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Diameter of the ductus arteriosus as a predictor of patent ductus arteriosus (PDA)

Research Article

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Abstract: Patent ductus arteriosus (PDA) is the most prevalent cardiovascular defect and is more often seen in females; premature babies are at increased risk. For both sexes, a relationship exists between the risk of this defect occurring and the higher dimensions of the ductus arteriosus. In this study, we examined the relationship between the dimensions of the ductus arteriosus (diameter, length, capacity) and sex. We analyzed a total of 223 fetuses, 108 males and 115 females, ranging in age from four to eight months of intrauterinal life. All fetuses of normal karyotype were obtained from spontaneous abortions. None of the analyzed specimens demonstrated any visible malformations. The increase in the length and diameters of the ductus is linearly related to gestational age. The volumetric growth of this vessel was dependent on fetal age, according to the exponential function. The large number of analyzed specimens allows reliable determination of the ductus arteriosus dimensions in consecutive months of fetal life. The data obtained could be of prognostic value during echocardiographic follow-up in the fetus. We found that the dimensions analyzed did not differ with regard to sex. It is a contradiction that, more frequently PDA in females is caused with the gender differences in the dimensions of ductus arteriosus.

Keywords: *Patent ductus arteriosus • Morphometry • Fetal development*

1. Introduction

Ductus arteriosus exists solely during fetal life when it plays a role in altered blood circulation during this period. The ductus arteriosus connects the pulmonary trunk with the aortic arch. Blood flows directly from the pulmonary trunk through the ductus arteriosus into the proximal part of the thoracic aorta [1,2]. Consequently, pulmonary circulation is omitted. This poorly oxygenated blood nourishes the inferior half of the body. Following parturition, the vessel closes off and contracts during the first 24 hours. As a result, its lumen becomes obliterated by proliferation of the intima. This process is thought to take up to 3 months leading to atrophy of the ductus arteriosus, which now becomes the arterial ligament [3-5].

However, blood flow does not always cease hence Patent Ductus Arteriosus (PDA) accounts for about 10% of all congenital heart diseases [6]. It is the most frequent congenital heart defect, and it is found three times more often in girls than in boys [7,8]. There are data showing that a larger dimension of the duct in premature babies conveys the risk of this defect's occurrence at an older age [9]. Therefore, the more common prevalence of the defect among girls should correlate with larger ductus arteriosus dimensions in female fetuses.

PDA can impair the relaxation and aeration of the lungs [10-12]. PDA impairs the perfusion of numerous organs [13], particularly in the abdomen (steal syndrome within the intestines and kidneys) and the nervous system. In the central nervous system PDA is associated with an increased risk of bleeding and leucomalatia around the cerebral ventricles [14].

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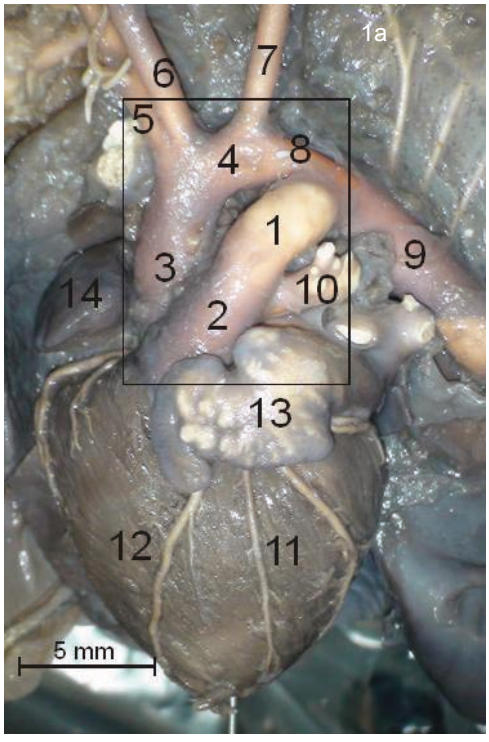
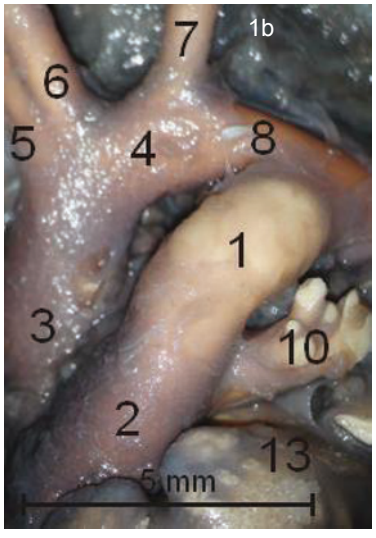
Figure 1. The great arteries of the fetal heart in a female fetus aged 28 weeks: 1 – ductus arteriosus, 2 – pulmonary trunk, 3 - ascending aorta, 4 – aortic arch, 5 - brachiocephalic trunk, 6 - left common carotid artery, 7 - left subclavian artery 8 – aortic isthmus, 9 - thoracic aorta, 10 - left pulmonary artery, 11 – left ventricle, 12 – right ventricle, 13 - auricle left atrium, 14 – auricle right atrium. Square area in fig. 1a zoom in figure 1b.





