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Length to width ratio of the ductus venosus in simple screening for fetal congenital heart diseases in the second trimester

Wei-Hsiu Chiu, MD[a,b,c,d], Shy-Ming Lee, MD[b], Tao-Hsin Tung, PhD[e,f], Xiao-Mei Tang, MD[g], Ren-Shyan Liu, MD[a], Ran-Chou Chen, MD[a,*]

Abstract

Antenatal diagnosis of congenital heart disease (CHD) is still low even though screening was first introduced over 25 years ago. The purpose of our study was to determine the efficacy of a second-trimester prenatal ultrasonographic method of screening for CHD.

From September 2012 to September 2013, the length and width of the fetal ductus venosus were measured sonographically in 1006 singleton fetuses, and the ratio of length to width was calculated. The accuracy of each fetal measurement and Doppler ultrasonography were determined. The standard fetal echocardiographic evaluations including 2-dimensional gray-scale imaging, color, and Doppler color flow mapping were performed. The transducer was aligned to the long axis of the fetal trunk to view the ductus venosus in its full length, including the inlet (isthmus) and outlet portions of the vessel. The diameters of the vessel inner wall and mid-point of the ductus venosus were measured using calipers. All scans and fetal measurements were conducted by a registered sonographer with more than 20 years of perinatal ultrasound screening experience.

Of the 1006 singleton fetuses between 19^{+0} and 28^{+6} weeks' gestation, 36 had CHD. The ductus venosus length/width ratio (DVR) for the first CHD screening was extremely sensitive at 88.90%, with a specificity of 99.10% for the cardiac abnormalities included in this study. Chromosomal anomalies accompanied CHD in 0.4% (4/1006) of all cases and 11.11% (4/36) of the CHD cases.

The DVR differed significantly between fetuses with CHD and normal fetuses during the second trimester. Careful assessment of the ratio should be a part of the sonographic examination of every fetus. In the case of a small DVR, advanced echocardiography and karyotype analysis should be performed. The ratio is a helpful tool for screening CHD abnormalities prenatally in the Chinese population.

Abbreviations: 3VT = 3-vessel and trachea, 3VV = 3-vessel view, CCAM = congenital cystic adenomatoid malformation, CCTCR = cardiothoracic circumference ratio, CHD = congenital heart disease, CI = confidence interval, DV = ductus venosus, DVa = ductus venosus A-wave velocity, DVL = ductus venosus length, DVR = ductus venosus length/width ratio, DVs = ductus venosus systolic velocity, DVW = ductus venosus width, FO = foramen ovale, GA = gestational age, LVOT = left ventricular outflow tract, NPV = negative predictive value, PAAOR = pulmonary artery/aorta ratio, PPV = positive predictive value, ROC = receiver operating characteristic, RVOT = right ventricular outflow tract, SD = standard deviation, TOF = tetralogy of Fallot.

Keywords: congenital heart diseases, ductus venosus, prenatal

1. Introduction

Fetal echocardiography is a widely used tool for routine screening and prenatal diagnosis of congenital heart disease (CHD).[1–3] The incidence of fetal CHD is 3 to 10 per 1000 live births.[1–4] Variation is the norm due to the use of different methods for detecting CHD. The leading causes of mortality and morbidity in the perinatal and infant population are related to CHDs.[5] In some studies, the chromosomal anomalies associated with CHD were trisomy 21, trisomy 13, trisomy 18, and so on. Still others had nonchromosomal malformations.[6] Methods of screening for CHD other than B-mode basic 4-chamber views of fetal echocardiography rely on the extended outflow tracts.[6–8] Varying detecting rates in different cases of CHD have been reported. Four-chamber view is the basic view used for the screening of 2 atrioventricular valves, ventricular septum, and right or left atrium and ventricle anomaly. The detection rate was 2.1% to 90.9%. In outflow tract views, assessment of the left ventricular outflow tract (LVOT) and right ventricular outflow tract (RVOT) is the routine method. Varying detection rates from 1.6% to 80.8% have been reported.[9] Three-vessel and trachea (3VT) view and 3-vessel view (3VV) could increase the detection

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[a] Department of Biomedical Imaging and Radiological Sciences, School of Biomedical Science and Engineering, National Yang-Ming University, [b] Department of Obstetrics and Gynecology, Chung Shan Hospital, Taipei, [c] Department of Obstetrics and Gynecology, Hungchi Women & Children's Hospital, Taoyuan, Taiwan, [d] Department of Obstetrics and Gynecology, Changsha Anzhen Women Hospital, Changsha, China, [e] Fu-Jen Catholic University, [f] Department of Medical Research and Education, Cheng Hsin General Hospital, Taipei, Taiwan, [g] Department of Obstetrics and Gynecology, the 1st Affiliated Hospital, Jinan University, Guangzhou, China.

