestational age, maternal height, maternal gravidity and maternal parity), suggesting that the observed associations were robust.
⇒ Three types of single fetus, including fetal growth restriction, small for gestational age and adequate for gestational age, were explored, which were compared by analysis of variance and post hoc pairwise comparative analysis.
⇒ A retrospective cross-sectional study design may lead to an inherent risk of selection bias (eg, information bias, confounding bias).
⇒ The number of fetuses in study groups in our study was small and a larger number of participants would be better.

to detect more than 25% of fetuses with late-onset FGR.[4 5] The possible reasons for failure to identify late-onset FGR might be that ultrasound examinations are performed in early third-trimester pregnancy,[5 6] and that measurement errors cause the inability to distinguish FGR from small for gestational age (SGA) prior to delivery.

The feto-placental circulation is crucial for fetal development and growth. At present, umbilical artery (UA) Doppler parameters, including the UA pulsatility index (UA-PI) and the ratio of the systolic peak value and the end-diastolic velocity of the UA, are commonly used for evaluating feto-placental circulation. However, unless the end-diastolic blood flow is elevated, absent or reversed, placental insufficiency in late-onset FGR often goes undetected by UA Doppler scan.[7 8] It is now widely acknowledged that large numbers of near-term SGA infants with normal UA

Doppler presentations are having identified as late-onset FGR and are at risk of APOs.[9–11]

Previous studies have confirmed that placental blood flow volumes are reduced in fetuses with FGR.[12–14] The decrease in placental blood flow volume might even occur before the increase in the UA-PI in fetuses with growth restriction.[15] One longitudinal study reported that UA velocities can reflect placental blood flow and thus feto-placental circulation.[16] However, to the best of our knowledge, it is not clear whether the UA velocities of fetuses with FGR are lower than those of fetuses with SGA.

Therefore, the main purpose of this study was to investigate the discordance of UA velocities of fetuses with FGR, SGA and adequate for gestational age (AGA) with normal UA Doppler at 37 weeks of gestation, and to investigate the value of using UA velocities for predicting FGR. We hypothesised that UA velocities might be decreased with the loss of fetal weight among the three groups, which can contribute to an early prediction of FGR with normal UA Doppler and distinguish FGR from SGA prior to delivery.

MATERIALS AND METHODS

This was a retrospective cross-sectional study in the Fetal Medicine Center of the First Affiliated Hospital of Chongqing Medical University in Chongqing, China, between January 2017 and May 2021.

SGA was defined as a customised birth weight between the 3rd and 10th percentiles, and FGR was defined as a birth weight of the <3rd percentiles.[17] Late-onset FGR is usually defined as FGR that is diagnosed at ≥32 weeks of pregnancy.[18] The APOs included emergency caesarean section for non-reassuring fetal status, a 5 min Apgar score <7 and neonatal acidosis at birth.[19] According to the American College of Obstetricians and Gynecologists guidelines,[20] all of the SGA fetuses with normal umbilical artery Doppler included in our study were delivered at approximately 37 weeks of gestation. The gestational age (GA) was determined according to the last menstrual period, and the first-trimester crown-rump length or the head circumference was determined when the first ultrasound examination was performed after 14 weeks of gestation.

The inclusion criteria for the three groups were as follows: singleton gestation; intact membranes; the absence of congenital or chromosomal abnormalities; the absence of pregnancy complications (ie, hypertensive disorders, diabetes); normal amniotic fluid; UA Doppler performed within the normal range for GA; and SGA and FGR fetuses were delivered at $37^{\pm2}$ weeks. Ultrasound examinations, including fetal biometry and UA velocities, were performed at $37^{\pm2}$ weeks for the three groups. The exclusion criteria were pregnant women with abnormal blood pressure, and pregnant women with viral infections such as rubella virus, herpes zoster virus and cytomegalovirus infections. The parameters of UA velocities included the UA end-diastolic velocity (UA-EDV), UA peak systolic velocity (UA-PSV), UA mean diastolic velocity (UA-MDV) and UA time-averaged maximum velocity (UA-TAMXV). The parameters of UA Doppler included the UA-PI, middle cerebral artery pulsatility index (MCA-PI) and cerebroplacental ratio (CPR).

