Original Article

The value of outflow tract flow tracing in early pregnancy in the screening of structural malformations of fetal cardiac great arteries

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Background: To explore the application value of outflow tract " ϐ " blood flow in screening fetal cardiac macrovascular structural malformations in early pregnancy.

Methods: A total of 3,356 pregnant women who underwent nuchal translucency (NT) screening during early pregnancy in the prenatal diagnosis center of General Hospital of Ningxia Medical University from January 2017 to December 2018 were taken as the research objects, and the fetuses were systematically screened by ultrasound. The display of four chamber cardiac blood flow, X-shaped blood flow of main pulmonary artery, V-shaped blood flow of three vessel trachea and " ϐ " shaped blood flow of outflow tract were observed and recorded. Fetal autopsy was performed after informed consent of those who terminated pregnancy. Follow up of fetuses and physical examination of newborns.

Results: A total of 3,356 cases underwent NT examination in early pregnancy, with an average age of 29.18±4.55 years and crown-rump length (CRL) (6.62±0.89 cm). A total of 66 cases of congenital heart disease (CHD) were detected, and the detection rate was 1.97%. There were 15 cases of conus trunk malformation, accounting for 22.7% of the total incidence of CHD. The sensitivity and the receiver operating characteristic (ROC) curve area (AUC =0.659) of " ϐ " blood flow of outflow tract in early pregnancy were higher than those of "X" Cross blood flow of main pulmonary artery and "V" blood flow of three vessel trachea.

Conclusions: " ϐ " Doppler superimposed blood flow in the outflow tract has high sensitivity in the screening of fetal cardiac macrovascular malformations, and has good predictive value for CHD. It can be used as a standard to evaluate whether fetal heart is accompanied by conus trunk malformation.

Keywords: Early pregnancy; congenital heart disease (CHD); conus trunk; " ϐ " shaped blood flow

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Introduction

Congenital heart disease (CHD) is the most common congenital defect, accounting for about 20% of all stillbirths and 30% of neonatal deaths caused by congenital defects (1). CHD is caused by genetic factors, environmental factors alone or both, of which 75–90% are caused by genetic and environmental factors (2). Fetal echocardiography is the only effective and noninvasive method to detect fetal heart structure, the function and hemodynamics. It can diagnose most abnormal heart structures during mid pregnancy

(18–24 weeks). However, how to improve the detection rate of CHD earlier is still an urgent problem to be solved (3).

Cardiac screening usually includes anatomical morphology and hemodynamics. Fetal four chamber view (4CV) is an important part of routine obstetric ultrasound structure screening (4), and it is also the common methods for screening CHD (5,6). On this section, CHD with abnormal cardiac axis, ventricular septal defect (VSD) in inflow tract and muscle, fatal single ventricle, atrioventricular septal defect (AVSD), ectopic pulmonary venous drainage (EPVD) and other CHD can be found. However, CHD with abnormal origin of conus muscle has low sensitivity (7-10), such as tetralogy of Fallot (TOF), double outlet right ventricle (DORV), transposition of great artery (TGA) and other complex CHDs, which need to be in left and right ventricular outflow tract and three vessel trachea (3VVT) isoarterial extension section screening. Although the fetal heart structure has begun to take shape after the 10th week of pregnancy (11,12), due to its small morphological structure and the development of cardiac malformation, the prenatal diagnosis rate of CHD before 11^{+6} weeks of pregnancy is still low (13).

The filling display of small blood vessel blood flow pattern in early pregnancy by color and power Doppler can make up for the deficiency of two-dimensional gray-scale imaging. Observing the shape of blood flow in and out of the heart through real-time and playback function is very important to improve the detection rate of four cardiac cavity structural abnormalities and conus trunk malformation. It has been reported that color and power Doppler display of three vessel trachea “V” shape and left and right ventricular outflow tract “X” sign can improve the detection rate of CHD in early pregnancy (14-16). Doppler can trace the shape of blood flow in the lumen in real time. The four-chamber view cardiac blood flow is in the same direction “II” shape. In the presence of large VSD, it shows the “H” shape blood flow pattern; Simulate and track the spatial blood flow direction mode of the main and pulmonary arteries. The aorta and pulmonary arteries originate from the left and right ventricular outflow tract behind the ventricle in the shape of “S” and “arc” respectively. After the upper and lower “X” cross walk, they converge in the left side of the descending aorta and trachea in the shape of “V” acute angle, and the blood flow trajectories can be traced in the shape of “ ზ ” (*Figure 1A*). The “ ზ ” Doppler flow diagram after image superposition can be obtained by slightly tilting to the right shoulder of the head end on the level of the four chamber cardiac section, It is a complete description of the blood flow trajectory of the “V” shape confluence at the three blood vessels and trachea after the blood flow passes through the “X” intersection of the left and right ventricular outflow tract (*Figure 1B*). The “ ზ ” blood flow image is easy to obtain in the apical or parasternal four chamber heart, and is easy to recognize. In CHD with abnormal outflow tract, this kind of cross collection relationship is usually in the shape of “⊃”, and the flood flow image of “ ზ ” cannot be displayed normally.