[*] Correspondence: Ran-Chou Chen, Department of Biomedical Imaging and Radiological Sciences, School of Biomedical Science and Engineering, National Yang-Ming University, Taipei, Taiwan (e-mail: chenranchou@yahoo.com.tw).

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rate up to 89% in 2 great vessel abnormality.[8,10,11] About 24% to 42% of overall CHD cases were detected before birth in recent studies.[2,12–16]

Recent reports suggested that the analysis of the fetal ductus venosus might help to identify fetuses at risk of CHD.[17–19] In utero, the fetal ductus venosus connects the intraabdominal umbilical vein and the inferior vena cava. The blood from the placenta through the umbilical vein is directed to the inferior vena cava via the ductus venosus, and empties into the right atrium, passing through the foramen ovale (FO) to the left side of the heart.[6] Approximately 20% to 30% of the oxygenated blood from the placenta is directed through the ductus venosus and enters the inferior vena cava.[6,20] Recently, due to improved image resolution techniques, the ductus venous diameter has been analyzed throughout gestation in human fetuses.[21,22] Previous reports showed a high correlation between the increase in ductus venosus width (DVW) and abnormal ductus venosus flow. Accordingly, DVW dilatation increases pressure in the central venous system due to ductus venosus sphincter relaxation.[23–25] Ductus venosus blood flow plays an important role in right ventricular preload and hemodynamics.[26,27] Ductus venosus assessment is a crucial part of a prenatal fetal heart activity assessment; it is a valuable initial diagnostic and screening tool for fetal CHD and associated chromosomal anomalies.[18,26,28,29]

Although guidelines have been formulated for performing fetal echocardiography including the assessment of the atria, ventricles, pulmonary venous return, and the ductal and aortic arches, the performance of fetal echocardiography requires significant training to perform; it is a highly specialized and time consuming examination.[1,30] Use of a simple screening plane and method could improve the prenatal detection rate of CHD. The aim of this study was to determine a normal range for fetal ductus venosus length/width ratio (DVR) among Chinese fetuses and to compare the DVR of fetuses with CHD to that of fetuses without CHD in order to assess the potential of the ratio as a screening tool.

2. Materials and methods

A retrospective study was conducted to determine the normal range of DVR. The fetal DVL and DVW were strictly measured in the sagittal view of the fetal trunk under appropriate image magnification (Fig. 1). The study was carried out in 2 community hospitals from September 2012 to September 2013. All procedures were performed in accordance with the guidelines of our institutional ethics committee and the tenets of the Declaration of Helsinki. All patient information was anonymous. The study was approved by the Hospital Human Subjects Review Board at Fu-Jen University. The requirement of informed consent was waived. The data were obtained from 1006 women with singleton pregnancies who underwent a fetal level II prenatal ultrasound examination, including detailed fetal echocardiography. The exclusion criteria were a history of fetal chromosome abnormalities or fetal extracardiac structural anomalies in previous pregnancy, maternal complications in present pregnancy, and uncertain gestational age (GA). The GA of the fetuses was calculated from the date of the last menstrual period as obtained from the patients. Some pregnant women had irregular menstrual cycles. Therefore, if the estimated GA from ultrasound and from the last menstrual period was more than 10 days, the women were excluded to avoid bias.[31] All the fetuses without cardiac defects were confirmed by clinical diagnosis in the neonatal hospital period after delivery.

