Application of two-dimensional echocardiography combined with enhanced flow in diagnosing fetal heart malformation

L. Liu[1], Y. He[2], Z. Li[2], L. Zhang[2]

[1]Department of Ultrasound in Medicine, Beijing Anzhen Hospital, Capital Medical University, Beijing
[2]Department of Ultrasound in Medicine, Henan Provincial Hospital, Zhengzhou (China)

Summary

Objective: The current study aims to evaluate the diagnostic accuracy of two-dimensional echocardiography combined with enhanced flow (e-flow) imaging for fetal heart malformation. *Materials and Methods:* A total of 1,639 pregnant women were enrolled. They were examined using fetal echocardiography combined e-flow. The obtained results were compared with those by postnatal examination or post-induction autopsy. *Results:* Complete data were obtained from 1,286 out of the 1,639 fetuses (78.46%). Two-dimensional echocardiography combined with e-flow imaging had sensitivity, specificity, a misdiagnosis rate, and a missed diagnosis rate of 98.0%, 99.3%, 2.0%, and 0.7%, respectively. It has a consistency evaluation Kappa value of 0.970 ($p = 0.000$). *Conclusion:* Two-dimensional echocardiography combined with e-flow is an accurate and reliable diagnostic method for fetal heart malformation. It has high sensitivity and specificity.

Key words: Fetal echocardiography; Congenital heart disease; Enhanced flow imaging.

Introduction

Fetal heart malformation is one of the congenital diseases seriously influencing fetal intrauterine development and neonatal survival; it has an incidence of 6‰ to 8‰ in live neonates [1]. Fetal echocardiography is a feasible, effective diagnostic method for heart malformations. It is of great significance for fetal intrauterine detection and intervention therapy, neonatal monitoring and corrective surgery, and perinatal neonatal mortality reduction. The diagnosis of fetal heart malformation is particularly important for the detection of the fine structure in fetuses during first- and second-trimester pregnancy. Although traditional color Doppler imaging can demonstrate the pulmonary venous blood flow and rate in third-trimester fetuses, its limitations in sensitivity and resolution influence its display of the pulmonary venous blood flow in first- and second-trimester fetuses. The pulmonary venous blood flow rate in first- and second-trimester fetuses is rather slow because of a quite thin vascular inner diameter. Meanwhile, the existence of channels, such as the foramen ovale, ductus arteriosus, and ductus venosus at fetal stage that maintains the fetal blood circulation system stable while keeping the pressures on the right and left heart systems equivalent to each other. This factor also entails difficulty in diagnosing fetal blood shunting to some degree.

Enhanced flow (e-flow) imaging is a technique which can clearly display low-speed blood signals; it enhances temporal and spatial resolutions by differentiating blood signals from tissue signals [2].

In the current study, two-dimensional echocardiography combined with e-flow imaging was used for fetal heart malformation screening. The accuracy of this method in diagnosing fetal heart malformation was then assessed.

Materials and Methods

Subjects

A total of 1,639 pregnant women that received fetal echocardiography at Henan Provincial Hospital and Beijing Anzhen Hospital were involved. Their ages ranged from 17 to 45 years with an average of 28.54 ± 4.41 years. Their gestational ages ranged from 16 to 40 weeks with an average of 26.36 ± 3.95 weeks. Subjects with complete data of prenatal echocardiography, postnatal echocardiography and related examination or surgery, autopsy after induction of labor, and so on were selected, whereas those with incomplete data were excluded.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Beijing Anzhen Hospital and Henan Provincial Hospital. Written informed consent was obtained from all the participants.

Guidelines and standards for screening

Fetal heart malformation was screened according to the guidelines and standards for fetal echocardiography recommended by the American Society of Echocardiography [3]. The standard views included the abdominal transverse plane, four-chamber view, left outflow tract plane, right outflow tract plane, short axis of both cardiac ventricles, three vessels and trachea view, long axis of the aortic arch, and long axis of the ductus arteriosus arch.

Case collection

Normal fetal echocardiograms: fetal echocardiography and physical examination were performed within one to 90 days after childbirth. The results were compared with those echocardiograms.

