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Diagnostic value of prenatal ultrasound parameters combined with serum apolipoprotein C1 and lamin A levels in the detection of fetal cardiac structural abnormalities and chromosomal abnormalities

Dijagnostički značaj kombinacije parametara prenatalnog ultrazvučnog pregleda i nivoa apolipoproteina C1 i lamina A u serumu u otkrivanju anomalija strukture srca fetusa i hromozomskih abnormalnosti

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Abstract

Background/Aim. Early screening for fetal cardiac structural abnormality (CSA) is crucial for improving prenatal outcomes. The aim of the study was to evaluate the diagnostic value of prenatal ultrasound parameters, combined with serum apolipoprotein C1 (APOC1) and lamin A (LMNA) levels, for detecting fetal CSA and chromosomal abnormality (CA). **Methods.** The research included 146 pregnant women (PW) admitted from July 2022 to March 2024, who were divided into two groups. The study group comprised 86 PW with a fetal CSA diagnosis, while the control group consisted of 60 PW with normal fetal cardiac structures who underwent prenatal examination during the same period. **Results.** Patients in the study group had lower ventricular systolic velocity (S), ventricular diastolic velocity (D), atrial systolic velocity (A), maximum A-wave velocity (TA_{max}), and serum LMNA levels, alongside a higher pulsatility index (PI) and serum APOC1 levels compared to the control group ($p < 0.001$). Serum APOC1 levels were negatively correlated with S, D, A, and TA_{max} ($r < 0$, $p < 0.001$) but positively correlated with PI ($r > 0$, $p < 0.001$). Conversely, serum LMNA levels were positively correlated with S, D, A, and TA_{max} ($r > 0$, $p < 0.001$), and negatively correlated with PI ($r < 0$, $p < 0.001$). For the diagnosis of CA, the areas under the curve – AUCs for S, D, A, TA_{max}, PI, serum APOC1, and serum LMNA levels alone, as well as the combination of all indicators reached, were 0.750, 0.817, 0.823, 0.802, 0.835, 0.796, 0.831, and 0.911, respectively. **Conclusion.** In the serum of PW carrying a fetus with CSA and CA, APOC1 levels were elevated, whereas LMNA levels were reduced. Combining prenatal ultrasound parameters with serum APOC1 and LMNA levels yields a significantly higher diagnostic value, which could be used for the early screening of high-risk pregnancies.

Keywords:
apolipoproteins c; biomarkers; chromosome aberrations; diagnosis; heart defects, congenital; ultrasonography, prenatal.

Apstrakt

Uvod/Cilj. Rani skrining strukturnih anomalija srca (*cardiac structural abnormality* – CSA) fetusa od ključnog je značaja za poboljšanje prenatalnih ishoda. Cilj rada bio je da se proceni dijagnostički značaj prenatalnih ultrazvučnih parametara u kombinaciji sa serumskim nivoima apolipoproteina C1 (APOC1) i lamina A (LMNA) u detekciji CSA fetusa i hromozomskih abnormalnosti (*chromosomal abnormality* – CA). **Metode.** Istraživanjem je obuhvaćeno 146 trudnica, hospitalizovanih od jula 2022. do marta 2024. godine, podeljenih u dve grupe. Ispitivanu grupu činilo je 86 trudnica sa dijagnozom CSA fetusa, dok je kontrolnu grupu činilo 60 trudnica sa normalnom strukturom srca fetusa, kojima je urađen prenatalni pregled u istom periodu. **Rezultati.** Kod ispitanica u ispitivanoj grupi utvrđeni su niža sistolna brzina komora (S), dijastolna brzina komora (D), sistolna brzina pretkomora (A), maksimalna brzina A-talasa (TA_{max}) i nivo serumskog LMNA, kao i viši pulsatilni indeks (*pulsatility index* – PI) i nivo serumskog APOC1, u odnosu na ispitanice