In both hospitals, fetal examinations were performed using the Voluson 730 ProV ultrasound platform (General Electric Medical Systems, Milwaukee, WI) with multifrequency transabdominal transducers. All scans and fetal measurements were conducted by the same sonographer who works for both hospitals. This sonographer had more than 20 years of experience in obstetric ultrasonography and more than 15 years of experience in fetal heart scanning. Intraobserver variations were assessed during the study; the reliability statistic was used to determine the consistency of intraobserver reliability between 2 repeated measurements taken by the same examiner. The reliability analysis was performed with 60 randomly selected fetuses during the ultrasound examinations.

The transducer was aligned with the long axis of the fetal body so that the ductus venosus was positioned for visualization in the full length plane and included the inlet (isthmus) and outlet portions of the vessel (Fig. 1). The diameters of the vessel inner wall and mid-point of the ductus venosus were measured by calipers during the procedure. Doppler investigations of the ductus venosus flow velocity were also performed for relevant diameter measurements. Pulsed Doppler waveforms were recorded in the absence of fetal activity and breathing movements.[23] The sonographer performed detailed fetal echocardiography (level II scan) at 19 to 28 weeks of gestation under the direct supervision of the obstetric doctor. The procedures for

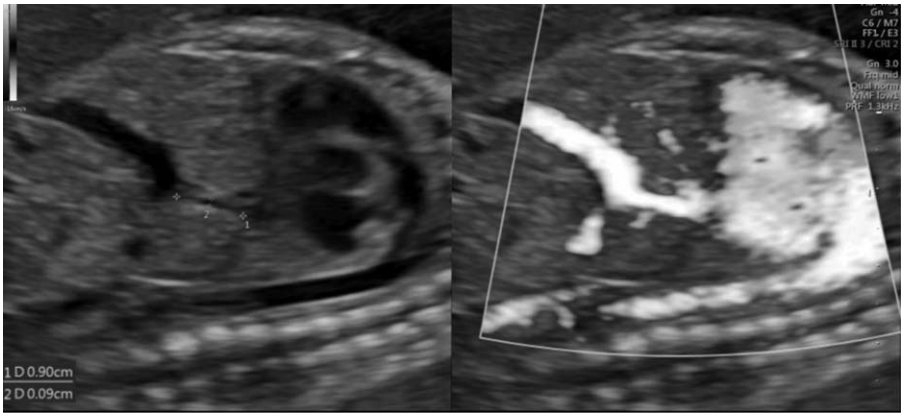

Figure 1. The full length of ductus venosus was identified in the mid-sagittal section of the fetal upper torso with B-mode and power Doppler mode ultrasonography.

evaluating fetal heart details and assessments for basic and extended cardiac screening are described elsewhere.[7,32] The standard fetal echocardiographic evaluation utilized 2-dimensional Gray-scale imaging, color, and color Doppler flow mapping. Two-dimensional B-mode echocardiography was used to examine the standard 4-chamber view, LVOT, RVOT, 3VV, and the basal short-axis view. All the fetuses with suspected CHD underwent diagnostic antenatal echocardiography within 1 to 2 weeks after the first routine screening ultrasound.

Statistical analysis was performed using SPSS (Ver. 13.0 for Windows, SPSS, Chicago, IL). Unless specific condition required otherwise, most of the data are expressed in mean and standard deviation (SD). Data were compared using independent *t* test as suitable. Performed correlation analysis between GA and DVR, as calculated using the Pearson correlation. A probability value of $P < 0.05$ was considered statistically significant.

3. Results

The median maternal age was 31 years (range, 18–43 years); the median maternal gravidity was 1 (range, 1–8); and median maternal parity was 0 (range, 0–3). The median gestation was 22^{+1} weeks (range, 19^{+0}–28^{+6} weeks).

Overall, the hearts of 970 singleton fetuses had a normal structure, and the hearts of 36 fetuses showed CHD (3.58%). The karyotype was normal in 1002 fetuses; the remaining 4 fetuses with CHD had abnormal karyotypes. Among the 4 fetuses with aneuploidy, all had trisomy 18.