Our study used the Standards for Reporting Diagnostic Accuracy reporting guidelines.[21] The normality of the data was determined by the Kolmogorov-Smirnov test. Continuous variables are expressed as the means±SDs or the medians (IQRs) as appropriate. Categorical variables are expressed as the numbers of patients. For multiple comparisons, one-way analysis of variance was performed for continuous variables, and Pearson's X^2 test was performed for categorical variables. Univariate and multivariate logistic regression analyses were performed to identify the predictive parameters for FGR. The sensitivity and specificity were calculated by receiver operating characteristic (ROC) curve analysis. Pearson correlations were performed to investigate the potential relationships between fetal weight and the UA velocities if the variables were normally distributed. Spearman correlation was performed if the variables were ordinal data or were not normally distributed. Moreover, linear correlation graphs were generated to evaluate the correlations between fetal weight and the UA velocities. All p values were two sided, and p values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS V.21.0 (IBM Corporation) and MedCalc V.11.4.2 (MedCalc Software, Ostend, Belgium).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

A total of 569 fetuses from singleton pregnancies were enrolled in our study, of which 39 (6.9%) had FGR, 57 (10.0%) were SGA and 473 (83.1%) were normal fetuses from singleton pregnancies. The maternal clinical and neonatal characteristics among the three groups are presented in table 1. The maternal height in the SGA group was the shortest among the three groups. The maternal height in the SGA group was significantly shorter than that in the AGA group (p<0.001); however, no significant differences were observed between the AGA group and FGR group or between the FGR group and SGA group (all p≥0.05). No significant differences in maternal age, gravida, parity, GA at delivery or APOs were observed among the three groups (all p≥0.05).

The parameters of UA Doppler and UA velocities among the three groups are presented in table 2. The UA-MDV, UA-TAMXV, UA-PSV, and UA-EDV in the AGA group, SGA group and FGR group decreased successively. There were significant differences in the UA-TAMXV and UA-PSV among the three groups (all p<0.05). There were significant differences in the UA-MDV and UA-EDV between the FGR group and AGA group, as well

Table 1 The maternal clinical and neonatal characteristics among three groups

Characteristics	FGR (n=39)	SGA (n=57)	AGA (N=473)	F/χ^2	P value
Maternal age (years)	28.9±4.4	30.1±4.1	30.4±3.9	2.994	0.051
Maternal gravidity (times)	1.9±1.3	2.4±1.5	2.3±1.4	0.959	0.384
Maternal parity (times)	1.2±0.4	1.3±0.5	1.3±0.5	1.463	0.232
Maternal height (cm)	157.9±5.4	156.6±5.3	159.2±4.9	7.753	<0.001*
Delivery gestational age	37.1±0.6	37.2±0.6	39.3±1.0	211.389	<0.001*†
Fetal weight (g)	2070.1±182.2	2371.8±69.2	3302.7±327.8	491.022	<0.001*†‡
5 min Apgar score <7 (%)	0 (0)	1 (1.8)	1 (0.2)	3.605	0.165
Neonatal metabolic acidosis (%)	1 (2.6)	0 (0)	1 (0.2)	5.917	0.052
Adverse perinatal outcome (%)	1 (2.6)	1 (1.8)	1 (0.2)	5.621	0.060

Values are given as the means±SDs or n (%). Groups compared using one-way ANOVA or Pearson's χ^2 test, with p<0.05 considered statistically significant.

*AGA versus SGA.
†AGA versus FGR.
‡SGA versus FGR.
AGA, adequate for gestational age; ANOVA, analysis of variance; FGR, fetal growth restriction; SGA, small for gestational age.

as between the SGA group and AGA group (all p<0.05). However, no significant difference was observed in the UA-MDV and UA-EDV between FGR group and SGA group (p≥0.05). There were no significant differences in the UA-PI, MCA-PI or CPR among the three groups (all p≥0.05). The univariable logistic regression analysis suggested that the UA-TAMXV, UA-PSV, UA-MDV, and UA-EDV and maternal height were predictive of SGA and FGR (all p<0.05). However, the multivariate logistic regression analysis suggested that only maternal height was an independent predicting factor of SGA (p=0.001) (table 3). A forward stepwise logistic regression analysis identified that only the UA-TAMXV was independently associated with FGR (p=0.029) (table 4).

As shown by the ROC curves, the UA-TAMXV had moderate predictive value for FGR. The area under the ROC curve was 0.82 (95% CI: 0.79 to 0.85), with a sensitivity of 74.40% and specificity of 77.60% (figure 1). There was a positive correlation between UA-TAMXV and fetal weight (r=0.286, p<0.001).

