Arch Gynecol Obstet (2016) 293:345–350
DOI 10.1007/s00404-015-3796-9

MATERNAL-FETAL MEDICINE

Effects of fetal cardiac anomalies on ductus venosus and aortic isthmus doppler profiles

Gülşah İlhan[1] · Ahmet Cem İyibozkurt[2] · Halil İbrahim Kalelioğlu[2] · Lemi İbrahimoğlu[2] · Ali Galip Zebitay[1] · Meryem Kürek Eken[3] · Ayşe Filiz Gökmen Karasu[4]

Received: 13 February 2015 / Accepted: 16 June 2015 / Published online: 25 June 2015

Abstract
Purpose To demonstrate the blood flow profiles of fetuses with cardiac anomalies at the level of Ductus venosus (DV) and Aortic isthmus (AI) to evaluate the effects of fetal cardiac anomalies on these profiles, and how these profile changes contribute to cardiac anomaly screening studies as a marker.
Methods DV and AI doppler studies were applied to 64 singleton pregnant women with fetal cardiac anomalies and 74 pregnant women with healthy fetuses. DV-PVIV (peak velocity index for veins) for DV and IFI (isthmic flow index) for AI were used.
Results DV doppler studies in fetuses with cardiac anomalies and healthy fetuses did not show statistically significant difference. But the results of the AI doppler studies had statistically significant difference in the fetal cardiac anomaly group with the exception of cases with dilatation and regurgitation. When right-sided heart anomaly and the remaining cases were compared with the control groups, AI doppler results also showed lower IFI values.
Conclusions DV doppler studies in the second or third trimester may not be suitable as a screening test for congenital heart disease, but AI doppler studies might be considered as a supporting parameter. But further studies are needed for routine clinical use.

Keywords Doppler · Ductus venosus · Aortic isthmus · Fetal cardiac anomaly

✉ Gülşah İlhan
gulsah.keskin.84@hotmail.com

Ahmet Cem İyibozkurt
Cem.iyi@yahoo.com

Halil İbrahim Kalelioğlu
i.kalelioglu.@gmail.com

Lemi İbrahimoğlu
lemi.ibrahimoglu.@gmail.com

Ali Galip Zebitay
galenusgz@hotmail.com

Meryem Kürek Eken
meryemkurek@yahoo.com

Ayşe Filiz Gökmen Karasu
afgokmen@gmail.com

[1] Suleymaniye Research and Education Hospital, Istanbul, Turkey

[2] İstanbul University İstanbul Medical Faculty, Istanbul, Turkey

[3] Zeynep Kamil Research and Education Hospital, Istanbul, Turkey

[4] Balıkesir State Hospital, Balıkesir, Turkey

Introductıon

Congenital heart disease (CHD) incidence is about 8–10 per 1000 live births. The incidence of CHD in stillbirths is 3–4, 10–25 % in abortion throughout all gestational weeks, 2 % in premature infants. Half of the children with congenital heart disease die in the first year of life. Therefore, early diagnosis, even in utero and early treatment planning is important in order to reduce the morbidity and mortality [1–6].

CHD can be classified as cyanotic and acyanotic according to the oxygenation of blood. It can also be classified with regards to the anatomic localization of the heart chambers, heart valves, and major vessels and with hemodynamic changes observed due to these settlements (Table 1) [7, 8].

Fetal echocardiography in the evaluation of congenital heart disease is the first choice in diagnostic terms. In addition to use of ultrasound, use of Doppler flow gives

Table 1 Classification of congenital heart disease according to anatomic localization of heart chambers, heart valves, and major vessels or hemodynamic changes (Kisslo et al. [8])