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kontrolne grupe ($p < 0,001$). Utvrđena je negativna korelacija serumskog APOC1 sa S, D, A i TA_{max} ($r < 0, p < 0,001$), ali pozitivna korelacija sa PI ($r > 0, p < 0,001$). Nasuprot tome, nivoi serumskog LMNA bili su u pozitivnoj korelaciji sa S, D, A i TA_{max} ($r > 0, p < 0,001$) i u negativnoj korelaciji sa PI ($r < 0, p < 0,001$). Za dijagnozu CA, *areas under the curve* – AUCs za S, D, A, TA_{max}, PI, nivoe serumskog APOC1 i LMNA, pojedinačno, kao i kombinaciju svih pokazatelja, iznosile su 0,750, 0,817, 0,823, 0,802, 0,835, 0,796, 0,831 i 0,911, redom. **Zaključak.** U serumu trudnica sa CSA i CA fetusa, nivoi APOC1 su bili povišeni, dok su nivoi LMNA bili sniženi. Kombinacija parametara prenatalnog ultrazvučnog pregleda i serumskih nivoa APOC1 i LMNA imala je veću dijagnostičku vrednost, što bi moglo biti od koristi za rani skrining trudnoća sa visokim rizikom.

Ključne reči:
apolipoproteini c; biomarkeri; hromosomi, aberacije; dijagnoza; srce, kongenitalne mane; ultrasonografija, prenatalna.

Introduction

Cardiac structural abnormality (CSA), a common type of fetal malformation, mainly refers to an abnormal cardiac structure during fetal development in the uterus, and its diagnosis in early pregnancy and pathogenesis have always been the focus of research in the field of obstetrics and gynecology [1]. Fetal CSA produces no obvious subjective symptoms in the mother initially, and it is mostly detected during prenatal examination, which has become an important factor influencing pregnancy outcomes and causing neonatal death, seriously reducing the quality of birth [2]. Therefore, early screening for CSA during fetal development is crucial, and identifying effective screening modalities is of primary importance. With the recent continuous development of clinical medical technology, prenatal ultrasound (PUS) has become a common method for diagnosing fetal CSA. It has been reported that cardiac function is closely related to bloodstream changes, and fetuses with CSA often develop hemodynamic abnormalities [3]. Nevertheless, blood flow spectral parameters obtained from PUS examination may serve as useful screening indicators for fetal cardiac structural abnormalities [4]. In addition, maternal serum biomarker testing, which is minimally invasive and timely, may complement ultrasound-based prenatal screening [5].

At present, no specific biological indicators are available for the clinical diagnosis of fetal cardiac abnormality. In recent years, protein molecules have been highly valued in the study of pregnancy markers, which can be used in the screening for fetal structural abnormalities [6]. Serum apolipoprotein C1 (APOC1) and lamin A (LMNA) are common protein molecules that have been confirmed to be associated with congenital cardiac malformations [7]. APOC1 is involved in lipid transport and lipid metabolism, and abnormal maternal lipid metabolism may influence placental-fetal metabolic homeostasis and embryonic cardiovascular development [5]. *LMNA* encodes lamin A/C, a nuclear lamina protein involved in nuclear architecture, chromatin organization, gene-expression regulation, and cardiomyocyte differentiation. Therefore, APOC1 and LMNA were selected as candidate maternal serum biomarkers because they may reflect biological changes related to abnormal fetal cardiac development [8]. Fetal growth and development is a dynamic process generally under the influence of a variety of factors, and chromosomal abnormality (CA) is recognized as one of the risk factors for fetal cardiac malformations [9]. Following the diagnosis of fetal CSA, whether to terminate the pregnancy should be determined according to the specific etiology. Surgery can be performed after birth if simple CSA occurs, while termination of pregnancy is usually recommended if it is caused by CA [10]. Therefore, prenatal diagnosis of CA is also important. Nevertheless, the diagnostic value of PUS parameters, combined with serum APOC1 and LMNA levels, for fetal CSA and CA has been rarely reported.

Therefore, the diagnostic value of PUS parameters combined with serum APOC1 and LMNA levels for fetal CSA and CA was investigated in this study, aiming to guide the early screening of high-risk pregnancies.

Methods

Subjects

The study was approved by the Ethics Committee of the Tongxiang Second People's Hospital, Tongxiang, Zhejiang, China (from July 12, 2022). Written informed consent was obtained from all participants.

The study included a total of 146 pregnant women (PW) admitted to our hospital from July 2022 to March 2024, who were divided into two groups. The first group, selected as a study group (SG), consisted of 86 PW carrying a fetus with CSA, while the control group (CG), selected as a healthy group, included 60 PW with normal fetal cardiac structure and received prenatal examination during the same period. The sample size was based on the consecutive enrollment of all eligible PW during the study period.

