Original Article

Reference Values of the Anterior Cerebral Artery Doppler Indices in Normal Fetuses

Kiatsuda D, MD[1], Saksiriwuttho P, MD[1], Komwilaisak R, MD[1], Ratanasiri T, MD[1]

[1] Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Objective: To establish reference values of anterior cerebral artery (ACA) Doppler indices in normal fetuses during the period between 20- and 37-weeks' gestation.

Materials and Methods: A prospective, cross-sectional study was conducted on low-risk singleton pregnancies with healthy fetuses. The ACA Doppler spectral waveforms were obtained using transabdominal Doppler sonography, just after the origin of the ACA from the internal carotid artery in the same plane as the middle cerebral artery. The putative normative data were analyzed and constructed for the median, fifth, and ninety-fifth percentiles of ACA Doppler indices for each gestational week.

Results: Three hundred fetuses were measured for ACA Doppler indices. The pulsatility index (PI) and resistance index (RI) continuously increased from 20-weeks' gestation until a period of relative stability at 28- to 32-weeks, followed by a gradual reduction thereafter. Peak systolic velocity (PSV) showed a constant increase with advancing gestational age. A quadratic analysis was performed to construct curve-fitted percentile charts for each of these variables.

Conclusion: Reference values of the fetal ACA Doppler indices are constructed. This nomogram may be a useful tool for early detection of the brain-sparing effect in growth-restricted fetuses.

Keywords: Doppler indices, Anterior cerebral artery, Reference values

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Fetal growth restriction (FGR) occurs when the fetus fails to achieve the biological growth potential, which is genetically determined as a result of impaired placental function[1,2]. FGR, defined as an estimated fetal weight below a threshold at the tenth percentile for gestational age, occurs in approximately 5% to 10% of pregnancies[2,3]. Fetuses affected by FGR have a greater risk of perinatal morbidity and mortality as well as poor long-term health outcomes[2,4-6].

Intrauterine surveillance and follow-up with Doppler ultrasound evaluation are the current standard practice for FGR because it is feasible, non-invasive, and safe. Doppler assessment is of great value for early detection of compromised placental or fetal circulation, which helps obstetricians determine proper management without delay to prevent and reduce adverse perinatal outcomes[7].

Hypoxia in growth-restricted fetuses leads to blood redistribution to vital organs, such as the brain, as a protective autoregulatory mechanism. Vasodilatation of cerebral vasculature results in reduction of blood flow impedance to allow nutrient and oxygen delivery to the fetal brain; this is referred to as the 'brain-sparing effect'[8]. Nowadays, measurement of middle cerebral artery (MCA) pulsatility index (PI) is a widespread method to detect this adaptive process[9].

However, recent studies suggest that the brain-sparing effect in growth-restricted fetuses can be detected earlier in the anterior cerebral artery (ACA) than in the middle cerebral artery. A significant proportion of fetuses had ACA PI values below the fifth percentile in spite of showing an MCA PI within the normal range[10]. For the evaluation of effectiveness of ACA Doppler indices in detection of this condition,

Correspondence to:

Saksiriwuttho P.

Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, 123 Mittraphap Road, Muang District, Khon Kaen 40002, Thailand.

Phone: +66-43-363030, **Fax**: +66-43-348395

Email: piyamassak@gmail.com

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it is essential that normal reference values are first constructed in the Thai population.

Therefore, the purpose of the present study was to establish reference values for ACA Doppler indices, particularly PI, in normal fetuses with gestational ages between 20 and 37 weeks.

Materials and Methods

The present prospective, cross-sectional study was approved by the Khon Kaen University Ethics Committee for Human Research (HE601428). Between February 1 and October 31, 2018, low-risk pregnant women were recruited from the antenatal clinic at Srinagarind Hospital, Khon Kaen University. All participants provided written informed consents.