When chambers and valves are in normal sequence and position	When chambers and valves are not in normal sequence or relationship
When shunting is predominant	Anomalies of relationships between atria and ventricles
Atrial septal defects (ASD)	Double inlet or right ventricle (with univentricular heart)
Ventricular septal defects (VSD)	Atrioventricular discordance (corrected transposition)
Atrioventricular septal defects (AV canal defects)	
When stenosis or obstruction is predominant	Anomalies or relationships between ventricles and great vessels
Absent atrioventricular connections (tricuspid and mitral atresia)	Tetralogy of Fallot
Absent or obstructed ventriculo-great arterial connections (pulmonary atresia,aortic)	Double-outlet right and left ventricles
	Truncus arteriosus
Obstructed great arteries (coarctation of the aorta, aortic atresia)	Ventriculo-great arterial discordance (transposition of the great vessels)
Obstructed venous inflow (total anomalous pulmonary venous return)	
Anomalous valve position (Ebsteins's anomaly)	

detailed information about fetal heart function. Early prenatal diagnosis of cardiac abnormalities has improved outcome of fetuses with severe cardiac malformations [9].

First-trimester DV wave analysis has been evaluated in many studies. These studies focus on detecting chromosomal anomalies with increased NT (Nuchal Thickness). As a result, cardiac anomalies with increased NT and abnormal DV wave patterns may have a common pathophysiological mechanism have been concluded [10–12]. Fewer DV studies are performed in the second trimester fetuses with cardiac anomalies [13–16]. Aortic isthmus Doppler studies are more likely related to placental insufficiency and intrauterine growth restriction (IUGR). Studies in the literature up to date aimed to detect fetuses with IUGR at early weeks in order to reduce mortality and morbidity by measuring the rate of aortic isthmus blood flow [17, 18]. In our study, we evaluated aortic isthmus Doppler profiles of fetuses with congenital heart disease by making a different study than done up to date in the literature.

In this study, we aimed to provide a new parameter that can shed light on fetal cardiac anomaly screening. For this purpose, we evaluated the effects of fetal cardiac anomalies on Ductus venosus (DV) and Aortic isthmus (AI) blood flow profiles and assessed how these profile changes can contribute to cardiac anomaly screening. We hypothesized that cardiac anomalies can make changes reflecting to the DV and AI flow profiles. They can also be used as a marker in screening studies.

Methods

The study was conducted at Istanbul Medical Faculty, Department of Perinatology, between April 2012 and August 2013. Following an ethics committee approval, 64 pregnant women between 19 and 39 weeks with fetal cardiac anomalies (Group A) and a control group of 74 pregnant women with healthy fetuses (Group B) were evaluated. Informed consents were taken from all patients. Fetal echocardiography and Doppler ultrasound were performed using Voluson 730 Expert with Multi-frequency convex transducer. Multiple pregnancies, fetuses smaller than 18 weeks of gestation and further along than 40 weeks of gestation, pregnant women with gestational diabetes, thyroid gland disease, preeclampsia, and problems of which may affect fetal hemodynamics were excluded. Fetuses with extra-cardiac anomalies, chromosomal anomalies, intrauterine growth retardation, and persistent non-sinus rhythm were also excluded.

DV doppler was performed transabdominally during fetal apnea when the heart rate range between 120 and 160 per minutes in the right ventral mid-saggital section. Fetal thorax and abdomen were enlarged to fill the entire screen. Pulsed Doppler cursor was placed on the DV where it originates from umbilical vein. The window was small enough (0.5–1 mm) to prevent contamination with adjacent veins. Insonation angle was kept less than 30°. At least three different series of systole-diastole (SD) waves were recorded and the average value was taken for analysis. The sampling interval (gate) was kept small enough to completely cover the vessel. Pathologic Doppler findings were defined as an increase in resistance of Pulsatility index (PIV > 95, $P > 2$ SD), increase in peak velocity index for veins (PVIV > 95, $P > 2$ SD), reversed a wave existence. In this study, we have used measurements of PVIV. It is calculated as [PVIV $= (S - A)/D$].

AI doppler was displayed in longitudinal cross section of the aortic arch, or three-vessel trachea view. Insonation angle was brought to less than 30°. Isthmic flow index (IFI) for the AI was calculated. Sampling interval (gate) was

kept small enough to completely cover the vessel. At least three different series of waves were recorded; the average value was taken for analysis. Average values of PSV (peak systolic velocity), EDV (end diastolic velocity), TAMXV (time-averaged maximum velocity), PI (pulsatility index), and RI (resistance index), and IFI were calculated. IFI was calculated by dividing the sum of the integrals of systolic (S) and diastolic (D) Doppler flow by the integrals of systolic (S) Doppler flow. In our study, we used IFI for evaluation of aortic isthmus blood flow.