The heart of the fetus during early pregnancy is small size, and the trajectory of the blood flow out of the channel can be displayed on the same level. As the pregnancy week increases, the heart volume is more and more big, the complete flow-out blood flow is difficult to display on the same horizontal surface, but we can be obtained through spatial and temporal image correlation (STIC) (*Figure 1C*). Therefore, it is easier to obtain images of the flow of blood during early pregnancy than during mid-pregnancy (*Figure 1D*).

This study intends to use transabdominal or combined transvaginal ultrasonography in the early pregnancy to study the application value of “ ზ ” shaped blood flow and other observation indexes in evaluating the detection of fetal cardiac structural malformations in early pregnancy through systematic screening.

We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/atm-21-6475).

Methods

Research object

Subjects 3,356 pregnant women (singleton or twin pregnancy) who underwent fetal NT examination in early pregnancy [$11–13^{+6}$ weeks of pregnancy, crown-rump length (CRL) 45–84 mm] and/or grade II or III structural screening in early middle pregnancy (16–18 weeks of pregnancy) were collected. Operators who measure NT need to obtain British Fetal Medicine Foundation (FMF) qualification certification and receive standardized prenatal screening training. The study is related with the project supported by the Research Fund of Ningxia Medical University, and the project number is XM2019086.

Exclusion criteria

Pregnant women were excluded based on the following

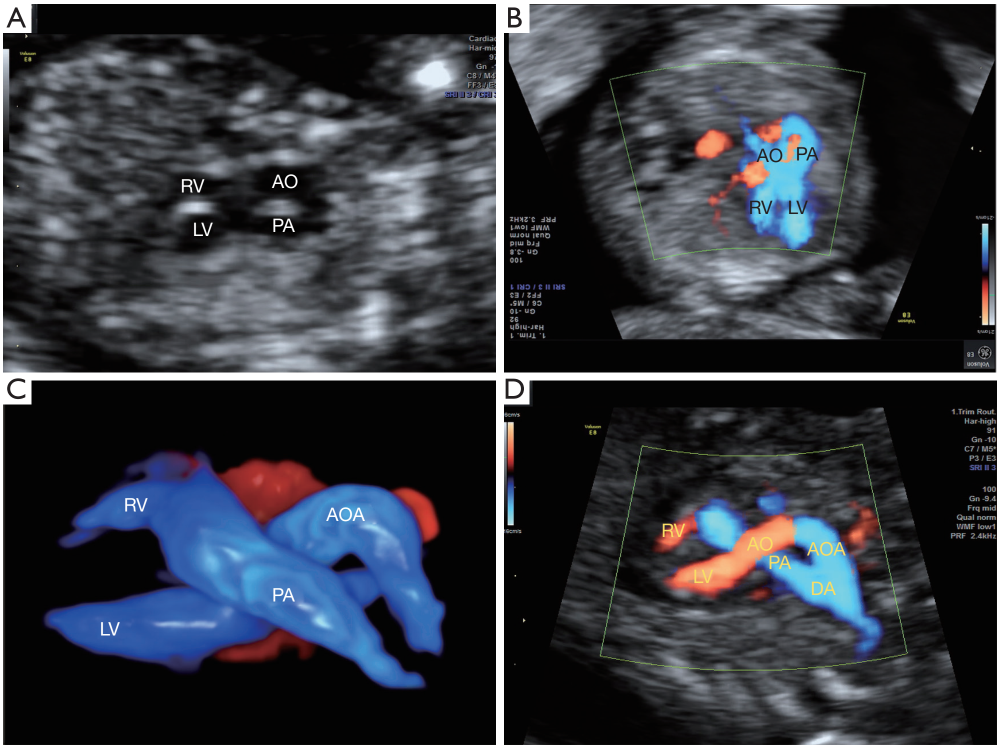

Figure 1 “ ɓ ” blood outflow. (A) Doppler “ ɓ ” shape blood outflow of figure by transabdominal, 12^{+4} weeks; (B) Doppler “ ɓ ” shape blood outflow of figure by transvaginal, 12 weeks; (C) Doppler “ ɓ ” shape blood outflow of figure by STIC, 22 weeks; (D) Doppler “ ɓ ” shape blood outflow of figure by Transvaginal, 14^{+5} weeks. STIC, spatial and temporal image correlation; PA, pulmonary artery; RV, right ventricle; LV, left ventricle; AO, aorta; AAO, ascending aorta.

criteria: (I) those with adverse pregnancy outcomes such as miscarriage or fetal death during pregnancy; (II) those with severe malformations, such as anencephaly and headless noncardiac sequence syndrome, unable to measure CRL; and (III) those who unable to perform cardiac examination. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ningxia Medical University General Hospital scientific research Ethics Committee and informed consent was taken from all the mothers.

Instrument method

The inspection instrument adopts Voluson E8 (GE Healthcare, Zipf, Austria), equipped with transabdominal and three-dimensional volume probes. It has the functions of local amplification, tissue harmonic, movie playback and dynamic storage. The power is less than 100 MW/cm^2. It can automatically optimize the image to achieve the best imaging. The frequency of transabdominal linear array probe is 2–8 MHz, that of transvaginal linear array probe is 4–9 MHz and that of abdominal volume probe is 4–8 MHz.