1.1. Aim of present research

We analyzed the development of the ductus arteriosus between the fourth and eighth month of human fetal life and how the dimensions of the ductus arteriosus changed with relation to sex.

2. Material and Methods

We examined 223 human fetuses, 108 males and 115 females, ranging in age from four to eight months of prenatal life. Whole material was derived from the Department of Histology and Embryology of the Collegium Medicum at Nicolaus Copernicus University in Bydgoszcz, Poland between 1994 and 2008. The fetuses had been conserved for a minimum period of three months in a 9% neutral solution of formaldehyde. All fetuses with normal karyotypes had been aborted spontaneously. None of them had any malformations or developmental abnormalities. 32 fetuses (19 without full clinical follow-up, 6 with external and 4 with cardiac malformation, and 3 with abnormal karyotypes - 2 with trisomy 21 (47,XX,+21), 1 with Turner syndrome - X monosomy (45,X)) were excluded from analysis of 255 fetuses. Proper consent was granted by the Bioethics Committee at Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland (KB/433/2004).

The age of each fetus was determined by crown-rump measurements (vertex-tuberale) using the polynomial proposed by Iffy [15]. All material was categorized according to its morphological age. Various numbers of fetuses were allocated to different, monthly age subgroups.

The vessel bed was filled with approximately 15–30 ml latex LBS 3060, without distortion of the dimensions of the vessel, using a catheter, which was introduced by dorsal access into the thoracic aorta. For specimen preparation a binocular magnifying glass (magnification 0.6-7 x 14, MBS-9, Russia) was used. The measurements were taken using electronic slide calipers (INCO, Poland) with an accuracy range of 0.01 mm. We measured the diameter and length of the ductus arteriosus (Figure 1). In order to exclude the impact of the difference between the diameters in the proximal and distal part of the vessel on vessel capacity, we used the arithmetical mean of the two diameters. We did this despite the findings of Szyszka and Wozniak, [16] who concluded that the ductus arteriosus had a constant diameter throughout its length. All measurements were taken twice by two independent investigators. For further analyses the arithmetical means of thus obtained values were used. We assumed that the arteries filled with latex were circular in cross-section. Subsequently, the vessel capacity was calculated using mathematical formula for cylinder volume based on the assumption of the vessel being a cylinder of known base diameter and height.

Table 1. Mean ductus arteriosus diameter (mm) in particular monthly age groups shown for the whole group and with regard to sex. Asteriks (*) indicates statistically significant difference of the marked group when compared to the younger group ($p<0.05$), N – number, X – parameter value, SD – standard deviation, p-value – indicates the differences between mean values in the female and male fetus in particular age groups ($p<0.05$).

age(m)	N			X + SD (mm)			p value
	all	male	female	all	male	female	
IV	18	8	10	1.12+0.25	1.11+0.26	1.13+0.25	0.8605
V	70	32	38	1.75+0.17*	1.78+0.18*	1.73+0.16*	0.1977
VI	105	50	55	2.46+0.24*	2.48+0.24*	2.44+0.25*	0.4078
VII	18	12	6	2.99+0.30*	2.99+0.29*	2.98+0.34*	0.9413
VIII	12	6	6	3.50+0.22*	3.55+0.29*	3.45+0.11*	0.4656
all	223	108	115	2.23+0.62	2.28+0.63	2.18+0.61	0.1635

