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THE DEVELOPMENT OF THE AORTIC ISTHMUS IN HUMAN FETAL LIFE

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ABSTRACT

Introduction. The aortic isthmus is a specific feature of fetal circulation. It undergoes regression by becoming wider postpartum. Developmental abnormalities of an isthmus may lead to congenital defects.

Aim. The aim of this work was a morphometric study of the aortic isthmus in human fetuses aged between 4 and 8 months of fetal life.

Materials and methods. We investigated 223 human fetuses, including 108 males and 115 females, aged between 4 and 8 months of fetal life. The entire material was obtained from the Department of Histology and Embryology at the Collegium Medicum, Nicolaus Copernicus University in Bydgoszcz, Poland. All fetal specimens had been conserved in a 9% formaldehyde solution for a period of more than 3 months. Only spontaneously aborted fetuses with a normal morphology and a normal karyotype were used in this study. We investigated the diameter of the aortic isthmus in human fetuses at different stages of prenatal life. We also analyzed the ratio of that diameter with regard to the diameters of other segments of the aorta and ductus arteriosus. We considered how these measurements varied depending on sex.

Results, Discussion and Conclusions. We found the growth of the aortic isthmus diameter to be linear in time. The measured diameters were similar in males and females. No significant differences with regard to sex were found between the ratios of that vessel's diameter to the diameters of the ascending and descending aorta

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and the ductus arteriosus. The relative ratio of the aortic isthmus diameter to the diameters of the ascending and thoracic aorta decreased with time. On the contrary, the ratio of the aortic isthmus diameter to the ductus arteriosus diameter increased over time.

Key words: aortic isthmus, prenatal development, human fetus

INTRODUCTION

The isthmus is a natural feature of the fetal aorta. Its embryogenesis is connected with the development of the aortic arch. It consists of three parts with different origins: the 4th left aortic arch, the 6th left aortic arch, and the left dorsal aorta. About 10% of fetal cardiac combined output (CCO) flows through the isthmus. As a result, oxygenated blood from the ascending aorta is primarily directed to the upper part of the body and, in particular, to the head and the central nervous system. The isthmus prevents excessive mixing of that blood with the desaturated blood from the distal aortic arch and the thoracic aorta [27]. The latter flows into the distal aorta through the ductus arteriosus and provides blood for the lower part of the body of the fetus [17, 23]. The complex organogenesis of the aortic isthmus leads to frequent developmental abnormalities. Among these, coarctation of the aorta above the ductus arteriosus is the most prevalent. According to Bonnet's classification (1903) this type of coarctation is called "infantile". Coarctation of the aorta accounts for 5–8% of all congenital heart defects, with the variant above ductus arteriosus being most prevalent. The defect is more often seen in boys than in girls [19]. Another, less frequently observed defect is the interrupted aortic arch (IAA). This accounts for about 1.5% of all defects. In 40–45% of cases a "type A" defect, directly correlated with isthmus abnormalities, is seen. It seldom occurs as an isolated defect. In 90–95% of cases it co-occurs with the interventricular septal defect. Also, concomitant patent ductus arteriosus (PDA) and defects obstructing the left ventricular outflow, such as bicuspid aortic valve, are frequently observed [15]. It is also worth noting that according to Hoffman et al.[11, 12], the incidence of an interrupted aortic arch is on the increase. Such plentitude of congenital defects arising from impaired embryogenesis of the aortic isthmus calls for intensive research concerning the changes this structure undergoes in fetal life [6, 18, 28].

AIM

The aim of this work was to determine the diameter of the aortic isthmus in human fetuses aged between 4 and 8 months of prenatal life. We calculated the ratios of the aortic isthmus diameter with respect to the diameters of the ascending and descending (thoracic) aorta and the ductus arteriosus. We also analyzed the differences of

obtained measurements and ratios with regard to the sex of the fetus.

MATERIALS AND METHODS

Research material consisted of 223 human fetuses, including 108 males and 115 females, aged between 4 and 8 months of prenatal life. Only spontaneously aborted fetuses with a normal karyotype were included in this study. None of the analyzed specimens demonstrated any visible malformations or developmental abnormalities upon close inspection. The entire material was homogenous in terms of race and skin color. All fetuses were obtained from the Department of Histology and Embryology at the Collegium Medicum, Nicolaus Copernicus University in Bydgoszcz, Poland. This study was approved by the Bioethics Committee at the Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland (resolution KB/433/2004). All fetuses had been conserved in a 9% formaldehyde solution for a period of at least 3 months. The morphological age of each fetus was estimated according to the crown-rump length (vertex--tubulare). To this end, we used a polynomial proposed by Iffy et al. [16]. All specimens were categorized into monthly subgroups according to the determined morphological age. Different numbers of fetuses were allocated to particular age groups. Random numbers were assigned to each fetus of each age group in the project.

