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The Effect of Fetal Heart Rate and Fetal Activity on the Middle Cerebral Artery Flow Velocity Waveforms in Normal Human Fetuses from 18 to 42 Weeks Gestation

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Objectives: The purpose of the study was to evaluate the effect of fetal heart rate (FHR) and fetal activity (FA) on the pulsatility index (PI) of fetal middle cerebral artery (MCA).
Methods: We examined 181 normal pregnant women from 18 to 42 weeks gestation with pulsed wave Doppler and color flow Doppler. Fetal activity was determined by ultrasound.
Results: The fetal MCA PI declines with advancing gestation after 25 weeks. MCA PI is significantly higher in the second than in the third trimester whereas the FHR is similar. MCA PI values are normally distributed and correlate best with gestational age and least with FHR but not at all with fetal activity (FA). Simple linear regression of MCA PI on FHR according to FA revealed this correlation to be stronger in active fetuses. During the second trimester, the MCA PI is lower in active than in quiet fetuses. In the third trimester, this difference is smaller. FHR shows similar responses in the two activity states. FHR in the entire group, however, is higher in active fetuses but MCA PI is similar in the two activity states.
Conclusions: Fetal MCA PI declines with advancing gestation significantly in the presence of an insignificant decline of the FHR. FHR and MCA PI relate differently in active than in quiet fetuses. The effect of activity on FHR and MCA PI is variable in second and third trimester fetuses.

Key words: Fetal heart rate—Fetal activity—Pulsatility index—Middle cerebral artery.

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Introduction

Recent advances in ultrasound and Doppler technologies have made the exploration of the fetal circulation possible for research and clinical purposes. A significant amount of research has demonstrated the clinical usefulness of umbilical artery flow velocity waveforms in the understanding and management of high-risk pregnancies.[1–3] More recently, a significant volume of research work described the characteristics of the intracranial fetal arterial flow velocity waveforms; several reports documented the changes that take place in the resistance of the middle cerebral artery (MCA) in fetuses with intrauterine growth retardation (IUGR).[4–9]

The majority of the studies reported thus far examined fetuses in the third trimester. The primary goal of these studies was to compare MCA resistance in normal and growth-retarded fetuses. There is limited information, however, in regard to the developmental changes during the second trimester and its relationship with the third trimester. Assessment of MCA resistance seems to be a useful clinical tool for the evaluation of the fetus with IUGR. The purpose of this prospective cross-sectional investigation was to evaluate the above-mentioned characteristics of the MCA pulsatility index (PI) and the effects of heart rate and fetal activity (FA) in normal human pregnancy and to establish normal reference values for clinical use.

Materials and Methods

Only patients with uncomplicated pregnancies at the time of the study were included. A total of 194 healthy pregnant women were enrolled in the study. The final analysis included only 181 patients whose pregnancies remained uncomplicated. Five patients were lost to follow-up, five were excluded due to pregnancy complications, and three were excluded due to fetal anomalies diagnosed after the Doppler study was completed

(one trisomy-18, one fetus with hydrocephalus, and one fetus developed ascites 10 weeks after the Doppler study). All neonates were appropriate for gestation and the 1- and 5-min Apgar scores were ≥7. All patients were examined once during the pregnancy. All of the 181 patients who were used in the analysis delivered at term, appropriate-for-gestation neonates. Birth weights were evaluated as normal according to the York county normal birth weight charts.[10] The majority of the patients (80%) were Caucasian, and the rest were black (12%), Hispanic (5%), and other (3%). The study was approved by the institutional review committee and all subjects gave informed consent.

The entire uterine cavity was scanned to rule out any gross fetal anomalies and to evaluate fetal growth. Fetal activity status was evaluated by real-time ultrasound for 5 min before we obtained the MCA flow velocity waveforms (FVWs). A modification of the fetal behavioral status as described by Nijhuis et al.[11] was used to classify the fetuses as active (AC) or inactive (IAC). Fetuses with absent gross body movements or quiescence, which may be interrupted regularly by startles, were classified as IAC. Fetuses with frequent and periodic gross body movements or vigorous, continual activity were classified as AC.