Group A was divided into Group A1, Group A2, Group A3, Group A4 subgroups—shunt-dominant group, stenosis or obstruction dominant group, dilatation or failure dominant group, ventricle and great artery anomalies group; respectively. In addition, Group A was divided into subgroups of isolated right heart anomalies (Group AA) and others (Group AB).

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) 17.0 for Windows. For comparisons, Mann–Whitney *U* and Kruskal–Wallis tests were used. The results were reported with 95 % confidence interval. $p < 0.05$ were considered statistically significant.

Results

64 cases had fetal cardiac anomalies (Group A) and 74 were healthy fetuses (Group B). Group A mean maternal age was 29.35 (18–42) and Group B mean maternal age was 30.25 (17–39), respectively. Mean gestational age of fetuses in group A was 27.9 (20–36) weeks. Mean gestational age of fetuses in Group B was 28.1 (20–36) weeks. Number of previous pregnancies for Group A was 1, 7; fetal sex male–female ratio was 2.2/1. Number of previous pregnancies for Group B was 1, 7; fetal sex male–female ratio was 2/3. None of the patients declared cardiotoxic drug use.

Group A included 13 Tetralogy of Fallot, 8 aortic stenosis, 7 AVSD, 4 hypoplastic left heart, 10 muscular VSD, 3 tricuspid insufficiency, 3 pulmonary stenosis, 1 ASD, 1 coarctation of the aorta and perimembranous VSD, 1 bicuspid aorta, 1 corrected transposition, 1 hypoplastic right heart, 1 mitral regurgitation, 1 truncus arteriosus, 5 double-outlet right ventricle, 2 Taussig Bing, 1 right ventricle Rhabdomyoma, and 1 Transposition of Great Arteries (TGA) patients.

Group A1 (left-to-right shunt-dominant group) included 1 ASD, 10 muscular VSD, and 7 AVSD patients. Group A2 (obstruction and stenosis dominant group) included 8 aortic stenosis, 4 hypoplastic left heart, 3 pulmonary stenosis, 1 coarctation of the aorta and perimembranous VSD, 1 hypoplastic right heart, 1 right ventricle Rhabdomyoma, and 1 bicuspid aorta patients. Group A3 (dilation or failure dominant group) included 3 tricuspid insufficiency, and 1 mitral regurgitation patients. Group A4 (ventricular-major vascular abnormalities group) included 13 Tetralogy of Fallot, 1 TGA patients, 2 Taussig Bing, 5 double-outlet right ventricle, 1 truncus arteriosus, and 1 corrected transposition patients.

Average DV-PVIV of Group A was not statistically different from that of the control group (Table 2). But IFI value of Group A was significantly lower than that of Group B.There was no statistically significant difference when comparing A1, A2, A3, A4, and the control groups in terms of DV-PVIV value. ($P^b = 0.391$). In addition, these results did not change in the paired comparison (Table 3).

Comparison of IFI values of A1, A2, A3, A4, and control groups showed statistically significant difference. Also there was statistically significant difference when comparing each group with control group separately, with the exception of Group A3 and the control group ($P^c = 0.991$) (Table 3).

In Table 3, when control group was not included and A1, A2, A3, and A4 groups were evaluated among themselves in terms of DV-PVIV and IFI values; there was no statistically significant difference. ($P^a = 0.749$ and $P^a = 0.496$, respectively).

While we could not find statistically significant difference in terms of DV-PVIV, we categorized the cases as right-sided cardiac anomalies (Group AA) and the rest (Group AB).There was no statistically significant difference between fetuses with Group AA, AB, and control group when compared in terms of DV-PVIV ($P^b = 0.197$). Also there was no significant difference when compared in pairs (Table 4).