The average normal fetal DVL/DVW ratio was 10.41 ± 0.74. Table 1 presents the number of cases, mean ± SD of the DVL, DVW, and the DVR at 19^{+0} to 28^{+6} weeks' gestation. Regression analysis (Fig. 2) revealed a constant relationship between the DVR and GA. The correlation coefficient of GA and DVR, as calculated using the Pearson correlation, was 0.038 ($P = 0.24$) (Table 2). In the assessment of ductus venosus blood flow velocity, the ductus venosus systolic peak velocity/systolic A-wave velocity ratio was 1.19 ± 0.18 for normal fetuses and 9.30 ± 13.68 for fetuses with CHD (Table 3).

Among the 970 fetuses without CHD, only 14 (1.44%) had a DVR greater than 2 SDs below the mean. Among the 36 fetuses with CHD, 32 (88.89%) had a DVR greater than 2 SDs below the mean (Table 3, Fig. 3). For the 4 aneuploid (trisomy 18) fetuses with CHD (1 coarctation of the aorta, 3 ventricular septal defect), the ductus venosus was dilated in 3 of the 4 fetuses (75.0%). Among the 36 fetuses with CHD diagnosed prenatally, 19.44% (7/36) also had extracardiac anomalies (hydrops fetalis, congenital cystic adenomatoid malformation (CCAM), congenital diaphragmatic hernia, choroid plexus cyst, and so on). Of the 36 fetuses with CHD, 4 died in utero (11%); of the remaining 32 (89%) fetuses with CHD, the women elected to terminate the pregnancies. Based on the receiver operating characteristic (ROC) analysis, decreased DVL/DVW ratios of ≤8.85 showed a significant area under the ROC curve (0.98), yielding sensitivity of 88.90% and specificity of 99.10% for detection of the 36 fetuses with CHD (Fig. 4). Using this simple cut-off would screen up to 88.90% of different types of CHDs (Table 4). The positive predictive value (PPV) and negative predictive value (NPV) were 78.05% and 99.59%, respectively. Of the 36 fetuses with CHD, 24 (66.67%) CHD fetuses were detected using conventional fetal echocardiography (4-chamber view with 2 ventricular outflow tracts) in our study.

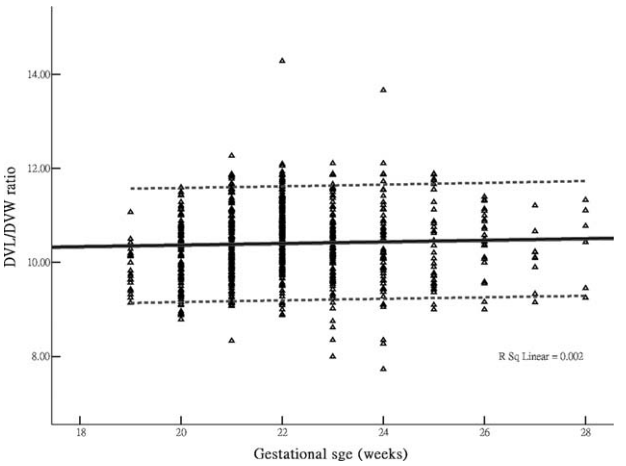

Figure 2. Relationship between ductus venosus length/ductus venosus width (DVL/DVW) ratio and gestational age in fetuses without CHD. Mean and 95% confidence interval (CI) are shown.

The intraobserver difference was assessed with 60 randomly selected fetuses during the ultrasound screening. The Cronbach alpha of intraobserver variability was 1.00 for DVL and 0.99 for DVW. The mean intraobserver variabilities of DVL and DVW were 0.0003 and 0.001, respectively.

4. Discussion

Neonatal morbidity and mortality rates are highly associated with increased prenatal detection rates of cardiac anomalies.[2,3]

Table 1

The mean and standard deviation for ductus venosus length, ductus venosus width, and ductus venosus length/ductus venosus width ratio at 19 to 28 weeks' gestation among fetuses without congenital heart disease (n = 970).

