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The Effect of Fetal Heart Rate on the Peak Systolic Velocity of the Fetal Middle Cerebral Artery: Does Heart Rate Matter?

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Abstract

Objective—To estimate the effect of an increase in the basal heart rate of the fetus on the middle cerebral artery-peak systolic velocity (MCA-PSV).

Study Design—Prospective longitudinal cohort. Patients between 14 and 36 weeks gestation were enrolled (N=66). Ultrasound examinations were performed monthly. MCA-PSV measurements were assessed at 0-degree angle of insonation at basal fetal heart rate and after application of vibroacoustic stimulation (VAS).

Results—A total of 514 MCA-PSV measurements were obtained in 66 fetuses. No difference in fetal heart rate pre- and post-VAS was noted prior to 27 weeks' gestation. A significant increase in fetal heart rate post-VAS was detected from a mean gestational age of 27.1 ± 1.3 weeks onward. A significant decrease in the MCA-PSV was noted between pre- and post-VAS measurements for examinations 3, 4, and 5 ($p < 0.001$, < 0.0001 , < 0.0001 , respectively).

Conclusion—Assessment of the MCA-PSV for the detection of fetal anemia, particularly in the third trimester, should be undertaken during a period of baseline fetal heart rate to avoid the potential of a false negative result.

Keywords

Middle cerebral artery; MCA; peak systolic velocity; fetus; Doppler; ultrasound; fetal heart rate; vibroacoustic stimulation

Introduction

Doppler ultrasound assessment of the middle cerebral artery peak systolic velocity (MCA-PSV) has evolved as the standard for the detection of fetal anemia in pregnancies complicated by maternal red cell alloimmunization.¹ Estimation of the MCA-PSV allows for a noninvasive method to detect the presence of moderate-to-severe fetal anemia. Normative data from retrospective, cross-sectional studies of the fetal MCA-PSV Doppler have established a threshold value of 1.5 multiples of the median (MOM) for the detection of moderate-to-severe fetal anemia.^{2,3} Prospective evaluations have demonstrated false positive rates of 13% and 18%, respectively. Sallout et al⁴ noted that an active fetal behavioral state was associated with a significant increase in the MCA-PSV as compared to the fetal resting state. The authors advised that the fetal behavioral state be taken into account when undertaking the measurement of the MCA-PSV in an effort to prevent a false positive result. Based on this data, we hypothesized that an increased fetal heart rate above expected normal ranges for any given gestational age would have an effect on MCA-PSV. We sought to estimate if an increase of the fetal basal heart rate was associated with an increase in the MCA-PSV.

Material and Methods

A prospective, longitudinal cohort study was conducted to compare Doppler ultrasound measurements of the MCA-PSV obtained at the fetal basal heart rate and during a period of increased fetal heart rate. The institutional review board of the University of North Carolina approved this study. Healthy women without medical comorbidities were recruited from December 2006 to November 2007 at the University of North Carolina Specialty Women's Center at Rex Hospital, a multidisciplinary women's referral center located in Raleigh, NC. Women with pre-existing conditions including hypertension, diabetes and thyroid disease were excluded from participation. A medication inventory was not conducted on the study participants. It is possible that medications that could affect fetal heart rate may have been taken by patients in the study population. Fetuses with anomalies, known aneuploidy, or intrauterine growth restriction were excluded from the study. Multiple gestations and patients with red cell sensitization were not eligible for participation. Written informed consent was obtained from each study participant before or at the time of the first study visit. Gestational age was confirmed by first trimester ultrasound in all subjects. Sonograms were performed every four weeks on each participant, beginning at 16–20 weeks through 34–38 weeks gestational age, totaling five study sonograms. Standard biometric parameters were also obtained at each visit. An estimated fetal weight of < 10% for gestational age using the formula of Hadlock et al. was used to define intrauterine growth restriction.⁵ Sonograms were performed using a 2.0–7.0 MHz convex transducer on the GE Voluson Expert (GE Medical Systems, Milwaukee, WI) by a single operator (AES).

Pulsed Doppler ultrasound was utilized to obtain a series of two separate MCA waveforms at the proximal segment of the near-field MCA at a 0-degree angle of insonation. Fetal heart rate was measured on the same spectral waveform as the initial MCA-PSV measurement. After initial MCA-PSV, vibroacoustic stimulation (VAS) was applied to the maternal abdomen in the region of the fetal head for a period of three seconds. A second series of MCA waveforms was then obtained and MCA-PSV and fetal heart rate were again measured. All MCA-PSV and fetal heart rate measurements were acquired manually for each of the waveforms in the series. The mean of the two MCA-PSV and fetal heart rates obtained pre-VAS was used as the initial MCA-PSV and basal fetal heart rate. The mean of the two MCA-PSV measurements and fetal heart rates acquired post-VAS was then obtained in a similar fashion.

