

Prediction of late-onset fetal growth restriction by umbilical artery velocities at 37 weeks' gestation

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Abstract

Objectives: To explore the predictive capacity of the umbilical artery velocities at 37 weeks' gestation in identifying fetal growth restriction (FGR), small-for-gestational-age (SGA) neonates and adverse perinatal outcome (APO). **Methods:** We retrospectively recruited FGR and SGA with normal umbilical artery Doppler at 37 weeks, and adequate-for-gestational age (AGA) controls in a tertiary referral center. All the parameters of the umbilical artery velocities were measured at about 37 weeks' gestation, including the umbilical artery end-diastolic velocity (UA-EDV), umbilical artery peak systolic velocity (UA-PSV), umbilical artery mean diastolic velocity (UA-MDV) and umbilical artery time-averaged maximum velocity (UA-TAMXV). **Results:** A total of 569 cases were included in the study and divided into three groups: FGR group, SGA group and AGA group. Of these, 39 (6.9%) were identified as FGR, 57 (10.0%) were SGA and 473 (83.1%) were AGA. Among the three groups, the UA-MDV, UA-TAMXV, UA-PSV, and UA-EDV were decreased with the severity of growth restriction. Multivariate logistic regression analyses showed that the UA-TAMXV was independent predicting factor of FGR. It had a moderate predictive value for FGR, with an area under the ROC curve of 0.821 [95% confidence interval (CI): 0.785-0.853]. **Conclusions:** The UA velocities were decreased with the severity of growth restriction and the UA-TAMXV was independently predictive of FGR. The results suggest that UA-TAMXV might be a new parameter to predict FGR.

1.INTRODUCTION

FGR accounts for approximately 5%–10% of singleton pregnancies¹. This growth disorder is associated with an increased risk of APO and long-term impacts^{2 3}. At present, prenatal recognition of small size by ultrasound, which minimizes rates of APO to some extent, is the most commonly method for identifying intrauterine growth disorders. However, it still fails to detect more than 25% of late-onset FGR⁴⁻⁶. One possible reason for failure to identify late-onset FGR is that the ultrasound examination was done in the early third-trimester pregnancy^{6 7}.

The fetoplacental circulation is crucial for fetal development and growth. At present, the umbilical artery (UA) Doppler studies, including the umbilical pulsatility index (UA-PI) and the ratio of the systolic peak value and the end-diastolic velocity of the umbilical artery (UA-S/D), is the primary method for evaluating fetoplacental circulation. However, as reported by some published studies, placental insufficiency in late-onset FGR often goes undetected by UA Doppler scan^{8 9}, which brings a problem in assessing APO of those SGA infants. It is now widely acknowledged that large numbers of near-term SGA infants with normal UA Doppler studies are identified as late-onset FGR, which are at risk of APO¹⁰⁻¹².

It is widely known that the placental volume blood flow is reduced in FGR. The decrease of placental volume blood flow might even occur before the increase of UA-PI in the fetuses with growth restriction¹³.

One longitudinal study reported that the UA velocities can reflect placental blood flow and thus the fetoplacental circulation¹⁴. However, to the best of our knowledge, whether the UA velocities are decreased in FGR has not been determined.

Therefore, the main purpose of this study was to investigate the discordances of UA velocities in the FGR, SGA and AGA with normal UA Doppler at 37 weeks' gestation, and to investigate the value of UA velocities for predicting FGR. We hypothesized that the UA absolute velocities might be decreased with the severity of growth restriction, even in those with normal UA Doppler, which can contribute to an early prediction of FGR with normal UA Doppler.

2 MATERIALS AND METHODS

This was a retrospective study in the Fetal Medicine Center of the First Affiliated Hospital of Chongqing Medical University in Chongqing, China, between January 2017 and June 2020. As this was a retrospective analysis of routinely collected anonymized clinical data, the local Ethics Committee confirmed that no ethical approval from the patients was necessary in accordance with the national regulations.

