

The Effect of Vibratory Acoustic Stimulation on Fetal Middle Cerebral Artery Impedance and Instantaneous Fetal Heart Rate: A Prospective Cross-Sectional Study From 20 to 42 Weeks' Gestational Age

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Objective: We sought to examine the response of fetal heart rate (FHR) and middle cerebral artery resistance (MCA PI) to vibratory acoustic stimulation (VAS).

Methods: We examined 160 normal pregnant women with uncomplicated pregnancies. We obtained baseline measurements of FHR and MCA PI before the application of a 3-s vibratory acoustic stimulus (commercially available artificial larynx); we then measured FHR and MCA PI change immediately after the stimulus. Real time ultrasonography with pulsed wave and color Doppler imaging was used for the execution of the study. Statistical evaluation was performed by comparison of the means and regression analysis.

Results: Fetuses ≤ 28 weeks did not exhibit any significant change in their heart rate or MCA PI after VAS (143 ± 2 vs 145 ± 2 for heart rate and 1.75 ± 0.07 vs 1.71 ± 0.07 for the MCA PI; $P =$ not significant). Fetuses > 28 weeks responded with significant changes (140 ± 1 vs 153 ± 1 for heart rate and 1.57 ± 0.03 vs 1.30 ± 0.03 for MCA PI; $P < 0.001$). Regression analysis revealed that FHR and MCA exhibited variable patterns of response to VAS with advancing gestation.

Conclusion: As the human fetus matures, its response to external VAS varies. FHR response follows a different pattern than MCA PI. Increasing auditory function and parasympathetic nervous system activity are thought to be important in the development of this gestational age-dependent pattern.

Key words: Pregnancy—Doppler—Cerebral

(VAS). Most of these reports have studied the effects of VAS on fetal heart rate (FHR) and the effects on fetal behavioral states, and one report presented the effect on the umbilical artery resistance.¹⁻⁶ Wladimiroff and Cheung reported on the effect of VAS on the resistance of the internal carotid artery between 36 and 39 weeks' gestation.⁷ The fetal neurologic system matures progressively with advancing gestational age, and fetal responses to various stimuli change as the fetal maturity level increases. Moreover, fetal auditory brain stem response improves with advancing gestation as a result of increasing functional maturation.⁸ Commercially available VAS devices are widely used as adjuncts to electronic FHR monitoring (EFM).

EFM in relation to fetal activity is the most commonly used method for the evaluation of fetal well-being. Recently, a number of reports indicate that EFM along with VAS may be a useful test for fetal well-being.⁹⁻¹¹ It is assumed that a sick fetus with a depressed central nervous system (CNS) will not respond to VAS, whereas a fetal response to VAS indicates a fetus with an intact CNS. Anencephalic fetuses fail to respond to VAS with any degree of appreciable heart rate or any fetal activity change, confirming the necessity of an intact CNS for appropriate fetal response to VAS.² With regard to fetal cerebral blood flow, it has been shown that regional fetal cerebral blood flow relates to fetal electrocortical activity.¹² This study was designed to examine how VAS affects FHR and middle cerebral artery impedance (MCA PI) from 20 to 42 weeks' gestation.

Introduction

Several studies in the medical literature have reported on fetal responses to external vibratory acoustic stimulation

Subjects and Methods

A total of 172 patients with normal pregnancies were examined for the completion of this study. All patients were recruited from a population of women referred to our Antenatal Testing Unit for fetal evaluation by ultrasound for various indications (prenatal diagnosis, growth evaluation, and gestational age determination). Only women with uncomplicated pregnancies and normally grown fetuses were

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Table 1. Responses of FHR and MCA PI according to gestational age.

Gestational age (weeks)	FHR (mean \pm SE)		MCA PI (mean \pm SE)	
	Control vs VAS	P^a	Control vs VAS	P^a
>28	140 \pm 1 vs 153 \pm 1	<0.001	1.57 \pm 0.03 vs 1.30 \pm 0.03	<0.001
\leq 28	143 \pm 2 vs 145 \pm 2	NS	1.75 \pm 0.07 vs 1.71 \pm 0.07	NS

Control, FHR before VAS; NS, not significant

^a Statistical significance at $P < 0.05$

enrolled in the study. Each fetus was examined only once (cross-sectional design). The study was approved by the Institutional Review Committee (IRC), and all women gave written informed consent.