Gestational age, wk	N	DVL	SD	DVW	SD	DVL/DVW ratio	SD
19^{+0}–19^{+6}	24	6.91	1.46	0.70	0.15	9.91	0.45
20^{+0}–20^{+6}	131	7.40	1.39	0.73	0.14	10.23	0.67
21^{+0}–21^{+6}	264	8.37	1.55	0.81	0.16	10.41	0.69
22^{+0}–22^{+6}	260	8.69	1.59	0.82	0.16	10.60	0.72
23^{+0}–23^{+6}	134	8.99	1.71	0.87	0.17	10.39	0.73
24^{+0}–24^{+6}	81	9.37	1.81	0.92	0.18	10.29	0.91
25^{+0}–25^{+6}	33	9.76	1.99	0.95	0.22	10.35	0.91
26^{+0}–26^{+6}	26	11.43	2.19	1.10	0.23	10.47	0.67
27^{+0}–27^{+6}	10	10.83	2.25	1.07	0.19	10.10	0.59
28^{+0}–28^{+6}	7	11.14	1.71	1.08	0.19	10.40	0.79

DVL = ductus venosus length, DVL/DVW ratio = ductus venosus length/ductus venosus width ratio, DVW = ductus venosus width, SD = standard deviation.

Table 2

The Pearson correlation coefficient of gestational age and ductus venosus length/ductus venosus width ratio, ductus venosus width, ductus venosus length.

		GA	DVR	DVW	DVL
GA	Pearson correlation	1	0.038	0.413*	0.436*
	Sig. (2-tailed)		0.242	0.000	0.000
DVR	Pearson correlation		1	−0.259*	0.072†
	Sig. (2-tailed)			0.000	0.025
DVW	Pearson correlation			1	0.942*
	Sig. (2-tailed)				0.000
DVL	Pearson correlation				1
	Sig. (2-tailed)				

DVL = ductus venosus length, DVR = ductus venosus length/ductus venosus width ratio, DVW = ductus venosus width, GA = gestational age.
* Correlation is significant at the 0.01 level (2-tailed).
† Correlation is significant at the 0.05 level (2-tailed).

In fetal echocardiographic screening, the detection rates of different structural abnormalities depend on specific training, skill, and experience.[30] In our study, we used a simple and objective method of screening for fetal CHD. We found that the DVR in the fetal sagittal view was an easy and reliable way to detect the majority of CHDs.

Several researchers reported the association of CHD with abnormal blood flow through the fetal DV.[18,19,33,34] Fetal DV Doppler flow reflects the central venous system pressure. It is highly correlated with CHD and has become the best method for the diagnosis of CHD. The merits of ductus venosus flow evaluation during fetal CHD screening in the early- and mid-second trimesters have been confirmed by large-scale trials.[19,33,34] In our study, the DV systolic peak velocity/systolic A-wave ratio was greater in the CHD group as compared with the normal group. Hung et al[19] evaluated the resistance of ductus venosus blood flow in fetuses with CHD during the second trimester of pregnancy and found that increased pulsatility index was highly correlated with fetal cardiac anomalies. Chelemen et al and Borrell et al used DV flow in detecting cardiac defects in the first trimester. They found that abnormal DV A-wave (absent or reverse A-wave) and abnormal DV pulsatility index were observed in fetuses with major cardiac defects.[33,34] Martinez et al reported using abnormal ductus venosus blood flow and normal NT for the detection of CHD at 11 to 13 weeks' gestation. However, the sensitivity and PPV associated with this technique were low.[35] The measurement of the ductus venosus flow by ultrasound is time consuming, requires specialized skills, and requires the fetus to be in a cooperative position during Doppler assessment.[1,17,23] Visualization of the fetal heart at the first trimester is difficult due to the following reasons: high maternal body mass index, unfavorable fetal position, placental location, retroversion of uterus, amniotic fluid volume, and operator experience. The above disadvantages are not encountered in the second trimester. The ductus venosus lumen can be easily identified in the ultrasound in the second trimester. The operators can measure the ductus venosus length and width in the fetal true sagittal view and detect the fetuses at risk of CHD easily.

Conventional fetal echocardiography can be used to diagnose prenatal CHD in the second trimester. However not all physicians possess the high skills required for fetal echocardiography and advanced ultrasound equipment. In our study, the sagittal view of the ductus venosus image was chosen because it was easy to obtain, and at this plane, the resulting dilatation would be obvious. Our study used a simple method, DVL/DVW ratio, to detect the fetuses at risk for CHD. We found that ductus venosus lumen measurement is easier than DV hemodynamic measurement.