Abnormal fetal echocardiograms: pregnancy continued. Fetal echocardiography and physical examination were performed

Revised manuscript accepted for publication April 18, 2013

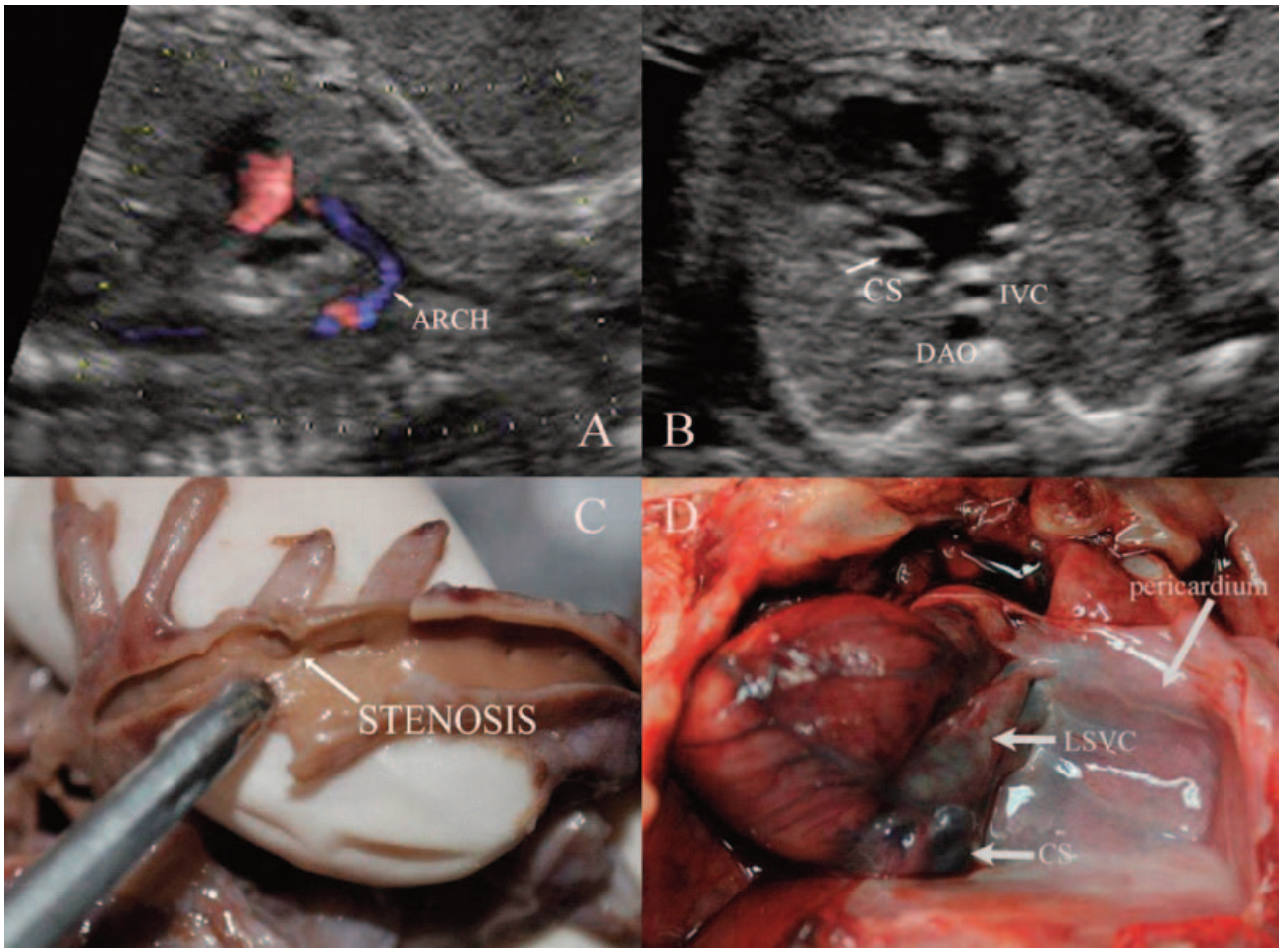

Figure 1. — Comparison between the echocardiography diagnosis (coarctation of the aortic arch, permanent left superior vena cava, and coronary sinus dilation) at the gestational age of 25 weeks and the autopsy pathology after induction in the same fetus. A: The plane of the long axis of the aortic arch shows a thin diameter at the aortic arch (the coarctation of the aortic arch is indicated by the arrow), but color Doppler examination does not show noticeably abnormal blood flow signals; B: the four chamber plane shows a widened coronary sinus in the left atrioventricular groove; C: post-induction autopsy shows a ridge between the subclavian artery and the left common carotid artery at the aortic arch which leads to diameter narrowing (the narrowed site is indicated by the arrow); and D: post-induction autopsy shows a downward connection between the permanent left superior vena cava and the coronary venous sinus outside of the left atrium and ventricle. ARCH: the aortic arch; DAO: the descending aorta; IVC: the inferior vena cava; LSVC: permanent left superior vena cava; and CS: the coronary venous sinus.

within 1 d to 90 days after childbirth. The results were compared with those echocardiograms. For the neonates subjected to cardiac surgical correction, pre-, intra-, and post-operative related data were collected and then compared with those echocardiograms.