Doppler flow studies of the MCA were carried out with a Toshiba 270-30A 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. When there was evidence of absent diastolic flow, the filter was reduced to 50 Hz to avoid artifactual elimination of low diastolic velocities. The power output was kept between 10 and 30% of the maximum. The maximum power output is 90 mW/cm². 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.¹³ During periods of fetal apnea, the range gate of the pulsed wave Doppler was placed at the midportion of the MCA and a 10- to 15-s recording of uniform MCA flow velocity waveforms was obtained. The pulsatility index (PI) was measured at a later time from uniform waveforms by means of the electronic calipers tracing two successive waveforms at a time and averaging the calculated values. Instantaneous heart rate was calculated similarly and automatically by measuring the time interval of the two flow velocity waveforms used for the measurement of the PI. Baseline (control) Doppler measurements were obtained after a few minutes of rest in left lateral tilt. All studies were performed during fetal apnea and fetal quiet sleep state. After the completion of baseline measurements, a 3-s vibratory acoustic stimulus was applied with a commercially available artificial larynx (Corometrics Model 146; Corometrics Medical Systems, Inc.). The audio frequency was 75 \pm 10% Hz, with harmonics ranging from 20 to 9,000 Hz, and the sound intensity was 74 dB at 1 m in air. The fetus was observed with real time ultrasound during the VAS. About 80% of fetuses responded with the first application, and the rest required a repeat 3-s VAS. Fetal responses consisted of startles and increased body movements. Immediately after the stimulation and not later than 3 min after it, Doppler studies were repeated as noted above.

The change of the heart rate was calculated by subtracting the instantaneous baseline heart rate from the instantaneous heart rate after VAS. A positive number indicates an

increase of the heart rate, and a negative number indicates a decrease. A FHR increase is the expected response. Similarly, for the MCA PI, the change was calculated by subtracting the baseline MCA PI value from the one after stimulation. A positive number indicates an increased MCA PI after stimulation, and a negative number indicates a decreased MCA PI after stimulation.

Statistical analysis was performed by means of a statistical program for the Macintosh personal computer (JMP version 2; Statistical Analysis Software Institute Inc., Cary, NC). The means of MCA PI and FHR before and after VAS were analyzed by a paired Student's *t*-test. Regression analysis was used to evaluate the relationships of the MCA PI with gestational age and FHR. $P < 0.05$ was considered statistically significant.

Results

A total of 160 patients were analyzed for the purpose of this study. We excluded 12 patients from the final analysis because of pregnancy complications that developed after the patients were examined (preeclampsia, diabetes, and preterm delivery for fetal or maternal indications). All remaining neonates were appropriate for gestational age, and no 5-min Apgar score was less than 8. The mean \pm SE gestational age at the time of delivery was 39 \pm 0.2 weeks (36–42 weeks), birth weight was 3,160 \pm 48 g (2,800–3,700 g), and gestational age at the time of the study was 34 \pm 0.4 weeks (20–42 weeks).

MCA PI after VAS was significantly lower than the baseline value (mean \pm SE; 1.35 \pm 0.03 vs 1.60 \pm 0.03; $P < 0.0001$), and FHR was significantly higher (mean \pm SE; 152 \pm 1 vs 141 \pm 1; $P < 0.0001$) when all patients were analyzed as one group. Gestational age-specific differences in the heart rate and MCA PI response to VAS are shown on Table 1.

Figure 1 reveals that between 22 and 25 weeks' gestation, the average heart rate change remains very close to zero. From 25 to 36 weeks' gestation, the average degree of change increases and the proportion of fetuses who respond with an increase in the heart rate increases. After 38 weeks' gestation, there is a combination of a gradual decline in the average degree of change and an increase in the proportion of fetuses who respond with a decline in the instantaneous heart rate (Fig. 1; third-degree polynomial, $r = 0.35$, $P < 0.00001$). Before 38 weeks' gestation, only 16% of fetuses respond with a decline in comparison to 35% after 38 weeks. After 40 weeks, the proportion of fetuses with a decline in the heart rate response increases to 67%, and at 42 weeks, it reaches 83%.