Inclusion and exclusion criteria

The inclusion criteria were as follows: PW who had abnormal results in PUS examination in SG; those who had normal results in PUS examination in CG; those with singleton pregnancy; those with natural pregnancy; and those who voluntarily signed the informed consent form.

The exclusion criteria involved the following: PW with severe liver or kidney dysfunction; those with concurrent gestational diabetes; those with hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia, or pre-existing chronic hypertension; those with an abnormal mental state; those with a history of threatened abortion; those with coagulation dysfunction; or those who had a history of alcohol consumption or smoking.

Prenatal ultrasound examination

PUS examination was performed at 11–13 weeks of gestation, as described in the text that follows. PW were instructed to lie in a supine position, and routine examinations were performed to detect the fetal heart rate, fetal movement, and development status using an E8 color Doppler ultrasound diagnostic instrument (GE, USA) equipped with a convex array probe (applied with couplant, frequency: 2–5 MHz). It was determined whether the examination results were consistent with the conditions at the corresponding gestational age (GA). Then the section was adjusted during a fetal resting state: at the sagittal plane of the midline of the upper abdomen, the long axis of the umbilical vein was displayed and traced toward the fetal head, and the umbilical venous duct was identified and measured for its length. Then, color Doppler flow imaging was performed at the entrance of the catheter (volume: 1–2 mm, beam-flow angle $< 30^{\circ}$), and the blood flow spectrum of more than 5 consecutive fetal cardiac cycles (< 5 min) was obtained. Finally, the following parameters were measured: ventricular systolic velocity (S), ventricular diastolic velocity (D), atrial systolic velocity (A), maximum A-wave velocity (TA_{max}), and pulsatility index (PI). A-wave reversal or disappearance suggested CSA. Fetuses with suspected CSA at 11–13 weeks of gestation were referred for detailed fetal echocardiography (FECG) during the second trimester. The final diagnosis of fetal CSA was based on detailed FECG and follow-up assessment. The type of cardiac anomaly, GA at first suspicion, GA at confirmation, chromosomal results, and pregnancy outcomes were recorded.

Detection of serum levels of APOC1 and LMNA

Fasting venous blood (3 mL) was drawn and placed into a sterile anticoagulant tube, followed by centrifugation using a TDZ5-WS centrifuge (Xiangyi Centrifuge Instrument Co., Ltd., Changsha, Hunan, China) for 10 min (radius: 20 cm, 3,000 revolutions *per* minute – rpm). The supernatant was harvested to determine serum levels of APOC1 and LMNA by the enzyme-linked immunosorbent assay – ELISA using kits provided by MultiSciences (Lianke) Biotech Co., Ltd., Hangzhou, Zhejiang, China. The analytical ranges were 3.2–50,000 pg/mL for APOC1 and 15.6–1,000 pg/mL for LMNA. After conversion to the fmol/mL units used in the present study, these ranges were 0.48–7,561 fmol/mL and 0.22–14.3 fmol/mL, respectively. The healthy PW in this study were used as the internal reference population for APOC1 and LMNA.

Diagnosis and confirmation of fetal cardiac structural abnormality

Fetal CSA was initially suspected based on PUS findings at the end of the first trimester. All suspected women were referred for detailed FECG and were re-evaluated during the second trimester. The final diagnosis of fetal CSA was established only when the anomaly was confirmed by second-trimester FECG and/or postnatal echocardiography or pathological examination after termination of pregnancy. Cases without confirmatory examination or incomplete follow-up information were excluded from the final analysis.

Chromosomal abnormality detection

PW in SG underwent genetic counseling after fetal CSA was suspected by PUS. Amniocentesis was performed during the second trimester to obtain fetal cells for chromosomal analysis. Chromosomal karyotyping was performed to determine the presence or absence of CA. The results of chromosomal karyotyping were used as the reference standard, and SG was further divided into two subgroups: the CA group and the chromosomally normal group.

