Correlation between developmental stages of the human heart and gestational ages

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ABSTRACT

Objectives: In this study we aimed to investigate the normal developmental pattern of the human fetal heart in second and third trimester, and to evaluate the correlation of the values with the gestational age (GA).

Methods: Seventy spontaneously aborted human fetuses with no external malformations were investigated and 11 parameters from each were assessed. The relationship of these parameters with the GA was evaluated by linear regression and correlation analyses using statistical methods. In addition, the values were compared to the gender and sides of the heart using Student t-test. This study was performed at the Department of Anatomy, Meram Medical Faculty, Selcuk University, Konya, Turkey, during the period from 2000 to 2004.

Results: There was a statistically significant linear relationship between the heart wall thicknesses, the development of the valves of the heart and GA. The mean values of the right side of the heart were found to be higher than those of the left side, and differences were statistically significant ($p<0.05$). Although, most of the parameters were found to be higher in females, only 2 of them were statistically significant. All parameters of the cardiac valves measured were significantly higher in the second trimester. There was no difference regarding the correlation ratio of the trimesters between the pulmonary valve diameter and GA. The measurement of the cardiac valves did not show any differences regarding the gender.

Conclusion: This study presents the normal values of the development of the fetal heart in second and third trimester that may provide useful background information for clinical approaches.

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Congenital heart malformations are the most common anomalies encountered in pediatric clinics in terms of both frequency and severity. The incidence of congenital heart abnormalities is 3-9 per 1000 livebirths.[1] That is why it is important to evaluate the developmental stages of the heart in order to assess any anomaly and to determine its cause. A number of morphometric studies on the development of heart during the intrauterine period, and the assessment of intracardiac anatomy and anomalies have been performed. Some of these studies were concerned with the right and left ventricular development,[2-6] others described interventricular,[3,4,7-9] and atrioventricular septa[10,11] or assessed the morphometry of atrioventricular valves.[9] Most studies have focused on the numbers of heart chambers, the measurements of length and width of the fetal heart during pregnancy,[12] and the functional development of heart.[13-17] Some of these studies have reported that the right side of the fetal heart is the dominant side.[6,18] There are some other studies that do not confirm this approach.[3,19] High-frequency vaginal ultrasound probes have improved embryonic imaging in the first trimester, making early detection of fetal malformations possible. In the second trimester, the 2-dimensional

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echocardiography allows more detailed visualization of the larger fetal cardiac structures. Until recently, prenatal diagnosis of fetal cardiac malformations was restricted to the second and third trimester.[20] The aim of this study was to determine the normal developmental model of the heart in the human fetuses during the second and third trimester, to measure the diameter of the valves of the heart, to establish the changes in the wall thicknesses of the right and left heart, and to study the correlation between the data obtained, the gender and the gestational ages (GA).

Methods. Seventy spontaneously aborted human fetuses (35 male and 35 female) that had apparently no pathologic feature were the material of the present study. They were fixed with formalin 10% using immersion technique. Fetuses were divided into 2 groups according to their GA estimated by crown rump length (CRL).[21] The first group comprised 49 fetuses (23 males and 26 females) in the second trimester, the second group comprised 21 fetuses (12 males and 9 females) in the third trimester (**Table 1**). The thoracic wall was opened, and the cavae and pulmonary veins were cut at their openings into the atria. The great arteries were cut immediately above their corresponding semilunar cusps. The heart was removed, and its chambers were carefully dissected. The growth of the fetal heart was studied by measuring several parameters with a caliper to the nearest 0.01 mm (**Figures 1 and 2**). The length and thickness values of the hearts were obtained sequentially from the determined places by the same person. The parameters were as follows: 1) Right atrial wall thickness (RAWT): measured from the lateral wall, excluding the thickness of the pectineal muscles, between the openings of the superior and inferior vena cavae. 2) Left atrial wall thickness (LAWT): measured from the lateral wall, excluding the thickness of the pectineal muscles. 3) Interatrial septum thickness (IAST): measured from the upper edge, including the thickness of the septum secundum and septum primum, after removal of the atrial walls. Maximal internal diameters of 4) mitral (MV) and 5) tricuspid (TV) valves measured, and maximal internal diameters of 6) aortic (AV) and 7) pulmonary valves (PV) measured immediately above their semilunar cups (**Figure 2**).