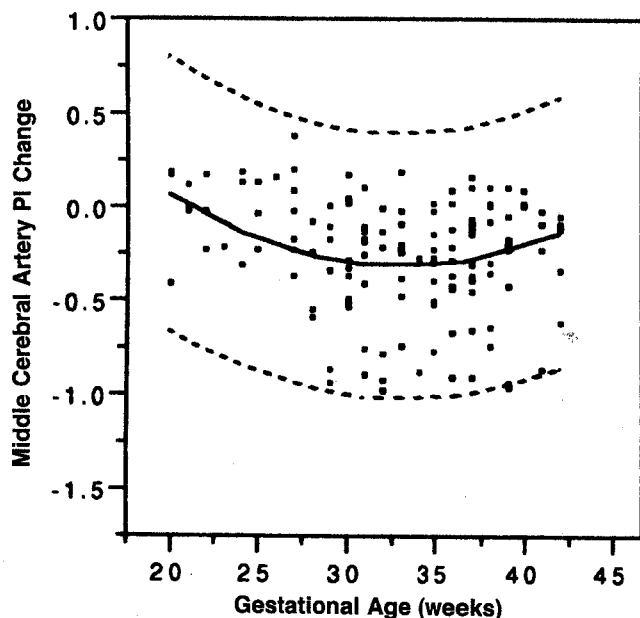


Fig. 1. FHR response to VAS in relation to gestational age.

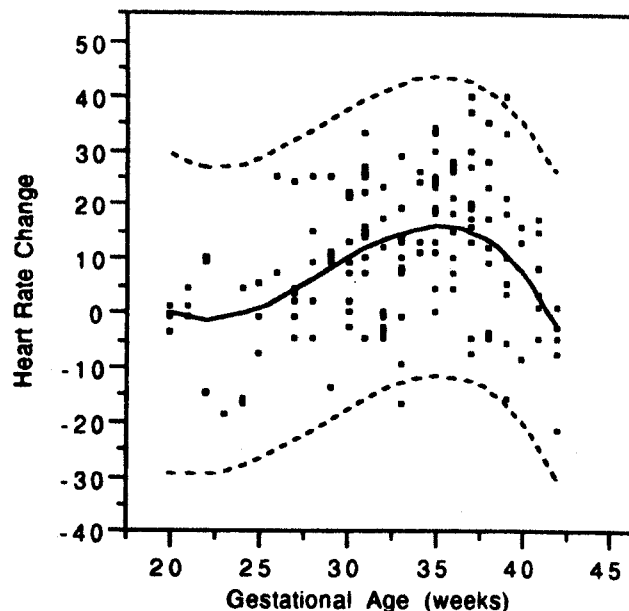


Fig. 2. Fetal MCA PI response to VAS in relation to gestational age.

Figure 2 reveals that the MCA PI declines more with advancing gestation until 36 weeks. Subsequently, and until 42 weeks, the average degree of decline of MCA PI lessens. To some extent, the MCA PI change mirrors the change in FHR between 25 and 42 weeks. This may imply that the MCA PI changes are the result of FHR changes. However, multiple regression analysis revealed that the change in the MCA PI after stimulation relates primarily to baseline MCA PI, with a smaller contribution from gestational age and an even smaller contribution from the change in FHR ($r = 0.68$, $P < 0.0001$; F ratios: 95.69, 20.06, and 8.50, respectively). The relationship between MCA PI change and gestational age is best expressed by a second-degree polynomial curve (Fig. 2, $r = 0.22$, $P < 0.02$).