In Table 4, for IFI, when AA, AB, and control groups were compared, there was statistically significant difference ($P < 0.01$). When compared in pairs, there was no statistically significant difference between group AA and control group ($P^c = 0.135$), but there was statistically difference between group AB and control group. IFI value of AB group was significantly lower as compared to the control group values ($P < 0.001$).

When AA and AB groups were compared to each other for DV-PVIV and IFI, a statistically significant relationship was not observed.

Discussion

First-trimester DV wave profiles have been analyzed in many studies focusing on detecting chromosomal anomalies with increased NT. In these studies, the sensitivity of increased NT in detecting chromosomal anomaly is around 65–90 % [19–22]. Studies examining NT above 95th percentile detected abnormal DV waveforms independent of

Table 2 Comparison of DV-PVIV and IFI values of Group A and Group B

	G	*N*	*A*	SD	*P*	95 % CI
DV-PVIV $(S - A)/D$	Group A	64	0.66	0.21	0.089	0.61–0.71
	Group B	74	0.75	0.31		0.68–0.83
IFI $(S + D)/S$	Group A	64	1.06	0.13	<0.001*	1.03–1.10
	Group B	74	1.12	0.03		1.11–1.12

G group, *N* number, *A* average, *SD* standard deviation, *CI* confidence interval

* $P < 0.001$; Mann–Whitney *U* test

Table 3 Comparison of DV-PVIV and IFI values of A1, A2, A3, A4, and C groups

	G	*N*	*A*	SD	P^a	P^b	P^c	95 % CI
DV-PVIV $(S - A)/D$	A1	18	0.63	0.13	0.749	0.391	A1 → C:0.127	0.57–0.70
	A2	19	0.72	0.27			A2 → C:0.746	0.60–0.85
	A3	4	0.65	0.26			A3 → C:0.496	0.25–1.06
	A4	23	0.63	0.19			A4 → C:0.121	0.55–0.71
	C	74	0.75	0.31				0.68–0.83
IFI $(S + D)/S$	A1	18	1.08	0.04	0.496	0.001*	A1 → C:0.002**	1.06–1.10
	A2	19	1.01	0.23			A2 → C:0.008**	0.90–1.12
	A3	4	1.12	0.05			A3 → C:0.991	1.05–1.20
	A4	23	1.084	0.045			A4 → C:0.002**	1.064–1.1032
	C	74	1.117	0.032				1.109–1.1241

G group, *N* number, *A* average, *SD* standard deviation, *CI* confidence interval, *C* control

* $P < 0.01$; Kruskal–Wallis test ** $P < 0.01$; Mann–Whitney *U* test

[a] A1, A2, A3, A4

[b] A1, A2, A3, A4 and C

[c] A1, A2, A3, A4 and C in pairs

Table 4 Comparison of DV-PVIV and IFI values of AA, AB, and C groups

	G	*N*	*A*	SD	P^a	P^b	P^c	95 % CI
DV-PVIV $(S - A)/D$	AA	21	0.66	0.27	0.673	0.197	AA → C:0.149	0.54–0.78
	AB	44	0.66	0.17			AB → C:0.152	0.60–0.71
	C	74	0.75	0.31				0.68–0.83
IFI $(S + D)/S$	AA	21	1.10	0.04	0.099	<0.001*	AA → C:0.135	1.08–1.12
	AB	44	1.06	0.13			AB → C: <0.001**	1.02–1.10
	C	74	1.12	0.03				1.11–1.12

G group, *N* number, *A* average, *SD* standard deviation, *CI* confidence interval, C control

* $P < 0.001$; Kruskal–Wallis tests ** $P < 0.001$; Mann–Whitney *U* test

[a] AA, AB

[b] AA, AB and C

[c] AA, AB and C in pairs

the type of the heart defect. Fetal cardiac problem had been identified in all of the cases showing abnormal DV wave pattern in a case series of NT above 95. percentile [10]. As a result, it has been concluded that cardiac anomalies with increased NT and abnormal DV wave patterns may have a common pathophysiological mechanism [11]. Furthermore, increased NT and abnormal DV waveforms have also been associated with poor fetal outcome [12].