The present study included singleton pregnant women, aged 18 years and older, between 20- and 37-weeks' gestation, as calculated from the certain last menstrual period based on a regular menstrual cycle without hormonal contraception for at least three months, or confirmed by sonographic measurement in the first trimester. No participants had experienced obstetric or medical complications in the current pregnancy before recruitment. Subjects with abnormal fetal growth, fetal anomalies, abnormal fetal karyotype, or unsatisfactory ACA Doppler waveforms were all excluded from the study.

A Voluson E8 (GE Healthcare, Milwaukee, WI, USA) ultrasound device with a transabdominal 2 to 5 MHz curvilinear transducer was used for ultrasound and Doppler studies by a single operator.

According to the study of Benavides-Serralde et al[10], there were no significant differences in any Doppler parameters between the first segment of the ACA (recorded just after its origin from the internal carotid artery in the same plane as the MCA) and the second segment (recorded distal to the outlet of the anterior communicating artery). However, in that study, the angle of insonation was lower, the time spent on examination was shorter, and reliability was higher for the first segment. For this reason, the authors decided to evaluate the first anatomical segment of the ACA in the present study.

For each participant, a standard ultrasound examination, including fetal biometry and anatomical survey, was initially performed to estimate fetal weight and detect any fetal anomaly. ACA Doppler spectral waveforms were then obtained using color and pulsed-wave Doppler capabilities. The recordings were acquired during absence of fetal breathing and body movements at a physiologic fetal heart rate of 110 to 160 bpm[11] without unnecessary pressure on the fetal head as it could affect blood flow velocities[12].

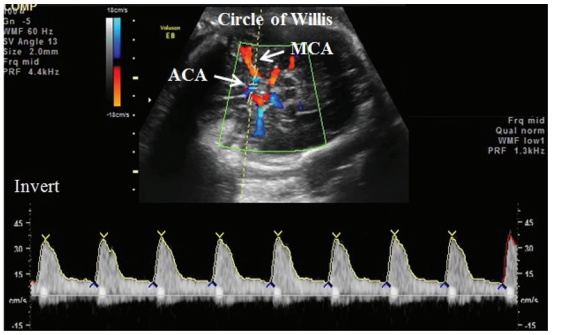

Figure 1. Location of the Doppler sample gate and acceptable Doppler waveforms of the anterior cerebral artery (ACA).

To locate the ACA, a transverse view of the fetal head was obtained at the level of the biparietal diameter. The transducer was then slightly directed towards the base of the skull at the level of the temporal and sphenoid bones. While the circle of Willis or MCA was visualized by color Doppler imaging, the ACA was also identified. The pulsed-wave Doppler gate was maintained at 2 to 3 mm and placed in the center of the vessel. Angle correction was optimized, and it was ensured that the angle of insonation was between 0° and 30°. The ACA Doppler waveforms were traced automatically over at least three consecutive uniform cardiac cycles (Figure 1), and the indices were calculated from the following computerized planimetry:

Pulsatility index (PI) = [peak systolic velocity (PSV) – end diastolic velocity] / time-averaged maximum velocity[13]

Resistance index (RI) = [peak systolic velocity (PSV) – end diastolic velocity] / peak systolic velocity[13]

In all fetuses, the PI, RI, and PSV values of ACA Doppler, with the angle of insonation and time spent to achieve acceptable waveforms, were recorded three times in succession and their mean values were calculated. Twenty randomly selected fetuses were measured by two operators for reproducibility analyses. The outcomes of pregnancy, including gestation at delivery and neonatal birth weight, were also noted.

The sample size calculation was based on the maximal standard deviation (SD) of the average of ACA PI during each gestational week (SD 0.33)[10] with 50% of SD allowance error. Therefore, at least 16 pregnant women for each gestational age were required.