Table 2. Mean proximal and distal part of ductus arteriosus diameter (mm) in particular monthly age groups shown for the whole group. N – number, X – parameter value, SD – standard deviation, p-value – indicates the differences between mean values the proximal and distal part of the arterial duct in particular age groups ($p<0.05$).

age(m)	N	X + SD (mm)		p value
		proximal	distal	
IV	18	1.14+0.76	1.10+0.55	0.2612
V	70	1.78+0.78	1.74+0.76	0.3937
VI	105	2.52+0.44	2.46+0.77	0.5087
VII	18	2.99+0.89	2.97+0.44	0.8571
VIII	12	3.45+0.91	3.55+0.31	0.5365
all	223	2.29+0.73	2.16+0.43	0.2347

2.1. Statistical Analysis

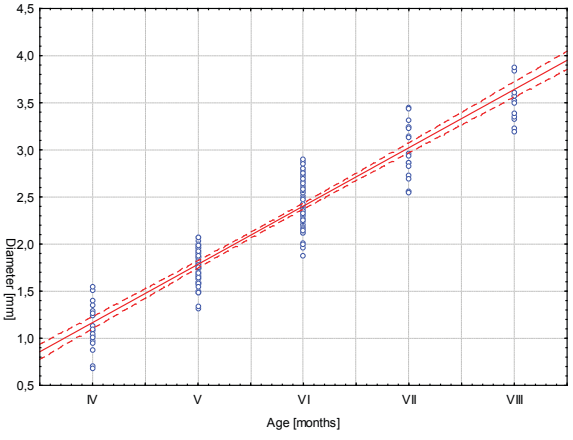
For statistical analysis of obtained data, Statistica 8.0 software (StatSoft Polska) was used. We calculated mean values and standard deviations for each age subgroup with respect to sex. In order to compare the means from particular groups we applied univariate (age) and bivariate (age and sex) analysis of variances (ANOVA) for independent variables and RIR Tukey post-hoc test for unequal populations. Statistical significance was defined as $p\leq0.05$.

Correlation coefficients (r) between the length or external diameter of the ductus arteriosus and fetal age, and the coefficient of determination (R^2) between volume and fetal age, were estimated.

3. Results

The growth of the ductus arteriosus diameter was linear in time and follows the regression curve (y=-61.3267+0.6188*x) with a correlation coefficient r=0.9265 and p<0.001 (Figure 2). The length of the ductus arteriosus increased according to a similar pattern (y=-158.9709+1.6045*x) with a correlation coefficient r=0.9238 and p<0.001 (Figure 3). The regression curve

Figure 2. Regression line for the diameter (y) of the ductus arteriosus versus fetal age (x); y=-61.3267+0.6188*x (r=0.9265; p<0.001) – continuous line, broken lines – 0.95 confidence interval.



reflecting the increase in ductus arteriosus capacity was exponential in time. $y=0.456*\exp^{0.8815*}x$, with a determination coefficient $r^2=0.7958$ (Figure 4). The diameter of the ductus arteriosus in the whole group was 2.23±0.62 mm. There were no significant sex-related differences with regard to this parameter p=0.1635. The diameter grew from 1.12±0.25 mm in the fourth month to 3.5±0.22 mm in the eighth month of fetal life. The mean diameter of the ductus arteriosus in females eight months old was 3.45±0.11 mm and was not significantly different in males (p=0.4656), where it was 3.55±0.29 mm (Table 1). There were no significant differences between the proximal and distal part of the DA (ductus arteriosus) (Table 2). The mean length of the ductus arteriosus in the investigated population was 5.89±1.61 mm; ranging from 3.00±0.66 mm in the fourth month subgroup to 9.15±0.56 mm in the eighth month subgroup. Similarly to the ductus arteriosus diameter, this measurement was also consistent in both sexes (p=0.0706) (Table 3). The ductus arteriosus capacity grew from 3.38±2.07 mm^3 in the fourth month to 84.96±16.56 mm^3 in the eighth month. The mean ductus arteriosus capacity in

Table 3. Mean ductus arteriosus length (mm) in particular monthly age groups shown for the whole group and with regard to sex. Asteriks (*) indicates statistically significant difference of the marked group when compared to the younger group ($p<0.05$), N – number, X – parameter value, SD – standard deviation, p-value – indicates the differences between mean values in the female and male fetus in particular age groups ($p<0.05$).