Fewer DV studies were performed in the second-trimester fetuses with cardiac anomalies. Devore et al. [14] have conducted a study of left ventricular hypoplasia in a fetus in the second trimester having normal DV flow pattern and found abnormal DV flow patterns in a fetus with main pulmonary artery atresia. In this study, sample size was too small. Borrel et al. [13] have reported a study of abnormal DV waveforms affecting mainly right heart

anomalies. In our study group, isolated right heart anomalies did not show a significant difference in the values of the DV-PVIV ($P^b = 0.197$).

Kiserud et al. [15, 16] reported that DV wave patterns of fetuses with CHD are altered. In the second and third trimesters, abnormal DV waveforms were detected in 64 % of fetuses with right ventricular inflow or outflow tract anomalies. DV flow velocity decreased with atrial contractions in 19 of 30 fetuses with cardiac anomalies. However, in this study, extra-cardiac malformations, aneuploidies, and arrhythmias were not excluded so leading to controversy. Therefore, in our study, subjects with maternal conditions that may affect fetal hemodynamics (gestational diabetes, thyroid gland disease, preeclampsia), concomitant non-cardiac abnormalities, chromosomal abnormalities, IUGR, and persistent non-sinus rhythm have been excluded.

Gembruch et al. reported a series of 146 fetuses with CHD. They concluded that Doppler studies of the ductus venosus in fetuses with isolated CHD do not present sufficient alterations to be a reliable marker for screening of CHD. Also, abnormal venous Doppler results were mainly attributed to myocardial dysfunction and also to severe right heart obstruction even in the absence of congestive heart failure. In our study, we eliminated fetuses with suggestive heart failure finding such as hydrops and cardiomegaly to left off DV changes secondary to heart failure [23].

When we could not find a significant difference between A1, A2, A3, A4, and control groups in terms of DV, we grouped subjects as isolated right heart anomalies (AA), and others as (AB). In a study which examined fetuses with isolated right heart anomalies, DV flow profiles remain unchanged in the presence of ventricular septal defect which equalizes the pressure between the two ventricles. Tricuspid atresia or Ebstein's anomaly without VSD, pulmonary stenosis, and pulmonary atresia will increase right atrial pressure and lead to increased pulsatility. In the absence of VSD, right-to-left shunt will increase and lead to closure of the foramen ovale. It will cause an increase in right atrial pressure and central venous pressure. Forward flow in diastole is reduced even if the atrium is in systole and disrupts the flow profile. It is also reported that increased flow resistance in DV in fetuses between 19 and 39 weeks with isolated right heart malformations has a sensitivity of 45 % [24]. In our study, there was no statistically significant difference between fetuses with right-sided cardiac anomaly (Group AA), the rest (AB), and control group when compared in terms of DV-PVIV ($P^b = 0.197$).

Aortic isthmus Doppler studies are more likely related to placental insufficiency and intrauterine growth restriction (IUGR). Under physiological conditions, the aortic isthmus doppler shows antegrade flow in both systole and diastole because placenta has less resistance than fetal upper body. In patients with progressive placental insufficiency, placental resistance increases and retrograde flow in the aortic isthmus is seen. Decreased aortic isthmus blood flow was observed in all IUGR fetuses. The studies up to date aimed to detect the fetuses with IUGR in the early weeks by measuring the rate of aortic isthmus blood flow. Early detection of fetal decompensation in growth-restricted fetuses by utilizing fetal aortic isthmus doppler before DV Doppler distortion in order to reduce mortality and morbidity constitutes the basis of the work done to improve the existing algorithms [11, 17, 25]. In our study, we evaluated aortic isthmus Doppler profiles of fetuses with congenital heart disease by conducting a different study than the previous ones in the literature.