Images of all measurements were recorded and stored to the ultrasound machine hard drive and within the ACERT 4.0 image archive and reporting system (CSC Group, Brecksville, OH). All MCA-PSV measurements were also recorded in a database specifically designed for the statistical analysis for this study.

Using a standard sample size formula for correlated data from Diggle et al⁶, a sample size of 50 women was deemed adequate.⁶ The outcome measures (pre/post VAS MCA-PSV) were assumed to be normally distributed and z-test two sample test was used for computing a sample size. The correlation of repeated measures over 5 exams is assumed to be 0.75. Under two-sided $\alpha=0.05$, $\beta=0.80$ and the effect size of 0.5, we need 50 women at each group. We anticipated 5% of women would not complete the study, and 5% of women would deliver at < 35 weeks gestation and thus not have all measurements performed. Therefore we planned to enroll 60 women to achieve our desired sample size.

Linear mixed models (Laird and Ware, 1983)^{7,8} were used first to investigate mean differences between MCA-PSV at basal fetal heart rate and post-vibroacoustic stimulation at each exam; Second, to evaluate mean differences between fetal heart rate pre- and post-vibroacoustic stimulation at each exam. *P* values < 0.05 were considered statistically significant for both fetal heart rate and MCA-PSV. All analyses were performed using SAS 8.0 statistical software (SAS Institute, Cary, NC).

Results

We enrolled 66 patients in the study. These patients were part of a previous investigation to estimate the influence of angle correction on the MCA-PSV.⁹ All five monthly ultrasound examinations were completed for 50 fetuses (76%). Sixteen patients did not complete all five monthly ultrasound examinations during the study (Table 1). The most common reason for incomplete examinations was patient withdrawal from the study. One fetus during the study was diagnosed with a congenital cystic adenomatoid malformation, and this patient was excluded from the study. No fetus developed intrauterine growth restriction as assessed by serial ultrasound growth parameters.

The mean gestational age for each of the five monthly ultrasound examinations was 18.5 ± 1.7 , 22.9 ± 1.5 , 27.1 ± 1.3 , 31.1 ± 1.1 and 35.2 ± 1.2 weeks, respectively. The mean basal fetal heart rate did not change significantly with advancing gestational age ($p=0.74$). The mean change in fetal heart rate associated with VAS was dependent on gestational age, ranging from 1 – 21 bpm. Significant fetal heart rate increases were noted for examinations # 3, 4, and 5 ($p < 0.001$, <0.0001 and <0.0001 , respectively), with fetal heart rate increases of 8, 13, and 21 bpm respectively (Figure 1) (Table 2). Post-VAS MCA-PSV measurements were significantly decreased compared to pre-VAS measurements for examinations #3, 4, and 5 ($p < 0.01$, <0.0001 and <0.0001 , respectively) with decrements of 3, 4, and 7 cm/s respectively. (Figure 2) (Table 3).

Spontaneous decrease in the fetal heart rate not related to VAS was observed seven times during the course of the study. In three of these cases, the heart rate was sufficiently low to meet the definition of fetal bradycardia (79 – 90 bpm). The MCA-PSV measurement during these bradycardic episodes was twice that of the MCA-PSV during basal fetal heart rate (basal MCA-PSV: 41.4 cm/sec; bradycardic MCA-PSV: 80.2 cm/sec). In the four remaining cases of decreased fetal heart rate post-VAS, the mean fetal heart rate decrease was 5 bpm. An increase in the MCA-PSV of 3.2 cm/s was observed during these periods of decreased fetal heart rate. None of the bradycardia events were included in the main analysis. MCA-PSV measurements were re-assessed when the fetal heart rate returned to a normal rate and

the subsequent velocities were then included in the main analysis. No fetuses were found to be aneuploid or anomalous after delivery.

Comment

Evaluation of the fetal MCA-PSV by Doppler ultrasound has become the gold standard of care in the screening and monitoring of fetal anemia. In the retrospective analysis of Mari et al⁴, a MCA-PSV of greater than 1.5 MOM was associated with a false positive rate of 10% for the detection of moderate to severe anemia. Zimmerman et al¹⁰ undertook a prospective multi-center trial and reported a similar false positive rate of 13%. Finally, Oepkes and coworkers¹¹ noted a slightly higher false positivity of 18% for the detection of severe fetal anemia when the MCA-PSV was greater than 1.5 MOM. Based on the observations of Sallout et al⁴, we hypothesized that fetal heart rate accelerations were associated with an increase in the MCA-PSV. Measurements during periods of an active fetal behavioral state could account for the previously reported rates of a false positive diagnosis of fetal anemia in association with an elevated MCA-PSV. However, our current investigation found the opposite to be true – fetal heart rate accelerations induced with VAS were associated with a decrease in the MCA-PSV.