Abnormal fetal echocardiograms: for the women whose pregnancy was terminated due to severe fetal heart malformation, the results of fetal autopsy were compared with those echocardiograms.

Statistical analysis

Data were analyzed using SPSS16.0 software. The diagnostic effectiveness of two-dimensional echocardiography combined with e-flow imaging for fetal heart malformation was evaluated using diagnostic test, and its diagnostic consistency for fetal heart malformation was evaluated using Kappa test.

Results

Clinical data

The pregnant women aged from 17 to 45 years with an average of 28.54 ± 4.41 years. Their gestational ages ranged from 16 to 40 weeks with an average of 26.36 ± 3.95 weeks. Complete data were obtained from 1,286 (78.46%) out of the 1,639 women and 353 (21.54%) were lost to follow-up.

The effectiveness evaluation

The diagnostic effectiveness evaluation results of two-dimensional echocardiography combined with e-flow imaging for fetal heart malformation are summarized in Table 1. Compared with the standard method, two-dimensional

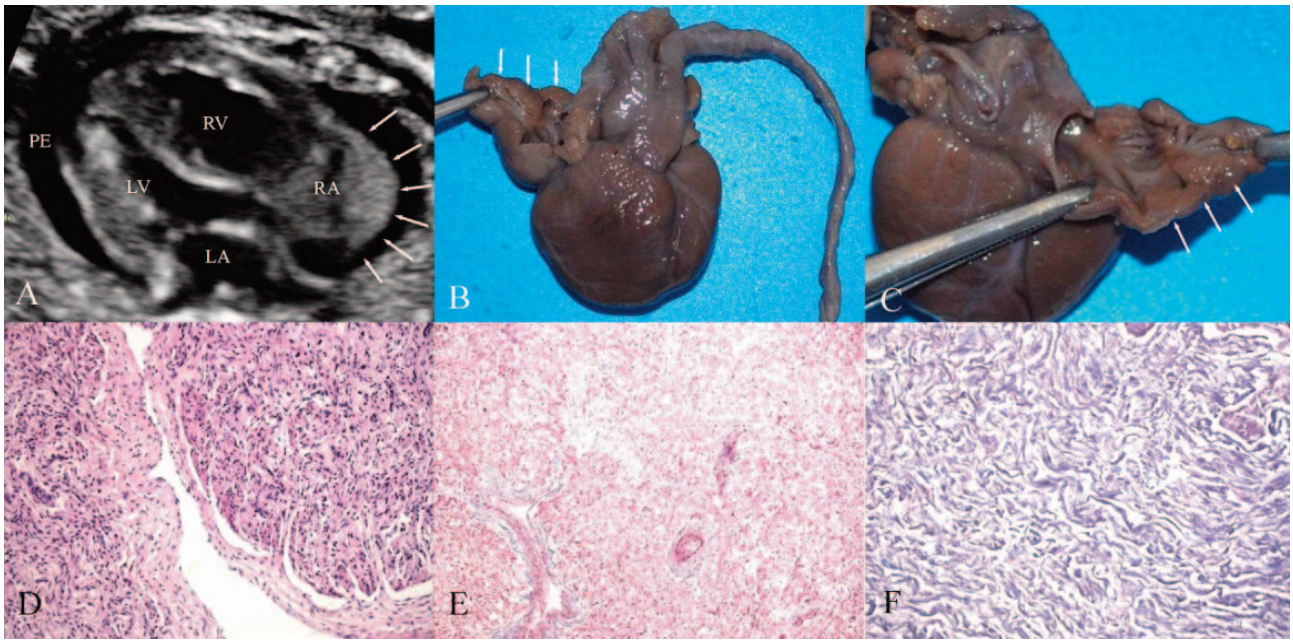

Figure 2. — Comparison between the echocardiography diagnostic results (right atrial aneurysm) at the gestational age of 26 weeks and the general and microscopic views after post-induction autopsy in the same fetus. A: The four chamber plane shows a thickened right atrial wall (indicated by the arrow) with a thickness of 3.8 mm and a small amount of hydrops in the pericardial cavity; B and C: The autopsy shows a thickened right atrial wall (indicated by the arrow); D: HE staining (×200) shows hyperplastic cells on the atrial wall in bunchy arrnangement with some deranged cells and vessels of different sizes distributed in the interstitia; E: PTAH staining (× 100) shows that the cells are striated muscle tissue cells; and F: Masson staining (× 100) shows that the cells are striated muscle tissue cells.