Doppler flow studies were carried out with a Toshiba 270-30 A-ultrasound system (Toshiba America, Yonkers NY). A 3.75 MHz transducer was used, with a 1- or 2-mm sample volume. A high-pass filter set at 100 Hz was used to filter out signals produced from slow-moving vessel walls and other structures. The power output was kept between 10 and 30% of the maximum. The maximum power output is 90 mW/cm^2. We obtained the MCA FVWs as follows: The patient was placed in a semirecumbent position with some left lateral tilt. An axial view of the fetal head was obtained at the biparietal diameter level. From this point on, color flow mapping was switched on and with a slight caudal displacement of the transducer, the MCA was identified. The Doppler beam was kept parallel to the axis of the MCA in either a temporal-occipital approach or occipital-temporal approach.[8] The range gate of the pulsed wave Doppler was placed at the midportion of the MCA and a 10 to 15-sec recording of appropriate MCA flow velocity waveforms was obtained. The PI was measured at a later time from two waveforms by means of the electronic calibers tracing two successive waveforms and averaging the calculated values. The heart rate was similarly calculated automatically by measuring the time interval of two successive waveforms. For storage of the data we used a computer data base until the study was completed.

Statistical analysis was performed by means of a statistical program for the Macintosh personal computer (JMP version 2, SAS Institute Inc., Cary, NC). Linear and polynomial regression analysis was used to evaluate the relationship of the MCA PI with gestational age and the fetal heart rate (FHR). Normality of the distribution of the MCA PI and FHR values was tested by the Shapiro-Wilk W test. Comparisons between the second and third trimester were performed by Student's T-test for independent groups. Ordinal logistic regression analysis and Wilcoxon/Kruskal-Wallis test (Rank Sums) were performed for the analysis of the nonparametric data. Differences between individual pairs were analyzed by Tukey-Kramer HSD test. A $P < 0.05$ was considered statistically significant.

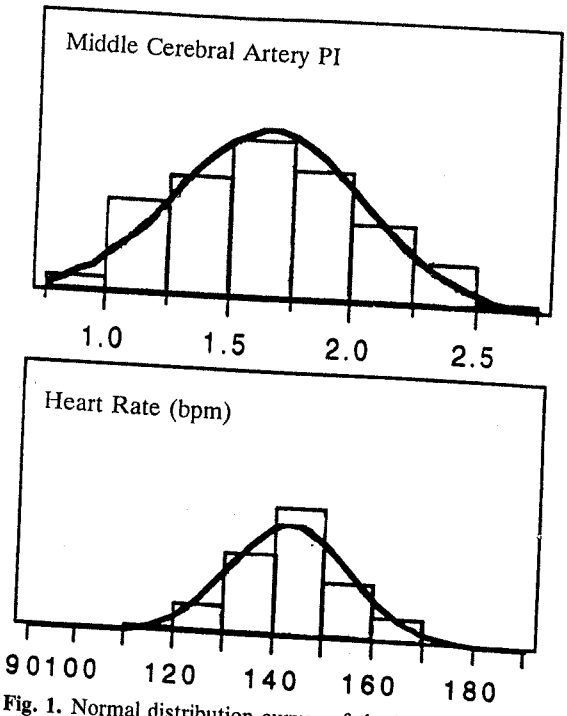

Fig. 1. Normal distribution curves of the MCA PI and FHR. Normality was tested by the Shapiro-Wilk W test.

Results

Data from 181 patients were analyzed. GA ranged from 18 to 42 weeks. MCA PI and the FHR values in this group of patients follow the normal distribution curve (Shapiro-Wilk W test) (Fig. 1). When MCA PI was plotted according to fetal activity, it was noted that active fetuses have normally distributed values but inactive fetuses do not (Fig. 2). Simple regression analysis (all patients) of the MCA PI on the GA revealed a moderate negative linear correlation ($r = -0.48$, $P < 0.0001$). A second-degree polynomial fit improved the correlation ($r = -0.58$, $P < 0.0001$) (Fig. 3). The polynomial fit shows clearly that prior to 25 weeks' gestation, the MCA PI is rather independent of gestation and from 25 weeks on, it declines with advancing gestation until 42 weeks. Linear regression analysis of the FHR on GA (all patients) revealed a statistically significant but very weak negative linear correlation ($r = -0.05$, $P < 0.02$), and a second-degree polynomial fit did not improve the relationship. This is in agreement with the known small decline of the FHR with advancing gestation after the mid-

