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Morphometric and volumetric analysis of the middle cerebral artery in human fetuses

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The morphometrical and volumetrical changes of the middle cerebral artery (MCA) during the fetal period of development were analyzed by digital-image analysis system (DIAS). Examinations were performed on 304 MCAs from 152 brains of human fetuses ranging from the 12th to 40th weeks of gestation. MCAs were analyzed with respect to its branching from the internal carotid artery and its division into the main cortical branches. No statistically significant differences were found between the mean values of the diameter, length and volume of the left and right M1 segments of the MCAs in all studied age groups.

Key words: middle cerebral artery, digital-image analysis, fetal brain, circle of Willis, anatomy, development

INTRODUCTION

Morphometrical and anatomical studies of the cerebral arteries development are important for the understanding of normal and variable growth of human fetal brain. A better morphological description of arteries development can also assist during prenatal diagnostic screenings. Previous studies of the morphological variations and current data of the middle cerebral artery (MCA), has been obtained from the research conducted on adults (Teal et al. 1973, Ciszek and Ząbek 1992). Very little emphasis has been given to the investigations of morphological and morphometrical changes of the MCAs during development. Embryologists (Padget 1947, 1948, Milenkovič et al. 1985, O'Rahilly and Müller 1992) studying the development of vascular system have often described the formation of the cerebral arterial circle (CAC) during the 6th and 7th weeks of human fetal gestational age (GA).

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During the past decade there has been great technological developments within the field of prenatal diagnostics (Gardiner 2001), combined with revolutionary advances in fetal surgical techniques, and an ability to visualize of development many vascular structures *in utero*. There is an increasing medical demand for the precise analysis of the cerebral vessels and its development during pregnancy, especially for the diagnosis of cerebral vascular pathologies (Kaplan 1981, Manusco 1989).

Arterial blood flow in prenatal Doppler-ultrasound analysis is generally employed to evaluate the overall state of the developing fetus (Mitchell et al. 1988). The morphometric (diameter, length) and volumetric analysis of the fetal vessels are very difficult to undertake using this method alone. The error level has been documented at approximately ±1 mm (Voight and Stoeter 1980, Rolfe et al. 1983) when compared to the mean value of the dimensions of fetal arteries, which are approximately 1 mm.

Accurate morphometrical description of normal development of the MCA is particularly crucial as a predicative marker for conditions such as fetal anemia

with the peak systolic velocity used as the predicative value for complications of intrauterine transfusions (Baytur et al. 2005). The pulsatility index of the MCA has also been shown to be helpful for the prenatal diagnosis of fetal hypoxemia or predication of perinatal outcome in fetuses suspected to have intrauterine growth restriction (Fong et al. 1999).

In both the adult and fetus the MCA is the main terminal branch of the internal carotid artery (ICA), which branch off from lateral part of the CAC. It is furthered divided into the insular and sphenoid branches. Various studies of the MCA have focused on the morphological variations of its origin from the ICA as a duplication, quadruplication, fenestration, and accessory middle cerebral artery (Abanou et al. 1984, Ciszek and Ząbek 1992). However, the brain specimens used in this research largely came from adults. Thus, the main focus of this particular study was the analysis of the development of the MCA in human fetuses at various GA groups. The main goal of this study was to analyze the growth of the MCA with respect to the various morphological and morphometrical parameters of the fetal brain. Synchronization of changes in the volume of the M1 segment of MCA and development of brain weight were also assessed. Furthermore, the effectiveness of our methods, using the digital-image analysis system, provided by the self-study algorithm of the vessels' edge detection, was assessed with new version Angio-Analyser software prepared by Olsztyn Digital-Image Analysis Laboratory.

METHODS

Studies were conducted on 304 MCAs taken from brains of 152 formalin-fixed human fetuses (83 males and 69 females) from a collection housed at the Department of Anatomy of the University of Warmia and Masuria. Cerebral vessels were injected with a mixture of 30% suspension latex (LBS 3060) and detergent. The mixture was then perfuse into the vessels according to a standard methodology (Radek 1990). Three weeks after the infusion, the brains were removed from skulls. The study group consisted of fetuses from both from spontaneous and therapeutic terminations of pregnancy. Specimens were screened for indications of external and internal malformations or abnormalities prior to taking images of cerebral vessels. The studies were approved by the Research Ethical Committee (L.DZ 61/98).

