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Application of Doppler ultrasound and pregnancy-associated plasma protein A in fetal growth restriction prediction

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► ***Original article***

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ABSTRACT

Background*:** To investigate the role of pregnant-associatedplasma protein A (PAPP-A) and uterine artery Doppler ultrasound in predicting fetal growth restriction (FGR). ***Materials and Methods*:** In total, 120 pregnant women diagnosed with FGR in Shijiazhuang Obstetrics and Gynecology Hospital from January 2021 to December 2023 were selected as the FGR group, and 120 normal pregnant women were selected as the control group during the identical time frame. Maternal serum pregnancy-related protein A combined with uterine artery Doppler ultrasonography was performed during the period from the 11th, to the 13th+6 weeks of pregnancy. The course of pregnancy was observed in both groups of pregnant women. ***Results: The FGR group exhibited significantly reduced rates of vaginal delivery and fetal survival compared to the control group, while experiencing higher rates of preterm delivery and cesarean section, with statistical significance (P<0.001). The pulsatility index of the uterine artery (UtA-PI) and the resistance index of the uterine artery and the FGR group exhibited a higher proportion of early blood diastolic incisors compared to the normal group, with statistical significance noted at a level of P<0.001. The concentration of PAPP-A was lower than that of normal group (P<0.001). The sensitivity of combining UtA-PI and PAPP-A to predict FGR was 81.6%, and the sensitivity of combining UtA-PI and PAPP-A is 82.9%, which is 1.3% higher, but there was no statistically significant distinction between the two approaches (P>0.05). ***Conclusion:*** The implementation the combination between PAPP-A and Doppler ultrasound is an effective method to predict FGR.

INTRODUCTION

Fetal limitations on growth (FGR) is characterized by the fetus falling short of attaining its anticipated growth rate, also known as fetal malnutrition syndrome or placental dysfunction syndrome. FGR is mainly manifested by a full-term fetus with a birth mass below 2500g, or below the 10th percentile of normal body mass after the same gestational age, or below two standard deviations of the average body mass during the same gestational age [1, 2]. The incidence of FGR in China is about 6.39%, and it is one of the major complications in the perinatal period. It not only affects the growth and development of the fetus, but also may lead to the increase of morbidity and mortality of the perinatal fetus. It is an important cause of intrauterine death or neonatal death [3]. Therefore, it is a hot topic in the field of obstetrics to investigate how to predict the occurrence of FGR in the first trimester and effectively control the progression and complications of the disease [4].

At present, it is widely believed that the occurrence of FGR is primarily related to poor placental function [5]. With the advancement of healthcare imaging science education, the detection of uterine artery blood flow by color Doppler flow imaging (CDFI) can effectively reflect the hemodynamic changes of the uterus and placenta, which can be applied to evaluate the status of utero-placenta circulation. The evaluation is of great value in its clinical application [6-8]. Ultrasound detection of multivessel blood flow parameters can effectively monitor the intrauterine status of fetuses with FGR, which is helpful for intrauterine status monitoring and therapeutic interventions for fetuses with FGR [9].Uterine arterial blood flow pulsatility index (UtA-PI) of pregnant women with FGR is higher than that of normal pregnant women, and monitoring of the UtA-PI is helpful for the early detection and prevention of FGR, the improve perinatal survival and health [10]. Absence or reversal of end-diastolic flow in the umbilical artery may lead to a poor outcome in fetal growth restriction (FGR); in pregnant women with FGR who have normal umbilical artery flow, regular prenatal ultrasound should be performed to monitor fetal growth, amniotic fluid, and umbilical arteries [11]. By studying uterine artery spectra at 19-22 weeks of gestation, it has been found that an increase in uterine artery resistance parameters or the presence of diastolic cut -offs in the spectra is a significant risk factor for

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adverse outcomes in fetal growth restriction (FGR) [12]. At the same time, pregnant-associated plasma protein A(PAPP-A), as a serum marker, can be identified in the blood of pregnant women during early pregnancy, and the serum concentration increases with week of gestation, and is mainly used in clinical evaluation of placental function[13,14]. The early prediction of the development of FGR and the effective control of the disease process and complications have garnered significant attention within the realm of obstetrics research.