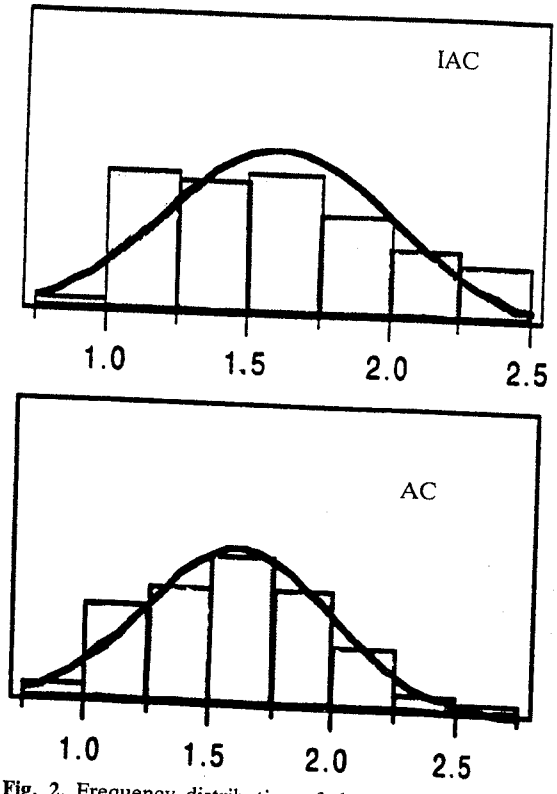

Fig. 2. Frequency distribution of the MCA PI according to fetal activity status. MCA PI in inactive fetuses is not normally distributed (Shapiro-Wilk W test).

second trimester, following a steeper decline between first and early second trimester. Simple regression analysis of MCA PI on FHR (all patients) revealed a weak but statistically significant negative linear correlation ($r = -0.25$, $P < 0.001$).

Comparison of the MCA PI according to FA status failed to reveal any significant difference; in contrast, FHR was found to be different in the two groups of activity (Table 1). Further analysis of the data according to FA status revealed significant differences between the two activity states. In quiet fetuses there is no correlation between MCA PI and FHR ($r = -0.005$, $P = 0.70$). In contrast, in active fetuses there is a moderate negative linear correlation ($r = -0.41$, $P < 0.001$, $n = 96$), (Fig. 4). FA, however, had a different effect in the relationship between MCA PI and gestational age (GA). In quiet fetuses, MCA PI correlates strongly with GA ($r = -0.58$, $P < 0.0001$), and this relationship weakens with FA ($r = -0.42$, $P < 0.0001$), (Fig. 5).

Ordinal logistic regression analysis of FA status according to GA revealed an increasing likelihood for a fetus to be active with advancing gestation ($r = 0.25$, $P < 0.0002$). Second trimester fetuses are less likely to be active than third trimester. MCA PI and FHR values are higher in second trimester than in third trimester fetuses (Table 2). Although in the second trimester, MCA PI is lower in active fetuses, the difference was not statistically significant. Power analysis showed that a sample of 215 second trimester fetuses would be