In the correlation analysis, the correlation coefficient between GA and DVW was calculated using the Pearson product–moment correlation ($r = 0.41$, $P = 0.00$) (Table 2); DVW increased with advancing gestation. These results are similar to those in some of the literatures. Chanthasenanont et al[22] assessed the DV diameter in late second- and third-trimester fetuses (17–37 weeks' gestation) and found that the ductus venosus diameter increased with GA.

Table 3

The mean and standard deviation of the fetal ductus venosus flow velocity for normal fetuses and fetuses with congenital heart disease.

	Normal (n = 970), mean (SD)	CHD (n = 36), mean (SD)	*t*	*P*
DVs (cm/s)	66.45 (19.76)	65.01 (18.81)	0.421	0.674
DVa (cm/s)	56.86 (17.99)	17.62 (12.54)	12.792	0.000
DVs/DVa ratio	1.19 (0.18)	9.30 (13.68)	−3.557	0.001

CHD = congenital heart disease, DVa = ductus venosus A-wave velocity, DVs = ductus venosus systolic velocity, SD = standard deviation.

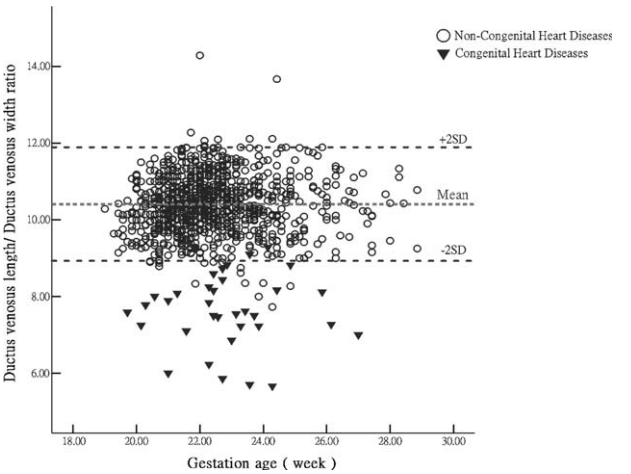

Figure 3. Relationship between ductus venosus length/ductus venosus width (DVL/DVW) ratio and gestational age in fetuses with congenital heart diseases and those without congenital heart diseases. Mean and ±2 SD are shown.

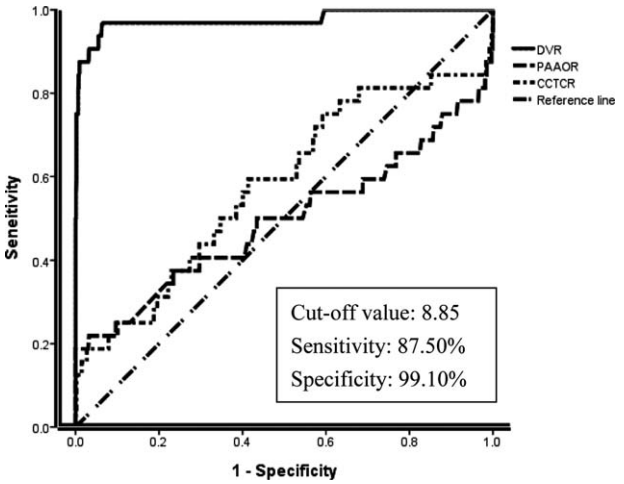

Figure 4. Receiver operating characteristic curve for the analysis of the length/width ratio of the ductus venosus in the prediction of congenital heart diseases with the conventional fetal echo results. CCTCR = cardiothoracic circumference ratio, PAAOR = pulmonary artery/aorta ratio.

Bellotti et al evaluated the size of the ductus venosus in human fetuses using ductus venosus flow measurements. They found a strong correlation between ductus venosus dilatation and reduced atrial velocity.[23] Both studies showed that high cardiac preload induced changes in the ductus venosus size, which then caused ductus venosus flow variation. Moreover, previous studies reported that in the second trimester, the dilatation of the DVW is a sonographic marker of extraordinary DV flow, and an exceptional ductus venosus waveform is associated with an increased risk of CHD.[18–20,34] Our results showed that the diameter of the DVW was linear across GA, but the regression analysis revealed that the DVR remained almost constant for the late second and early third trimesters for normal fetuses (adjusted $R^2 = 0.00$, $P = 0.26$). In addition, the correlation coefficient between GA and DVR was calculated using the Pearson product–moment correlation ($P = 0.26$).