The aim of this investigation is to assess the clinical utility of utilizing both Doppler ultrasound of uterine arteries and Pregnancy-related plasma proteins A concentration in the first trimester of pregnancy (specifically from the 11^{th} to 13^{th}+6 weeks) for the prediction of inhibited fetal development. This study skillfully combines two techniques, Doppler ultrasound and PAPP-A, to provide a new perspective on the prediction of fetal growth restriction. Previously, most studies have focused on the application of only a single aspect of ultrasound or blood biomarkers, whereas the present study combines the two seamlessly, promising a more accurate prediction of the risk of fetal growth restriction. In addition to methodological innovations, the study is also a theoretical breakthrough. It may challenge or complement existing theories of fetal growth restriction prediction. Through the combined application of Doppler ultrasound and PAPP-A, researchers may reveal new biological mechanisms or pathways, leading to a deeper understanding of the etiology and pathophysiological processes of fetal growth restriction.

MATERIALS AND METHODS

Materials of study

The FGR group in this study were 120 pregnant women diagnosed with FGR in Shijiazhuang Obstetrics and Gynecology Hospital from January 2021 to December 2023. Besides, the control group of this study was composed of 120 normal pregnant women who came to this hospital for pregnancy examination during the same period. The key criteria to choose FGR group and control group are summarized as follows.

Meeting the relevant criteria in Expert Consensus on Fetal Growth Restriction (The edition of 2019) [15].
Risk of fetal malformation;
(3) The pregnancy is 11 to 13+6 weeks;
(4) Single pregnancy;
(5) Complete clinical data (exclusion criteria).

The pregnant women with the following features should not be included in the research samples in this study.
(1) Pregnant women with the diseases that can cause FGR, such as gestational hypertension, chronic hypertension, etc.
(2) Fetal death during pregnancy;
(3) The pregnant woman with mental dysfunction.
Approval has been granted for the study by the Medical Ethics Committee of the Fourth Hospital of Shijiazhuang (01.03.2021, Ethics No: 20210030), and all the patients have signed an informed consent form.

Methods

All pregnant women chosen as research samples in this study received maternal serum PAPP-A and uterine artery ultrasound Doppler examination during the gestation period from 11 to 13^{th+6} weeks.
1. Ultrasound examination
(1) Instrument: In this study, the key equipment is the GE VolusonE8 color Doppler ultrasonic diagnostic instrument (the brand name is Zhongyi Kanghui (Beijing) and the International Trading Code is Co. X150). The frequency of the abdominal probe is 1 ~ 5MHz.
(2) Detection via Uterine artery color Doppler blood flow: before the examination, the quiet test has to be done and to last for at least 5 minutes. Trans abdominal test was adopted. The subject was supine with a small amount of bladder filling. The cervix was first located and the image was locally enlarged. The probe was moved to one side of the uterine body and the cervical junction level to show Ascending branches of the uterine artery. The typical uterine artery blood flow waveform for 3 consecutive cardiac cycles was obtained. The measurements of uterine artery pulsatility index (UtA-PI) and uterine artery resistance index (UtA-RI) were recorded. Then, the probe was moved back to the cervix, the ascending branch of the contralateral uterine artery was found and measured. During the measurement, it was observed that the width of the pulse Doppler sampling gate was set to 2mm, and the Angle between the ultrasonic beam and the blood flow was less than 30°. More details are shown in figure 1.

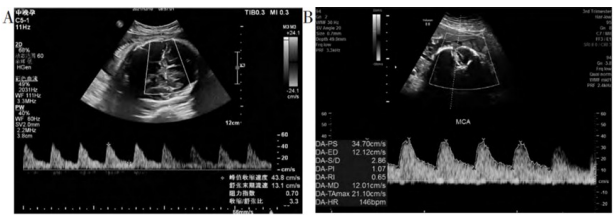

Figure 1. Schematic diagram of colour Doppler blood flow testing. A shows a normal fetus and B shows a FGR fetus.

Detection of PAPP-A

Quantitative enzyme-linked immunosorbent assay [16] was used, and the main experimental instruments were: Addcare ELISA 1100 fully automated enzyme immunoassay system, Beckman Coulter AU5821 fully automated biochemical analyzer. The main kits used were: PAPP-A test kit (CUSABIO, lot number: C0102110178), which was operated strictly

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according to the instruction of the kit.

Evaluation criteria

1. Calculation of ultrasonic parameters: the following information was recorded in this study, including the pregnancy-related information about medical history, uterine artery-related Doppler ultrasound measurement parameters (bilateral UtA-RI and UtA-PI, with or without early diastolic incisure) and PAPP-A concentration of each pregnant woman. The resistance index (RI) and the pulsatility index (PI) [RI=(S-D)/S; PI=2(S-D)/(S+D)] were calculated according to the peak systolic (S) and end-diastolic (D) values of arterial blood flow. Among the statistics above, the average value of UtA-RI and UtA-PI was taken from both sides, and the identification of an initial diastolic indentation on either side of the uterine artery was regarded as affirmative.
2. Follow-up: the pregnancy process and outcome of the enrolled pregnant women were followed up, and the gestational termination week and maternal and infant outcomes were recorded. The diagnostic criteria for fetal growth restriction was that the birth weight of a full-term fetus should be below 2500g, the 10th percentile of normal body mass at an equivalent stage of gestation, or the two standard deviations of the average body mass of the fetus at the same gestational age.