Collection of clinical data

Age, GA, primipara/multipara, body mass index (BMI), PUS parameters (S, D, A, TA_{max}, and PI), and serum levels of APOC1 and LMNA were recorded and compared between the CA and chromosomally normal groups.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software. Measurement data were expressed as mean ± standard deviation (SD) and analyzed using the independent-samples *t*-test. Count data were represented as numbers (percentages) and compared using the χ^2 test. Bivariate Pearson correlation analysis was conducted to evaluate the correlations between serum APOC1 and LMNA levels and PUS parameters. Receiver operating characteristic (ROC) curves were plotted to analyze the diagnostic value of PUS parameters combined with serum APOC1 and LMNA levels for fetal CSA and CA. A value of $p < 0.05$ was considered statistically significant.

Results

In SG, PW were aged 25–34 years, with an average of 28.56 ± 2.34 years. The GA ranged from 11 to 13 weeks, with an average of 12.02 ± 0.25 weeks. There were 56 primiparas and 30 multiparas. The BMI was 22–27 kg/m^2, with an average of 23.48 ± 1.14 kg/m^2. In CG, PW were aged 26–34 years, with an average of 28.74 ± 2.41 years. GA ranged from 11 to 13 weeks, with an average of 12.00 ± 0.24 weeks. There were 41 primiparas and 19 multiparas. The BMI was 22–27 kg/m^2, with an average of 23.53 ± 1.20 kg/m^2. The general data were well balanced between the two groups ($p > 0.05$).

Characteristics of diagnosed fetal cardiac structural abnormalities

Among the 86 fetuses with CSA, the initial suspicion was made based on PUS findings at a mean GA of 12.04 ± 0.43 weeks. All cases were subsequently re-evaluated and

confirmed by detailed FECG during the second trimester at a mean GA of 21.36 ± 2.18 weeks. The diagnosed fetal cardiac anomalies included ventricular septal defect in 22 cases, atrial septal defect in 8 cases, atrioventricular septal defect in 10, tetralogy of Fallot in 9, double outlet right ventricle in 7, transposition of the great arteries in 6, hypoplastic left heart syndrome in 5, pulmonary stenosis or pulmonary atresia in 6, aortic stenosis, coarctation of the aorta, or interrupted aortic arch in 5 cases, and single ventricle or complex congenital heart disease in 8 cases.

CA were detected in 26 fetuses, whereas 60 fetuses had normal chromosomal findings. CA included trisomy 21 in 10 cases, trisomy 18 in 6, trisomy 13 in 3, Turner syndrome in 2, and other CA in 5 cases. Regarding pregnancy outcomes, 49 pregnancies continued to live birth, 31 pregnancies were terminated after multidisciplinary counseling, 3 cases resulted in intrauterine fetal death, and 3 were lost to follow-up.

Prenatal ultrasound parameters and serum APOC1 and LMNA levels in study and control groups

PW in SG had lower S, D, A, TA_{max} values and serum LMNA levels, and higher PI values and serum APOC1 levels than patients in CG ($p < 0.001$) (Table 1).

Correlations of serum APOC1 and LMNA levels with prenatal ultrasound parameters

The results of Pearson correlation analysis showed that APOC1 levels were negatively correlated with S, D, A, and TA_{max} ($r < 0$, $p < 0.001$) but positively correlated with PI ($r > 0$, $p < 0.001$). Serum LMNA levels were positively correlated with S, D, A, and TA_{max} ($r > 0$, $p < 0.001$), and negatively correlated with PI ($r < 0$, $p < 0.001$) (Table 2).

Diagnostic value of prenatal ultrasound parameters combined with serum APOC1 and LMNA levels for fetal cardiac structural abnormality

ROC curves were plotted with the presence or absence of fetal CSA as a state variable (abnormal/normal = 1/0) and S, D, A, TA_{max}, PI, and serum APOC1 and LMNA levels as test variables.

ROC curve and its areas under the curve (AUCs) values for S, D, A, TA_{max}, PI, serum APOC1 levels, and serum LMNA levels alone and the combination of all indicators were 0.812, 0.798, 0.685, 0.846, 0.781, 0.784, 0.811, and 0.915, respectively, for the diagnosis of fetal CSA (Table 3 and Figure 1).