SGA was defined as a customized birth weight between the 3rd and 10th centiles, and FGR was defined as a birth weight < 3rd centile¹⁵. Late-onset fetal growth restriction (FGR) is usually defined as that diagnosed >32 weeks of pregnancy. Adverse perinatal outcomes included emergency cesarean section for non-reassuring fetal status, 5-min Apgar score < 7 and neonatal acidosis at birth¹⁶. According to the ACOG guideline¹⁷, all of the SGA with normal umbilical artery Doppler included in our study were delivered at about 37 weeks of gestation. The gestational age (GA) was determined according to the last menstrual period, the first-trimester crown-rump length or the head circumference when the first ultrasound examination was performed after 14 weeks of gestation.

The inclusion criteria for three groups were as follows: (1) singleton gestation, (2) intact membranes, (3) absence of congenital or chromosomal abnormalities, (4) absence of pregnancy complications (i.e. hypertensive disorders, diabetes), (5) normal amniotic fluid, (6) the UA-PI within the normal range for GA, (7) SGA and FGR were delivered at 37 ± 2 weeks and (8) an ultrasound examination, including fetal biometry and UA velocities, was performed at 37 ± 2 weeks for all fetuses. The parameters of UA velocities included the umbilical artery end-diastolic velocity (UA-EDV), umbilical artery peak systolic velocity (UA-PSV), umbilical artery mean diastolic velocity (UA-MDV) and umbilical artery time-averaged maximum velocity (UA-TAMXV).

The normality of the data was determined by Kolmogorov-Smirnov test. Continuous variables were expressed as the means $\pm$ standard deviations or the Medians (interquartile ranges) as appropriate. Categorical variables were expressed as the numbers of cases. For multiple comparisons, one-way analysis of variance (ANOVA) was performed for continuous variables, and Pearson's chi-square test was performed for categorical variables. Logistic regression analysis was performed to identify the predictive factors of FGR. The predictive performance for FGR was determined by receiver-operating characteristics (ROC) curve analysis. $P < 0.05$ was considered to be statistically significant. All P values were two-sided, and P values of less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA) and MedCalc version 11.4.2 (MedCalc Software, Ostend, Belgium).

3 RESULTS

A total of 569 singleton pregnancies were enrolled in our study, in which 39 cases were FGR, 57 were SGA and 473 were normal singleton pregnancies. The maternal clinical and neonates characteristics among the three groups are presented in Table 1. The maternal height in SGA group is shortest among the three groups. The maternal height in SGA group was significantly shorter than that in the AGA group ($P < 0.001$), however, no significant differences were observed AGA group and FGR group or between FGR group and SGA group ($P > 0.05$). No significant differences in maternal age, gravida, parity and APO were observed among the three groups ($P > 0.05$).

The parameters of UA velocities among the three groups are presented in Table 2. The UA velocities param-

eters were decreased with the severity of growth restriction. The UA-TAMXV and UA-PSV were reduced successively in AGA, SGA and FGR (all $P < 0.05$). Multivariate logistic regression analysis suggested that the maternal height was predictive of SGA ($P = 0.001$) (Table 3). However, all of the UA velocities parameters were not independent predicting factors of SGA ($P > 0.05$). The UA-TAMXV was an independent predicting factor of FGR ($P = 0.029$) (Table 4). However, there was no significant correlation between maternal height and FGR ($P > 0.05$). As showed by the receiver operating characteristic (ROC) curves, the UA-TAMXV had moderate predictive value for FGR, with an area under the ROC curve of 0.821 [95% confidence interval (CI): 0.785-0.853], with sensitivity of 74.40% as well as specificity of 77.60%, respectively (Figure 1).

4.DISCUSSION

In this study, we mainly found that UA velocities were decreased with the severity of growth restriction and the UA-TAMXV was independent predicting factor of FGR. To our knowledge, this is the first study to assess associations between the UA velocities and growth disorders.

In this study, the absolute UA velocities is decreased with the severity of growth restriction, that's to say, it is decreased in SGA group and further decreased in FGR group when compared with AGA group at 37 weeks, suggesting that the absolute UA velocities was associated with the fetoplacental blood flow. As all of the fetuses enrolled in our study presented normal UA Doppler spectrums, our finding suggested that UA velocities, particularly UA-TAMXV and UA-PSV, might be more predictive of late-onset FGR and SGA than the conventional UA Doppler parameters, such as UA-PI and UA-S/D.