Statistical processing

SPSS 23.0 software package was applied for data analysis. The measurement data was expressed as mean±standard deviation, and the counting data were compared by χ^2test. The mean values of 3 or more samples was analyzed by means of ANOVA. P<0.05 was considered to be statistically significant.

RESULTS

General Information

Among the 120 patients in this explore, the pregnant women in the FGR group were 25-34 years old, with a mean age of (25.75±2.05) years. The body mass index (BMI) was 19.5-27.3kg/m^2, with an average age of (25.01±4.98) kg/m^2. The women comparison group who were pregnant ranged from 24 to 34 years old, with a mean age of (26.02±2.15) years, and the BMI was 19.4-28.6kg/m^2, with an average age of (25.68±5.02) kg/m^2. In comparison, the mean age did not exhibit a statistically significant difference (P>0.05), mean BMI, and number of deliveries of the two groups showed. However, the pregnant women in FGR group ended pregnancy earlier than those in normal group (P<0.01). The fetal birth weight within the FGR group demonstrated significantly lower compared to control (P<0.01), table 1.

Table 1. Comparison of general data between the two groups ($\bar{x}$ ±s).

Indicators	FGR Group (n=60)	Control Group (n=60)	*t*	*P-value*
Age /yrs	25.75±2.05	26.02±2.15	0.704	0.483
BMI/(kg·m^2)	25.01±4.98	25.68±5.02	0.734	0.464
Duration of termination of pregnancy /week	36.35±2.65	37.95±3.45	2.849	0.005
Number of births/ times	2.10±1.00	2.00±1.00	0.548	0.585
Fetal birth weight/kg	2.41±0.35	3.65±0.81	10.885	0.000

Notes: BMI: Body Mass Index; Statistical features were determined through a Student t-test, involving a comparison between the control group and FGR group.

Comparison of Doppler-measured parameters and PAPP-A concentrations

The mean values of UtA-PI and UtA-RI in FGR group were respectively 1.89±0.52, 0.79±0.12, and the percentage of early uterine artery diastolic incisor in FGR group was 61.67%, which were significantly higher than 1.70±0.45, 0.71±0.16 and 41.67% in control group (P<0.05). The concentration of PAPP-A (MoM) in FGR group was 0.82±0.11. This value was less than 1.25±0.67 in the control group. The disparity among the pair of factions reached statistical significance (P<0.01). More details were shown in table 2.

Table 2. Comparison between uterine artery doppler measurement parameters and PAPP-A concentration in the two groups.

Indicators	FGR group (n=60)	Control group (n=60)	t / χ^2	*P-value*
UtA-PI	1.89±0.52	1.70±0.45	2.140	0.034
UtA-RI	0.79±0.12	0.71±0.16	3.098	0.002
Early diastolic notch /(n,%)	37 (61.67%)	25 (41.67%)	4.038	0.044
PAPP-A(MoM)	0.82±0.11	1.25±0.67	4.906	0.000

Notes: FGR: fetal growth restriction; UtA-PI: uterine artery pulsatility index; UtA-RI: uterine artery resistance index; PAPP-A: pregnancy-associated plasma protein A; "Statistical characteristics" were calculated using the Student's t-test and χ^2 to facilitate comparisons between the control and FGR groups.

Comparison of AUC for each parameter to predict FGR

In our results, the AUC of UtA-PI and UtA-RI values were 0.748 and 0.714, respectively, and the predictive effect of UtA-PI values was significantly better than that of UtA-RI values (P<0.05). The sensitivity of FGR obtained by PAPP-A and combined with UtA-PI was 80.5%, and the sensitivity of FGR obtained by PAPP-A and combined with UtA-PI combined with early blood diastole notch was 82.6%. However, no substantial difference was observed among the pair of factions (P > 0.05). More details are shown in table 3.

Comparison between the pregnancy outcomes of the two groups

There were 16 preterm deliveries and 36

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cesarean deliveries in the FGR group, which were significantly higher than those in the control group, and the difference was statistically significant (P<0.05). In addition, there were 39 cases of normal delivery in the control group, which was significantly higher than that in the FGR group, and the difference was statistically significant (P<0.05). In the end, 59 fetuses survived in the control group and 52 fetuses survived in the FGR group, with a statistically significant difference (P<0.05), table 4.