Discussion

Animal experimentation has helped us realize many of the recent advances in perinatal medicine. Whenever possible, studies performed on human fetuses provide valuable insights on human fetal physiology to a degree that animal experimentation cannot. Doppler methodology has improved substantially and provides us with a real time "physiology dissecting tool." VAS has been studied extensively. We have significant evidence describing normal and abnormal fetal responses to VAS. In this report, FHR measurements reflect instantaneous values obtained immediately before and after VAS and not continuous recordings. Therefore, we were unable to evaluate the presence or absence of heart rate decelerations or accelerations in the form of electronic heart rate monitoring. Any direct comparison of our findings with the findings of other studies whereby different methodology was used may be inappropriate and possibly misleading. To our knowledge, this is the first study to use a relatively large number of fetuses, ranging in gestation from 20 to 42 weeks, in contrast to previous studies

whereby gestational age was limited to a portion of the third trimester.

This report demonstrates that fetuses respond to VAS in different ways depending on the gestational age. Fetuses with gestational age ≤ 28 weeks have clearly failed to achieve the degree of response that the older ones have. The pattern of heart rate response we have observed in this study is in agreement with that of previous related reports.^{1,8} It seems that as fetuses mature with advancing gestation, concurrent changes in the maturity of the CNS may alter fetal cardiovascular response to external stimuli.

Analysis of the data by comparison of the means indicates that MCA PI changes may be the result of FHR changes. Although heart rate changes may affect vascular resistance indices,^{14,15} in this study, the effect of heart rate change on MCA PI was negligible. Regression analysis revealed certain interesting points. It seems that the degree and direction of change in the heart rate vary according to gestational age. Advancing gestation is associated with increasing responsiveness to VAS after 25–28 weeks and up until 36 weeks. This may be the result of maturing auditory function.^{1,8} After 36–38 weeks, the proportion of fetuses who respond with decreasing heart rate increases. Decelerative responses of the FHR after VAS have been observed in term patients in labor.^{16,17} This finding has clinical implications in the interpretation of fetal vibratory acoustic response as a test of fetal well-being. We speculate that the relationship between the heart rate response and gestational age is the product of a complex interaction between increasingly maturing auditory function and increasing parasympathetic nervous system activity.

MCA PI response relates also to gestational age but with a weaker relationship. Before 25 weeks, the average MCA PI change is insignificant, because equal proportions of fetuses respond with either an increase or a decrease in the MCA PI and a small number of fetuses do not respond at all to VAS. After 25–28 weeks, most of the fetuses respond

with a drop in value of MCA PI and this pattern remains unchanged until 42 weeks' gestation, although the average degree of change gets smaller after 36 weeks. At 42 weeks, the average reduction in the MCA PI values approaches zero. This is in part at variance with the pattern of the FHR change. Multiple regression analysis made it clear that the baseline MCA PI value is the most significant contributor to the change after stimulation. The effect of increasing heart rate is the least significant, and the effect of gestational age is in between the other two. Because the heart rate and the MCA PI follow different patterns, we are tempted to speculate that the drop of the impedance in the cerebral vessels may be caused in part by a mechanism different from the one that causes the change in the heart rate. Cangon et al.⁶ described umbilical artery impedance changes after VAS. In that study, the decline of the impedance in the umbilical artery was attributed to the concurrent increase in the heart rate. Wladimiroff and Cheung⁷ reported on VAS and internal carotid artery impedance in normal fetuses between 36 and 39 weeks. They found a decline in the impedance that was attributable to the concurrent heart rate increase. This contrasts with our findings. Although this may be true for a limited gestational age range close to term, it did not seem to be the case when we examined a wider range of gestational ages. This may be the result of variable fetal responses at different maturational levels. Finally, different methodology may be responsible in part for these differences. With increasing gestational age, an increasing proportion of fetuses responded with a decline in the MCA PI, regardless of the direction of change in the heart rate. The discordance in the expected FHR and MCA PI response was most evident at 40 weeks and beyond, when despite the fact that most fetuses responded with a decline in the heart rate, the average MCA PI also declined. If FHR were to influence the MCA PI value, the latter should have increased with declining FHR. The mechanism of this response is not clearly understood, but it may be reasonable to speculate that it is the result of complex cardiovascular and CNS interactions.¹⁸ The information provided by this study may justify further studies with the pharmacologic manipulation of the parasympathetic and sympathetic nervous systems to clarify the possible mechanism of the observed interactions. The study design allows interpretation only with regard to acute fetal responses from a physiologic point of view and not for clinical use.

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