Transabdominal ultrasound screening was performed on fetuses undergoing NT examination in early pregnancy. If the image quality is poor or suspected to be abnormal due to too small head and hip, posterior uterus, obese pregnant women and other factors, transabdominal combined transvaginal ultrasonography shall be performed with the informed consent of pregnant women. Four chamber Doppler flow, X-shaped flow of aorta and pulmonary artery, V-shaped flow of three vessel trachea and “ ɓ ” shaped flow Doppler of outflow tract were observed and displayed at 11–14 weeks. The sensitivity, specificity, positive predictive value, negative predictive value and positive likelihood ratio of the above four sections were compared and analyzed. The suspected abnormal fetuses were re-examined by echocardiography at 15–16 weeks, and the blood flow of outflow tract was observed and recorded. If the structure of the outflow tract is normal, the “ ɓ ”-shaped blood flow

Table 1 Cardiac structural abnormalities and diagnostic sections

Cardiac anomalies	Cases	Diagnosis aspect	Outside the heart malformations
VSD	33	4CV, section of outflow tract	Lymphadenoma, whole forebrain, omphalocele, giant bladder, deadly dwarf
AVSD	6	4CV	Lymphadenoma, visceral antithesis, laryngotracheal atresia
TA	6	Section of outflow tract	Whole forebrain, Dandy-Walker syndrome
TOF	4	Section of outflow tract	Lymphatic water cyst, Pentalogy of Cantrell, giant bladder
Single ventricle	4	4CV	Lymphatic water sac tumor, Pentalogy of Cantrell, small mandible
DORV	4	Section of outflow tract	Lymphatic hydrocystic tumor, whole forebrain
HLHS	3	4CV, section of outflow tract	Lymphadenoma, whole forebrain, Dandy-Walker syndrome
HRHS	2	4CV section of outflow tract	Lymphadenoma, omphalocele
Right aortic arch	2	3VVT	Giant bladder
TGA	1	Section of outflow tract	None
PLSVC	1	3VVT	Giant bladder

4CV, fetal four chamber view; 3VVT, three vessel tracheas; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; TOF, tetralogy of Fallot; TA, truncus arteriosus; DORV, double outlet right ventricle; TGA, transposition of great artery; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; PLSVC, perpetuate the left superior vena cava.

can be displayed, but if the heart structure is abnormal, the “ ɓ ”-shaped blood flow cannot be displayed, and the optimal time to perform flow tracing in the screening for heart is form 11 to 16 weeks.

Statistical analysis

SPSS 24.0 statistical software was used for statistical analysis. The count data is expressed in rate. If the measurement data conforms to the normal distribution, it is expressed by the mean ± standard deviation for normally distributed continuous variables; otherwise, expressed by the median (interquartile interval). The test level is α=0.05.