Mild-to-moderate left ventricular dysfunctions such as aortic stenosis or stenosis of the left ventricular outflow tract will reduce output and therefore the forward current of isthmus. Decreased output (IFI >1) will lead to reduced isthmic flow, and the flow is forward in systole and diastole [26]. In severe aortic stenosis, reverse flow in the aortic isthmus is observed [27]. The most extreme example of this situation is hypoplastic left heart syndrome. Left ventricle accounts for a large portion of cardiac output in right ventricular dysfunction or outlet obstruction; so isthmic forward flow is increased. In this situation, IFI changes are variable [26, 27]. In our study, IFI values of Group A (fetuses with CHD) were significantly lower than that of Group B (normal fetuses). Comparison of IFI values of A1, A2, A3, A4, and control groups showed statistically significant difference. Also there was statistically significant difference when comparing each group with the control group seperately. Only there was no difference between A3 and the control group. When comparing A1, A2, A3, and A4 groups in pairs in terms of IFI, there was no difference.

As a result, DV doppler studies in fetuses with cardiac anomalies are not a reliable predictor. But the results of the Aortic isthmus Doppler studies have shown statistically significant difference in the fetal cardiac anomaly group with the exception of cases with dilatation and regurgitation (A3). Tetralogy of Fallot, aortic stenosis, atrioventricular septal defect, hypoplastic left heart, muscular Ventricular septal defect (VSD), pulmonary stenosis, atrial septal defect, aortic coarctation, and perimembranous VSD, bicuspid aorta, corrected transposition, hypoplastic right heart, truncus arteriosus, double-outlet right ventricle, Taussig Bing, rhabdomyoma and Transposition of Great Arteries (TGA) showed lower IFI values. When right-sided heart anomalies (Group AA) that were tetralogy of Fallot, tricuspid insufficiency, rhabdomyoma of right ventricle, hypoplastic right ventricle, pulmonary stenosis, and the remaining cases (Group AB) were compared with control

groups, Aortic isthmus doppler results showed also lower IFI values.

According to our study results, Ductus Venosus Doppler studies in the second and third trimesters may not be suitable as a screening test for any CHD group, although Aortic isthmus Doppler (IFI) studies may be considered as a supporting parameter. Measuring lower IFI values might be a clue for a structural heart disease and the physician should give more attention to the fetal heart. Moreover, after a normal fetal echocardiography, checking AI doppler profiles may serve as a safety valve mechanism for overlooked congenital heart diseases. But further studies are needed to determine the appropriate gestational age for examination and to clarify the test reproducibility.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. The authors have full control of all primary data and they agree to allow the journal to review their data if requested.

Ethics committee approval Ethics committee approval was received for this report from the local ethics committee.

Informed consent Written informed consent was obtained from patient who participated in this study.