The vessel beds were filled with latex LBS 3060, without distorting the dimensions of the vessels, at an amount of approximately 15–30 mL, through a catheter, which was inserted by dorsal access into the thoracic aorta. All measurements were performed by two investigators who, with the aid of binocular magnifying glasses (MBS-9, Russia, magnification 0.6–7 × 14), used digital calipers (INCO, Poland, resolution 0.01 mm) to collect all measurements required with an accuracy range of 0.01 mm. All measurements were taken twice by each investigator for consistency and verification purposes. The mean value of the two obtained values was used for further quantitative analysis.

Statistica 8.0 software (StatSoft Polska) was used for statistical analysis of the obtained data. The results obtained were analyzed by the two-way ANOVA test for unpaired data and Tukey's HSD post hoc test for non-equal populations. Statistical significance was defined as $p \leq 0.05$.

RESULTS

The mean diameter of the aortic isthmus for the entire group was 1.75±0.47 mm. In male fetuses it was 1.78±0.49 mm, and in females 1.72±0.46 mm. The differences in diameter values between males and females were not significant, either in the entire group ($p = 0.2658$) or in any monthly age groups investigated ($p > 0.05$) (Tab. 1). The aortic isthmus diameter increased through the investigated time period in a linear pattern ($y = -47.494 + 0.4794x$), with a correlation coefficient ($r = 0.9276$) and a high level of statistical significance ($p < 0.001$) (Fig. 2). The aortic isthmus diameter grew significantly in consecutive months for both sexes and for the entire group ($p < 0.05$) (Tab. 1).

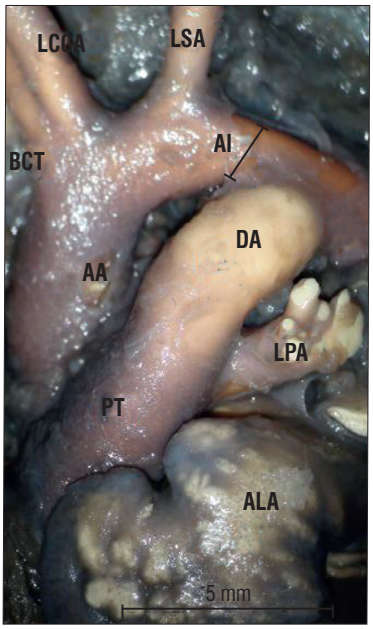

Fig. 1. The great arteries of the fetal heart in a 28-weeks old female fetus. Comments: AA – ascending aorta, AI – aortic isthmus, TA – thoracic aorta, BCT – brachiocephalic trunk, LCCA – left common carotid artery, LSA – left subclavian artery, DA – ductus arteriosus, PT – pulmonary trunk, LPA – left pulmonary artery, ALA – auricle left atrium

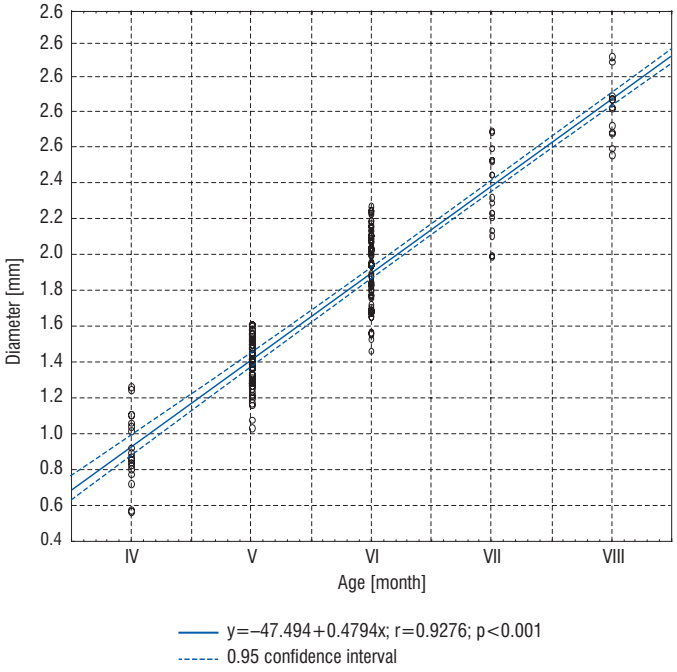

Fig. 2. Regression curve for the diameter of the isthmus of the aorta versus fetal age (x)

