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Original Article

Fetal middle cerebral artery peak systolic velocity as a predictor of fetal anemia in unselected women giving birth at or near term

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ABSTRACT

Objective: This study was performed to evaluate the application of fetal middle cerebral artery peak systolic velocity (MCA-PSV) for prediction of newborn anemia with umbilical cord blood hemoglobin concentration at birth (UCB-Hb) < 10.0 g/dL among infants born at gestational week (GW) ≥ 36 to unselected women.

Materials and methods: We reviewed the medical charts of 699 women giving birth to singleton infants at GW ≥ 36 with available data on MCA-PSV measured at GW ≥ 25 at the discretion of the attending physician. Multiple of the median (MoM) MCA-PSV (MCA-PSV MoM) > 1.5 was defined as a positive MCA-PSV test result.

Results: The MCA-PSV test was applied 2309 times (313 and 1996 times during second and third trimesters, respectively) in 699 women. The results were positive in 4.4% (102/2309) of tests and at least once in 9.9% (69/699) of women. Anemic infants were born to one (1.4%) and six (1.0%) of 69 and 630 women with and without at least one positive test result, respectively. MoM determined 4, 3, and 2 weeks before birth showed significant weak negative correlations with UCB-Hb at birth (correlation coefficient: 0.298–0.325).

Conclusions: Among unselected women giving birth at or near term, the MCA-PSV test was unsatisfactory for prediction of newborn anemia in this retrospective observational study.

Introduction

The fetal middle cerebral artery (MCA) is easily visualized with an angle close to 0° between the ultrasound beam and the direction of blood flow, and this measurement has low intra- and interobserver variability [1]. Determination of fetal MCA peak systolic velocity (MCA-PSV) is a non-invasive means of detecting fetal anemia in pregnancies complicated by not only maternal blood group immunization [1], but also placental mesenchymal dysplasia [2] and fetomaternal hemorrhage [3–7]. As absolute MCA-PSV value increases with advancing gestation [8,9], the degree of MCA-PSV abnormalities can be transformed to multiples of the median (MCA-PSV MoM) according to gestational week (GW) at determination [8] allowing comparison between two measurements at different GWs.

MCA-PSV determination (MCA-PSV test) has very high sensitivity with a low false positive rate for prediction of fetal anemia among selected cases, i.e., fetuses at risk of anemia due to maternal red cell alloimmunization [8]. However, high fetal MCA-PSV can occur in cases of preterm fetal growth restriction (FGR) [10]. It is possible that problems not associated with fetal anemia can cause high fetal MCA-PSV, and positive MCA-PSV test results do not necessarily imply fetal anemia in preterm FGR [11].

To our knowledge, there have been no detailed studies regarding whether MCA-PSV beginning at the second trimester is useful for predicting anemic infants born at or near term. This retrospective observational study was performed to validate abnormal MCA-PSV results in unselected women and the correlation between MCA-PSV MoM and umbilical cord blood hemoglobin concentration at birth (UCB-Hb).

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Material and methods

The Hokkaido University Hospital Institutional Review Board approved this study and publication (015-0032, June 15, 2015).

Participants

Medical chart review was performed in all cases fulfilling all of the following three inclusion criteria: (1) giving birth to a singleton infant on or after GW 36 at Hokkaido University Hospital during the 3-year study period between January 1, 2012, and December 31, 2014; (2) data were available for MCA-PSV determined on and after GW 25, and UCB-Hb at birth; and (3) no proven chromosomal aberrations in newborn infants. Demographic characteristics were also reviewed. Light for gestational age (LGA) was diagnosed in newborns based on normative birthweight for Japanese newborns [12]. Newborn anemia was defined as UCB-Hb < 10.0 g/dL.

Fetal MCA-PSV measurement (MCA-PSV test)

At our hospital, ultrasound (including Doppler ultrasound) studies were performed after obtaining inclusive informed consent from all pregnant women at the beginning of pregnancy and the MCA-PSV test was given at the attending physician's discretion. The measurements were performed according to the method of Mari et al. [1] at the unilateral MCA closer to the probe within 2 mm from the circle of Willis using RAM™ or C1-5-D™, Voluson E8 (GE Healthcare Co. Ltd., Tokyo, Japan), prosound α7™, UST-9130 (Hitachi-Aloka Medical Co. Ltd., Tokyo, Japan) or prosound SSD 3500 plus™, UST-9123 (Hitachi-Aloka Medical Co. Ltd.). The procedure was repeated at least three times, and the highest MCA-PSV value at the smallest insonation angle (<20°) was used as the datum for each procedure. The MCA-PSV value was transformed to multiples of the median (MoM) using the median MCA-PSV values according to GW as proposed by Mari et al. [8]. Positive test result on MCA-PSV was defined as MoM >1.5 in this study.