Table 1

Prenatal ultrasound parameters values and serum levels of APOC1 and LMNA in the study and control groups

Group	S	D	A	TA_{max}	PI	APOC1	LMNA
Study (n = 86)	30.25 ± 1.99	22.35 ± 4.05	7.01 ± 2.53	18.76 ± 3.61	1.73 ± 0.75	32.25 ± 10.36	0.16 ± 0.07
Control (n = 60)	34.25 ± 2.18	27.56 ± 4.72	8.63 ± 1.82	26.15 ± 4.88	1.05 ± 0.46	21.56 ± 9.68	0.29 ± 0.14
t-test	11.488	7.142	4.250	10.517	6.247	6.300	4.879
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

APOC1 – apolipoprotein C1; LMNA – lamin A; S – ventricular systolic velocity; D – ventricular diastolic velocity; A – atrial systolic velocity; TA_{max} – maximum A-wave velocity; PI – pulsatility index; n – number.
All values are given as mean ± standard deviation.
Values are expressed as cm/s for S, D, A, and TA_{max}, and as fmol/mL for APOC1 and LMNA.

Table 2

Correlations of serum APOC1 and LMNA levels with prenatal ultrasound parameters

Variable	S	D	A	TA_{max}	PI
APOC1					
r	-0.512	-0.502	-0.613	-0.571	0.555
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
LMNA					
r	0.519	0.610	0.612	0.615	-0.542
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

For abbreviations, see Table 1.

Table 3

Diagnostic value of prenatal ultrasound parameters combined with serum APOC1 and LMNA levels for fetal cardiac structural abnormality

Index	AUC	SE	Cut-off	95% CI	*p*-value
S	0.812	0.035	31.856	0.743–0.881	< 0.001
D	0.798	0.038	24.361	0.724–0.872	< 0.001
A	0.685	0.043	7.356	0.600–0.770	< 0.001
TA_{max}	0.846	0.032	20.458	0.783–0.909	< 0.001
PI	0.781	0.037	1.426	0.708–0.854	< 0.001
APOC1	0.784	0.039	28.561	0.706–0.861	< 0.001
LMNA	0.811	0.041	0.261	0.730–0.891	< 0.001
Combination	0.915	0.027	-	0.862–0.968	< 0.001

AUC – area under the curve; SE – standard error; CI – confidence interval.
For other abbreviations, see Table 1.

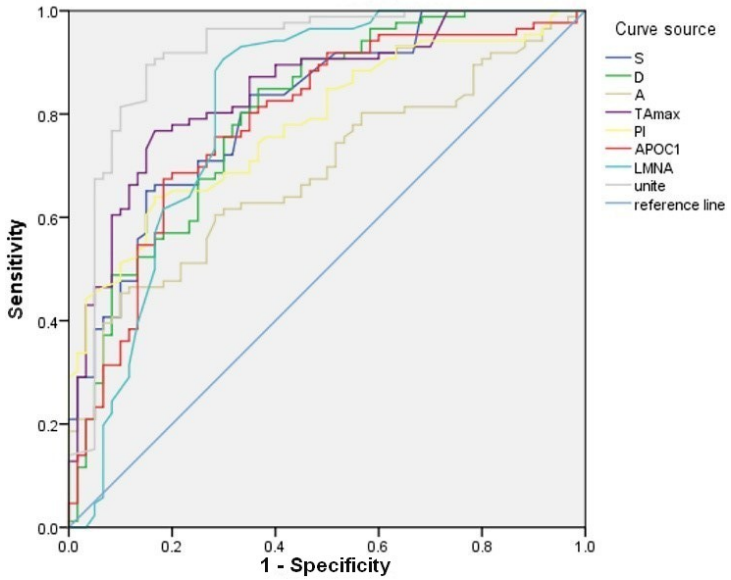

Fig. 1 – Receiver operating characteristic (ROC) curves of prenatal ultrasound parameters combined with serum APOC1 and LMNA levels for the diagnosis of fetal cardiac structural abnormality. For other abbreviations, see Table 1.