By comparing the sensitivity, specificity, positive predictive value, negative predictive value and positive likelihood ratio of scanning sectional blood flow Doppler and other observation indexes in early pregnancy, the prediction accuracy of these diagnostic indexes for CHD is evaluated.

Results

A total of 3,356 pregnant women with CHD were included in the NT examination, with an average age of 29.18±4.55 and an average head hip length of 6.62±0.89 cm. A total of 66 cases of CHD were detected among the 3,356 fetuses, with a detection rate of 1.97%. Of these, there were 15 cases of conus trunk malformation, accounting for 22.7% of the total number of CHD cases. All fetuses suspected of cardiac structural abnormalities in early pregnancy and fetuses re-examined by echocardiography at 15–16 weeks were jointly consulted by 1–2 fetal prenatal ultrasound diagnostic experts. Sixty-five cases of induced labor. Among the 8 missed cases, 1 case was born and 7 cases were induced labor.

Blood flow display and CHD diagnosis in heart screening section

Thirty-three cases (50%) of VSD, 6 cases (18.2%) of ASD, 4 cases (6%) of single ventricle, 3 cases (5%) of hypoplastic left heart syndrome (HLHS), and 2 cases (3%) of hypoplastic right heart syndrome (HRHS) were detected in four chamber cardiac section. Moreover, 15 cases of DORV, TGA, truncus arteriosus (TA) and TOF were also detected in the section of outflow tract (22.7%), as well as 2 cases of right aortic arch and 1 case of Perpetuate the left superior vena cava (PLSVC) were detected on the three-vessel trachea section (*Table 1*). Abnormal “ ɓ ” blood flow in outflow tract, cross of “X” aorta and pulmonary artery, and “V” blood flow in the trachea with three vessels were mostly seen in the conus trunk malformation (*Table 2*).

In this study, the display rates of four chamber “II” shape blood flow, aorta and pulmonary artery “X” cross, three vessel trachea “V” shape blood flow and outflow tract “ ɓ ” shape Doppler blood flow were 93.30%, 96.81%, 97.53%, and 96.39%, respectively. The sensitivity, negative predictive value, and the ROC curve area (AUC =0.659) of outflow tract “ ɓ ” shape blood flow were higher than those of the “X” cross of the aorta and pulmonary artery and the “V” shape of the three vessels trachea (see *Table 3*, *Figures 2,3*).

Table 2 Scan the sections and the associated CHD

Scanning plane	CHD
4CV	Single ventricle, larger VSD, AVSD, obvious valve abnormalities
Abnormal “X” sign in aorta and pulmonary artery crossing	aorta/pulmonary stenosis/atresia, VSD with aortic straddling, TGA, and DORV
Abnormal “V” sign in 3VVT	right arch aorta, aberrant subclavian artery, TA
Abnormal Outflow tract “ ზ ”	Outflow stenosis/atresia, TGA, DORV, TA, right arch aorta

4CV, fetal four chamber view; 3VVT, three vessel tracheas; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; TGA, transposition of great artery; TA, truncus arteriosus; CHD, congenital heart disease.

Table 3 Blood flow display and congenital heart disease (CHD) diagnosis in heart screening section

Scan cross-sectional blood flow Dop	Cases	CHD (case)	Norm/ heart	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio
4CV “II” blood flow Dop				65.15	94.47	19.11	99.27	11.78
4CV “II” shape blood flow does not show	225	43	182					
4CV “II” shape blood flow shows	3,131	23	3,108					
Total	3,356	66	3,290					
“X” cross flow Dop				30.30	97.36	18.69	98.58	11.47
The aorta and pulmonary artery “X” shape blood flow does not show	107	20	87					
The aorta and pulmonary artery “X” shape blood flow shows	3,249	46	3,202					
Total	3,356	66	3,290					
3VVT “V” blood flow Dop				31.82	98.12	25.30	98.63	16.93
3VVT “V” shape blood flow does not show	83	21	62					
3VVT “V” shape blood flow shows	3,273	45	3,228					
Total	3,356	66	3,290					
Outflow tract “ ზ ” Dop				34.85	97.02	19.01	98.67	11.69
Outflow tract “ ზ ” shape, blood flow does not show	121	23	98					
Outflow tract “ ზ ”, blood flow shows	3,235	43	3,192					
Total	3,356	66	3,290					

CHD, congenital heart disease; 4CV, fetal four chamber view; 3VVT, three vessel tracheas.

