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Changes in middle cerebral artery velocimetry of fetuses diagnosed postnatally with mild or moderate hemolytic disease

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Key words
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Conflicts of interest
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Abstract

Objectives. To determine the longitudinal trends of middle cerebral artery peak systolic velocity (MCA PSV) in fetuses with mild or moderate hemolytic disease according to the need for postnatal therapy. *Design.* Prospective cohort study. *Setting.* University referral center. *Sample.* Twenty-three fetuses from singleton alloimmunized pregnancies. *Methods.* Serial measurements of MCA PSV were performed. After delivery, newborns were grouped by the need for postnatal management into mild hemolytic disease, which required no or only phototherapy (n = 14, group 1), and moderate hemolytic disease, where postnatal top-up or exchange transfusions were required (n = 9, group 2). *Main outcome measures.* Serial Doppler MCA PSV data transformed to multiples of the median, analyzed with linear regression and exponential models. *Results.* We performed 83 measurements in group 1: 3-8 per fetus; mean GA at inclusion, 23 weeks and 65 measurements in group 2: 4-15 per fetus; mean GA at inclusion, 22 weeks. The estimated mean slopes of the MCA PSVs increased with the degree of postnatal therapy required (group 1: MCA PSV = 0.003 GA + 1.298; group 2: MCA PSV = 0.035 GA + 0.436). The relative average increments (RAI) were 4.7% and 7.1%, respectively. The two groups exhibited significant differences in mean slope and RAI ($p<0.05$). *Conclusions.* Fetuses that required postnatal transfusions due to hemolytic disease showed an enhanced progressive increase in MCA PSVs compared to those without transfusion requirement. This information might enable their identification during pregnancy.

Abbreviations: AAI, absolute average increment; GA, gestational age; HDN, hemolytic disease of newborns; MCA, middle cerebral artery; MoM, multiples of the median; PSV, peak systolic velocity; RAI, relative average increment.

Introduction

Middle cerebral artery (MCA) peak systolic velocity (PSV) Doppler velocimetry is a standard method for noninvasively diagnosing fetal anemia. Accelerated blood velocity in the MCA enables identification of anemic fetuses (1–3). Previous studies have demonstrated a

Key Message

Fetuses that will require postnatal transfusions due to hemolytic disease show progressive elevations in middle cerebral artery peak systolic velocity. This feature provides a tool that can be used during the pregnancy to determine whether the fetus will require transfusion therapy after delivery.

correlation between the MCA PSV and fetal hemoglobin levels (4–8). In mild fetal anemia, there is very little or no increment in blood velocity in the MCA; however, in moderate and severe fetal anemia, the MCA blood velocity increases and the detection accuracy of anemia improves. When anemia becomes very severe (hemoglobin levels of 10–30 g/L), the velocity does not increase further (7). A single MCA PSV measurement below 1.5 multiples of the median (MoM) of the Mari nomogram cannot reassure the investigator about the future well-being of fetuses at risk of hemolytic disease, as it does not describe how rapidly the anemia develops (9). Therefore, serial measurements are necessary. Nevertheless, 70% of fetuses at risk of anemia due to red blood cell alloimmunization of the mother will either have no anemia or will become only mildly anemic during the pregnancy and will therefore not require transfusion (2). To our knowledge, only one previous retrospective study analyzed longitudinal measurements (9). There it was demonstrated that by examining the slope of the values over time, instead of individual values, one could detect in advance which fetuses were at risk of developing anemia. The objective of the present study was to describe the longitudinal trends in MCA PSV Doppler measurements in fetuses diagnosed with mild or moderate hemolytic disease postnatally, and managed according to the degree of disease and to determine whether fetuses that will postnatally require top-up or exchange transfusions could be noninvasively identified during pregnancy.

Material and methods

The data were prospectively collected at the tertiary care center at the Department of Obstetrics and Gynecology, University Hospital Ostrava, Ostrava, Czech Republic. We included fetuses with red blood cell maternal alloimmunization clinically relevant antibodies in significant titer (D $\geq$ 1:32, Kell $\geq$ 1:8, other non-D antibodies $\geq$ 1:32). In one case, prenatal fetal genotyping was performed from free-fetal DNA isolated from the mother; in the remaining cases, the neonatal blood group phenotype was identified after birth. All fetuses underwent a detailed prenatal ultrasound evaluation. The expected date of delivery was established by first trimester crown–rump length. All fetuses were followed up with a minimum of three or more serial MCA PSV measurements. The first three measurements were done weekly. When the MCA PSV was <1.5 MoM and the slope of the MCA PSV did not indicate that it would cross 1.5 MoM within the next 2–3 weeks, we extended the interval to 2–3 weeks. Apart from that, the levels of antibodies were monitored every second to fourth week depending on the antibody titer. During every visit a basic ultrasound scan was performed. The decision about delivery was based on the consensus of at least two specialists in maternal fetal medicine depending on cardiotocogram, PSV and biophysical profile. Two sonographers performed the measurements on one ultrasonographic machine (Voluson E8 BT08; General Electric, GE Healthcare Technologies, Wauwatosa, WI, USA).