Table 4

Prenatal ultrasound parameters values and serum levels of APOC1 and LMNA among CG, chromosomally normal fetuses with CSA, and chromosomally abnormal fetuses with CSA

Variable	CG (n = 60)	Fetuses with CSA		*F*	Overall *p*-value	*Post-hoc* comparison
		chromosomally normal (n = 60)	chromosomally abnormal (n = 26)			
S	34.25 ± 2.18	33.26 ± 5.13	28.56 ± 3.85	19.667	< 0.001	abnormal < healthy and normal
D	27.56 ± 4.72	24.13 ± 3.02	20.42 ± 2.16	35.652	< 0.001	normal < healthy; abnormal < normal < healthy
A	8.63 ± 1.82	7.80 ± 1.20	6.21 ± 0.75	25.879	< 0.001	normal < healthy; abnormal < normal < healthy
TA_{max}	26.15 ± 4.88	21.26 ± 2.69	17.30 ± 2.51	57.288	< 0.001	normal < healthy; abnormal < normal < healthy
PI	1.05 ± 0.46	1.50 ± 0.27	1.85 ± 0.24	51.551	< 0.001	normal > healthy; abnormal > normal > healthy
APOC1	21.56 ± 9.68	28.26 ± 1.80	35.69 ± 2.74	46.358	< 0.001	normal > healthy; abnormal > normal > healthy
LMNA	0.29 ± 0.14	0.24 ± 0.06	0.14 ± 0.07	19.605	< 0.001	normal < healthy; abnormal < normal < healthy

CG – control group; CSA – cardiac structural abnormality; n – number. For other abbreviations, see Table 1.
All values are given as mean ± standard deviation.
Values are expressed as cm/s for S, D, A, and TA_{max}, and as fmol/mL for APOC1 and LMNA.

Prenatal ultrasound parameters and serum APOC1 and LMNA levels among the control group, chromosomally normal fetuses with cardiac abnormality, and chromosomally abnormal fetuses with cardiac abnormality

To further evaluate the diagnostic value of PUS parameters and serum APOC1 and LMNA levels in different fetal subgroups, SG was divided into chromosomally normal and CA fetuses with ultrasonographically detected CSA, and both subgroups were compared with CG. As shown in Table 4, there were significant overall differences among the three groups in S, D, A, TA_{max}, PI, serum APOC1 levels, and serum LMNA levels ($p < 0.001$). Compared with CG, chromosomally normal fetuses with CSA showed lower D, A, TA_{max}, and LMNA levels, and higher PI and APOC1 levels. Chromosomally abnormal fetuses with CSA showed more marked changes, including lower S, D, A, TA_{max}, and LMNA levels and higher PI and APOC1 levels than the other two groups. Overall, these findings suggest a stepwise alteration in fetal cardiac hemodynamic parameters and maternal se-rum biomarkers, progressing from healthy controls to chromosomally normal fetuses with CSA, and further to those with both CSA and CA (Table 4).

Diagnostic value of prenatal ultrasound parameters combined with serum APOC1 and LMNA levels for identifying chromosomal abnormality among fetuses with cardiac structural abnormality

ROC curves were further constructed to evaluate the ability of PUS parameters and serum APOC1 and LMNA levels to identify CA among fetuses with ultrasonographically detected CSA. As shown in Table 5 and Figure 2, the AUCs of S, D, A, TA_{max}, PI, APOC1, and LMNA were 0.750, 0.817, 0.823, 0.802, 0.835, 0.796, and 0.831, respectively. The combined model achieved the highest diagnostic performance, with an AUC of 0.911, indicating that the combined assessment may help further stratify the risk of CA in fetuses with CSA.

Discussion

With the continuous improvement of ultrasound technology, ultrasound, characterized by non-invasiveness, simple operation, and repeatability, has been widely employed in prenatal examination, which is safer than invasive examination and thus favored by PW. PUS examination can observe fetal development from multiple directions and sections, and take advantage of color Doppler blood flow imaging technology to visually display the distribution of blood flow in the heart and vessels [11, 12]. S, D, A, TA_{max}, and PI are common parameters of PUS, and cardiac condition can be reflected by measuring blood flow velocity of the umbilical venous duct [4]. Under normal physiological conditions, ductus venosus S-wave, D-wave,

Table 5

Diagnostic value of prenatal ultrasound parameters combined with serum APOC1 and LMNA levels for identifying chromosomal abnormalities among fetuses with CSA