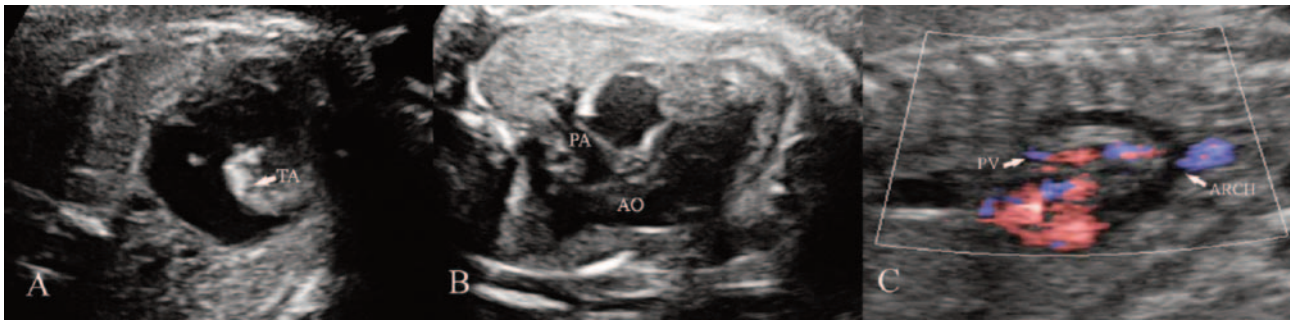

Figure 3. — Fetal echocardiography diagnostic results of one fetus at the gestational age of 29 weeks (total anomalous pulmonary venous drainage (supracardiac type), functional single atrium (right heart auricle isomerism), right atrioventricular valvular closure, single ventricle, pulmonary artery atresia, and right aortic arch complicated with vascular ring formation). A: The four chamber plane does not show high-level echoes other than one muscular strong echo from the tricuspid valve area (the tricuspid valvular closure is indicated by the arrow); B: the five chamber plane shows the aorta located on the right side of the pulmonary artery (right transposition of the great arteries) and the closure at the pulmonary artery opening; and C: The plane of the long axis of the aortic arch shows the abouchement of the pulmonary veins into the superior vena cava. TA: tricuspid atresia; AO: the aorta; PA: the pulmonary artery; PV: pulmonary veins; and ARCH: the aortic arch.

echocardiography combined with e-flow imaging had sensitivity of 98.0%, specificity of 99.3%, a misdiagnosis rate of 2.0%, a missed diagnosis rate of 0.7%, a total coincidence of 99.1%, a Youden index of 97.3%, a positive predictive value of 97.9%, and a negative predictive value of 99.3%.

The respective true positive, false negative, and false positive cases before childbirth, as well as during follow-ups by two-dimensional echocardiography combined with e-flow imaging are summarized in Tables 2, 3, and 4. Two hundred and thirty-nine cases (18.6%) were true positive, 1035 (80.5%) were true negative, seven (0.5%) were false negative, and five (0.4%) were false positive. Among the true positive cases, one manifested coarctation of the aortic arch, permanent left superior vena cava, and coronary sinus dilation (Figure 1), and one by right atrial aneurysm (Figure 2). The false negative cases presented with common pulmonary vein atresia (Figures 3 and 4).