Fetuses aging between 12–40 weeks in GA were subdivided into 7 Gestational Age Range Groups (GARG) encompassing four weeks stage. The fetal age estimation was based on clinical documentation (Naegele's Rule) and the examination was compatible to Gruenwald's (1966) and Thomsen's (1977) method. The somatic development of the fetuses were determined by crown-rump length, crown-heel length and brain weight measurements (Thompson et al. 1970).

The fetal brain base arteries were carefully dissected under a stereoscopic microscope (Nikon SMZ-10A) and digital-images were stored (Nikon D300) in uncompressed data format (TIFF) at 3872 × 2592 pixels reso-

Table I

Somatic parameters of fetuses

Age Group (weeks)	*n*	CRL (mm)	SD	BW (g)	SD	BRW (g)	SD
12–16	11	96.2	10.8	48.1	17.8	4.5	1.64
17–20	33	180.3	11.7	159.6	46.5	15.9	6.29
21–24	50	189.7	26.4	345.5	71.4	32.3	15.03
25–28	21	213.6	10.6	568.2	103.9	50.9	21.87
29–32	12	264.8	12.8	887.3	158.6	76.4	17.44
33–36	13	289.3	15.6	1250.8	223.5	196.4	47.23
37–40	12	321.2	16.2	2408.2	593.2	275.8	55.20

(CRL) crown-rump length; (BW) body weight; (BRW) brain weight; (SD) standard deviation

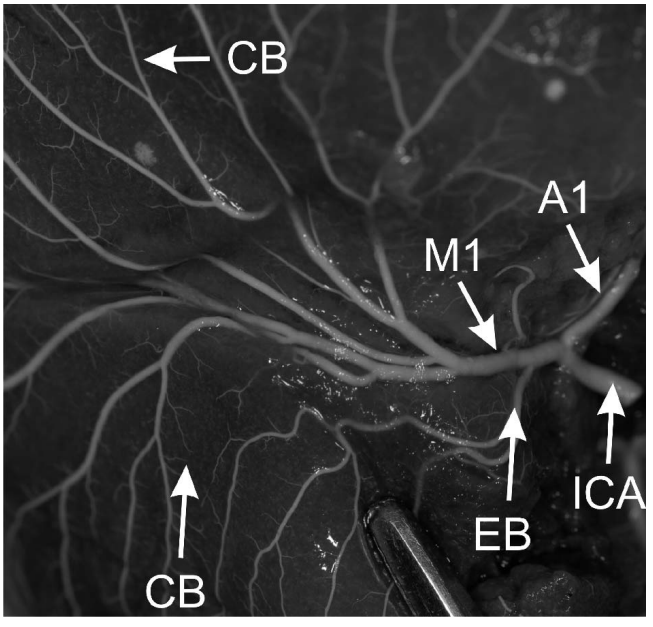

Fig. 1. Division of the right middle cerebral artery of during development. (A1) precommunicating segment of the anterior cerebral artery; (CB) cortical branch; (EB) early branch; (M1) the first (sphenoidal) segment of the middle cerebral artery; (ICA) internal carotid artery.

lution (10 MPX). The digital-images of the MCAs were used to compute the average diameter, length, and volume of the MCA using Angio-Analyser 08 software which was specially designed for this study.

The MCA was exposed from the meninges and the M1 segment was measured from its origin point at the ICA to its division into terminal branches. In case of the MCA duplication the parameters of the smaller diameter vessel have been excluded from the statistical analysis. The MCA was analyzed taking into consideration the growth characteristics of morphometric (diameter, length) and volumetric parameters of vessels and brain weight of fetuses. The growth curves fitting was carried out using a least-squares regression method. Differences between mean values each GARGs were performed using the *post-hoc* analysis with the Scheffe's test at the P=0.05 statistical significance level. The correlation coefficients were established using the Snedecore test with P<0.05 as statistically significant value.

RESULTS

The somatic parameters of all fetuses were summarized in Table I.

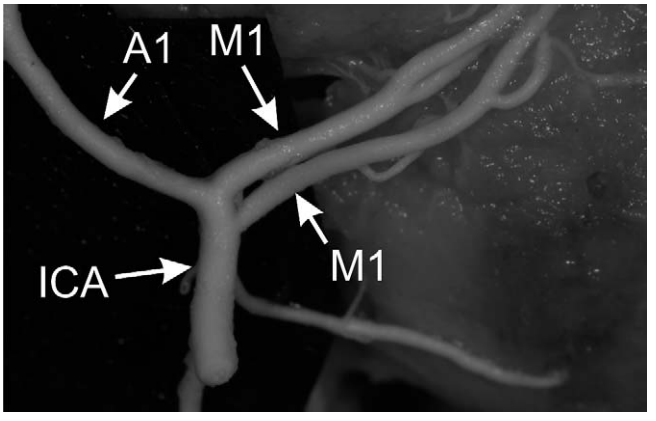

Fig. 2. Duplication of the left middle cerebral artery during development. (M1) the first (sphenoidal) segment of the middle cerebral artery; (ICA) internal carotid artery.