Discussion

Evaluation of the value of “ ზ ” Doppler blood flow of outflow tract in CHD screening in early pregnancy

The prenatal screening of CHD is based on three orthogonal planes of the heart. Multiplane scanning can verify the structure of the heart chamber, the connection sequence of atrium-ventricle, ventricle-aorta and the shape of aortic arch (17,18). In all CHD, the incidence of conic truncus malformation is as high as 10–30%. The mechanism is that during embryogenesis and development, a series of pyramidal arterial septal defects are caused by abnormal migration of cardiac nerve crest cells (19-22). The most common malformations include TOF, TGA, DORV and TA. Identifying the ventricular-great artery connection in fetuses with conic truncus malformations is still one of the great challenges faced by prenatal ultrasound.

Most routine echocardiographic examinations include 4CV and outflow tract section scan. The 4CV is an important part of fetal heart examination. The section of the left and right ventricular outflow tract are considered to be part of routine cardiac screening in the second trimester. The CHD with abnormal four-chamber gray scale and Doppler echocardiography included bicuspid and tricuspid atresia, Ebstein’s Anomaly, AVSD, larger VSD, single ventricle, total anomalous pulmonary venous return (TAPVR), cardiac tumor and so on. Abnormal left and right ventricular outflow tract is commonly seen in complex CHD such as outflow tract VSD, aortic straddle, TGA, DORV, TA and so on. It is an important section for the diagnosis of complex CHD such as conic truncus malformation. The three-vessel trachea is an important section to observe the spatial connection, position arrangement and lumen size of the aorta and pulmonary artery to the arterial ductal arch, the transverse and isthmus of the aortic arch, the superior vena cava and the trachea from left to right. Color or energy Doppler can be used to detect abnormal arterial and venous blood flow in the upper mediastinum, some complex CHD (such as vascular ring, interrupted aortic arch, TA) have diagnostic specificity.

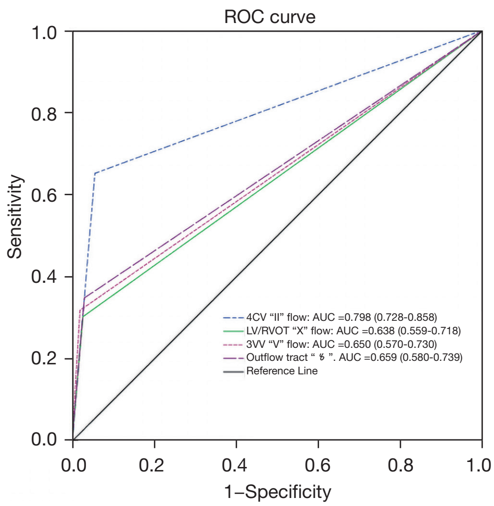

Figure 2 ROC curve comparison of CHD screening for each section. ROC, receiver operating characteristic; CHD, congenital heart disease.

In early pregnancy, major cardiac structural abnormalities include AVSD, HLHS, TOF, DORV, TGA, and coarctation of the aorta (COA). These six types of CHD account for 50% to 70% (23). Due to different diagnostic sections, the detection rates of different types of CHD are quite different, in which the detection rate of HLHS is as high as 50–100%, while the detection rate of TOF, TGA, COA and so on is only 16–18% (24).

Due to the small size of the fetal heart in early pregnancy, complex morphology and continuous exercise