Tab. 1. Mean aortic isthmus diameter in monthly age subgroups shown for the entire group and with regard to sex

Age [month]	N			X±SD [mm]			P value
	total	male	female	total	male	female	
4	18	8	10	0.91±0.19	0.91±0.21	0.92±0.2	0.9154
5	70	32	38	1.39±0.13*	1.38±0.14*	1.39±0.12*	0.7473
6	105	50	55	1.92±0.19*	1.93±0.19*	1.90±0.19*	0.4754
7	18	12	6	2.32±0.23*	2.33±0.23*	2.32±0.27*	0.9328
8	12	6	6	2.8±0.17*	2.84±0.23*	2.76±0.09*	0.4659
Total	223	108	115	1.75±0.47	1.78±0.49	1.72±0.46	0.2658

Comments: * – indicates statistically significant difference of the marked subgroup when compared to the immediately younger subgroup ($p < 0.05$), N – number, X – parameter dimension, SD – standard deviation, P value – the differences between the mean values in the male and female fetuses within particular age groups ($p < 0.05$).

The mean ratio of the aortic isthmus diameter to the ascending aorta diameter in the entire group was 0.73±0.09 (Tab. 2). When analyzed within particular monthly subgroups, it ranged between 0.74±0.03 in the 5th month to 0.69±0.05 in the 8th month. These values were similar for both sexes ($p > 0.05$). The mean ratio values for particular subgroups did not differ significantly from the ratios calculated for the consecutive younger subgroups (Tab. 2). The ratio of the aortic isthmus diameter to the thoracic aorta diameter for the entire group was 0.79±0.11. When analyzed within particular monthly age subgroups, it ranged between 0.8±0.03 in the 4th month to 0.78±0.05 in the 8th month. This ratio was not different between sexes, nor for particular monthly age subgroups ($p > 0.05$) (Tab. 3).

Tab. 2. The ratio of aortic isthmus diameter to the ascending aorta diameter (x)

Age [month]	N	X	SD	P value
4	18	0.73	0.04	0.3751
5	70	0.74	0.03	0.4859
6	105	0.72	0.06	0.8321
7	18	0.69	0.07	0.7395
8	12	0.69	0.05	0.0813
Total	223	0.73	0.09	0.2819

Comments: SD – standard deviation. Lack of significant difference between the immediately, younger monthly age subgroups, P value – sex related differences, level of significance ($p < 0.05$).

Tab. 3. The ratio of the aortic isthmus diameter and the thoracic aorta diameter (x)

Age [month]	N	X	SD	P value
4	18	0.80	0.03	0.0685
5	70	0.79	0.07	0.1298
6	105	0.79	0.06	0.4219
7	18	0.78	0.03	0.7617
8	12	0.78	0.05	0.0939
Total	223	0.79	0.11	0.4138

Comments: SD – standard deviation. Lack of significant difference between the immediately, younger monthly age subgroups, P value – sex related differences.

The mean ratio of the aortic isthmus diameter to the diameter of the ductus arteriosus was 0.85±0.13. This value grew gradually for consecutive age subgroups from 0.85±0.06 in the 4th month to 0.9±0.07 in the 8th month. However, the differences between the consecutive months did not reach a level of statistical significance ($p > 0.05$). Also, there were no significant differences between sexes ($p > 0.05$) (Tab. 4).

Tab. 4. The ratio of the aortic isthmus diameter and the diameter of the ductus arteriosus (x)

Age [month]	N	X	SD	P value
4	18	0.85	0.06	0.1989
5	70	0.86	0.04	0.7320
6	105	0.86	0.05	0.4183
7	18	0.88	0.04	0.6734
8	12	0.90	0.07	0.4290
Total	223	0.85	0.13	0.6432

Comments: SD – standard deviation. Lack of significant difference between the immediately, younger monthly age subgroups, *P* value – sex related differences.

DISCUSSION

In our research material we found no sex related differences of the aortic isthmus diameter ($p > 0.05$) (Tab. 1). Similar conclusions were reached by Szpinda [24, 25], Ursell et al. [26], and also Gielecki et al. [9, 10].