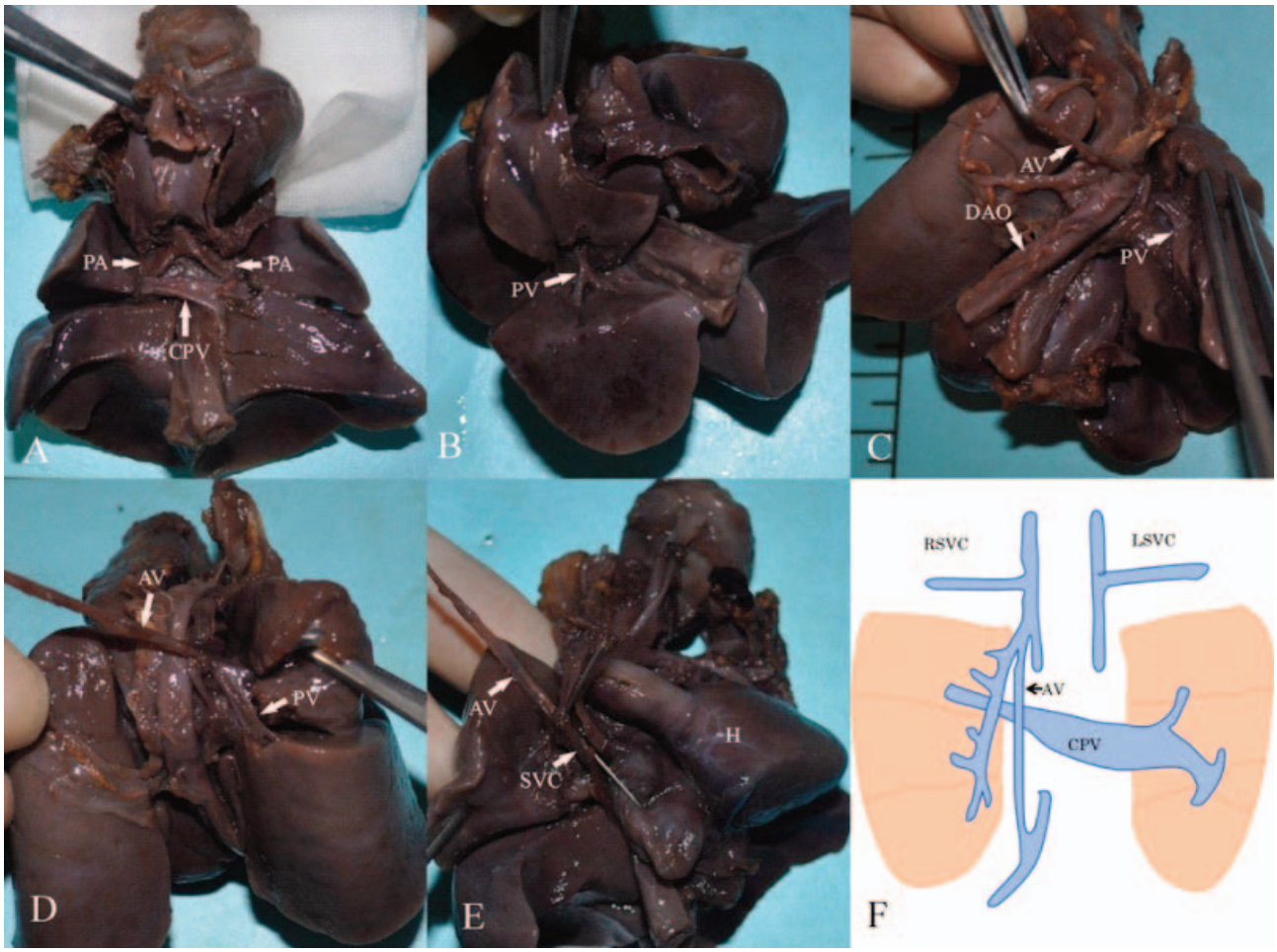

Figure 4. — The autopsy results of the same fetus in Figure 3 (partial common pulmonary vein atresia (atresia of the common cavity of the left superior, left inferior, and right superior pulmonary veins), supracardiac partial anomalous pulmonary venous drainage (the right inferior, middle, and superior branches converge into the azygos vein and then into the superior vena cava), permanent left superior vena cava (innominate venous absence), unroofed coronary sinus syndrome (total type), single atrium, tricuspid atresia, single ventricle, pulmonary artery atresia, right aortic arch, aortopulmonary collateral formation, and ductus arteriosus absence). A is the anterior view: the heart upturns, and the left superior, left inferior, and right superior pulmonary veins converge to form a common cavity which has no connection with the heart; B, C, D, and E, respectively, display the convergence of the right inferior, middle, and superior pulmonary veins into the azygos vein and then into the superior vena cava; and F is the view of partial common pulmonary vein atresia and supracardiac partial anomalous pulmonary vein drainage. CPV: common pulmonary vein atresia; PA: the pulmonary artery; PV: pulmonary veins; AV: the azygos vein; DAO: the descending aorta; SVC: the superior vena cava; H: the heart; RSVC: the right superior vena cava; and LSVC: the left superior vena cava.

Table 1. — *Comparison between two-dimensional echocardiography combined with e-flow imaging and follow-up examination in diagnosing fetal heart malformation (cases).*

Methods		Postnatal recheck, operation, and autopsy after induction Positive	Negative	Total
E-flow	Positive	239	5	244
	Negative	7	1035	1042
	Total	246	1040	1286

The consistency evaluation

The consistency between two-dimensional echocardiography combined with e-flow imaging and the standard method in diagnosing fetal heart malformation is summarized in Table 1. The consistent Kappa value was 0.970 ($p = 0.000$) which indicates that two-dimensional echocardiography combined with e-flow imaging had good consistency with the standard method in fetal heart malformation diagnosis.