age(m)	N			X + SD (mm)			p value
	all	male	female	all	male	female	
IV	18	8	10	3.00+0.66	3.07+0.71	2.95+0.65	0.7044
V	70	32	38	4.57+0.45*	4.68+0.47*	4.47+0.41*	0.0529
VI	105	50	55	6.44+0.65*	6.55+0.64*	6.35+0.64*	0.1085
VII	18	12	6	7.75+0.78*	7.81+0.76*	7.63+0.88*	0.8771
VIII	12	6	6	9.15+0.56*	9.26+0.76*	9.05+0.28*	0.5280
all	223	108	115	5.89+1.61	6.03+1.62	5.69+1.57	0.0706

Table 4. Mean ductus arteriosus volume (mm) in particular monthly age groups shown for the whole group and with regard to sex. Asteriks (*) indicates statistically significant difference of the marked group when compared to the younger group ($p<0.05$), N – number, X – parameter value, SD – standard deviation, p-value – indicates the differences between mean values in the female and male fetus in particular age groups ($p<0.05$).

age(m)	N			X + SD (mm^3)			p value
	all	male	female	all	male	Female	
IV	18	8	10	3.38+2.07	3.41+2.27	3.36+2.03	0.9630
V	70	32	38	11.31+3.17*	11.98+3.43*	10.75+2.85*	0.1047
VI	105	50	55	31.53+9.07*	32.54+8.91*	30.61+9.19*	0.2769
VII	18	12	6	55.89+16.52*	56.34+16.19*	55.00+18.72*	0.6610
VIII	12	6	6	84.96+16.56*	93.07+22.32*	84.85+8.06*	0.4155
all	223	108	115	27.97+21.98	30.29+23.33	25.78+20.50	0.1251

Figure 3. Regression line for the length (y) of the ductus arteriosus versus fetal age (x); $y=-158.9709+1.6045*x$ ($r=0.9238$; $p<0.001$) – continuous line, broken lines – 0.95 confidence interval.

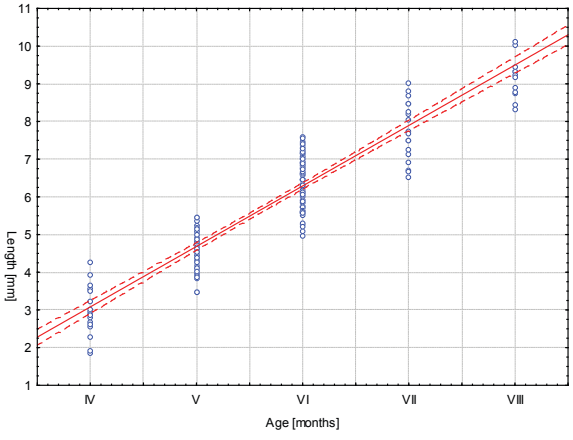
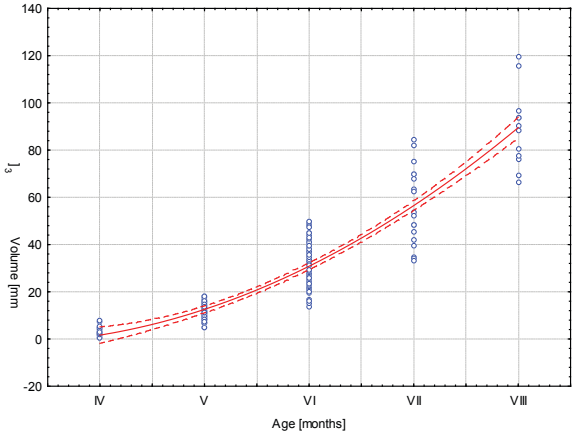


Figure 4. Regression line for the volume (y) of the ductus arteriosus versus fetal age (x); $y=0.456*\exp^{0.8815*x}$; $r^2=0.82$) – continuous line, broken lines – 0.95 confidence interval.



the whole study group was 27.97±21.98 mm^3. Similarly to the other parameters, these values were not different between sexes in the whole group ($p=0.1251$) and also within particular age subgroups ($p>0.05$) (Table 4).

In the whole group, both in males and females, all dimensions of the ductus arteriosus (diameter, length and capacity) increased significantly between consecutive months i.e. fifth vs. fourth, sixth vs. fifth, seventh vs. sixth, eighth vs. seventh (Tables 1, 3, 4).