Table 3. Comparison of AUC for each parameter predicted FGR.

Indicators	AUC (%)	Sensitivity (%)	Specificity (%)	*P value*					
				UtA-PI	PAPP-A	Early diastolic notch	UtA-PI+ early diastolic notch	PAPP-A+UtA-PI	PAPP-A+UtA-PI+ early diastolic notch
UtA-RI	71.4	70.1	68.2	0.0270	0.0140	0.0080	0.0070	0.0030	0.0020
UtA-PI	74.8	76.9	71.5		0.0160	0.0060	0.0580	0.0230	0.0010
PAPP-A	63.4	47.3	74.7			0.0370	0.0190	0.0010	0.0004
Early diastolic notch	57.1	31.1	80.6				0.0013	0.0011	0.0001
UtA-PI+ early diastolic notch	77.2	77.6	71.4					0.3050	0.0290
PAPP-A+UtA-PI	78.5	81.6	70.6						0.4750
PAPP-A+UtA-PI+ early diastolic notch	79.2	82.9	64.2						

Notes: BMI: Body Mass Index; Statistical features were determined through a Student t-test, involving a comparison between the control group and FGR group.

Table 4. Comparison of pregnancy outcomes between two groups [number of cases (%)].

Groups	Premature Birth	Natural birth	Cesarean section	Midwifery	Fetal survival
FGR group (n=60)	16 (26.67)	24 (40.00)	36 (60.00)	0 (0.00)	52 (86.67)
Control group (n=60)	2 (3.33)	39 (65.00)	19 (31.67)	2 (3.33)	59 (98.33)
χ^2	11.046	6.550	8.593	0.508	4.324
P-value	0.001	0.010	0.003	0.476	0.038

Notes: FGR means fetal growth restriction;"Statistical characteristics" were calculated using the χ2 to facilitate comparisons between the control and FGR groups.

DISCUSSION

FGR is a significant obstetric complication and a major cause of perinatal fetal death. Although clinical researchers consider placental insufficiency as the primary contributing factor, it is difficult to make precise pathogenesis of FGR. Additionally, FGR can be triggered by perinatal asphyxia, hypothermia, hypoglycemia, and other conditions that can impact long-term nervous system development. Recent studies have indicated that early pregnancy intake of low-dose aspirin effectively prevents and reduces the incidence of FGR [17]. However, it has been a hot topic in obstetric studies to identify early predictors of FGR to effectively manage fetal growth associated complications continues.

Owing to its safety and reliability, the detection of uterine artery by ultrasonic Doppler is of great value in clinic. In the past two decades, a large number of literature have been published on the prediction of FGR by uterine artery ultrasound in early and middle pregnancy, but the sensitivity and specificity in these studies is not the same. Despite of the large number of the researches in this area, high-risk groups are still not well prevented. Therefore, it is a crucial topic of obstetric studies to investigate the prediction of FGR at early stage so as to prevent FGR. With the popularization of one-stop screening services for Down syndrome in early pregnancy, it has become a convenient means of examination to detect uterine arteries by Doppler ultrasound during the period from 11th to 13^{th+6} week of gestation. Ultrasound Doppler provides objective information about the uterine artery blood flow of pregnant women. Besides, its shows quantitative information about the changes of placental blood flow dynamics. The data above enable doctors to objectively evaluate the blood circulation of pregnant women's uterus and placenta. Therefore, it is reliable and non-invasive to use ultrasound Doppler for clinical examination. Findings from this investigation revealed that the uterine artery Doppler blood resistance during the period from 11th to 13th+6 weeks of gestation in the FGR the observed levels in the experimental group surpassed those in the standard control group, while the uterine artery blood resistance in the normal pregnant group decreased with the increase of gestation week [18]. The result proves that the changes of uterine and placental hemodynamics in early gestation could be identified by ultrasonic Doppler blood flow monitoring of the artery supplying the uterus.