Discussion

Fetal heart malformation is the most common congenital disease that seriously influences fetal intrauterine development and neonatal survival [4]. Fetal echocardiography is a technique which was first applied and whose clinical value was confirmed by Winsberg in 1972 [5]. Since then, M-mode

Table 2. — *True positive cases of fetal heart malformation diagnosed by two-dimensional echocardiography combined with e-flow imaging and their follow-up examination.*

Case types	Case number	Follow-up examination		
		Postnatal echocardiography	Postnatal operation	Autopsy
Ventricular septal defects	45	39	6	-
Total endocardial cushion defects	21	5	-	16
Single ventricle	15	2	-	13
Hypoplastic left heart	10	-	-	10
Hypoplastic right heart	7	2	-	5
Aortic stenosis	13	3		10
Pulmonary artery stenosis	15	5	2	8
Pulmonary atresia with intact ventricular septum	2	–	–	2
Ebstein's anomaly	8	–	–	8
Fallot tetrad	12	5	2	5
Persistent truncus arteriosus	15	2	–	13
Complete transposition of great arteries	10	–	–	10
Anomalous pulmonary vein drainage	10	2	–	8
Double outlet right ventricle	20	5	–	15
Ductus arteriosus early shrinkage	15	15	–	–
Heart neoplasms	11	1	–	10
Vascular ring	7	5	–	2
Valvular mucinous degeneration	2	–	–	2
Inferior vena cava interruption	1	–	–	1
Total	239	91	10	138

Table 3. — *False negative cases of fetal heart malformation diagnosed by two-dimensional echocardiography combined with e-flow imaging and their follow-up examinations.*

Fetal echocardiography	Follow-up examination
Total anomalous pulmonary vein drainage (intracardiac type) and permanent left superior vena cava	Autopsy: Severe hypoplastic right lung and permanent left superior vena cava
Total anomalous pulmonary vein drainage (supracardiac type), total endocardial cushion defects, persistent truncus arteriosus, left pulmonary artery stenosis, and permanent left superior vena cava	Autopsy: common pulmonary vein atresia (total type), total endocardial cushion defects, persistent truncus arteriosus, left pulmonary artery branch stenosis, and permanent left superior vena cava
Total anomalous pulmonary vein drainage (intracardiac type), single atrium (right auricle isomerism), tricuspid atresia, single ventricle, pulmonary artery atresia, and complicated pulmonary artery ostial stenosis	Autopsy: partial common pulmonary vein atresia, partial anomalous pulmonary vein drainage (supracardiac), single atrium, tricuspid atresia, single ventricle, pulmonary artery atresia, and aortopulmonary collateral formation
Pulmonary valve stenosis, pulmonary artery trunk and branch aneurysmal dilatation, ventricular septal defect, and tricuspid regurgitation	Autopsy: Pulmonary valve defects, pulmonary artery trunk and branch aneurysmal dilatation, and ventricular septal defect
Left ventricle glare points	Postnatal echocardiography: mild pulmonary valve stenosis
Left ventricle glare points	Postnatal echocardiography: mild pulmonary valve stenosis
Normal	Postnatal echocardiography: ventricular septal defects complicated with membranous aneurysm formation and mild tricuspid regurgitation

two-dimensional spectral Doppler, color Doppler, tissue Doppler, harmonic wave power Doppler, spatio-temporal image correlation, high-resolution blood flow imaging, two-dimensional gray scale imaging of blood flow, and three-dimensional imaging have emerged; these techniques all play an important role in evaluating fetal heart structure, blood circulation, and heart function [6-12].

E-flow employs the broadband reception technique and adds motion artifact suppression to coherent imaging. It successfully differentiates the color signal zone and the two-dimensional zone from each other. This differentiation enhances sensitivity; meanwhile, it avoids the problem of blood flow signal spillover during traditional color Doppler imaging, which radically improves temporal and spatial resolutions to enable the fine blood circulation to be reflected and thus to effectively prevent blood flow signal spillover under high sensitivity. In this study, the application of the e-flow technique to fetal echocardiography demonstrates that it improves the resolution of the display of the micro-vessels and low-velocity blood flows and reduces the spillover of color blood flow signals in fetal pulmonary vein and ductus venosus imaging.

Table 4. — *Five false positive cases of fetal heart malformation diagnosed by two-dimensional echocardiography combined with e-flow imaging and their follow-up examination.*

Two-dimensional echocardiography	Follow-up examination
Ebstein abnormalities, tricuspid regurgitation (severe), pulmonary valve absence, ventricular septal defect (membranous)	Autopsy: Ebstein abnormalities, no pulmonary valve absence, and no ventricular septal defect
Aortic dysplasia and ventricular septal defect	Autopsy: aortic root stenosis without ventricular septal defect
Ventricular septal defect (membranous)	Postnatal echocardiography: normal
Ventricular septal defect (peri-membranous)	Postnatal echocardiography: normal
Ventricular septal defect (muscular)	Postnatal echocardiography: normal

Forbus *et al.* evaluated the diagnostic accuracy of two-dimensional color Doppler for fetal heart malformation and obtained an accuracy rate of 89.5% [13]. They further classified misdiagnosed and missed cases: the missed diagnosis or misdiagnosis rates of single ventricle deformity, septal defects, valvular deformity, and conotruncal defects were 5%, 8%, 11%, and 25%, respectively. Only prenatal four-chamber views are not sufficient with some heart abnormalities [14]. Extra scanning of the left and right outflow tracts can improve the detection rate of fetal heart malformation [15-17]. However, even after this extra strategy is applied based on four-chamber view, the missed diagnoses of some fetal heart malformations can still occur. Based on the aforementioned, to increase the correct diagnosis rate for fetal heart malformation and to reduce the missed diagnosis and misdiagnosis rates, the e-flow technique was applied based on the planes in the guidelines and standards for fetal echocardiography recommended by the American Society of Echocardiography in this study.