DISCUSSION
In this study, we mainly found that the UA velocities decreased with the loss of fetal weight among the three groups and that the UA-TAMXV was an independent predicting factor for FGR. To our knowledge, this is the

Table 2 The comparison of conventional Doppler and UA velocity parameters at 37 weeks' gestation among three groups

Parameters	FGR (n=39)	SGA (n=57)	AGA (N=473)	F	P value
UA-PI	0.85±0.1	0.83±0.2	0.83±0.2	0.629	0.533
MCA-PI	1.47±0.2	1.48±0.3	1.48±0.3	0.023	0.977
CPR	1.77±0.4	2.02±1.7	1.91±1.1	0.580	0.560
UA-MDV	14.3±3.3	15.9±3.9	19.5±5.1	30.795	<0.001*†
UA-TAMXV	23.9±4.9	26.8±5.9	32.0±7.2	34.874	<0.05*†‡
UA-PSV	36.7±6.8	40.6±8.0	46.8±10.2	26.655	<0.05*†‡
UA-EDV	14.9±3.4	16.7±4.3	20.6±5.6	31.400	<0.001*†

Values are given as the means±SDs, with p<0.05 considered statistically significant.
*AGA versus SGA.
†AGA versus FGR.
‡SGA versus FGR.
AGA, adequate for gestational age; CPR, cerebroplacental ratio; FGR, fetal growth restriction; MCA-PI, middle cerebral artery pulsatility index; SGA, small for gestational age; UA-EDV, umbilical artery end-diastolic velocity; UA-MDV, umbilical artery mean diastolic velocity; UA-PI, umbilical artery pulsatility index; UA-PSV, umbilical artery peak systolic velocity; UA-TAMXV, umbilical artery time-averaged maximum velocity.

Table 3 Multivariable logistic regression analysis of the UA velocities and maternal height in the SGA group

Variables	Regression coefficient	SE	Wald value	P value	OR	95% CI
UA-MDV	−0.016	0.096	0.026	0.871	0.985	0.817 to 1.187
UA-TAMXV	0.069	0.055	1.581	0.209	1.071	0.962 to 1.193
UA-PSV	−0.017	0.032	0.292	0.589	0.983	0.923 to 1.046
UA-EDV	0.137	0.086	2.554	0.111	1.147	0.969 to 1.357
Maternal height	0.097	0.030	10.651	0.001	1.101	1.039 to 1.167

With p<0.05 considered statistically significant.
SGA, small for gestational age; UA-EDV, umbilical artery end-diastolic velocity; UA-MDV, umbilical artery mean diastolic velocity; UA-PSV, umbilical artery peak systolic velocity; UA-TAMXV, umbilical artery time-averaged maximum velocity.

first study to assess associations between UA velocities and growth disorders.

The placental blood flow volume is reduced in fetuses with FGR.[12–14] A published study showed that there is a significant positive association between the placental blood flow volume and UA velocities independent of GA.[16] In this study, we found a weak and positive correlation between the UA-TAMXV and fetal weight, suggesting that the UA velocities, which was associated with the feto-placental blood flow, decreased with the loss of fetal weight. The conventional UA Doppler parameters presented no significant differences among the three groups. Our findings suggested that the UA velocities, particularly the UA-TAMXV, might be more predictive of late-onset FGR than the UA resistance indices, such as the UA-PI, MCA-PI and CPR.

As described in previous studies, the placental blood flow volume could also be assessed by umbilical venous velocities.[22 23] However, the umbilical venous velocities are prone to errors and still need to be standardised.[24] One longitudinal study demonstrated that the UA-TAMXV was best correlated with the umbilical vein blood flow volume.[16] Our study showed that the UA-TAMXV was decreased in fetuses with FGR, which was consistent with a previous study.[16] In routine UA Doppler examinations, the UA velocities can be easily and quickly acquired simultaneously. However, these indicators have not been widely considered in clinical practice. When the placental blood flow resistance increases, the end-diastolic blood flow decreases. Therefore, the UA-EDV might be absent and cannot be detected in severely growth-restricted fetuses,

whereas the UA-TAMXV can still be readily detected in fetuses with this condition. Our findings suggested that the UA-TAMXV might be of predictive value for FGR. Therefore, the UA-TAMXV might be a more preferred parameter for evaluating the placental blood flow volume as well as the degree of fetal ischaemia.

Previous studies reported that fetal growth disorders are associated with an increased risk of APOs.[2 3] Unfortunately, no obvious APOs were found in our study. The possible reasons might be as follows. First, the CPR was a predictor of APOs in fetuses with late-onset FGR.[25] However, all of the fetuses in our study had normal UA resistance indices including CPR, UA-PI and MCA-PI values, which indicated to some extent that the fetus was not seriously compromised. Furthermore, the timing for delivering SGA fetuses was at 37 weeks of gestation rather than terminating the pregnancy unless the fetus was severely damaged. A large study reported a significantly increased risk of fetal death in SGA infants delivered at >37 weeks of gestation compared with those delivered at 37 weeks of gestation.[26] Another study including 92 218 singletons found that the fetal death rates were lower in fetuses with detected FGR than in those with undetected FGR.[2] It follows that the key to preventing APOs is the early detection of FGR and timely delivery. Nevertheless, further studies with more fetuses are required to observe the relationships among UA velocities, fetuses with FGR with advanced GA and APOs.