The MCA PSV was evaluated with the standardized technique, previously described by Mari et al. (10). In brief, a transverse section of the brain, which included the thalamus and the cavum septi pellucidi, was identified during a period of fetal rest, and the circle of Willis was imaged with color Doppler ultrasonography. The MCA proximal to the transducer was enlarged until it occupied more than 50% of the image, and could be visualized over its entire length; the sample volume (1 mm) was superimposed on the MCA, 2 mm after its origin from the internal carotid artery. The angle between the direction of blood flow and the ultrasound beam was maintained as closely as possible to 0°, and when uniform waveforms (between 15 and 30) were recorded, the highest point of the waveform (the PSV) was measured.

All newborns underwent clinical examination. Neonatal blood counts from the umbilical vein were performed immediately after delivery. Hemolytic disease of newborns (HDN) was confirmed by positive Coombs test, anemia and/or elevated bilirubin at birth or its sharp rise within 24 hours of birth. Further management and treatment indications were performed according to the American Academy of Pediatrics guidelines and the Czech Society of Neonatology guidelines (11,12). The newborns were later assigned to one of two groups: group 1 required no therapy or phototherapy only (mild HDN); group 2 required a postnatal top-up or exchange transfusion (moderate HDN).

Data analysis

Two types of the mathematical analyses were performed for both groups, based on an exponential model and a linear model. Serial Doppler measurements of MCA PSV from individual fetuses were analyzed with the exponential model ([MCA PSV] = $K.e^{RAI.GA}$), where K is a proportional parameter, RAI is the relative average increment and GA is gestational age. The data were fitted with the model to determine the rate of change. From these data, the RAI in the MCA PSV as a function of GA was calculated for the two groups. The mean RAI in the MCA PSV as function of GA was calculated for each group with the confidence interval (CI), and exponential trends were modeled.

The measurements from individual fetuses were analyzed with a simple linear regression model ([MCA PSV] = $AAI.GA + L$), where L is a proportional parameter and

Table 1. Maternal and neonatal clinical characteristics in groups with different degrees of hemolytic disease of newborn.

Parameter	Mild HDN (n = 14)	Moderate HDN (n = 9)	p-value[a]
Maternal age (years)	29 (22–41)	32 (27–38)	0.33
Parity	2 (1–7)	2 (2–5)	0.49
Gestational age at inclusion (weeks)	21.5 (18–32)	22 (18–29)	0.59
Gestational age at delivery (weeks)	38 (35–41)	36 (34–37)	0.01
Birthweight (g)	3090 (2500–3800)	2450 (1950–3420)	0.01
Number of measurements	6.5 (3–8)	7 (4–15)	0.42
Hemoglobin UV (g/L)	152 (121–179)	116 (97–173)	<0.01
Total bilirubin UV (μmol/L)	39.9 (27.2–54.9)	78.8 (58.1–107.4)	<0.01
Reticulocytes UV (%)	3.8 (1.3–7.6)	4.6 (0.2–11.3)	0.12
Neonatal intensive care unit (days)	0 (0–6)	6 (2–23)	<0.01
Phototherapy (hours)	0 (0–316)	201 (107–399)	<0.01
Neonates who received transfusions	0	9	–

Data represent the median (range).
HDN, hemolytic disease of newborn; UV, umbilical vein.
[a]Mann–Whitney *U*-test for independent samples.

AAI (absolute average increment) represents the mean rate of change in the MCA PSV (mean slope). The mean slope of the MCA PSV as a function of GA was calculated for each group,and longitudinal trends were modeled.

Differences between and within the groups were evaluated with the Mann–Whitney *U*-test for independent samples. The values of MCA PSV were expressed in units of MoM, according to Mari et al. (2). A p-value <0.05 indicated statistical significance. MedCalc software (Version 12.7.5.0; MedCalc Software, Mariakerke, Belgium) and Office Excel 2007 (Microsoft Corporation, Redmond, WA, USA) were used for calculations and trend modeling.