The statistically significant increase in the fetal heart rate in response to VAS is similar to that reported by Kisilevsky et al¹². In that study, a maturation of the fetal heart rate response to VAS was noted with advancing gestational age at a threshold of 26 weeks' gestation. In our study, we did not detect a significant increase in heart rate until 27.1 ± 1.3 weeks' gestation.

Other explanations must be sought for the inverse relationship between the MCA-PSV and fetal heart rate. An active fetal behavioral state is noted with advancing gestational age. It is defined as the presence of frequent accelerations of the fetal heart rate associated with fetal movement as well as increased baseline variability. In the only study to date that assessed the relationship between MCA-PSV and fetal behavioral state, an active fetal behavioral state was associated with an increased MCA-PSV¹³. In that study however, Shono and colleagues found that the baseline fetal heart rate in the active state was not statistically different from the heart rate in the resting state. Additional MCA Doppler findings in the Shono cohort included an increase in the diastolic velocity, pulsatility index and resistance index. These findings may represent a reduction in fetal cerebral vascular resistance in accordance with increased cerebral blood flow. In our study, an acute increase in fetal heart rate after VAS may be associated with an increase in fetal cardiac output. We conjecture that the fetal cerebral circulation reacts in a protective mechanism to prevent overdistension of the cerebral vessels. In these cases, one would expect a decrease in both the MCA-PSV as well as the PI due to an increase cerebral resistance. Unfortunately the latter parameter was not measured in our current investigation to confirm this hypothesis. Another explanation for our findings might related to decreased myocardial recovery time associated with increased fetal heart rate, resulting in decreased velocities. Indirect measures of myocardial recovery in-utero include TEI index. A prospective study of the affects of increased fetal heart rate on TEI index may prove or disprove this hypothesis.

In conclusion, our data suggest that there is an inverse relationship between fetal heart rate and MCA-PSV. Assessment of the fetal heart rate should be conducted in concert with assessment of the MCA-PSV, particularly in the third trimester of pregnancy. Fetal heart rates above the basal heart rate during a spontaneous acceleration may contribute a false negative screen for fetal anemia. This finding may be particularly useful in situations where the MCA-PSV is borderline and approaching but below velocities of MoM. As such, repeated MCA-PSV after accelerations have subsided may result in an elevated velocity

above 1.5 MoM indicating severe fetal anemia making the patient a candidate for referral to a center where fetal transfusion therapy may be undertaken.

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Figure 1.
Comparison of basal and post-vibroacoustic stimulation fetal heart rate as a function of advancing gestational age.

Figure 2.
Comparison of MCA-PSV as a function of advancing gestational age at basal fetal heart rate and post-vibroacoustic stimulation.

Table 1

Number of subjects completing examinations 1–5.

Exam	Number of patients
1	66
2	61
3	56
4	53
5	50

Table 2

Mean fetal heart rate pre- and post-vibroacoustic stimulation at each exam, adjusted by gestational age

Exam	fetal heart rate pre- vibroacoustic stimulation (SE)	fetal heart rate post- vibroacoustic stimulation (SE)	P-value [†]
1	143.61 (3.603)	144.36 (3.626)	0.6593
2	142.61 (2.040)	145.21 (2.076)	0.1283
3	143.10 (1.333)	151.27 (1.379)	<.0001
4	145.07 (2.325)	158.49 (2.343)	<.0001
5	146.43 (3.949)	167.20 (3.937)	<.0001

* Based on the mixed-model adjusted for gestational age

[†] For the mean differences between and post-vibroacoustic stimulation fetal heart rates at each exam

Table 3

MCA-PSV at basal fetal heart rate and post-vibroacoustic stimulation at each exam

Exam	Mean MCA-PSV at basal fetal heart rate (SE)	Mean MCA-PSV at post-vibroacoustic stimulation (SE)	P-value [†]
1	30.50 (1.061)	29.55 (1.061)	0.1128
2	31.15 (1.034)	31.47 (1.034)	0.6016
3	39.37 (1.022)	36.35 (1.023)	<.0001
4	44.75 (1.039)	40.51 (1.039)	<.0001
5	51.67 (1.067)	44.64 (1.067)	<.0001

* Based on the mixed-model adjusted for gestational age

[†] For the mean differences between and post-vibroacoustic stimulation fetal heart rates at each exam