As recent studies have shown, maternal height was significantly and inversely associated with the risk of SGA and was a stronger predictor of birth weight than

Table 4 Multivariable logistic regression analysis of the UA velocities and maternal height in the FGR group

Variables	Regression coefficient	SE	Wald value	P value	OR	95% CI
UA-MDV	−0.128	0.153	0.698	0.404	0.880	0.652 to 1.188
UA-TAMXV	0.155	0.071	4.797	0.029	1.168	1.016 to 1.342
UA-PSV	−0.013	0.042	0.099	0.753	0.987	0.908 to 1.072
UA-EDV	0.271	0.147	3.384	0.066	1.311	0.982 to 1.750
Maternal height	0.054	0.036	2.222	0.136	1.056	0.983 to 1.134

With p<0.05 considered statistically significant.
FGR, fetal growth restriction; UA-EDV, umbilical artery end-diastolic velocity; UA-MDV, umbilical artery mean diastolic velocity; UA-PSV, umbilical artery peak systolic velocity; UA-TAMXV, umbilical artery time-averaged maximum velocity.
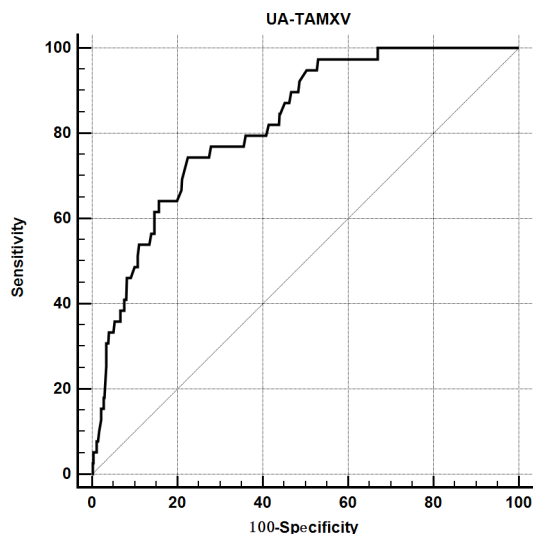
Figure 1 Receiver operating characteristic curves of the UA-TAMXV for identifying FGR. FGR, fetal growth restriction; UA-TAMXV, umbilical artery time-averaged maximum velocity.

ethnicity.[27 28] In our study, the maternal height of the SGA group was the shortest among the three groups and was independently predictive of SGA rather than FGR, which was consistent with the above research results.[27 28] Conversely, compared with maternal height, the UA-TAMXV was independently predictive of FGR. We speculated that maternal height was more closely associated with SGA, whereas the UA-TAMXV was more closely related to FGR. Therefore, the UA-TAMXV could distinguish FGR from SGA when the women had the same maternal height.

According to the American College of Obstetricians and Gynecologists guidelines,[20] 37 weeks of gestation is a critical time to decide whether to continue or terminate a pregnancy with suspected growth restriction. In clinical practice, it is quite difficult to distinguish FGR from SGA, which may result in SGA being early terminated. In our study, we monitored the UA velocities at approximately 37 weeks of gestation, and we found that the UA-TAMXV could distinguish FGR from SGA. Our finding suggested that the UA-TAMXV might be a useful parameter for the management of pregnancies with suspected growth disorders, thus avoiding neonatal complications related to early term delivery in SGA infants and severe damages associated with continued pregnancy in FGR infants.

Several limitations of our study should be mentioned. First, most of the pregnant women with fetuses with SGA and FGR were transferred from other hospitals, so it was not always possible to collect actual primary UA Doppler spectra and serial data. Second, as this was a retrospective study, the retrospective design can lead to an inherent risk of selection bias. Last, because all fetuses were delivered at approximately 37 weeks of gestation rather than waiting until a more advanced GA, the pregnancy outcome assessment could not be objectively assessed.

CONCLUSIONS

The UA velocities decreased with the loss of fetal weight, and the UA-TAMXV was independently predictive of FGR. Our findings suggested that the UA-TAMXV might be a new parameter to predict FGR, which might provide a better discrimination of FGR from SGA and a better management of pregnancies with suspected growth disorders, thus avoiding neonatal complications related to early term delivery in SGA infants and severe damages associated with continued pregnancy in FGR infants. However, further studies are needed to confirm these questions.

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