The screening of 1,286 cases of fetal heart malformation in this study shows that the e-flow technique can demonstrate fetal low-velocity blood flow such as that in the pulmonary veins, foramen ovale, aortopulmonary collaterals, ductus venosus, and therefore has a great advantage in the diagnosis of pulmonary venous lesions, small collateral flow in persistent truncus arteriosus, interatrial shunt right before foramen ovale atresia, interruption of the inferior vena cava, vascular ring, and so on. However, there were still false positive and false negative cases in this study. Reasons for this phenomenon were analyzed as follows:

1) *A lack of the knowledge of rare heart malformations:* In this study, two cases with total anomalous pulmonary venous drainage according to prenatal diagnosis were confirmed with common pulmonary vein atresia by post-induction autopsy. Common pulmonary vein atresia is a type of rare heart malformation which often leads to neonatal death shortly after birth if not corrected timely [18]. Lucas *et al* first reported three neonates with common pulmonary vein atresia in 1962 and according to them, the deaths of the three neonates occurred at 3, 22, and 28 days after birth, respectively [19]. Deshpande *et al* detected three cases of common pulmonary vein atresia out of 1,326 collected congenital heart disease samples [20]. In common pulmonary vein atresia, the formed common cavity lies at the posterior wall of the left atrium. Thus, the blood flow signal in this common pulmonary vein is likely to be erroneously identified connected to the heart atrium or the systemic veins by ultrasonography and consequently, the malformation is misdiagnosed as anomalous pulmonary venous drainage. Therefore, under such a condition, the pulmonary veins should be carefully observed to ensure whether they are connected with the atrium or not;

2) *Influence of the special structure and hemodynamic properties at fetal stage:* In this study, two cases with normal prenatal pulmonary valvular flow rate were observed with mild pulmonary valvular stenosis after birth. The possible reason may be as follows: most blood flow signals from the inferior vena cava flow into the left heart atrium via the foramen ovale, and a small part flow into the right ventricle and pulmonary artery through the right atrium; during fetal period, lungs are unexpanded and do not communicate with the external environment, and the pulmonary vascular bed presents high resistance; with the closure of the foramen ovale after birth, the majority blood that originally enters into the left atrium from the inferior vena cava via the foramen ovale completely flows into the right ventricle and pulmonary artery rather than shunt; meanwhile, as the neonate develops, and the blood volume increases, and so does the blood flow entering into the pulmonary artery via the pulmonary valve. Because of these structural and hemodynamic changes, the phenomenon that a normal flow rate at the pulmonary valve orifice during fetal period turns into an increased flow rate at the same site is likely to occur;

3) *Influence of extracardiac malformation on the intracardiac structure:* In this study, one case with anomalous pulmonary venous drainage according to the prenatal diagnosis was confirmed with severe right lung dysplasia by the post-induction autopsy. The possible reason was analyzed: Unilateral lung dysplasia can lead to pulmonary venous unilateral absence; the left atrium can only receive unilateral pulmonary venous blood backflow; this condition results in an increase in the diameter of the left atrium rather than anomalous pulmonary venous drainage. Therefore, when fetal echocardiography is performed for fetal

heart malformation screening, to increase its diagnostic accuracy, secondary cardiac structure changes caused by extracardiac organ lesions, apart from intracardiac structure abnormalities, should be carefully observed.

To summarize, two-dimensional echocardiography combined with the e-flow technique is an effective, reliable diagnostic method for fetal heart malformation andhas high specificity and sensitivity; furthermore, the application of the e-flow technique on the recommended planes in the standard diagnostic method can reduce missed diagnosis and misdiagnosis of fetal heart malformation and increase diagnostic accuracy. However, a larger sample size is required to further summarize and analyze the causes for false and negative positivity, increase ultrasonic diagnostic skills, and provide a more reliable basis for the application of the new ultrasound technique to the diagnosis of fetal heart malformation.

Acknowledgement

This study was supported by The National Natural Science Fund (81171350).

References

[1] Gardiner H.M.: "Fetal echocardiography: 20 years of progress". *Heart*, 2001, *86*, II12.