Table 1. Normal reference values for the anterior cerebral artery Doppler indices with respect to gestational age

GA (weeks)	PI			RI			PSV		
	P5	P50	P95	P5	P50	P95	P5	P50	P95
20	1.15	1.30	1.46	0.66	0.71	0.78	14.20	20.08	26.87
21	1.08	1.22	1.45	0.65	0.69	0.74	18.45	20.26	24.93
22	1.05	1.37	1.63	0.63	0.74	0.81	16.93	21.53	31.32
23	1.19	1.42	1.88	0.66	0.75	0.85	17.89	24.92	32.07
24	1.28	1.54	1.77	0.72	0.76	0.82	19.20	25.70	38.70
25	1.38	1.55	1.99	0.71	0.78	0.85	20.42	23.92	35.15
26	1.20	1.48	1.79	0.69	0.76	0.82	18.59	25.85	33.27
27	1.33	1.53	1.84	0.70	0.77	0.82	19.42	28.97	34.80
28	1.39	1.68	2.03	0.74	0.80	0.85	23.61	32.53	43.27
29	1.48	1.64	1.94	0.75	0.80	0.87	25.45	35.48	52.97
30	1.35	1.64	2.06	0.73	0.79	0.88	27.86	36.83	45.97
31	1.32	1.59	1.88	0.70	0.79	0.84	25.03	39.70	52.64
32	1.40	1.69	1.95	0.74	0.80	0.87	29.09	37.90	49.97
33	1.45	1.64	1.84	0.75	0.81	0.85	28.90	44.17	53.77
34	1.23	1.69	1.95	0.73	0.81	0.85	27.50	42.72	58.57
35	1.21	1.60	1.96	0.69	0.80	0.85	33.70	45.47	59.49
36	1.01	1.33	1.70	0.63	0.72	0.81	29.73	38.12	48.57
37	0.97	1.32	1.76	0.61	0.73	0.84	33.20	44.03	60.57

GA=gestational age; PI=pulsatility index; RI=resistance index; PSV=peak systolic velocity; P=percentile

Statistical analysis was performed using Stata statistical software (StataCorp (2007) Stata Statistical Software: Release 10, StataCorp LP, College Station, TX). Descriptive statistics were analyzed for all parameters. The putative normative data were analyzed and constructed for the median, fifth, and ninety-fifth percentiles of ACA Doppler indices for each gestational week. Regression models were also provided to estimate the relationship between Doppler variables and gestational age. Reproducibility was evaluated with the interclass and intraclass correlation coefficients (CCs) and 95% confidence intervals (CI) by comparing the results of the two operators. Furthermore, 95% limits of agreement between observers were calculated according to the method proposed by Bland and Altman[14].

Results

Three hundred eleven healthy singleton pregnant women were recruited into the present study. Eleven were excluded due to fetal growth abnormalities, fetal structural anomalies, or inability to obtain proper ACA Doppler waveform. The remaining 300 fetuses, 16 to 18 fetuses per weeks of gestation, were evaluated by Doppler ultrasonography. Mean maternal age was 28.97±5.02 years old (18 to 42) and mean pre-pregnancy body mass index (BMI) was 21.63±3.71 kg/m^2. One hundred thirty-six women (45.3%) were nulliparous. Most women (81%) had not used contraception before pregnancy and their gestational ages were mostly calculated based on crown-rump length (68.3%) by first-trimester ultrasonography. Unexpectedly, seven women (2.3%) had gestational diabetes mellitus and one woman (0.3%) had pre-eclampsia after the examination. Mean gestational age at delivery and birth weight were 38.51±1.19 weeks and 3,183.83±376.96 grams, respectively. Two babies (0.7%) with low birth weight (lower than 2,500 grams) were born prematurely due to maternal preterm labor and preterm pre-labor rupture of membranes (PPROM). Their weights were appropriate for their respective gestational ages.