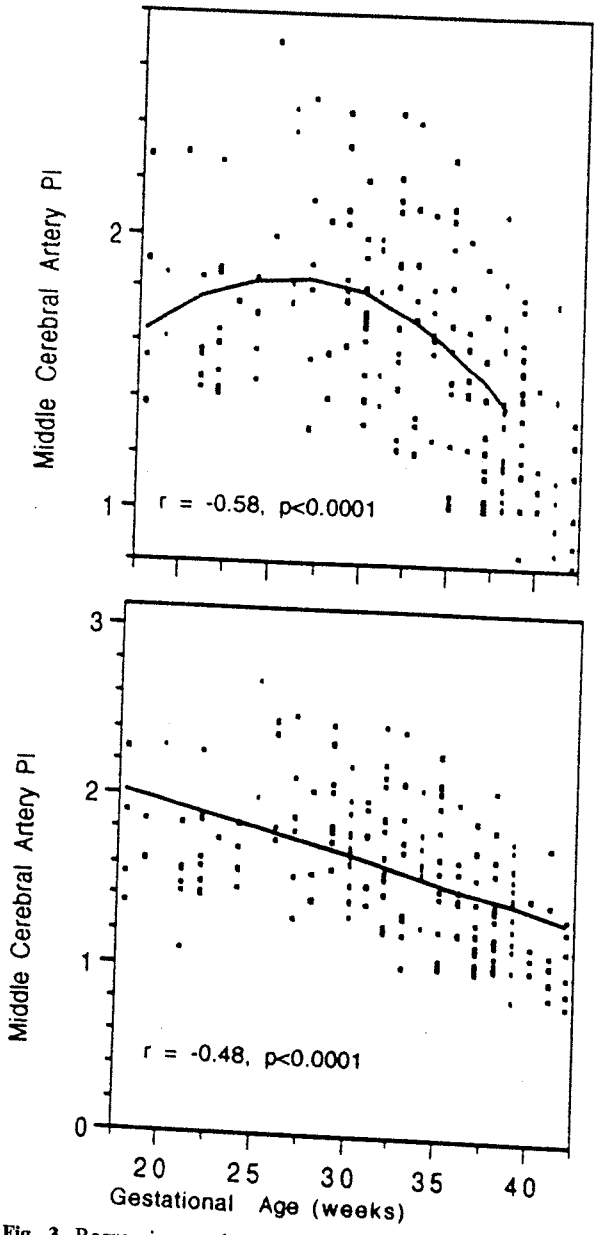

Fig. 3. Regression analysis of MCA PI on gestational age in all patients. Upper panel represents a second degree polynomial fit and the lower panel the linear model.

Table 1. Comparison of MCA PI and fetal heart rate between active (AC) and inactive (IAC) fetuses.

	IAC ($n = 85$)	AC ($n = 96$)	P value
MCA PI (mean ± SD)	1.59 ± 0.04	1.59 ± 0.04	NS
FHR (mean ± SD)	139.82 ± 10.19	144.71 ± 11.12	0.003

necessary for significant difference at $P = 0.05$. In third trimester fetuses this difference is even smaller, and the necessary sample size is 615 third trimester fetuses. FHR differences in the two activity states in the two trimesters were closer to significance, with

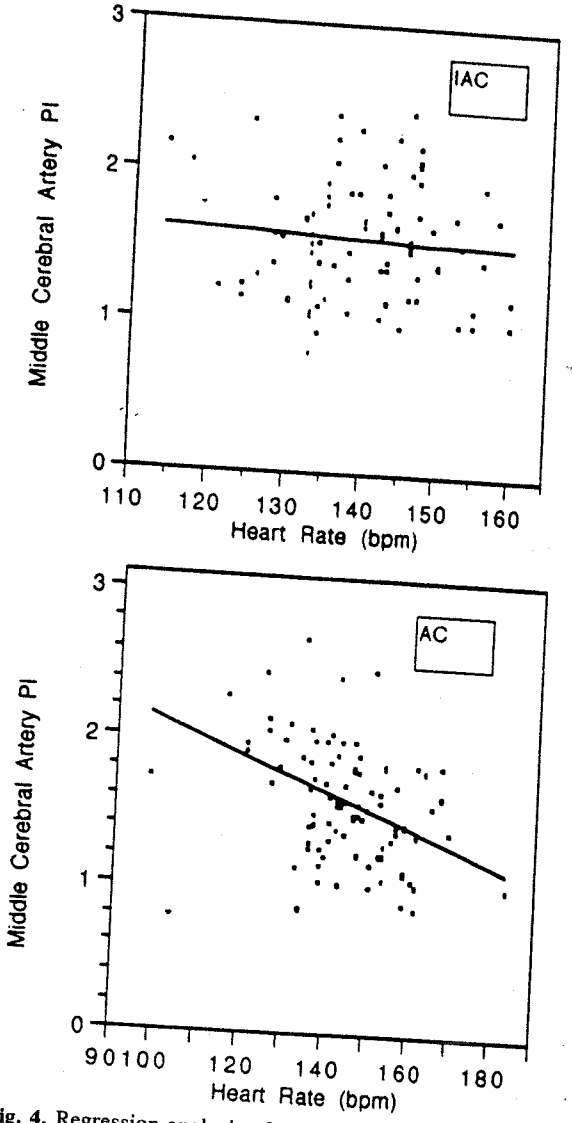

Fig. 4. Regression analysis of MCA PI on FHR. Upper panel represents inactive and lower panel active fetuses.