Results

A total of 148 measurements were performed on 23 fetuses. Group 1 (mild HDN) included 14 fetuses with 83

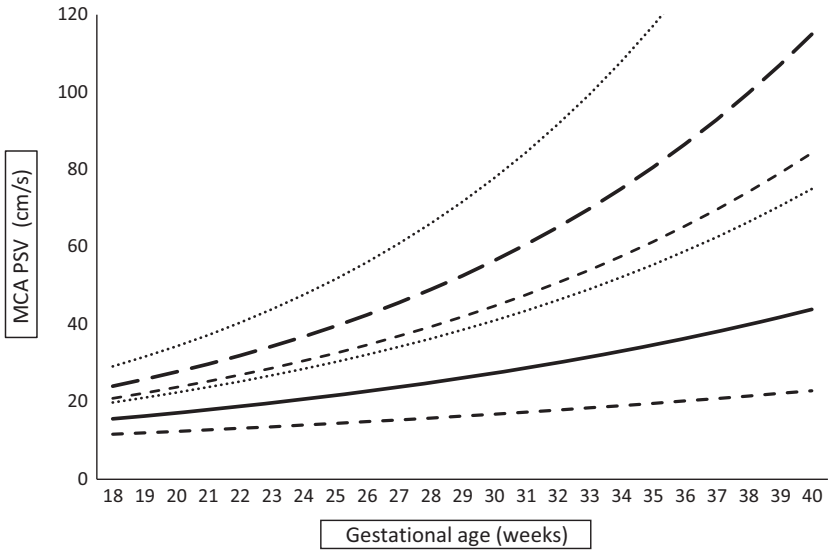

Figure 1. Serial Doppler measurements of the middle cerebral artery peak systolic velocity (MCA PSV) increased exponentially as a function of gestational age (GA). Each heavy line represents the average exponential fit to data from fetuses with either mild hemolytic disease of the newborn (continuous line, MCA PSV = $K e^{0.047 \cdot GA}$) or moderate hemolytic disease of the newborn (heavy dashed line, MCA PSV = $K e^{0.071 \cdot GA}$). Only the exponential lines that were fitted to at least three serial measurements were included in the average lines shown. The dotted lines represent the confidence limits.

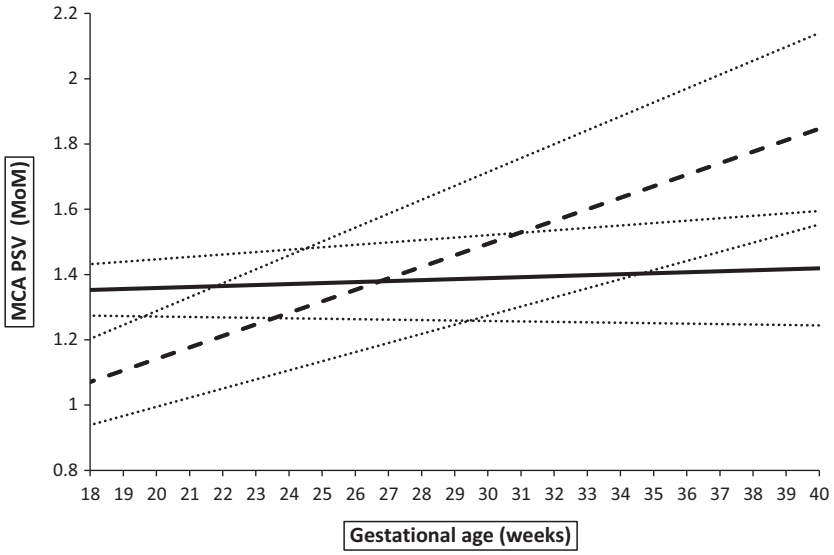

Figure 2. Serial Doppler measurements of the middle cerebral artery peak systolic velocity (MCA PSV) observed over time were transformed to multiples of median (MoM) units, according to the Mari reference curve. Lines represent the average linear regression fits for data from fetuses with either mild hemolytic disease of the newborn (continuous line, MCA PSV = 0.003.GA + 1.298) or moderate hemolytic disease of the newborn (heavy dashed line, MCA PSV = 0.035.GA + 0.436), where GA is gestational age. Only the linear regression lines that were fitted to at least three serial measurements were included in the average lines shown. The dotted lines represent the confidence limits.

measurements (range 3–8/fetus). Group 2 (moderate HDN) included nine fetuses with 65 measurements (range 4–15/fetus). The characteristics of the study population are given in Table 1. All women were Caucasian. All fetuses were delivered after 34 weeks of gestation. Red cell alloantibodies observed in the mild HDN group included D (n = 8), c (n = 1), E (n = 2), K (n = 2) and s (n = 1). Those observed in the moderate HDN group included D (n = 8) and E (n = 1). The umbilical venous blood hemoglobin levels differed significantly between the groups.