Index	AUC	SE	Cut-off	95% CI	*p*-value
S	0.750	0.054	29.689	0.644–0.856	< 0.001
D	0.817	0.046	30.157	0.727–0.907	< 0.001
A	0.823	0.045	22.148	0.736–0.911	< 0.001
TA_{max}	0.802	0.048	19.057	0.707–0.896	< 0.001
PI	0.835	0.046	1.680	0.746–0.924	< 0.001
APOC1	0.796	0.062	31.172	0.675–0.917	< 0.001
LMNA	0.831	0.048	0.175	0.737–0.925	< 0.001
Combination	0.911	0.031	-	0.850–0.972	< 0.001

CSA – cardiac structural abnormality; AUC – area under the curve; SE – standard error; CI – confidence interval.
For other abbreviations, see Table 1.
Values are expressed as cm/s for S, D, A, and TA_{max}, and as fmol/mL for APOC1 and LMNA.

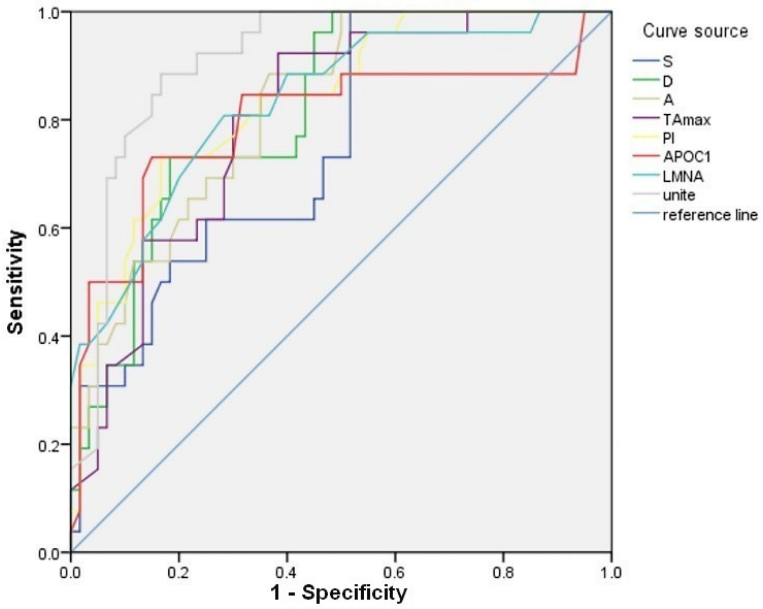

Fig. 2 – Receiver operating characteristic (ROC) curves of prenatal ultrasound parameters combined with serum APOC1 and LMNA levels for diagnosis of chromosomal abnormality.
For other abbreviations, see Table 1.

A-wave, and TA_{max} values show GA-related changes at 11–13+6 weeks of gestation. In contrast, PI for veins remains relatively stable during this gestational period [13]. In case of fetal CSA, the normal physiological needs cannot be met, resulting in hemodynamic abnormality and increased cardiac load [14]. Brickmann et al. [15] found that abnormal blood flow parameters of the umbilical venous duct were important indicators of fetal cardiovascular abnormalities, and that these parameters were most susceptible to right atrial structural abnormality. Chimoriya et al. [16] believe that fetal CSA would lead to changes in blood flow of the umbilical venous duct, mainly manifested as reduced blood flow velocity, and A-wave reversal or decline. In this study, S, D, A, and TA_{max} were lower, while PI was higher in SG than in CG, suggesting that PUS parameters are expected to be effective indicators for diagnosing fetal CSA. Because fetal cardiac anomalies are difficult to classify definitively by the end of the first trimester, the 11–13-week ultrasound findings in this study were considered screening results, and suspected cases were further confirmed by detailed FECG in the second trimester.

Peripheral blood screening for pregnancy-related markers is also an ideal method for prenatal examination. Proteomics can quantitatively analyze the expression of disease-related protein molecules, thereby guiding disease diagnosis and targeted therapy [17]. APOC1, an important apolipoprotein in plasma, can be implicated in plasma lipid transport. Increased APOC1 levels may reflect altered maternal-fetal lipid metabolism and inflammatory status, which may influence placental function and fetal cardiovascular development [5]. In the present study, APOC1 was negatively correlated with S, D, A, and TA_{max}, but positively correlated with PI, suggesting that increased APOC1 may be associated with impaired fetal hemodynamics. Research suggests that high serum APOC1 levels increase the risk of coronary heart disease and are closely associated with heart disease [18, 19]. It is inferred that serum APOC1 levels probably have a certain correlation with fetal CSA. In this study, serum APOC1 levels were higher in SG than in CG, indicating that serum APOC1 levels are elevated in PW carrying a fetus with CSA. However, its specific mechanism of action remains to be further verified. The results of Pearson correlation analysis showed that serum APOC1 levels were negatively correlated with S, D, A, and TA_{max}, but positively correlated with PI in PW carrying a fetus with CSA, demonstrating its association with fetal cardiac structure.