The heart was then transected perpendicular to its long axis midway between apex and the middle of the atrioventricular valves and the following measurements were obtained: 8) right (RVWT) and 9) left ventricular wall thickness (LVWT): includes only the compact ventricular myocardial mass and not the ventricular trabeculation and papillary muscle;[4] 10) muscular part of the interventricular septum length (MuL); between the apex of the heart and limbus marginalis (where the membranous and muscular parts of the interventricular septum unite) (11) muscular part of the interventricular septum thickness (MuT); obtained from the mid-point of muscular part (**Figure 1**).

The data were presented as the mean ± standard deviation in **Table 2 to 4**. Relationships between the fetal heart measurements and GA were evaluated by linear regression and correlation analysis in order to estimate cardiac growth rates. Furthermore, Student t-test was applied to make comparisons between all heart measurements and the gender, and sides of the hearts.

Table 1 - The distribution of fetuses according to trimester.

Second trimester N=49			Third trimester N=21		
CRL (mm)	GA (week)	FN	CRL (mm)	GA (week)	FN
120-129	14	2	270-274	28	1
130-139	15	2	275-279	29	1
140-149	16	2	280-289	30	2
150-159	17	2	290-299	31	2
160-169	18	3	300-309	32	2
170-179	19	4	310-319	33	2
180-199	20	4	320-329	34	2
200-209	21	3	330-339	35	2
210-219	22	5	340-349	36	2
220-229	23	3	350-359	37	1
230-239	24	4	360-369	38	1
240-249	25	5	370-374	39	2
250-259	26	6	375-379	40	1
260-269	27	4			

CRL - crown-rump length,
GA - gestational age, FN - fetus number

Results. There was a significant linear relationship between the thickness of wall of the heart and the GA (**Table 2**). When we evaluated the rate of linear relationship between the used parameters and GA for each trimester, a significant degree and moderate correlation were determined for whole parameters of the fetal heart wall in the second trimester. But, in the third trimester, moderate/mild correlation was determined only in LVWT, RVWT and MuL (**Table 2**). These data indicate that the growth rate of the heart wall is more rapid in the second than in the third trimester. The difference in the atrial and ventricular wall thicknesses between the right and left side of the fetal heart were statistically significant, and the

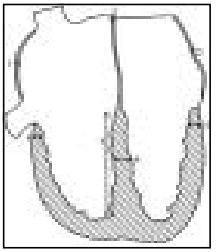

Figure 1 - A schematic drawing of a frontal section of the human fetal heart showing the measured parameters. 1. Right atrium wall thickness, 2. left atrium wall thickness, 3. interatrial septum thickness 4. right ventricular wall thickness, 5. left ventricular wall thickness, 6. muscular part of the ventricular septum length, 7. muscular part of the ventricular septum thickness.

Figure 2 - The valves of the fetal heart measured at 27th weeks (crown rump length was 26 cm) of gestation (fetus no: 113). MV - mitral valve diameter, TV - tricuspid valve diameter, AV- aortic valve diameter, PV - pulmonary valve diameter.

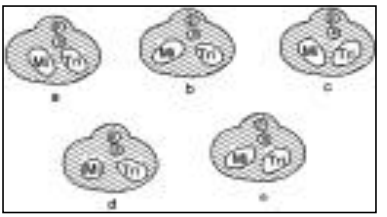

Figure 3 - A schematic drawing shows the varying localization and relationship of the heart valves to each other and to the interventricular septum; **a)** The TV was close to the IVS anteriorly and to the MV posteriorly, **b)** the atrioventricular valves were close to each other and to the IVS anteriorly, **c)** the atrioventricular valves were close to each other and the to IVS posteriorly, d) the TV was close to the IVS anteriorly; the MV was round and in the middle, **e)** The MV was close to the IVS anteriorly and to the TV posteriorly. Mi - mitral, Tri - tricuspid, a - aortic, p - pulmonary valves, MV - mitral valve diameter, TV - tricuspid valve diameter, IVS - interventricular septum