The MCA originates at the terminal bifurcation of ICA as a larger and more lateral branch (Fig. 1). In the study a duplication of M1 segment was observed twice on the left side only (Fig. 2). Early division of M1 segment was present four times on both sides. In one case M1 segment of right MCA had a small fenestration (Fig. 3). Diameter of M1 segment of the MCA increases approximately 3 times according linear function $y = -0.0705455 + 0.0043678*x$ with r=0.65 from 12 to 40 weeks of gestation (Fig. 4). Analysis showed statistically significant differences mean value of M1 segment diameter between all GARGs. There is no statistically significant difference between diameters of left and right and of M1 segment of MCA in each GARG (Table II).

No significant differences in vessel volume, length and dimensional values were noted with respect to the gender of the fetus or with respect to the left or right M1 segment (Table II, III, IV).

The length of M1 increased linearly according to the function $y = -0.159 + 0.01627x$ with r=0.50. The mean volume of the M1 segment for the youngest GA group (12–16 weeks) was recorded as 0.181 mm^3, with a mean diameter of 0.37 mm, and a mean length of 1.43 mm (Fig. 1). The mean volume in the oldest GA group (37–40 weeks) was 5.45 mm^3, with a mean diameter of 1.08 mm, and a mean length of 4.4 mm (Fig. 2).

The volume of the M1 segment was found to increase exponentially according to the following function $y = \exp(-3.40443 + 0.0186825*x)$ with r=0.75. The M1 diameter was found to increase linearly according to the function $y = 0.12x + 0.13$ where r=0.65.

Table II

Differences between age groups in diameter of M1 segment of the middle cerebral during fetal development

Age Group (weeks)	*n*	Diameter of M1 segment (mm)					
		Mean	SD	Min.	Max.	10th PCT	90th PCT
12–16	22	0.37	0.08	0.20	0.51	0.27	0.45
17–20	66	0.52	0.08	0.28	0.70	0.41	0.60
21–24	100	0.62	0.11	0.34	0.98	0.48	0.77
25–28	42	0.69	0.13	0.40	1.07	0.56	0.83
29–32	24	0.83	0.14	0.59	1.12	0.67	0.99
33–36	26	0.95	0.21	0.67	1.46	0.69	1.23
37–40	24	1.22	0.21	0.85	1.60	0.93	1.50

(Min.) minimum value; (Max.) maximum value; (PCT) percentile

In consecutive age groups, a statistically significant M1 segment volume increase was found, with an exception between the age groups of 17–20 weeks and 21–24 weeks. The variability coefficient for age groups 21–24 and 33–36 weeks was found to exceed 50%.

The mean values of successive age groups showed statistically significant increases, with an exception between the age groups 29–32 and 33–36 weeks. The mean values were statistically significant between all gestational age groups, except the groups of 21–24 weeks and 25–28 weeks (Fig. 3).

When comparing the measurement parameters of the MCA to other arteries at the base of the brain, correlations of the volume, dimension and length with the same parameters in the A1 segment of the anterior cerebral artery (ACA) showed no statistical significance. The lowest correlation coefficient was found to be between the volume of the M1 segment and the length of the anterior communicating artery.

Table III

Differences between age groups in length of M1 segment of the middle cerebral artery during fetal development

Age Group (weeks)	*n*	Length of M1 segment (mm)					
		Mean	SD	Min.	Max.	10th PCT	90th PCT
12–16	22	1.43	0.46	0.72	2.77	1.10	2.06
17–20	66	2.03	0.58	0.78	3.22	1.27	2.77
21–24	100	2.53	0.81	0.61	4.12	1.65	3.81
25–28	42	2.61	0.60	1.52	4.40	1.91	3.36
29–32	24	3.24	0.74	1.90	4.86	2.40	4.30
33–36	26	3.79	1.10	1.90	6.03	2.35	5.44
37–40	24	4.41	1.01	2.76	6.02	3.00	6.00

(Min.) minimum value; (Max.) maximum value; (PCT) percentile

Table IV

Differences between age groups in volume of M1 segment of the middle cerebral artery during fetal development