4. Discussion

Available literature documents growth of the length and diameter of fetal arteries as linear in time [17-23]. The increase of ductus arteriosus capacity is described as exponential in time and following a regression curve [24-26]. Our research confirms these general patterns of development of arterial vessels in the specific

case of the ductus arteriosus. Van Meurs-van Woezik and Krediet [17] in their study on 126 subjects aged between 21 weeks of gestation to 10 years found that the diameter of the ductus arteriosus was proportional to body length. Alvarez et al. [27] demonstrated that the fetal ductus arteriosus circumference (in its middle part) grew according to a linear pattern with regard to body weight. Also, the length of the ductus arteriosus grew in a linear fashion. Hyett et al. [28] plotted a regression curve for the ductus arteriosus diameter as it grew in fetuses aged between three and five months of prenatal life. Szpinda et al. [25,29] found the diameter and length of the ductus arteriosus growth linear in time. According to different authors [1,30-35] the length of the ductus arteriosus fluctuates between 1 to 20 mm. This was confirmed in our material. Szpinda et al. [25] examined 131 human fetuses aged between four and nine months and found the length of the duct to range between 4 to 12 mm. The same author concluded that the capacity of the vessel grew according to exponential regression from 7.25±2.26 mm^3 to 103.52±13.81 mm^3. According to Castillo et al. [23], in a group of fetuses aged between four and five months, the diameter of the ductus arteriosus was 1.2-2.45 mm. A similar value was reported by Szpinda [29] – he found that the diameter in similarly aged fetuses to be 1.48-2.00 mm. Also in our group the diameter of the duct in fetuses aged between four and five months was 1.2 to 1.8 mm. Also in other age subgroups our data meet results reported by Szpinda [29]. According to Szpinda, [29] this diameter was 2.48±0.27 mm at six months, 2.64±0.31 mm at seven months and 3.00±0.24 mm at eight months.

Also in echocardiographic study [36] this data are confirmed. According Mielke and Benda [36] diameter of ductus arteriosus between 12-16 weeks (four months) was 1.5 mm, in 28-32 weeks (eight months) was 3.7 mm. Length of the duct in the same periods range between 2 mm and 5 mm [36]. This data confirm that increase of the length of the DA with advancing gestational age was found Mielke and Benda [36] and Alvarez et al. [27]. Another prenatal sonographic studies concerning on ductal diameter are based on a small number of cases. For example on 38 fetuses in Tan et al [37], 21 cases in Sutton et al. [38], and in Rasanen et al. [39] on 63 fetuses. Our study confirms sonographic data [36].

In methodology we determined that diameter of proximal and distal part of the duct are constant and similar [17]. In our study this assumption turned out correct. In Mielke and Benda [30] study proximal DA was smaller than distal part of this vessel (for about 2,5%). According Hyett at al 1995 [28] the diameter of the proximal part of the ductus was greater than the diameter of the distal part.

There is scarce data published with regard to sex related differences in ductus arteriosus dimensions. According to Szpinda [25,29], no significant gender differences were found. This is further confirmed by our results ($p>0.05$). The lack of sex-related differences in the ductus arteriosus anatomy, together with the well established fact of greater prevalence of patent ductus arteriosus in females remains in opposition to the assumption made by Kluckow and Evans, [9] who claimed the risk of future patency to be related to the fetal ductus arteriosus diameter. These authors were planning to conduct an echocardographic follow-up in prematurely born babies within the first 19 hours of life. The available data suggest that this parameter could be of diagnostic significance up to 28 weeks i.e. to the beginning of the eight month of prenatal life – which fully includes the time period we investigated. If the parameter proposed by Kluckow and Evans [9] were to convey prognostic value, then the dimensions (and the diameter in particular) of the duct among female subjects should be significantly larger. However, this is not the case, and therefore the assumption made by Kluckow and Evans [9] seems unjustified. Moreover, there is no research to date that would support this hypothesis.

5. Conclusion

Our data show that, there is a linear increase in the diameters and the length of the ductus arteriosus. Its volume increases according to the exponential function throughout gestation.

Therefore, the development of ductus arteriosus follows the same rules that had been described in the case of other fetal arteries. Lack of differences in vessel dimensions between males and females indicates that the greater prevalence of patent ductus arteriosus among females is not related to the vessel size in the fetus.

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