mean values of the right side of the heart were greater in all parameters (**Table 3**). The difference between the LAWT and RAWT was only significant at the second trimester. Thus, the increase of the LAWT was greater than the increase of the RAWT in the third trimester (**Table 3**). Distributions of the values in relation to gender are shown in **Table 4**. The differences of LAWT were significantly higher in females in the second trimester ($p<0.05$). In the third trimester, the IAST was greater in females and differences were significant ($p<0.05$) (**Table 4**). Five different types of spatial relationships of the heart valves to each other and to the interventricular septum (IVS) were found. Accordingly, the TV was close to the IVS anteriorly and to the MV posteriorly in 32 (45.7%) hearts, the atrioventricular valves were close to each other and to the IVS anteriorly in 32 (45.7%) hearts, the atrioventricular valves close to each other and to the IVS posteriorly in 4 (5.71%) hearts, the TV was close to the IVS anteriorly and the MV was round and in the middle in one (1.42%) heart, the MV was close to the IVS anteriorly and to the TV posteriorly in one (1.4%) heart (**Figure 3**). The relationship between the GA and the heart valve measurements was tested, the correlation coefficient of all parameters, except the PV diameter, was found to be greater in the second trimester (**Table 1**). The relationship between the PV diameter and GA was not significant. There was no significant difference between the cardiac valve measurements and gender (**Table 4**). The fetal heart valve measurements showed a high degree of significant relationship between each other ($p<0.001$). There were highly positive correlation between the MV and the PV, the AV, the TV (r=0.78; r=0.81; r=0.92). High positive correlations were determined between the TV and the PV, the AV (r=0.84 for both of them). There was also a significant correlation (r=0.91) between the AV and the PV.

Discussion. During the fetal period, the size of the heart increased with the GA. The previous studies established that this increase play an important role in the whole cardiac parameters.[3-6,8,19] Detailed examination of the fetal heart is of great importance, as much as congenital heart disease remains the most common serious anomaly at birth.[12] Meanwhile, there are few morphometric data of the heart development during the intrauterine period, and these are based on either clinical ultrasonographic or echocardiographic data or studies on the hearts of aborted fetuses.[12,15-17,20] The present study added the new parameters to the previous studied parameters. Differences between the right and left side of the heart in both gender, the correlation between the GA and the data on the fetal heart were also obtained and compared to the results of previous studies.

Table 2 - Relationship between the fetal heart measurements (mean ± standard deviation) and gestational age.

Parameters	Second trimester N=49		Third trimester N=21		Second and Third trimester N=70	
	mm	r	mm	r	mm	r
LVWT	2.96 ± 0.79	0.54‡	3.70 ± 0.72	0.57†	3.18 ± 0.84	0.62‡
RVWT	3.53 ± 1.19	0.58‡	5.11 ± 0.56	0.56†	4.00 ± 1.50	0.68‡
MuL	16.09 ± 3.62	0.72‡	21.51 ± 3.15	0.45*	17.71 ± 4.27	0.79‡
MuT	3.35 ± 0.87	0.48‡	4.64 ± 1.19	0.36	3.34 ± 1.14	0.64‡
LAWT	0.62 ± 0.25	0.46‡	0.94 ± 0.53	0.12	0.72 ± 0.38	0.42‡
RAWT	0.82 ± 0.30	0.41‡	1.10 ± 0.36	0.36	0.91 ± 0.34	0.51‡
IAST	1.07 ± 0.32	0.42‡	1.50 ± 0.54	0.23	1.20 ± 0.44	0.53‡
MV	6.01 ± 1.88	0.73‡	8.98 ± 1.66	0.24	6.90 ± 2.27	0.78‡
TV	6.10 ± 2.09	0.80‡	10.55 ± 1.78	0.37	7.44 ± 2.86	0.87‡
AV	4.09 ± 1.10	0.69‡	5.86 ± 0.73	0.56	4.62 ± 1.43	0.82‡
PV	4.33 ± 1.21	0.72‡	6.24 ± 0.93	0.69	4.90 ± 1.43	

r = correlation coefficient, **p*<0.05, †*p*<0.01, ‡*p*<0.001
LVWT - left ventricular wall thickness, RVWT - right ventricular wall thickness, MuL - muscular interventricular septum length, MuT - muscular interventricular septum thickness, LAWT - left atrial wall thickness, RAWT - right atrial wall thickness, IAST - interatrial septum thickness, MV - mitral valve diameter, TV - tricuspid valve diameter, AV - aortic valve diameter, PV - pulmonary valve diameter.

Table 3 - Fetal heart measurements (mean ± standard deviation) in relation to gestational age and side.