In the exponential model, the estimated mean average increment for mild HDN (MCA PSV = K e $^{0.047.GA}$) was 4.7% and for moderate HDN (MCA PSV = K e $^{0.071.GAx}$) 7.1% (Figure 1). In individual cases RAI increased with the requirement for more intense postnatal therapy and was significantly different between fetuses with mild and those with moderate hemolytic disease ($p < 0.05$).

In the linear model, the estimated mean rate of change for both mild HDN (MCA PSV = 0.003.GA + 1.298) and moderate HDN (MCA PSV = 0.035.GA + 0.436) increased with the degree of required postnatal therapy. The mean slopes were 0.3 and 3.5% for fetuses with mild and moderate HDN, respectively (Figure 2) and were significantly different between the two groups ($p < 0.05$; Figure 3).

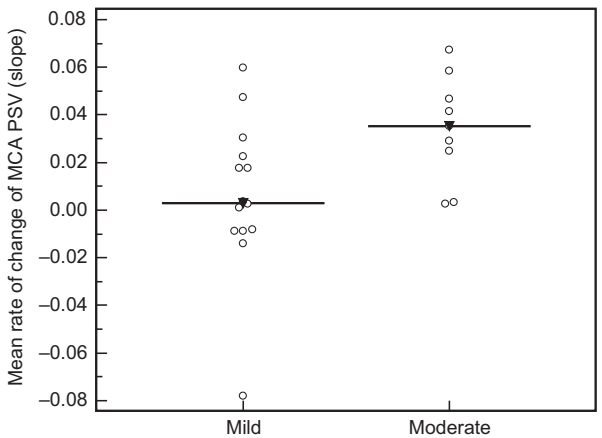

Figure 3. Mean rates of change in the middle cerebral artery peak systolic velocity in fetuses with mild or moderate hemolytic disease of newborn. Individual values and medians are shown.

Discussion

This study demonstrated that the plot of at least three serial MCA PSV measurements over time exhibited a slope that increased with the degree of HDN. We found a significant difference in mean slope and RAI of MCA PSV between fetuses with mild and moderate HDN. This finding suggested that it may be possible to differentiate between fetuses that develop mild HDN but require little or no postnatal therapy and fetuses that develop moderate HDN, which requires a top-up or exchange transfusion

after delivery. This information might be useful in the management of at-risk pregnancies, because it can identify which fetuses will benefit from closer surveillance during pregnancy and better planning of the delivery. For example, identification of a fetus with mild HDN that will require low-intensity therapy could provide a basis for postponing the delivery, which would decrease the risk of preterm delivery. In fact, the more advanced GA in the mild HDN group (38 vs. 36 weeks; Table 1) reflects such a policy.

To our knowledge, to date, only one previous retrospective study by Detti et al. showed that, by determining the slope of the line joining at least three measurements, it was possible to identify a fetus that had developed moderate or severe anemia. They showed that the rate of increase in MCA PSV values was greater in moderate or severe anemia than when there was mild or no anemia (9). In the present study, we aimed to extend that observation. Our results showed that Doppler measurements were sufficiently sensitive to clearly distinguish between fetuses with moderate hemolytic disease and those with mild hemolytic disease. This finding represents a means to determine whether a fetus will require transfusion after delivery.

The main strengths of this study were the prospective collection of the data, the comparatively large number of measurements, that all measurements were performed with one type of ultrasound machine and only two sonographers who used one standardized protocol. The primary weakness of the study was the limited reproducibility of the results due to its monocentric character. Larger, multicenter studies are needed to confirm our findings.

We support the caution stated by Detti et al. that a single MCA PSV measurement below the cut-off point of 1.50 MoM should not reassure the investigator about the future well-being of a fetus at risk for anemia. Instead of focusing on a single value, the investigator should consider the RAI in the MCA PSV. The rate of increase informs the investigator in advance of whether the fetus is at risk for developing HDN, even when the MCA PSV values are in the healthy range. Patient counseling or planning the next visit can be based on the calculated trend in the MCA PSV, and the physician can project the approximate time that anemia is likely to develop.

We have demonstrated that fetuses that are likely to require postnatal transfusion due to hemolytic disease show a more rapid increase in MCA PSV than those who will manage without transfusions. This feature provides a tool that can be used during the pregnancy to determine whether the fetus will require transfusion therapy after delivery.

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