Gestational age-specific reference values for the fifth, fiftieth, and ninety-fifth percentiles of the anterior cerebral artery PI, RI, and PSV were established as shown in Table 1. A quadratic analysis was performed

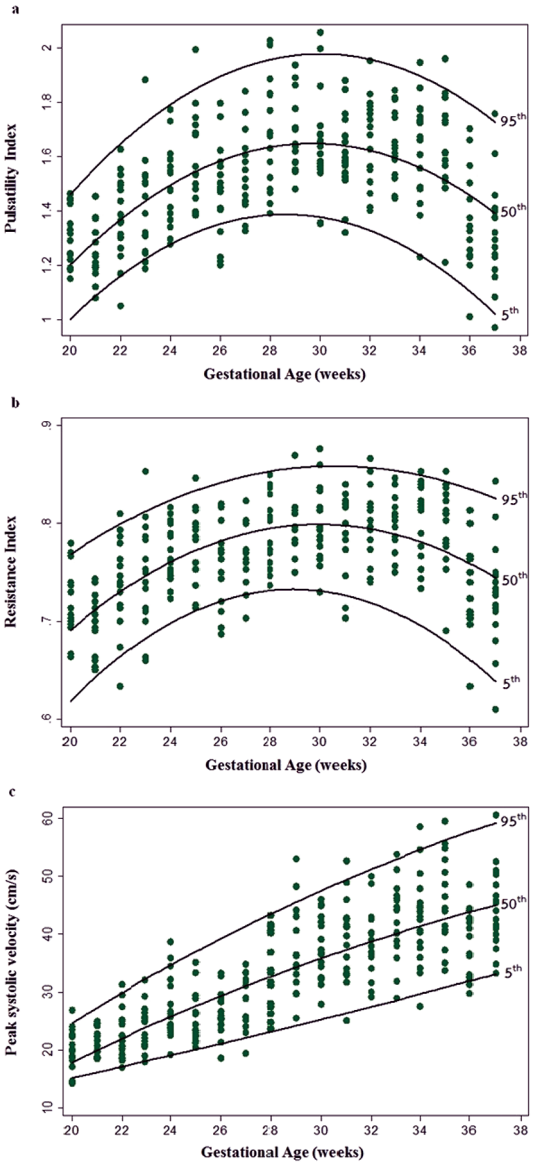

Figure 2. Plots of anterior cerebral artery Doppler indices with normal values at the 5th, 50th, and 95th percentiles for the pulsatility index (a), resistance index (b), and peak systolic velocity (c) throughout gestation.

cm/s=centimeters/second

to construct curve-fitted percentile charts for each of these variables (Figure 2). Notably, the PI and RI continuously increased from the 20-weeks' gestation until relatively stable at 28- to 32-weeks, followed by a gradual reduction thereafter, while the PSV showed a constant increase with advancing gestational age.

In all cases, the mean angle of insonation used in the present study was 20.09±7.43°, and the mean

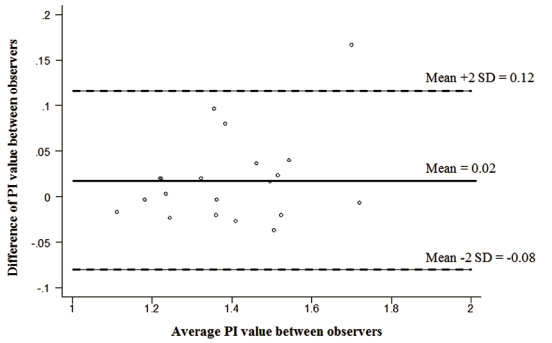

Figure 3. Limits of agreement between observers in assessing the PI of ACA.

PI=pulsatility index

time spent since identification of the correct plane of the fetal head until the achievement of acceptable waveforms was 1.47±0.96 minute.

Reproducibility analysis showed that the inter-class CCs in ACA PI, RI, and PSV assessment were 0.95 (95% CI 0.89 to 0.98), 0.94 (95% CI 0.85 to 0.98), and 0.97 (95% CI 0.91 to 0.99), respectively. The respective intraclass CCs were 0.90 (95% CI 0.88 to 0.92), 0.88 (95% CI 0.85 to 0.90), and 0.91 (95% CI 0.90 to 0.93). These results indicated good to excellent reliability in all Doppler indices. A Bland-Altman plot of the agreement between observers showed the mean difference for the measurement of ACA PI was 0.02 (95% CI –0.01 to 0.04), which was not statistically significant (Figure 3).