In our work, UtA-PI values were significantly better predictors than UtA-RI values due to the fact that PI values not only reflect total vascular resistance beyond the point of measurement, but also provide information on placental size and total placental vascular cross-section [19]. The sensitivity of screening for FGR using uterine artery early diastolic notch alone was only 31.1%, which may be attributed to the fact that the appearance of uterine artery early diastolic notch is related to vascular compliance, whereas UtA-PI is related to terminal vascular resistance, and abnormal uterine arterial flow in early

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pregnancy is mainly related to an increase in terminal vascular resistance [20]. In this study, we showed that the combined UtA-PI values and early diastolic cutoff of uterine arterial flow were more sensitive in predicting FGR than the prediction using UtA-PI values alone, but the difference in validity between the 2 groups was not statistically significant. It has been suggested that this is related to the inconsistency in the criteria for judging the presence of early diastolic cuttings in uterine artery flow detected by Doppler, and how to quantify this has been reported differently by various authors [21-23].

In addition, at present, uterine height and fetal body mass are used as indicators to predict the occurrence of FGR, but they are affected by many factors. Besides, there are errors in measurement, which affect the prediction effect. With the improvement of serum test technology, PAPP-A has been used in the screening program of Down syndrome. It is helpful for the diagnosis of fetal malformation, and is related to fetal growth. PAPP-A is a zinc-bound metalloproteinase, which is mainly secreted by placental syncytiotrophoblast in pregnant women and produced by corpus luteum in non-pregnant period. It can be detected from maternal serum in early pregnancy. The decrease of PAPP-A is associated with the increase of growth factor resembling insulin binding protein-4 and decreased levels of hormone similar to insulin in its growth-promoting effects Such changes affect fetal growth and development by controlling the absorption of glucose amino acids and the secretory and paracrine effects of trophoblastic infiltration. The results of this study suggest that low PAPP-A value is associated with adverse perinatal outcomes during the development of the placenta during pregnancy. The decrease of serum PAPP-A levels can be used as an indicator to predict the risk of FGR.

In one study, after excluding the differences in age and body mass index between the two groups of pregnant women, the birth weight of the newborn was positively correlated with maternal serum PAPP-A, and pregnant women in the FGR group had low PAPP-A concentrations. Since the decrease of PAPP-A level is related to the increase of hormone that mimics the effects of insulin binding protein 4 and the decrease of hormone that mimics the effects of insulin. The hormone that mimics the effects of insulin affects fetal growth and development by means of controlling the absorption of glucose amino acids and the secretory. The paracrine effects in the process of trophoblastic infiltration. PAPP-A is related to the onset of gestational diabetes mellitus, preeclampsia and FGR. Hence, it is easy to detect during pregnancy. If this indicator is abnormal, clinical intervention should be performed before the onset to improve pregnancy outcomes [24]. Therefore, in the prenatal screening stage of pregnant women, the influence of chromosome and fetal structure should be excluded. Besides, the changes of serum markers during pregnancy should be paid with more attention. In case of abnormal PAPP-A levels of pregnant women, it is necessary to make examinations of placental function in time to prevent from adverse pregnancy outcomes.However, some studies have also reported that reduced PAPP-A concentrations (below the 5th percentile) were found in only 8% to 33% of pregnant women who developed FGR. The data indicates that the serum PAPP-A concentration of pregnant women in early gestation cannot effectively predict FGR [25].

In this study, about 47.3% of FGR could be detected by serum PAPP-A concentration alone, while the detection rate became 82.9% after combining UtA-PI and early diastolic incisor. It is worth noting that the AUC and sensitivity of the combined prediction of serum PAPP-A, UtA-PI and early diastolic notch in pregnant women were higher (0.792, 82.9%) than the combined prediction of the first two indexes (0.785, 81.6%), however, there was no statistically noteworthy distinction between the outcomes of the two prediction methods. Although the combination of multiple indicators in early pregnancy can effectively improve the sensitivity of screening FGR, its clinical application is not as effective as that of quantitative indicators (UtA-PI, UtA-RI and maternal serum PAPP-A). An important reason is that the early diastolic notch of uterine artery Doppler blood flow is a qualitative indicator and there is no unified quantitative standard. Therefore, it is still necessary to investigate how to quantify the early diastolic notch of uterine artery Doppler blood flow uniformly.

CONCLUSION

The combination of maternal serum pregnancy-associated protein A, uterine artery Doppler ultrasonography, and flow-diastolic early tracing at 11^{th} to 13^{th}+6 weeks of gestation is the best method for predicting FGR. However, the qualitative indicator, uterine artery diastolic early tracing, was less clinically effective than the quantitative indicator.

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***Author Contributions*:** The study conception and design involved contributions from all authors. F.L., F.F.L., W.H.S., and H.Y.L. participated in material preparation, data collection, and analysis. The initial manuscript draft was penned by F.L. and F.F.L. All authors provided input on earlier manuscript versions, and their final approval was obtained after all authors read and reviewed the manuscript.

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