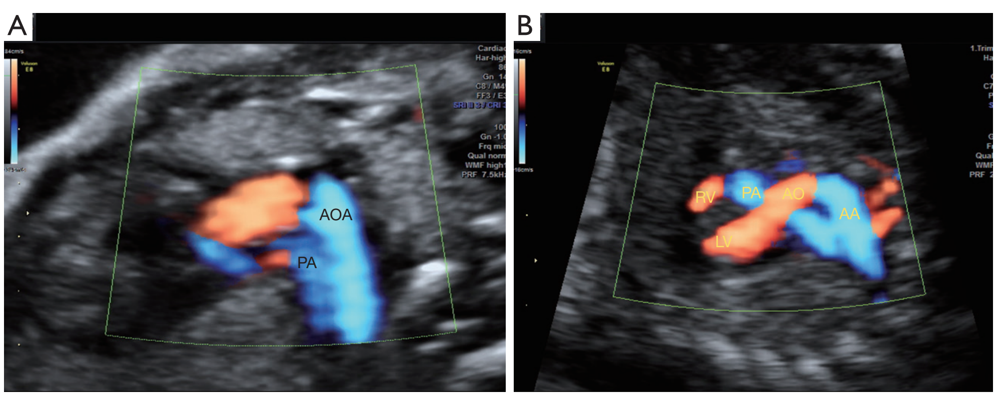

Figure 3 Comparison of abnormal outflow tract blood flow graph with normal outflow tract “ ზ ” shape blood flow graph. (A) DORV, the parallel shape of the aortic arch and the pulmonary artery, and the confluence of the aortic arch and ductus arteriosus in “ ɔ ” shape, 15^{+2} weeks ultrasonic duplicate check; (B) confluence of blood flow in the normal outflow tract with “ ზ ” shape (transvaginal ultrasound), 14^{+5} weeks. DORV, double outlet right ventricle; AOA, aorta; PA, pulmonary artery; RV, right ventricle; LV, left ventricle; AO, aorta; AAO, ascending aorta.

make it more difficult to evaluate the fetal heart. Image resolution and accurate identification of anatomical details are not only important factors affecting the diagnosis, but also the difficulty of echocardiography in early pregnancy. The optimized color or highly resolution Doppler was used to display the blood flow pattern in the large vessels to make up for the defect that the inner diameter of the left and right ventricular outflow tract was too small to be displayed by two-dimensional ultrasound. Although the "X" shape of the left and right ventricular outflow tract Doppler is easy to show, it is difficult to distinguish the anatomical position relationship between the aorta and pulmonary arteries because the internal diameter of the left and right ventricular outflow tract is too much small and the anatomical orientation is unreliable in early pregnancy.

In this study, we analyzed and summarized the blood flow pattern trajectory of the outflow tract as follows: through the superposition image of the " ৬ " outflow from two ventricles to the outflow tract, the "X"-shaped intersection of the left and right ventricular outflow tract and the "V"-shaped confluence of the aorta and pulmonary artery on the left side of the trachea are all part of the outflow tract blood flow pattern trajectory, and the complete trajectory can be described as a " ৬ " shape. In the second trimester, the blood flow patterns of the left and right outflow tract are difficult to display completely in the same section, so it is necessary to dynamically and continuously observe the confluence pattern of the left and right ventricular outflow tract, but because of the small size of the heart in the early pregnancy, it is easier to obtain the superimposed static and dynamic " ৬ " shape blood flow images of the left and right ventricular outflow tract than the second trimester, and can quickly identify the spatial relationship between the aorta and pulmonary arteries according to the different blood flow patterns. And in the apical and parasternal four-chamber cardiac section, slightly tilted to the right shoulder of the fetus, the " ৬ "-shaped blood flow image can be obtained, which is convenient, fast and easy to operate.

The display rates of four kinds of blood flow images of four-chamber heart "II", left and right ventricular outflow tract "X", three-vessel trachea "V" and outflow tract " ৬ " were compared. the data showed that the display rate of the superimposed image of the " ৬ " outflow tract was 96.88% in the normal fetal heart, and its sensitivity and specificity were higher than those of the main pulmonary artery "X" cross and the three-vessel trachea "V" blood flow Doppler display. In the conic artery trunk malformations, such as stenosis or atresia of left and right ventricular outflow tract, DORV, TGA and TA, the cross shape " ৬ " of conic truncus artery changed or did not show. This study shows that the " ৬ " blood flow convergence image of the outflow tract shows the inherent blood flow pattern of fetal echocardiography Doppler, which is the characteristic embodiment of the out-of-shape trend of the tube from the cardiac cavity in large blood. It can be used as a criterion for screening conic truncus artery malformations to evaluate whether the fetal heart is associated with conic truncus artery malformations. However, the detection rate of outflow tract VSD is low.

The Doppler superimposed blood flow image of the " ৬ " outflow tract completely records the blood flow trajectory of the outflow tract, which can help us to grasp the anatomical details of the heart more clearly when screening the cardiac structure, and establish the spatial thinking of the blood flow pattern of the cardiac cavity and outflow tract. And familiar with the normal Doppler blood flow pattern, can quickly judge the abnormal blood flow pattern in early pregnancy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-6475). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ningxia Medical University General Hospital scientific research Ethics Committee and informed consent was taken from all the mothers.

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