Discussion

In addition to the MCA, the ACA is another vessel of choice to assess fetal cerebral circulation. The authors have established the reference ranges of three ACA Doppler indices, i.e., PI, RI, and PSV, for each gestational week. The authors' study found the resistance in ACA, either PI or RI, increased from week 20 to relatively stable values at weeks 28 to 32, then gradually decreased up to term. Values for PSV increased steadily with time, consistent with advancing gestational age.

Similar to the present results, Benavides-Serralde et al reported the PI values in both ACA segments increased until 28- to 32-weeks of gestation and then decreased until the end of pregnancy, and that PSV increased between 20- and 40-weeks of gestation[10]. Likewise, Contag et al also demonstrated an increase in the value of ACA PI from 24-weeks until 28- to 32-weeks of gestation[15]. Although, the authors' reference values of PI (Table 1) are a bit lower and

different from those previously reported[10,15], they have the same trend and curve pattern throughout the gestation (Figure 2). The difference could probably be explained by racial factors or the use of different equipment. However, the differences in insonation angles are not likely as an explanation for different values. Their average angle used[10] was 18°, similar to the authors' (20°). Another study, using only a small number of cases (n = 31), found unchanged PI values in the ACA between weeks 28 and 33, followed by a significant drop at weeks 34/35 and thereafter remained stable[16]. It is possible that each population group may require its own normal reference values for clinical applications.

The authors observed minor fluctuations of the normal values in some gestational weeks (Table 1). The authors' study was not a longitudinal study, so it could not control the effect of any potential confounding factors among participants. In the present study, the authors also included seven cases of gestational diabetes mellitus and one case of pre-eclampsia, which later developed after the examination because all of those fetuses had normal growth at the time of measurement and were finally born with appropriate weight for their gestational ages.

The authors found identification of the ACA to be usually simple and quick, as for the MCA, except when the fetal head is in an improper position such as occiput anterior or engagement into the pelvis as seen in near-term gestation or during labor. Therefore, measurement of ACA Doppler indices can be achieved in almost all fetuses and reproducibility is nearly perfect as presented by inter- and intraclass CCs, consistent with previous study[10].

The strengths of the present study are 1) it provides the first nomogram of fetal ACA Doppler indices in a Thai population, 2) the sample size for each gestational week is adequate, 3) it contains sufficient information about the study population and complete neonatal data, 4) the authors display not only the PI values but also RI and PSV, and 5) low interobserver variation suggests high reproducibility of this measurement.

A limitation of the present study is that the authors did not include and follow the outcomes of the fetuses from which acceptable ACA Doppler waveforms could not be obtained. Those fetuses may in fact have experienced normal outcomes and their Doppler values can probably be used as a part of this reference values.

The authors believe that this nomogram provides reference values for fetal ACA Doppler indices, especially PI, and will be useful in early detection of the brain-sparing effect in growth-restricted fetuses. Further evaluation is required regarding the accuracy of ACA PI in detection of the fetal brain-sparing effect. In addition, short- and long-term consequences of a decrease in ACA PI values below the normal range in fetuses with FGR, need to be assessed.

Conclusion

Reference values of fetal ACA Doppler indices between 20- and 37-weeks' gestation are determined. These may be useful in early detection of the brain-sparing effect in growth-restricted fetuses.

What is already known on this topic?

The fetal brain-sparing effect resulting from hypoxia is associated with increased risk of adverse neurodevelopmental outcomes. Detection of this effect in growth-restricted fetuses can be done earlier in the ACA than in the MCA.

Though normal reference values for fetal ACA Doppler parameters have been published in several countries, there seems to be some variation of these values according to nationality. Therefore, the authors need their own normative data for evaluation of fetuses in the Thai population.

What this study adds?

This study has established, for the first time in Thailand, reference values of fetal ACA Doppler indices (PI, RI, and PSV) for the median, fifth, and ninety-fifth percentiles between 20- and 37-weeks' gestation. More research should be conducted to determine the precision of ACA PI in detection of the brain-sparing effect in fetuses with FGR.

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Conflicts of interest

The authors declare no conflict of interest.

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