Previous studies have shown that abnormal fetal middle cerebral artery may occur in 20% of term SGA fetuses with normal UA Doppler results¹⁸⁻¹⁹. It has certain value for clinical management of FGR²⁰, however, its role in predicting FGR with normal UA Doppler spectrums remains unclear. As described in previous studies, the placental volume blood flow could also be assessed by the umbilical venous velocities²¹⁻²². However, the umbilical venous velocities were prone to errors and still need to be standardized²³. One longitudinal study demonstrated that the UA-TAMXV was best correlated with the umbilical vein volume blood flow¹⁴. Our study showed that UA-TAMXV was decreased in the FGR and was consistent with previous studies. In routine ultrasound examination, as the UA circulation Doppler has been generally used to assess the fetoplacental blood circulation, the UA velocities can be easier and quicker to acquire than the umbilical vein velocities. As we know, 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 this condition. Our findings suggested that the UA-TAMXV might be of predictive value for the FGR. Therefore, the UA-TAMXV might be a more preferred parameter for evaluating the placenta volume blood flow as well as the degree of fetal ischemia.

Previously studies reported that fetal growth disorders are associated with an increased risk of APOs²⁻³. Unfortunately, no obvious APOs were found in our study. The possible might be as follows. Firstly, this negative finding may be related to the small sample size. Furthermore, all of the fetuses in our study had normal UA Doppler spectrums, which indicates that the fetus was not seriously compromised. Lastly, the timing for delivering in SGA fetus is at 37 weeks or so rather than terminating the pregnancy until the fetus is severely damaged. A large study reported a significantly increased risk of fetal death in SGA delivered >37 weeks compared to those delivered at 37 weeks²⁴. Another study including 92,218 singletons found that the fetal death rates were lower in detected than those in undetected FGR². It follows then that the key to preventing APOs is detection of FGR and timely delivery. Nevertheless, further researches with more cases are required to observe the relationships among the UA velocities, FGR with advanced GA and APOs.

It was showed that the maternal height was significantly and inversely associated with risk of SGA²⁵. A previous reporting suggested that the maternal height was a stronger predictor of birth weight than ethnicity²⁶. Consistent with previous studies²⁵⁻²⁶, the maternal height of SGA was shortest among the three groups, and was independently predictive of SGA rather than FGR in our study. Conversely, the UA-TAMXV was independently predictive of FGR rather than the maternal height. We speculated that the maternal height was

more closely associated with SGA, whereas the UA-TAMXV was more closely related to FGR. Therefore, UA-TAMXV could figure out FGR from SGA when the women were at the same maternal height.

There are some limitations in our study. Firstly, most pregnancies with SGA and FGR were transferred from other hospitals, so it was not always possible to collect actual primary UA Doppler spectrums and serial data. Secondly, as this was a retrospective study, the retrospective design can lead to an inherent risk of selection bias. Lastly, because all of fetuses were delivered at about 37 weeks' gestation, the pregnancy outcome assessment could not be objectively assessed.

In conclusion, the UA velocities were decreased with the severity of growth restriction and the UA-TAMXV was independently predictive of FGR. The results suggested that the UA-TAMXV might be a new parameter to predict FGR, which might provide a theoretical basis for earlier prediction and better management FGR as well as distinguishing FGR from SGA. Moreover, it might help to determine the optimum time for surgical intervention as well as to select those pregnancies which are in need of close monitoring. However, further studies are needed to confirm these questions.

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None.

Conflicts of interest

The authors have no conflicts of interest.

Authors' contributions: Hong-Li Liu is first author and Hong-Bo Qi obtained the funding. Lan Zhang and Hong-Li Liu designed the study. Hong-Li Liu, Shuai Huang and Jun-Nan Li collected the data. Hong-Li Liu and Lan Zhang analyzed the data. Hong-Li Liu drafted the manuscript. Lan Zhang contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript. Lan Zhang is the study guarantor.

Ethics approval

This was a retrospective analysis of routinely collected anonymized clinical data, the local Ethics Committee confirmed that no ethical approval from the patients was necessary in accordance with the national regulations.

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