Gestational age	LVWT mm	RVWT mm	LAWT mm	RAWT mm
Second trimester (N=49)	2.96 ± 0.79	3.53 ± 1.19*	0.62 ± 0.25	0.82 ± 0.30*
Third trimester (N=21)	3.70 ± 0.72	5.11 ± 1.59*	0.94 ± 0.53	1.10 ± 0.36
Second and third trimester (N=70)	3.18 ± 0.84	4.00 ± 1.50*	0.72 ± 0.38	0.91 ± 0.34*

**p*<0.01, LVWT - left ventricular wall thickness, RVWT - right ventricular wall thickness, LAWT - left atrial wall thickness, RAWT - right atrial wall thickness

Table 4 - Distribution of fetal heart measurements (mean ± standard deviation) in relation to gestational age and gender.

Parameters	Second trimester		Third trimester	
	Male (n=23) mm	Female (n=26) mm	Male (n=12) mm	Female (n=9) mm
LVWT	2.80 ± 0.77	3.10 ± 0.79	3.76 ± 0.73	3.62 ± 0.75
RVWT	3.31 ± 1.12	3.72 ± 1.23	5.23 ± 2.05	4.94 ± 0.68
MuL	15.88 ± 3.76	16.28 ± 3.56	21.64 ± 3.26	21.33 ± 3.18
MuT	3.21 ± 0.67	3.48 ± 1.02	4.37 ± 1.29	5.00 ± 1.00
LAWT	0.57 ± 0.18	0.66 ± 0.30*	1.03 ± 0.67	0.81 ± 0.22
RAWT	0.81 ± 0.23	0.84 ± 0.36	1.13 ± 0.43	1.07 ± 0.27
IAST	0.95 ± 0.26	1.18 ± 0.33	1.43 ± 0.39	1.57 ± 0.71*
MV	5.90 ± 1.99	6.20 ± 1.83	9.45 ± 1.59	8.36 ± 1.63
TV	5.80 ± 2.09	6.38 ± 2.09	10.68 ± 1.95	10.37 ± 1.63
AV	3.93 ± 0.97	4.23 ± 1.20	5.82 ± 0.72	5.92 ± 0.79
PV	3.98 ± 1.02	4.64 ± 1.29	6.31 ± 1.04	6.14 ± 0.82

**p*<0.05, LVWT - left ventricular wall thickness, RVWT - right ventricular wall thickness, MuL - Muscular interventricular septum length, MuT - muscular interventricular septum thickness, LAWT - left atrial wall thickness, RAWT - right atrial wall thickness, IAST - interatrial septum thickness, MV - mitral valve diameter, TV - tricuspid valve diameter, AV - aortic valve diameter, PV -pulmonary valve diameter.

St John Sutton et al[6] and Kim et al[3] examined the heart development parameters in normal developed hearts of aborted fetuses and reported that the RVWT and the LVWT increased linearly with the increase of GA, and did not differ from each other. They also stated that these results did not support the hypothesis that the right ventricle was dominant during the development of the heart in human fetuses. In another study,[19] the development of the fetal heart and its functions were examined using echocardiography. The authors suggested that the fetal heart wall thickness, the diameters of heart chambers and the left ventricle muscle mass increased with the GA, but the right ventricle was not dominant during the fetal period because of the determined similarities of the right and left ventricular valves. Our results confirmed that there is a positive correlation between the GA and other parameters. The present results suggest a significant increase in the growth rate of the heart size in the second trimester but not in the third trimester. Differently from the previous studies mentioned above, we reported that the measured values of the RVWT and the RAWT were significantly higher than the values of the LVWT and the LAWT ($p<0.05$). Our data also confirmed the results of the study carried out on the aborted fetuses by Alvarez et al[2] who reported that the RVWT was greater than the LVWT until the 39th week of intrauterine life. The only exception in our findings is that the RAWT was found to be greater than the LAWT, the difference was not significant ($p>0.05$) in the third trimester. These findings confirm the results of the report of St John Sutton et al[22] and Smolich[18] that the right ventricular function was dominant. There are other studies which do not support the idea of the dominance of the right side of the heart.[3,19] Mandarim-de-Lacerda[5] studied the linear relation between the development of fetal heart and CRL, and reported that the developmental rate was greater in females than in males. The present study suggested that the mean value was greater in all parameters in females and the differences were statistically significant in case of the LAWT in the second and in case of the IAST in the third trimester ($p<0.05$). Accordingly, our results seem to confirm the data of Mandarim-de-Lacerda.[5] Kim et al[3] determined that the IVS thickness had a positive correlation with GA. In the present study, there was a significant correlation between the MuT and GA in the second trimester, and the developmental rate of thickness in the third trimester was lower than in the second trimester. Therefore, our results paralleled with the results of Kim et al.[3]