Furthermore, about 95% of trisomy 18 abnormalities are associated with cardiac defects.[6] We identified 4 fetuses with aneuploidy, and 3 of the 4 (75.00%) had trisomy 18; they all had significantly different DVRs. Therefore, the DVR helps to identify CHD in fetuses with chromosomal abnormalities. We recommend that all fetuses diagnosed prenatally with CHD undergo karyotyping as early as possible. On the other hand, cardiac anomalies are often associated with extracardiac malformations. Among all 36 fetuses with CHD, 19.44% (7/36) also had extracardiac anomalies.

Our research concerned mainly cardiac structural malformations potentially detectable using DVR. If the DVR was less than 8.85, there was a 99.10% probability that the heart structure was normal. Using this simple cut-off would screen up to 88.90% of all congenital cardiac abnormalities (Table 4). The sensitivity of the DVR was 88.90% and the specificity was 99.10%, with the PPV and NPV being 78.05% and 99.59%, respectively. Of the 36 fetuses with CHD, 24 were detected using conventional fetal echocardiography (4-chamber view with 2 ventricular outflow tracts), and 32 were detected using the DVR method in our study. The detection rate with conventional fetal echocardiography was less than that with the DVR method. According to the 2013 sonographic screening examination of the fetal heart practice guidelines of ISOUG, in conventional fetal echocardiography, a high level of experience in fetal heart scanning and 15 to 20 minutes per scan are required.[8] However, there is no special skill required for DVL and DVW measurement, and the procedure requires less than 5 min.

DVR can provide a prompt differentiation of fetuses at risk of CHD. Our method does not provide the final diagnosis; we simply offer a quick and easy CHD screening method for the operator who is not very experienced or has no fetal heart screening training. The performance characteristics of the DVR for fetal CHD risk assessment in the second trimester of pregnancy show that the ratio is a valuable and effective screening tool for prenatal CHD detection.

There are 2 limitations to our study. First, we could not include all the different types of fetal CHDs. Second, autopsies were not done on the fetuses with CHD for Chinese cultural reasons. However, all the fetuses with suspected CHD underwent antenatal diagnostic echocardiography within 1 to 2 weeks after the first routine screening ultrasound. The real benefits of this additional method of fetal vital CHD assessment can only be measured in prospective, randomized studies; thus future studies are needed.

In conclusion, we found a strong correlation between fetal DVL and DVW in the late second and early third trimesters and a lower DVR in fetuses with CHD than that in fetuses without CHD at 19 to 28 weeks' gestation. We recommend using 8.85 as a cut-off value for the DVR for detecting fetal CHD in the late second and early third trimesters in the Chinese population.

Table 4

Ductus venosus length/ductus venosus width ratios for different types of congenital heart diseases.

Congenital heart disease	n	DVR	DVR < 8.85, n (%)
LVOT/RVOT disease	13	5.67–8.82	13 (100.00%)
CCAM with congenital heart disease	5	7.50–9.26	4 (80.00%)
TOF	7	6.23–9.29	6 (85.71%)
Trisomy 18 with congenital heart disease	4	7.23–9.10	3 (75.00%)
Other cardiac diseases	7	6.86–10.57	6 (85.71%)
Total	36	5.67–10.57	32 (88.89%)

CCAM = congenital cystic adenomatoid malformation, DVR = ductus venosus length/ductus venosus width ratios, LVOT = left ventricular outflow tract, RVOT = right ventricular outflow tract, TOF = tetralogy of Fallot.

LVOT/RVOT disease (transposition of the great arteries, double outlet right ventricle, pulmonary artery stenosis, pulmonary stenosis, aortic stenosis, common truncus), CCAM with congenital heart disease (ventricular septal defect, dextrocardia, compressed heart).

Trisomy 18 with congenital heart disease (coarctation of the aorta, ventricular septal defect). Other cardiac diseases (pericardio effusion, complex congenital heart disease, hypoplasia right ventricle, atrioventricular septal defect, hypoplastic left heart syndrome, Ebstein anomaly, total anomalous pulmonary venous return).

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