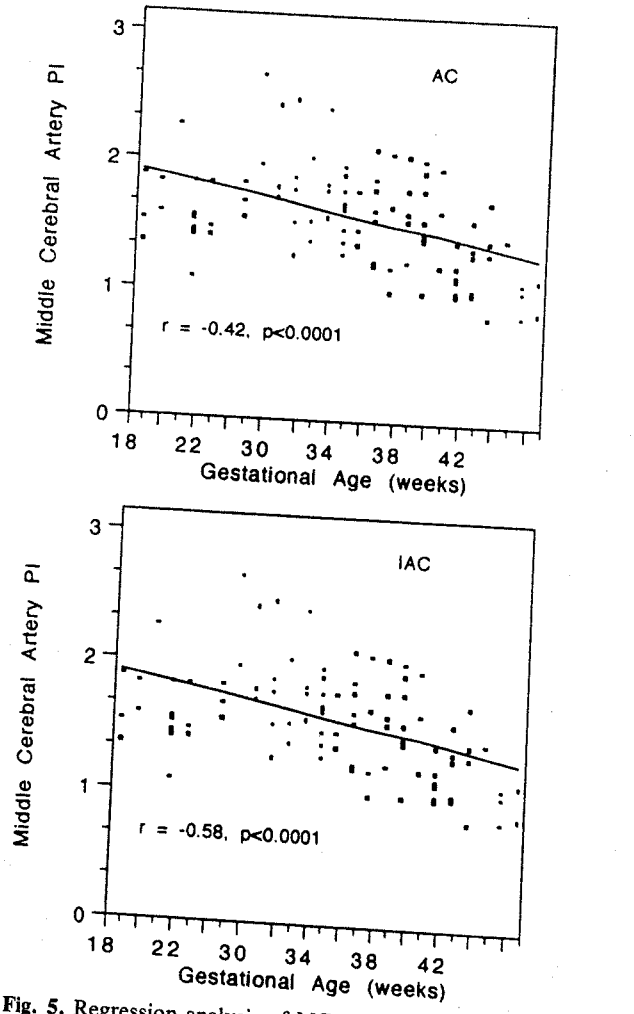

Fig. 5. Regression analysis of MCA PI on gestational age. Upper panel represents active and lower panel inactive fetuses.

required sample sizes of 153 and 142 for the second and third trimester, respectively (Table 3).

Simple regression analysis of the MCA PI on the GA in patients ≥25 weeks gestation ($n = 154$) revealed a strong negative linear correlation ($r = -0.63$, $P < 0.0001$) (Fig. 6). Predicted normal values for MCA PI from 25 to 42 weeks gestation with the 5th% and 95th% confidence bands (mean ± 1.65 SD) were developed by the regression equation,

$$\text{MCA PI} = 3.477 - 0.055 * \text{GA}$$

with a standard error (SE) above and below the predicted mean of 0.196. Figure 7 is a graphic depiction of the predicted values of MCA PI from 25 to 42 weeks' gestation along with the 95th percentile confidence bands, and Table 4 presents the numerical values. When the same group of patients (25–42 weeks' gestation) were analyzed according to activity status, a

Table 2. Comparison of MCA PI and FHR between second and third trimester.

	2nd trimester	3rd trimester	*P* value
MCA PI (mean ± SD)	1.81 ± 0.35	1.51 ± 0.36	<0.0001
FHR (mean ± SD)	145.82 ± 11.74	140.77 ± 10.54	<0.001

better correlation was found between GA and MCA PI in inactive ($n = 76$) fetuses than in active ($n = 78$) ones ($r = -0.67$, $P < 0.0001$ vs $r = -0.61$, $P < 0.0001$). However, the SE above and below the predicted mean in both conditions is larger than in the whole group [IAC group 0.300, ($n = 76$); AC group 0.269 ($n = 78$); all patients between 25 and 42 weeks 0.196 ($n = 154$), respectively]. This leads to a significantly wider range of normal values and it may be the result of smaller numbers (Table 5).

The 5th, 50th, and 95th percentiles of each group (IAC, AC, and all patients together >25 weeks' gestation) were compared among the three groups and significant differences were found (Table 6).

Table 3. Comparison of MCA PI and FHR according to fetal activity in the second and third trimester.