In our study, it was observed that there were differences in the heart valve location which had not been identified in the previous studies. When the correlation of the heart valves compared with each other and with the IVS, 5 various types of location were determined as follow: (i) the TV was close to the IVS anteriorly and to the MV posteriorly, (ii) the atrioventricular valves were close to the each other and to the IVS anteriorly, (iii) the atrioventricular valves were close to the each other and to the IVS posteriorly, (iv) the TV was close to the IVS anteriorly and the MV was round and in the middle, (v) the MV was close to the IVS anteriorly and to the TV posteriorly.

St John Sutton et al[19] reported that the diameter of the AV increased from the 20th week to term, much enough to have a high correlation (r=0.91) with the GA. In other studies investigating the development of the AV and the PV by echocardiography in fetuses, the diameter of the PV was reported to be greater than the diameter of the AV.[5,14,22] In a similar study[23] the AV and the PV diameters were found to increase linearly with GA. Fernandez et al[13] measured the diameters of the TV, MV, AV and PV with echocardiography in fetuses and reported that there was a positive correlation (r>0.7) between all parameters and GA. Alvarez et al[2] determined in a rather extensive study carried out on the hearts of aborted fetuses that the atrioventricular valves, AV and PV showed a linear relation with the GA. In both studies, it was determined that the diameter of the TV was greater than that of the MV. Also, the diameter of the PV was greater than that of the AV. The results of our study concerning heart valves support the results of the previous studies.[2,13] Similarly, the present study evaluated the relationship between heart parameters and GA and found a linear relation between them. The growth rate was greater in the second trimester except for the PV. The fact that the correlation rate of the PV was not significantly different between the second and third trimester (r=0.72, r=0.69), while the correlation rate of the AV was different between the second and third trimester (r=0.69, r=0.56), seems to support the report of Alvarez et al[2] that the growth rates of the AV and PV diameters are not the same. It was suggested that the growth rate of the cardiac valves was greater in the second trimester than in the later periods of gestation, with the least difference in case of the PV diameter. The growth of the PV diameter, which is the sign of the growth of the right ventricle, continues at a similar rate in the third trimester. The finding that the PV diameters are greater than the AV diameters in both trimesters may be considered as a preparation for the growth of the right side of the heart which has to resist the pulmonary pressure after the delivery. The present study suggested that there were no significant difference between the gender and all heart valve measurements the same conclusion was suggested by Leslie et al.[4] However, these results contradicted with the results of Mandarim-de-Lacerda[5] who suggested that the growth rate of heart parameters including the valves were greater in females.

We have tried to find whether or not there is a linear correlation between the growth rate and the GA. Obviously, this question should be answered with yes; however, the present study underlines that the right side of the heart undergoes a different developmental pattern, due to the tasks and the function of the right ventricle and its valves are different during fetal life than after delivery. The results confirm the hypothesis of a positive correlation between the GA and the measured parameters. There is a significant increase in the growth rate of the heart and the cardiac valves being greater in the second trimester. The results of the present study presented the morphometric data of the normal growth rate of heart walls and valves in the second and third trimester. This information may provide useful background information for looking at cardiac function, fetal cardiac imaging, clinical approaches and help understanding of the congenital cardiac anomalies.