[2] Dong F.Q., Zhang Y.H., Li Z.A., Hou Z.Z., He X.J., Guo Y.Z.: "Evaluation of normal fetal pulmonary veins from the early second trimester by enhanced-flow (e-flow) echocardiography". *Ultrasound. Obstet. Gynecol*., 2011, *38*, 652.

[3] Rychik J., Ayres N., Cuneo B., Gotteiner N., Hornberger L., Spevak P.J. *et al*.: "American society of echocardiography guidelines and standards for performance of the fetal echocardiogram". *J. Am. Soc. Echocardiogr*., 2004, *17*, 803.

[4] Hoffman J.I., Kaplan S.: "The incidence of congenital heart disease". *J. Am. Coll. Cardiol*., 2002, *39*, 1890.

[5] Winsberg F.: "Echocardiography of the fetal and newborn heart". *Investigative radiology*, 1972, *7*, 152.

[6] Lenz F., Chaoui R.: "Reference ranges for doppler-assessed pulmonary venous blood flow velocities and pulsatility indices in normal human fetuses". *Prenat. Diagn*., 2002, *22*, 786.

[7] Pooh R.K.: "Normal anatomy by three-dimensional ultrasound in the second and third trimesters". *Semin. Fetal Neonatal Med*., 2012, *17*, 269.

[8] Martins W.P., Welsh A.W., Falkensammer P., Raine-Fenning N.J.: "Re: Spatio-temporal imaging correlation (STIC): technical notes about STIC triggering and choosing between Power Doppler or high-definition color flow". *Ultrasound Med. Biol*., 2013, *39*, 549.

[9] Simioni C., Nardozza L.M., Araujo Júnior E., Rolo L.C., Terasaka O.A., Zamith M.M. *et al*.: "Fetal cardiac function assessed by spatio-temporal image correlation". *Arch. Gynecol. Obstet*., 2011, *284*, 253.

[10] Hata T., Tanaka H., Noguchi J.: "3D/4D sonographic evaluation of amniotic band syndrome in early pregnancy: a supplement to 2D ultrasound". *J. Obstet. Gynaecol. Res*., 2011, *37*, 656.

[11] Volpe P., Tuo G., De Robertis V., Campobasso G., Marasini M., Tempesta A. *et al*.: "Fetal interrupted aortic arch: 2D-4D echocardiography, associations and outcome". *Ultrasound Obstet. Gynecol*., 2010, *35*, 302.

[12] Markov D.: "Spatio-temporal image correlation (STIC) and tomographic ultrasound imaging (TUI)-combined clinical implementation in 3D/4D fetal echocardiography". *Akush. Ginekol. (Sofiia)*, 2010, *49*, 3.

[13] Forbus G.A., Atz A.M., Shirali G.S.: "Implications and limitations of an abnormal fetal echocardiogram". *Am. J. Cardiol*., 2004, *94*, 688.

[14] Nelson N.L., Filly R.A., Goldstein R.B., Callen P.W.: "The aium/acr antepartum obsterical sonographic guidelines: expectations for detection of anomalies". *J. Ultrasound Med*., 1993, *12*, 186.

[15] Carvalho J.S., Mavrides E., Shinebourne E.A., Campbell S., Thilaganathan B.: "Improving the effectiveness of routine prenatal screening for major congenital heart defects". *Heart*, 2002, *88*, 387.

[16] Buskens E., Grobbee D.E., Frohn-Mulder I.M., Stewart P.A., Juttmann R.E., Wladimiroff J.W. *et al*.: "Efficacy of routine fetal ultrasound screening for congenital heart disease in normal pregnancy". *Circulation*, 1996, *94*, 67.

[17] Stümpflen I., Stümpflen A., Wimmer M., Bernaschek G.: "Effect of detailed fetal echocardiography as part of routine prenatal ultrasonographic screening on detection of congenital heart disease". *Lancet*, 1996, *348*, 854.

[18] Zhu Q.Y.: "Congenital heart disease pathological anatomy (Edition I)". Beijing: People's Medical Publishing House, 2001, 255.

[19] Lucas Jr R.V., Woolfrey B.F., Andersonrc R.C., Lester R.G., Edwards J.E.: "Atresia of the common pulmonary vein". *Pediatrics*, 1962, *29*, 729.

[20] Deshpande J.R., Kinare S.G.: "Atresia of the common pulmonary vein". *Int. J. Cardiol*., 1991, *30*, 221.

Address reprint requests to:
Y. HE, M.D.
Department of Ultrasound in Medicine
Beijing Anzhen Hospital
Capital Medical University
Beijing 100029 (China)
e-mail: yihuahecn@126.com