Trimester	No.	MCA PI (mean ± SD)			FHR (mean ± SD)		
		AC	IAC	*P*	AC	IAC	*P*
Second	68	1.76 ± 0.33	1.86 ± 0.31	0.27	145.45 ± 11.52	141.57 ± 10.60	0.19
Third	113	1.44 ± 0.35	1.50 ± 0.39	0.41	143.10 ± 14.08	139.23 ± 9.19	0.08

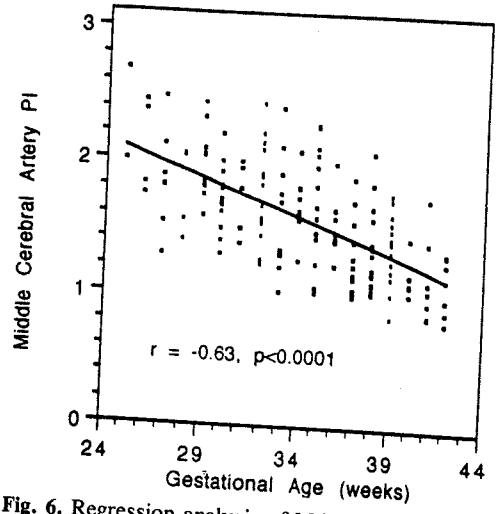

Fig. 6. Regression analysis of MCA PI on GA in patients who are equal to or greater than 25 weeks' gestation.

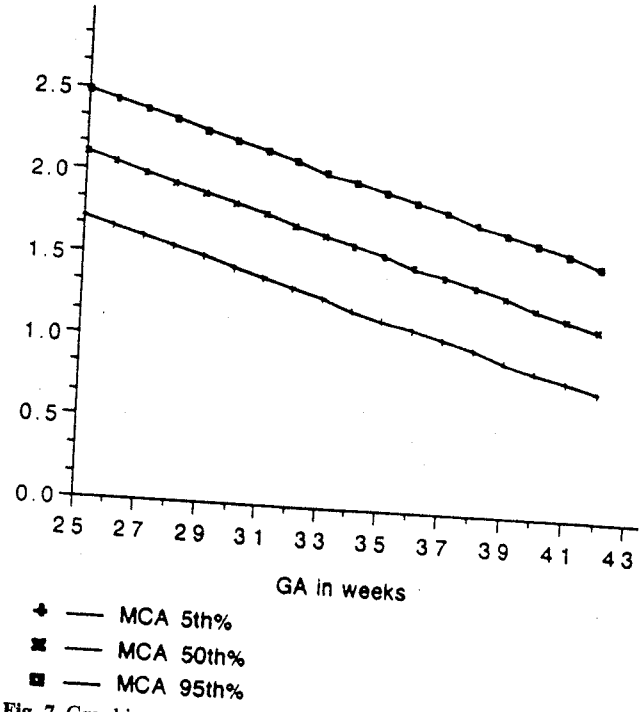

Fig. 7. Graphic representation of 95th percentile confidence bands of MCA PI from 25 to 42 weeks' gestation.

Discussion

The MCA is the largest branch of the internal carotid artery and perfuses a significant portion of the human brain. Its main arterial branches include the anterolateral ganglionic, inferior external frontal, ascending frontal, ascending parietal, and parietotemporal arteries.[12] There is little known on the development of the cerebral vasculature of the human fetus after 24 weeks' gestation, although significant changes take place in the cerebral growth and vascular development.[13]

Doppler methodology is a significant recent development which offers the capability of noninvasive in vivo studies of intracranial flow patterns. Although the evolution of the cerebral blood flow is complex, evaluating vascular resistance by Doppler can provide valuable information and improve our understanding of the physiologic and pathologic aspects of fetal cerebral flow. The PI is an expression of peripheral vascular resistance. We elected to use the PI instead of the resistance index (RI) or the systolic-diastolic ratio (S/D) for two reasons. First, the bulk of the fetal cerebral blood flow studies used PI, and secondly, PI is the most appropriate for vessels that may display absent or reverse flow during diastole.

The statistical properties of the MCA PI have not been reported before. It is known from studies of the umbilical artery resistance that the different resistance indices (PI, S/D, and RI) do not always follow the gaussian distribution curve.[14,15] This is particularly important in the development of normal reference values. Our data show that the MCA PI is normally distributed in pregnancies from 18 to 42 weeks when fetal activity status is ignored, but this is not the case when fetuses are classified according to their activity. It seems that inactive fetuses exhibit clustering of MCA PI values within a narrow range probably because of a decreased heart rate variability which is characteristic of quiet fetuses. This hypothesis is further enhanced by the fact that there is no correlation between FHR and MCA PI in inactive fetuses. In contrast, active fetuses exhibit increased variability in the FHR with a more symmetrical distribution and a significant correlation with the corresponding MCA PI values. The effect of fetal activity on the relationship between MCA PI and GA is of interest; increasing GA is more likely to be associated with an active fetus. The introduction of the effect of the increased FHR variability on the MCA PI blunts the effect of GA and weakens the relationship.