References

1. Bronshtein M, Siegler E, Yoffe N, Zimmer EZ. Prenatal diagnosis of ventricular septal defect and overriding aorta at 14 weeks' gestation, using transvaginal sonography. ***Prenat Diagn*** 1990; 10: 697-702.
2. Alvarez L, Aranega A, Saucedo R, Contreras JA. The quantitative anatomy of the normal human heart in fetal and perinatal life. ***Int J Cardiol*** 1987; 17: 57-72.
3. Kim HD, Kim DJ, Lee IJ, Rah BJ, Sawa Y, Schaper J. Human fetal heart development after mid-term: Morphometry and ultrastructural study. ***J Mol Cell Cardiol*** 1992; 24: 949-965.
4. Leslie J, Shen S, Thornton JC, Strauss L. The human fetal heart in the second trimester of gestation: A gross morphometric study of normal fetuses. ***Am J Obstet Gynecol*** 1983; 145: 312-316.
5. Mandarim-de-Lacerda CA. Morphometry of the human heart in the second and third trimesters of gestation. ***Early Hum Dev*** 1993; 35: 173- 182.
6. St John Sutton MG, Raichlen JS, Reichek N, Huff DS. Quantitative assessment of growth and function of the cardiac chambers in the normal human fetal heart: a pathoanatomic study. ***Circulation*** 1984; 70: 935-941.
7. Hutchins GM, Meredith MA, Moore GW. The cardiac malformations. Double inlet left ventricle and corrected transposition explained as deviations in the normal development of the interventricular septum. ***Hum Pathol*** 1981; 12: 242-250.
8. Figueria RR, Prates JC, Hayashi H. Development of the pars membranacea septi interventricularis of the human heart. II. Thickness change. ***Arch Ital Anat Embriol*** 1991; 96: 303-307.
9. Wenink AC. Quantitative morphology of the embryonic heart: an approach to development of the atrioventricular valves. ***Anat Rec*** 1992; 234: 129-135.
10. Espinosa-Caliani JS, Alvarez-Guisado L, Munoz-Castellanos L, Aranega-Jimenez A, Kuri-Nivon M, Sanchez RS et al. Atrioventricular septal defect: quantitative anatomy of the right ventricle. ***Pediatr Cardiol*** 1991; 12: 206-213.
11. Nguyen H, Leroy JP, Vallee B, Person H, Nguyen HV. The muscular atrioventricular septum (abstr). ***Bull Assoc Anat (Nancy)*** 1982; 66: 373-377.
12. Mandarim-de-Lacerda CA, Boasquevisque EM. Sonographic quantitative analysis of the heart in the third trimester of gestation. ***Surg Radiol Anat*** 1993; 15: 139-143.
13. Fernandez Pineda L, Tamariz-Martel Moreno A, Maitre Azcarate MJ, Lopez Zea M, Cazzaniga Bullon M, Rico Gomez F et al. Heart growth in the normal human fetus. A two-dimensional echocardiographic study (abstr). ***An Esp Pediatr*** 1996; 44: 475-481.
14. Mandorla S, Narducci PL, Bracalente B, Pagliacci M. Fetal echocardiography. A horizontal study of biometry and cardiac function in utero (abstr). ***G Ital Cardiol*** 1986; 16: 487-495.
15. Rane HS, Purandare HM, Chakravarty A, Pherwani AV. Fetal echocardiography- norms for M- mode measurements. ***Indian Heart J*** 1990; 42: 351-355.
16. Tan J, Silverman NH, Hoffman JI, Villegas M, Schmidt KG. Cardiac dimensions determined by cross-sectional echocardiography in the normal human fetus from 18 weeks to term. ***Am J Cardiol*** 1992; 70: 1459-1467.
17. Veille JC, Sivakoff M, Nemeth M. Evaluation of the human fetal cardiac size and function. ***Am J Perinatol*** 1990; 7: 54-59.
18. Smolich JJ. Ultrastructural and functional features of the developing mammalian heart: a brief overview. ***Reprod Fertil Dev*** 1995; 7: 451-461.
19. St John Sutton MG, Gewitz MH, Shah B, Cohen A, Reichek N, Gabbe S et al. Quantitative assessment of growth and function of the cardiac chambers in the normal human fetus: a prospective longitudinal echocardiographic study. ***Circulation*** 1984; 69: 645-654.
20. Gembruch U, Knöpfle G, Chatterjee M, Bald R, Hansmann M. First-trimester diagnosis of fetal congenital heart disease by transvaginal two-dimensional and Doppler echocardiography. ***Obstet Gynecol*** 1990; 75: 496-498.
21. Hensinger RN. Standards and measurements of fetus and neonate. In: Polin RA, Fox WW, editors. Fetal and neonatal physiology. Philadelphia (PA): W.B. Saunders; 1992. p. 1687-1696.
22. St John Sutton MG, Gill T, Plappert T, Saltzman DH, Doubilet P. Assessment of right and left ventricular function in terms of force development with gestational age in the normal human fetus. ***Br Heart J*** 1991; 66: 285-289.
23. Hyett J, Moscoso G, Nicolaides K. Morphometric analysis of the great vessels in early fetal life. ***Hum Reprod*** 1995; 10: 3045-3048.