References

1. Aydoğan Ü (2000) Fetal ve neonatal dolaşım. In: Dadaloğlu T (ed) Neonataloji. Nobel tıp kitapevleri, Ankara, pp 387–390
2. Bernstein D (2000) Epidemiology and genetic basis of congenital heart disease. In: Berhman RE, Kliegman RM, Jenson HB (eds) Nelson texbook of pediatrics, 16.baskı. W.B. saunders Company, Philadephia, pp 1499–1502
3. Brennan P, Young ID (2001) Congenital heart malformations: etiology and associations. 6:17–25
4. Dawes GS (1962) The umbilical circulation. Am J Obstet Gynecol 84:1634
5. Guyton AC, Hall JE (1996) Fetal ve neonatal fizyoloji. In: Guyton AC, Hall JE. Çeviri Ed. Çavuşoğlu H (eds) Tıbbi Fizyoloji, 19. baskı (Türkçe), Nobel Kitap evi, İstanbul, pp 1047–1056
6. Gürakan B (2004) Konjenital kalp hastalıklarının değerlendirilmesi. In: Yurdakök M, Erdem G (eds) Neonataloji. Ankara 63, pp 503–512
7. Edwards WD (2001) Classification and terminology of cardiovascular anomalies. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ (eds) Moss & Adams heart disease in infants, children, and adolescent including the fetus and young adult, 6.baskı. Lippincott Williams and Wilkins, Philadelphia, pp 118–137
8. Kisslo J, Adams D, Leech G (2000) The use of echocardiography in congenital heart disease. Essentials of echocardiography http://www.echoincontext.com
9. Kovalchin JP, Silverman NH (2004) The impact of fetal echocardiography. Pediatr Cardiol 25(3):299–306
10. Brown R, Di Luzio L, Gomes C, Nicolaides KH (1998) The umbilical artery pulsatility index in the first trimester: is there an association with increased nuchal translucency or chromosomal abnormality? Ultrasound Obstet Gynecol 12:244–247
11. Haak MC, Twisk JW, Bartelings MM, Gittenberger-de Groot AC, van Vugt JM (2003) Ductus venosus flow velocities in relation to the cardiac defects in first-trimester fetuses with enlarged nuchal translucency. Am J Obstet Gynecol 188:727–733
12. Huisman TWA, Bilardo CM (1997) Transient increase in nuchal translucency thickness and reversed end-diastolic ductus venosus flow in a fetus with trisomy 18. Ultrasound Obstet Gynecol 10:397–399
13. Borrell A (2004) The ductus venosus in early pregnancy and congenital anomalies. Prenat Diagn 24:688–692
14. DeVore GR, Horenstein J (1993) Ductus venosus index: a method for evaluating right ventricular preload in the secondtrimester fetus. Ultrasound Obstet Gynecol 3:338–342
15. Kiserud T (2001) The ductus venosus. Semin Perinatol 25:11–20
16. Kiserud T, Rasmussen S, Skulstad S (2000) Blood flow and the degree of shunting through the ductus venosus in the human fetus. Am J Obstet Gynecol 182:147–153
17. Fouron JC, Gosselin J, Amiel-Tison C et al (2001) Correlation between prenatal velocity waveforms in the aortic isthmus and neurodevelopmental outcomes between the ages of 2 and 4 years. Am J Obstet Gynecol 184:630–636
18. Makikallio K, Jouppila P, Rasanen J (2003) Retrograde aortic isthmus net blood flow and human fetal cardiac function in placental insufficiency. Ultrasound Obstet Gynecol 22:351–357
19. Antolín E, Comas C, Torrents M, Muñoz A, Figueras F, Echevarría M, Cararach M, Carrera JM (2001) The role of ductus venosus blood flow assessment in screening for chromosomal abnormalities at 10–16 weeks of gestation. Ultrasound Obstet Gynecol 17:295–300
20. Bilardo CM, Müller MA, Zikulnig L, Schipper M, Hecher K (2001) Ductus venosus studies in fetuses at high risk for chromosomal or heart abnormalities: relationship with nuchal translucency measurement and fetal outcome. Ultrasound Obstet Gynecol 17:288–294
21. Borrell A, Antolin E, Costa D, Farre T, Martinez JM, Fortuny A (1998) Abnormal ductus venosus blood flow in trisomy 21 fetuses during early pregnancy. Am J Obstet Gynecol 179:1612–1617
22. Matias A, Gomes C, Flack N, Montenegro N, Nicolaides KH (1998) Screening for chromosomal abnormalities at 10–14 weeks: the role of ductus venosus blood flow. Ultrasound Obstet Gynecol 12:380–384
23. Gembruch U, Meise C, Germer U, Berg C, Geipel A (2003) Venous Doppler ultrasound in 146 fetuses with congenital heart disease. Ultrasound Obstet Gynecol 22:345–350
24. Berg C, Kremer C, Geipel A (2006) Ductus venosus blood flow alterations in fetuses with obstructive lesions of the heart. Ultrasound Obstet Gynecol 28:137–142
25. Bonnin P, Fouron JC, Teyssier G, Sonesson SE, Skoll A (1993) Quantitative assessment of circulatory changes in the fetal aortic isthmus during progressive increase of resistance to umbilical blood flow. Circulation 88:216–222
26. Ruskamp J, Fouron JC, Gosselin J, Raboisson MJ, Infante-Rivard C, Proulx F (2003) Reference values for an index of fetal aortic isthmus blood flow during the second half of pregnancy. Ultrasound Obstet Gynecol 21:441–444
27. Mari G, Deter RL (1992) Middle cerebral artery flow velocity waveforms in normal and small-for-gestational-age fetuses. Am J Obstet Gynecol 166:1262–1270