As a nucleoskeleton protein, LMNA plays an important role in the morphological development of the nuclear membrane. Its expression is induced during the differentiation of embryonic stem cells into neural cells and cardiomyocytes, thereby facilitating cardiomyocyte development and contributing to the pathogenesis of multiple cardiovascular diseases [20]. According to the results of this study, serum LMNA levels were lower in SG than in CG, suggesting that PW carrying a fetus with CSA exhibit decreased serum LMNA levels. LMNA is involved in nuclear lamina stability, chromatin organization, and cardiomyocyte differentiation. Decreased LMNA expression may disturb embryonic cardiovascular cell differentiation and normal cardiac morphogenesis [8, 21]. It is inferred that fetal CSA may be attributed to a structural disorder of the nuclear fiber layer induced by decreased LMNA expression, thereby inhibiting embryonic stem cell differentiation [8]. In addition, it was found that serum LMNA levels were positively correlated with S, D, A, and TA_{max}, and negatively correlated with PI, implying that serum LMNA levels are also closely linked to fetal CSA and involved with serum APOC1 in the process of cardiac structural changes. To further evaluate the diagnostic value of PUS parameters combined with serum APOC1 and LMNA levels for fetal CSA, ROC curve analysis was performed. For the diagnosis of fetal CSA, the results revealed that the AUCs for S, D, A, TA_{max}, PI, serum APOC1 levels, and serum LMNA levels, both alone and in combination, were 0.812, 0.798, 0.685, 0.846, 0.781, 0.784, 0.811, and 0.915, respectively. These findings further confirmed the high value of PUS parameters, combined with serum APOC1 and LMNA levels, in the diagnosis of fetal CSA.

In addition, chromosomes are an important player in fetal organ and functional development. CA can also lead to fetal cardiac developmental delay, also manifested as A-wave reversal or disappearance [22]. Following the diagnosis of fetal CSA, non-invasive deoxyribonucleic acid (DNA) or amniocentesis is often recommended to identify the etiology and the presence or absence of CA. However, non-invasive DNA testing is expensive, and amniocentesis is invasive and carries certain risks, so their widespread adoption and use as routine examinations are limited. In case of fetal CSA caused by CA, it is often necessary to terminate pregnancy by induction of labor to reduce the risk of neonatal malformations [23]. Therefore, it is particularly important to seek an effective screening method for CA. As revealed in this study, lowered S, D, A, TA_{max}, and serum LMNA levels, along with elevated PI and serum APOC1 levels, were detected in the abnormal group compared with those in the normal group, indicating that both PUS parameters and serum APOC1 and LMNA levels can serve as screening indicators for CA. Furthermore, AUCs of 0.750, 0.817, 0.823, 0.802, 0.835, 0.796, 0.831, and 0.911 corresponding to S, D, A, TA_{max}, PI, serum APOC1, and serum LMNA levels alone and the combination of all indicators were obtained for the diagnosis of CA. It can be seen that combining PUS parameters with serum APOC1 and LMNA levels yields a higher diagnostic value for CA.

Limitations of the study

This study has several limitations. First, this was a single-center observational study, and the sample size was based on consecutive enrollment rather than a prospective *a priori* sample-size calculation. Second, the diagnostic model requires further validation in larger multicenter cohorts.

Conclusion

Apolipoprotein C1 levels were high, and lamin A levels were low in pregnant women with fetal cardiac structural and chromosomal abnormalities, which were closely associated with prenatal ultrasound parameters. The combined assessment of these parameters exhibits a higher diagnostic value, making it a promising tool for the early screening of high-risk pregnancies.

Conflicts of interest

The authors declare no conflict of interest.

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