Age Group (weeks)	*n*	Volume of M1 segment (mm^3)					
		Mean	SD	Min.	Max.	10th PCT	90th PCT
12–16	22	0.18	0.07	0.06	0.43	0.09	0.25
17–20	66	0.43	0.17	0.14	0.91	0.25	0.64
21–24	100	0.86	0.49	0.08	2.62	0.38	1.48
25–28	42	0.93	0.39	0.33	1.95	0.51	1.53
29–32	24	1.94	0.74	0.89	3.39	1.12	2.87
33–36	26	2.95	2.08	0.89	9.11	1.12	6.46
37–40	24	6.55	2.89	1.73	11.02	2.74	10.00

(Min.) minimum value; (Max.) maximum value; (PCT) percentile

Other morphometrical parameters of vascular segments and fetal somatic parameters showed statistically significant correlations to volume, length and dimension of the M1 segment. The lowest correlation was noted with respect to the length of the P1 segment of the posterior cerebral artery (PCA).

In the present study, a comparison was made between the dynamic growth in the volume of the M1 segment of the MCA and brain weight. It was found that the brain's growth dynamic (coefficient of 4.17) was higher than the growth dynamic of the main artery of the base of brain. The MCA had a growth dynamic coefficient of 3.37, the highest of the arteries at the base of the brain, but lower than the growth dynamic coefficient of the brain. In comparing the vascular indices indicating the relative growth of the brain vessels, we found that within the prenatal period, the MCA and other arteries at the base of the brain showed a twofold or threefold decrease of the vascular index during development. This can be explained due to the asynchronous growth of the vessels and brain matter.

DISCUSSION

The MCA is one of the terminal branches of ICA forming an important component of the CAC. The literature reports the similar morphological variation of the MCA as a duplication or quadruplication of the M1 segment or M1-premature (early) division (Teal et al. 1973, Ciszek and Ząbek 1992). The research conducted on arteries at the base of the brain mostly target structures of the CAC, their symmetry and the differences between the left and right hemispheres. Medical studies have examined the asymmetry of the CAC with respect to stenosis of one of its arteries and the occurrence of aneurysms (Ferguson 1972, Stehbens 1972). Moreover, it was determined that asymmetry of the left and right segments of MCAs could be responsible for hemispheric dominance development. The smaller part of the CAC can lead to poor blood supply

Table V

Vascular indices of the M1 segment of the middle cerebral artery during fetal development

Gestational Age Group (Weeks)	Vascular index of M1 (mean)
12–16	0.04
17–20	0.03
21–24	0.03
25–28	0.02
29–32	0.02
33–36	0.02
37–40	0.02

Table VI

Vascular diameter ratio of the M1 segment of the middle cerebral and the internal carotid arteries during fetal development

Age Group (weeks)	*n*	Vascular diameter ratio of M1 segment (%)					
		Mean	SD	Min.	Max.	10th PCT	90th PCT
12–16	22	78.1	12.5	48.1	95.5	61.7	90.6
17–20	66	82.9	9.3	54.9	96.7	71.9	94.2
21–24	100	81.6	9.6	52.2	96.4	66.7	93.5
25–28	42	79.1	10.6	55.5	96.4	59.5	93.1
29–32	24	75.4	11.6	49.3	93.3	61.5	91.8
33–36	26	74.2	11.6	49.3	93.3	61.5	92.9
37–40	24	72.4	10.7	52.6	93.7	56.4	82.4

(Min.) minimum value; (Max.) maximum value; (PCT) percentile

which can "weaken" the hemisphere receiving perfusion from these vessels (Khamlichi et al. 1985, Fujimoto and Tanaka 1989). Examples throughout the scientific literature demonstrate that enlarged contralateral aspects of the CAC could contribute to the development of the second hemisphere. Neuroscientists describe cases of growth advantages in the arteries of the left hemisphere including the ICA, anterior, middle and posterior cerebral arteries in adult brains (Kamath 1981, Orlandini et al. 1985) and in fetuses or children (Tolgskaya 1953, Dovgiallo and Pekar 1966). This has served as a confirmation of left hemispheric dominance, which is observed in most of the population. Such studies currently describe infants and fetuses (van Overbeeke et al. 1991) or children at the age of 4 month to 14 years of age, and did not corroborate findings regarding lateral preference in development between the left and right sides of the brain. Similarly, the present study does not confirm the statistically significant differences in size of the left and right segments of the MCA.