Our data revealed that the growth of the aortic isthmus diameter was linear in time (Fig. 2). This is confirmed by Hyett et al. [14, 15] who found that diameter, in the period between the 9th and 18th week of gestation, to be growing according to a linear regression curve. Also Achiron et al. [1, 2] and Nomiyama et al. [21] described the increase of the aortic isthmus diameter as linear in time. Alvarez et al. [3] discovered that the circumference of the aortic isthmus in the fetus with relation to the body mass also grew linearly. Szpinda [25] found that the growth of the aortic isthmus diameter with regard to time followed a linear regression curve. A similar

relation concerning isthmus growth with regard to body length was observed by van Meurs-vanWoezik and Krediet [20].

Castillo et al. [5] noted that in fetuses aged between 4 to 7 months, the aortic isthmus diameter ranged between 1.45 mm to 3.0 mm. These data correspond with our results. Other research also supports these conclusions. According to Ursell et al. [26], the diameter was 0.5 mm in the 3rd month, 1.1 mm in the 5th month, 1.5 mm in the 6th month, and 1.8 mm in the 7th month. Szpinda [25] found that diameter to, be 0.92 mm in the 4th month, 1.71 mm in the 5th month, 2.84 mm in the 6th month, 3.26 mm in the 7th month, and 4.39 mm in the 8th month. On the other hand, Hornberger et al. [13] found the aortic isthmus diameter to be independent of age and equal to 3.6 mm.

Two contradictory trends with respect to the changing ratio of the aortic isthmus to other aortic diameters are to be found in available literature. One trend shows the relative growth of the aortic isthmus diameter. This trend is confirmed in the research conducted by Hyett et al. [14], where the relative isthmus diameter was found to be growing from 0.6 mm to 0.8 mm in the time period between 3rd and 5th months of fetal life. Similar findings were reported by Szpinda [25], who found the relative isthmus diameter (in relation to the diameter of the proximal ascending aorta) to be growing from 0.45±0.1 mm in the 4th month to 0.72±0.07 mm in the 6th month of fetal life. He found this to be also true in terms of the ratio of the isthmus diameter to the proximal thoracic aorta diameter; by the 9th month that ratio increased from 0.73±0.1 to 0.88±0.09 [25].

On the contrary, our research supports the opposite trend – the ratio of the aortic isthmus diameter to the proximal and thoracic aorta decreased with time (Tab. 2, 3). Similar conclusions were also drawn by other authors. Ursell et al. [26], Nomiyama [21], and Gielecki et al. [10] concluded that the ratio of the aortic isthmus diameter to the diameters of the ascending and thoracic aorta decreased over time. According to Ursell et al. [26], in fetuses aged between 4 and 6 months, the ratio of the isthmus diameter to the diameter of the ascending aorta ranged between 0.61 and 0.65 and decreased to 0.58 by the 7th month. Also, the mean ratio of the isthmus diameter to the diameter of the thoracic aorta ranged between 0.71 and 0.78. Nomiyama et al. [21] found that in fetuses aged between 7 and 10 months, the ratio of the aortic isthmus diameter to the proximal thoracic aorta diameter decreased over time. According to Gielecki et al. [10], the ratio of the isthmus diameter to the ascending aorta diameter decreased from 0.64 in fetuses aged 5 months to 0.45 in fetuses aged 6–7 months. These authors also found that the ratio of the aortic isthmus diameter to the thoracic aorta diameter decreased from 0.8 to 0.76.

According to some investigators [5], in fetuses aged between 5 and 7 months, the ratio of the aortic isthmus diameter to the diameters of the ascending and thoracic aorta is highly variable and falls within a range of 0.66 and 0.99. On the other hand,

Angelini et al. [4] calculated that the relative diameter of the aortic isthmus exceeded 0.6. They did not, however, consider the variability associated with age.

Ursell et al. [26] believe that the relative decrease of the aortic isthmus diameter implies that the majority of left ventricle stroke volume is forwarded to the encephalon. Szpinda [25], who found the relative dimensions of the aortic arch ramifications to be growing, concurs with this reasoning. On the basis of our results, we also agree with Ursell et al. [26]. Nevertheless, we do not fully agree with the reasoning presented by Ursell et al. [26] in their work. It is true that the ratio of the dimensions of the aortic isthmus to the ascending aorta decreases, but at the same time a similar phenomenon is to be observed with regard to the ratio of the aortic isthmus to the thoracic aorta. This may indicate that the isthmus limits excessive blood flow between the ascending and thoracic aorta, thus preventing the oxygenated and desaturated blood from mixing; consequently, this results in a privileged flow of oxygenated blood to the upper part of the body. When evaluating the function of the isthmus it is important to correctly asses the direction of the blood flow. Physiologically the blood flows from the ascending aorta into the thoracic aorta. However, in the case of a defect this flow may be bidirectional [7, 8].