During the second trimester, fetuses are less likely to be active and have higher mean heart rate and mean MCA PI values. There is a statistically significant declining trend in the FHR with advancing gestation although the degree of decline is small. Second trimester

Table 4. Reference values for MCA PI from 25 to 42 weeks gestation regardless of fetal activity status.

Gestational age	MCA PI 5th %	MCA PI 50th %	MCA PI 95th %
25	1.78	2.10	2.41
26	1.72	2.05	2.35
27	1.67	1.99	2.30
28	1.61	1.94	2.24
29	1.56	1.88	2.19
30	1.50	1.83	2.13
31	1.45	1.77	2.08
32	1.39	1.72	2.09
33	1.34	1.66	1.97
34	1.28	1.61	1.91
35	1.23	1.55	1.86
36	1.17	1.50	1.80
37	1.12	1.44	1.75
38	1.06	1.39	1.69
39	1.01	1.33	1.64
40	0.95	1.28	1.58
41	0.90	1.22	1.53
42	0.84	1.17	1.47

Table 5. Predicted lowest, highest, and range values for MCA PI in the two groups of activity and in all patients together regardless of activity status in patients between 25 and 42 weeks gestation.

Value	GA	IAC (n = 85)	AC (n = 96)	All
Lowest	42	0.58	0.56	0.77
Highest	25	2.82	2.57	2.48
Range	25–42	2.24	2.01	1.71

All: All patients regardless of fetal activity

Table 6. Comparisons of the average 5th, 50th, and 95th percentile values among the three groups.

Percentile	IAC	AC	All	P value (group)
5th	1.06 ± 0.28[c]	0.99 ± 0.25[c]	1.19 ± 0.25	<0.01
50th	1.65 ± 0.28	1.52 ± 0.25[b]	1.58 ± 0.25[b]	<0.01
95th	2.24 ± 0.28	2.05 ± 0.25[a]	1.96 ± 0.24[a]	<0.01

Each percentile category represents the mean ± SD of all gestational ages from 25 to 42 weeks for the respective activity group
Wilcoxon/Kruskal-Wallis test (Rank Sums)
[a,b,c] Not different pairs (Tukey-Kramer HSD)

fetuses exhibit a poor relationship between MCA PI and advancing gestation. In contrast, after 25 weeks' gestation, MCA PI declines significantly with advancing gestation. This finding is in harmony with the fact that fetal brain vasculature exhibits significant changes as a result of extensive branching of the existing arterial tree.[13] Between 18 and 25 weeks' gestation one may consider MCA PI values to be similar, regardless of GA. However, after 25 weeks, MCA PI is GA dependent and one should only use GA-specific normal values.

Our data demonstrate that fetal activity exerts a significant effect on the MCA PI in ways that are not evident by direct comparisons of MCA PI values between active and inactive fetuses. In contrast, it is clear that activity alters the statistical properties of MCA PI and its relationship with FHR and GA. We attempted to develop appropriate normal reference values according to fetal activity status. However, we realized that the effect of fetal activity not only changes the predicted mean values but also leads to a significant increase in the variance of the test which leads to very wide ranges between the lowest and highest values for each GA. It is possible that this effect may alter the sensitivity and specificity of the test in its clinical application in unpredictable ways. Our intention is to utilize normal reference values generated by ignoring the fetal activity until we get the opportunity to evaluate the activity related values in clinical practice.

The effect of FHR on the MCA PI values seems to be clinically insignificant. It is clear that although MCA PI declines with increasing heart rate, only 6% of the decline noted on the MCA PI can be attributed to the increase noted on the FHR. This is in agreement with previously published data on the relationship between FHR and umbilical artery resistance.[16,17] Therefore, we believe that FHR need not be taken into account when one evaluates MCA PI for clinical use.

In conclusion, we report the effects of FHR and fetal activity status on the MCA PI values in normal pregnancy. In addition, we evaluated the statistical aspects of these parameters in normal human fetuses from 18 to 42 weeks' gestation and developed normal reference values according to the above aspects.

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