Scientific studies about the measurement of arterial morphometric parameters are difficult to compare, because different methods and statistical analysis steps are in use. In fetal studies, confounding variables could be created because of different methods of dividing the experimental/age groups. Ziółkowski's technique, which was based on fetal organ growth is most commonly used (Ziółkowski et al. 1988), and allows for the classification of 5 fetal age groups. In our research we delineated 7 age groups by four week intervals, which is more useful in correlating findings to the clinical practice. Other problems could arise in the metering of fetal arteries, as their size is quite small. Current vital research uses new imaging techniques like computerized tomography (CT) and magnetic resonance imaging (MRI) to better visualize such structures. Fetal artery visualization and measuring is also possible in ultrasound imaging (USG) (Mitchell et al. 1988, Mari and Deter 1992); but the lack of exact morphometric descriptions makes the evaluation of the images difficult and less imprecise. Sonographic methods are complicated and can carry high error levels: 30–40%, ± 1 mm in a vessel of 1–3 mm in diameter in an old GA group. This explains why USG is more indicative of the quantitative blood flow measures in relatively big vessels (Arström et al. 1989, Lewisky et al. 1991, Noordam et al. 1994a). Fetal vessels have a diameter of about 0.1 mm in younger GA groups, thus, it is only possible to measure such vessels by computerized techniques (Brayden 1994, Gielecki et al. 1996). The digital-image analysis that we used in this research provides reliable information on comparative data that can be further used for other anatomical studies (Castleman 1979).

Contemporary morphometric descriptions of the cerebral blood vessels (Arduini and Rizzo 1990, Macchi and Catini 1994) are not accurate enough to be used in prenatal diagnostics. Seydel (1964) compared the size of CAC segments as a relative index to the diameter of the ICA. Other studies showed values of

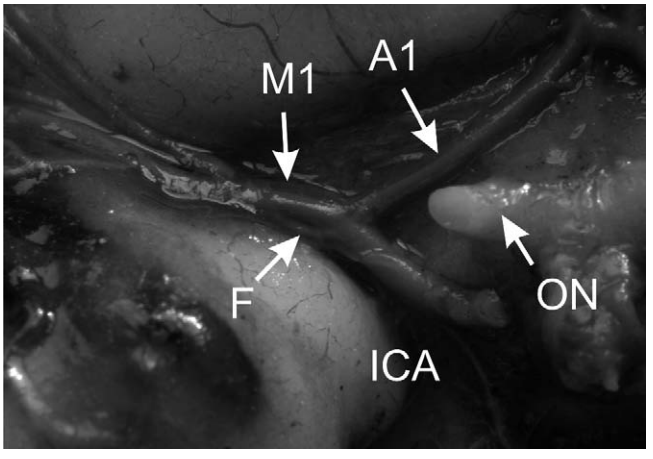

Fig. 3. Fenestration of right middle cerebral artery. (M1) the first (sphenoidal) segment of the middle cerebral artery; (ICA) internal carotid artery; (F) fenestration; (ON) optic nerve.

the measured arteries not corresponding to the size of fetal arteries (Noordam et al. 1994b). Furthermore, many authors still stand by the hypothesis of a more significant growth of the arteries on the left side of the CAC, whilst in the present study no such data was noted.

The present study also examined differences in brain development and the development of the arteries at the base of brain. In our research we demonstrated that the growth dynamic coefficient of the MCA is higher than that of the basilar artery. However, the growth dynamic coefficient of the anterior and posterior cerebral arteries shows a greater growth dynamic than the basilar artery (Cytowski et al. 2008). It seems this phenomenon can be associated with a smaller/slower growth dynamic of the brainstem and cerebellum during the prenatal period, as compared to the other brain components (Dobbing and Sands 1973). The changes of the arterial vascular indices point to the asynchronous increase of the cerebral vessels' volume when compared to the brain weight, which has been confirmed before in research on animals (Materka and Gielecki 1989).