Hyett et al. [14] analyzed the ratio of the aortic isthmus diameter with respect to the diameter of the distal ductus arteriosus. Their data corresponded with our findings. They found this ratio to be growing linearly in time. This may indicate the capacity of the ductus to obliterate postpartum. This is also reflected by the decrease of CCO from 40% to 30% through the ductus arteriosus in the period between the 20^{th}–30^{th} weeks of prenatal life [22]. These data may reveal the role of the isthmus as a restrictive structure creating a pressure gradient between the ascending and the thoracic aorta, thus regulating fetal circulation. Our results are in strict concordance with those observations made by Ursell et al. [26] and Gielecki et al. [10]. In certain areas our data support the results demonstrated by Hyett et al. [14] and Szpinda [25].

CONCLUSIONS

1. The diameter of the aortic isthmus in a fetus aged between 4 and 8 months grows linearly in time.
2. No differences with regard to dimensions of this vessel were found in both males and females.
3. The ratio of the aortic isthmus diameter with respect to the diameters of the ascending and thoracic aorta decreases in time, whereas the ratio of the aortic isthmus diameter to the diameter of the ductus arteriosus increases.

REFERENCES

1. Achiron R., Golan-Porat N., Gabbay U., Rotstein Z., Heggesh J., Mashiach S., Lipitz S.: *In utero ultrasonographic measurements of fetal aortic and pulmonary artery diameters during the first half of gestation.* Ultrasound Obstet. Gynecol., 1998; 11 (3): 180–184.
2. Achiron R., Zimand S., Hegesh J., Lipitz S., Zalel Y., Rotstein Z.: *Fetal aortic arch measurements between 14 and 38 weeks' gestation: in-utero ultrasonographic study.* Ultrasound Obstet. Gynecol., 2000; 15 (3): 226–230.
3. Alvarez L., Aránega A., Saucedo R., Contreras J. A., López F., Aránega A. E.: *Morphometric data concerning the great arterial trunks and their branches.* Int. J. Cardiol., 1990; 29 (2): 127–139.
4. Angelini A., Allan L. D., Anderson R. H., Crawford D. C., Chita S. K., Ho S. Y.: *Measurements of the dimensions of the aortic and pulmonary pathways in the human fetus: a correlative echocardiographic and morphometric study.* Br. Heart J. 1988; 60, 221–226.
5. Castillo E. H., Arteaga-Martínez M., García-Peláez I., Villasis-Keever M. A., Aguirre O. M., Morán V., Vizcaíno A.: *Morphometric study of the human fetal heart. I. Arterial segment.* Clin. Anat., 2005; 18 (4): 260–268.
6. Del Río M., Martínez J. M., Figueras F., López M., Palacio M., Gómez O., Coll O., Puerto B.: *Reference ranges for Doppler parameters of the fetal aortic isthmus during the second half of pregnancy.* Ultrasound Obstet. Gynecol., 2006; 28 (1): 71–76.
7. Fouron J. C.: *Blood flow through the fetal aortic isthmus: a new physiological concept with many clinical implications.* Med. Sci. (Paris), 2007; 23 (11): 950–956.
8. Fouron J. C., Siles A., Montanari L., Morin L., Ville Y., Mivelaz Y., Proulx F., Bureau N., Bigras J. L., Brassard M.: *Feasibility and reliability of Doppler flow recordings in the fetal aortic isthmus: a multicenter evaluation.* Ultrasound Obstet. Gynecol., 2009; 33 (6): 690–693.
9. Gielecki J. S., Wilk R., Syc B., Musiał-Kopiejka M., Piwowarczyk-Nowak A.: *Digital-image analysis of the aortic arch's development and its variations.* Folia Morphol. 2004; 63 (4): 449–454.
10. Gielecki J. S., Syc B., Wilk R., Musiał-Kopiejka M., Piwowarczyk-Nowak A.: *Quantitative evaluation of aortic arch development using digital-image analysis.* Ann. Anat., 2006; 188 (1): 19–23.
11. Hoffman J. E., Christiansen R. R.*: Congenital heart disease in a cohort of 19 502 birth in long term follow up.* Am. J. Cardiol., 1978; 42: 641–647.
12. Hoffmann J. I.: *Incidence, mortality and natural history.* In: R. Anderson (ed.) *Pediatric Cardiology.* Churchill Livingstone, London–Edinburg, 2002.
13. Hornberger L. K., Sanders S. P., Sahn D. J., Rice M. J., Spevak P. J., Benacerraf B. R., McDonald R. W., Colan S. D.: *In utero pulmonary artery and aortic growth and potential for progression of pulmonary outflow tract obstruction in tetralogy of Fallot.* J. Am. Coll. Cardiol., 1995; 25 (3): 739–745.
14. Hyett J., Moscoso G., Nicolaides K.: *Morphometric analysis of the great vessels in early fetal life.* Hum. Reprod., 1995; 10 (11): 3045–3048.
15. Hyett J., Moscoso G., Nicolaides K.: *Increased nuchal translucency in trisomy 21 fetuses: relationship to narrowing the aortic isthmus.* Hum. Reprod., 1995; 10: 3049–3051.
16. Jakobovits A., Westlake W., Iffy L., Wingate M. B., Caterini H., Kanofsky P., Menduke H.: *Early intrauterine development: I. The rate of growth of Caucasian embryos and fetuses between the 6th and 20th weeks of gestation.* Pediatrics, 1975; 56: 173–186.
17. Karolczak M. A. (ed.): *Wykłady o sercu i kardiochirurgii wad wrodzonych* [*Lectures on heart and heart surgery of the congenital heart disease*]. Wydawnictwo Czelej, Lublin, 2008.
18. Kennelly M. M., Farah N., Turner M. J., Stuart B.: *Aortic isthmus Doppler velocimetry: role in assessment of preterm fetal growth restriction.* Prenat. Diagn., 2010; 30 (5): 395–401.
19. Kubicka K., Kawalec W. (eds.): *Kardiologia dziecięca* [*Pediatric cardiology*]. PZWL, Warszawa, 2003.
20. van Meurs-van Woezik H., Krediet P.: *Measurements of the descending aorta in infants and children: comparison with other aortic dimensions.* J. Anat., 1982; 135 (Pt. 2): 273–279.
21. Nomiyama M., Ueda Y., Toyota Y., Kawano H.: *Fetal aortic isthmus growth and morphology in late gestation.* Ultrasound Obstet. Gynecol., 2002; 19 (2): 153–157.