The results taken from Doppler examinations usually do not include the numerical data of the fetal vessels' morphometric parameters. Others researchers have analyzed the blood flow, speed, pulsation and respective vessel resistance coefficients (Hadijev et al. 1992, Noordam et al. 1994b). One group (Veille et al. 1993) has displayed the trends as growth curves of the MCA for fetuses ranging in age from 16 to 40 weeks. The results of that work are comparable to those

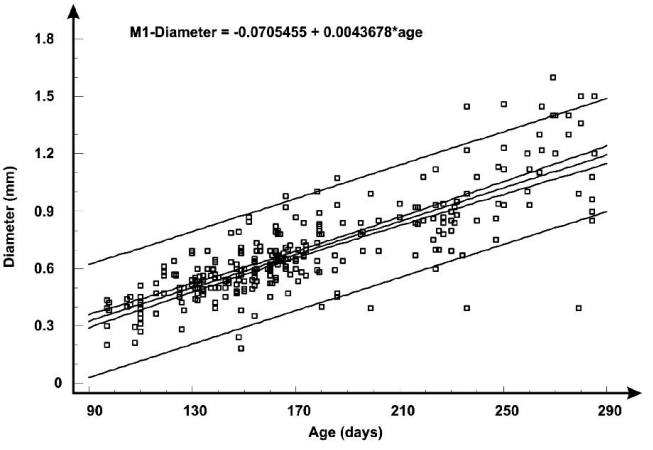

Fig. 4. Diameter of the M1 segment of middle cerebral artery during development

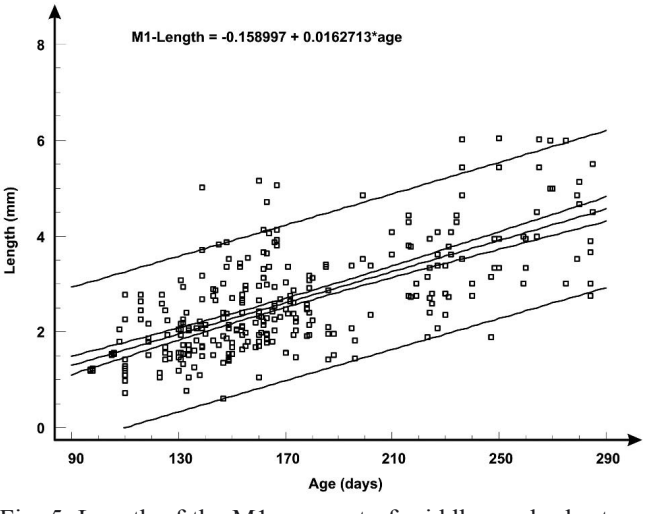

Fig. 5. Length of the M1 segment of middle cerebral artery during development

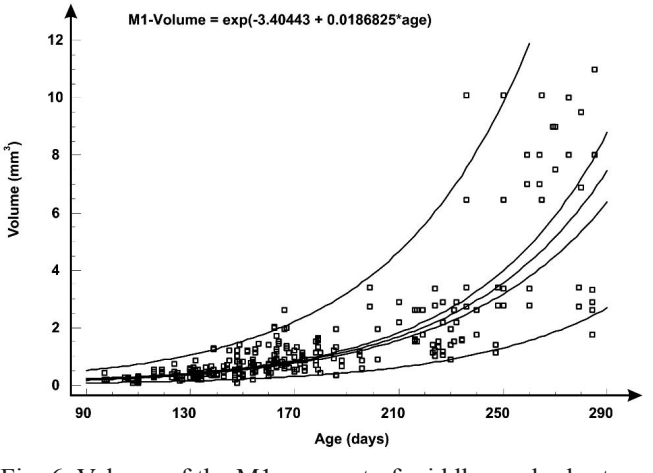

Fig. 6. Volume of the M1 segment of middle cerebral artery during development

obtained in the present study. The functions are linear; however, the individual values are half of what was recorded in this study. Differences probably could be due to inaccuracies in the method used to measure the vessels' diameter. Doppler ultrasound was employed, which is a method already known to be consistent but not accurate. This particular method gives us information about the state of the fetal vessels based on blood flow, speed and direction (Degani et al. 1994). Nevertheless, the quantitative and qualitative changes of the fetal vascularization, without precise morphological descriptions, can lead to erroneous interpretation and misdiagnosis (Padayachee et al. 1986, Cynober et al. 1992).

CONCLUSIONS

In the present study, morphometric data about the development of the MCA in human fetuses according to appropriate age groups was analyzed. Furthermore, a comparison was made between the variability of some developmental parameters of the middle, anterior, posterior and basilar cerebral arteries during prenatal development. This study showed a higher growth dynamic of the diameter and volume of the MCA in comparison to the basilar artery. The comparison of the growth rate of the arteries at the base of brain and brain weight show a distinct developmental asynchrony, as the brain weight growth rate coefficient is higher than the volume growth rate coefficient of the arteries. Additionally, the effectiveness of DIAS was proven as an accurate estimate of the morphometric and morphologic parameters of the fetal cerebral vasculature.

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