22. Rasanen J., Wood D. C., Weiner S., Ludomirski A., Huhta J. C.: *Role of the pulmonary circulation in the distribution of human fetal cardiac output during the second half of pregnancy*. Circulation, 1996; 94 (5): 1068–1073.
23. Sadler T. W.: *Langman's Medical Embryology.* Lippincott Wiliams & Wilkins, Philadelphia–Baltimor–New York–London–Buenos Aires–Hong Kong–Sydney–Tokyo, 2009.
24. Szpinda M., Elminowska-Wenda G., Wiśniewski M.: *Morphometric study of the aortic and great pulmonary arterial pathways in human fetuses.* Ann. Anat., 2006; 188 (1): 25–31.
25. Szpinda M.: *Badania morfometryczne wielkich tętnic klatki piersiowej u płodów ludzkich* [*Morphometric study of the great arteries of the chest in the human fetus*]. Rozprawa habilitacyjna. Wydawnictwo CM UMK, Bydgoszcz, 2006.
26. Ursell P. C., Byrne J. M., Fears T. R., Strobino B. A., Gersony W. M.: *Growth of the great vessels in the normal human fetus and in the fetus with cardiac defects.* Circulation, 1991; 84 (5): 2028–2033.
27. Vimpeli T., Huhtala H., Wilsgaard T., Acharya G.: *Fetal aortic isthmus blood flow and the fraction of cardiac output distributed to the upper body and brain at 11–20 weeks of gestation.* Ultrasound Obstet. Gynecol., 2009; 33 (5): 538–544.
28. Yagel S., Silverman N. H., Gembruch U. (eds.): *Fetal cardiology: embryology, genetics, physiology, echocardiographic evaluation, diagnostic and perinatal management of cardiac diseases.* Informa Healthcare Publisher, London, 2008.