Statistical methods

Statistical analyses were performed using the JMP Pro11© statistical software package (SAS, Cary, NC). Differences in the means between groups were tested using Wilcoxon's rank sum test, and differences in frequencies were examined using Fisher's exact test. Pearson's product − moment correlation coefficient was used to measure linear correlations between two variables. In all analyses, $P < 0.05$ was taken to indicate statistical significance. However, a significant finding regarding a linear correlation between two variables was defined as that meeting both $P < 0.05$ and correlation coefficient (R-value) > 0.2.

Results

A total of 699 cases met the inclusion criteria (Table 1). The 699 infants corresponded to 89% of all 786 infants with no proven chromosomal aberrations born on or after GW 36 at our hospital during the study period. Median (range) GW at delivery was 38 (36–42), and median birthweight was 2.95 (1.49–4.44) kg in the 699 infants born to the 699 women. Sixty-seven newborn infants (9.6%) were LGA and 19 women (2.7%) had Rh blood type incompatibility or irregular antibodies. The MCA-PSV test was applied 2309 times in these 699 cases by 22 physicians. The median (range) number of tests per case was 3 (1–15), and 86% of tests were performed during the third trimester of pregnancy (Table 1). In 699 newborn infants, median (range) UCB-Hb level was 14.8 (6.3–20.1) g/dL, and UCB-Hb < 10.0 g/dL, <11.0 g/dL, <12.5 g/dL, and <13.5 g/dL occurred in 1.0% (7/699), 3.3% (23/699), 12% (81/699), and 24% (165/899) of all newborns, respectively (Table 1).

Table 1
Demographic characteristics in 699 study subjects.

Maternal age (years)	33 (17–48)
Nulliparous	399 (57.1%)
Body height (m)	1.58 (1.33–1.80)
Pre-pregnancy weight (kg)	52 (32–128)
Pre-pregnancy BMI	20.6 (13.7–48.8)
Gestational week at delivery	38 (36–42)
Light for gestational age (LGA)	67 (9.6%)
Rh blood type incompatibility[a]	19 (2.7%)
Infant birthweight (kg)	2.95 (1.49–4.44)
<2500	96 (13.7%)
Apgar score (5 min)	9 (1–10)
<8	22 (3.1%)
UCB-Hb (g/dL) at birth	14.8 (6.3–20.1)
<13.5	165 (23.6%)
<12.5	81 (11.6%)
<11.0	23 (3.3%)
<10.0 (newborn anemia)	7 (1.0%)
Determination of fetal MCA-PSV	
Total no. of tests	2309
No. of tests per woman	3 (1–15)
No. of tests during 2nd trimester	313 (13.6%)
No. of tests during 3rd trimester	1996 (86.4%)

Data are presented as the median (range). UCB-Hb, umbilical arterial cord blood hemoglobin concentration.
[a] Including 7 with Rh blood type incompatibility and 12 with irregular antibodies (anti-E antibody in 6 women, anti-M antibody in two women, anti-Lea antibody in two women, and anti-Jra antibody in two women).

Among the 2309 tests applied in the 699 cases, positive results were observed in 4.4% (102/2309) of tests and at least once in 9.9% (69/699) of all fetuses; in 19 women (2.7%) in the first test and in another 50 women (7.2%) in repeat tests following negative test result(s) (Table 2). Seven anemic infants (1.0%) were born; to one of 69 women with at least one positive test result and to six of 630 women with negative test results (Table 2). Thus, MCA-PSV test yielded sensitivity of 14% (1/7), specificity of 90% (624/692), positive predictive value of 1.4% (1/69), and negative predictive value of 99% (624/630) for prediction of newborn anemia.

The number of tests applied was significantly greater in those with than without at least one positive test result, possibly due to repeat tests given in cases with one positive test result (4 [1–15] vs. 3 [1–12] times per case, respectively, $P < 0.0001$) (Table 2). Among the 69 women with at least one positive test result, the total number of positive test results was 102 and the number of positive test results per case was 1 (1–10); once in 57 cases, twice in eight cases, and three or more times in four cases. Although the rate of positive test results was 2.7% (19/699) for the first test, the rates of positive test results according to GW varied from 1.7% (at GW 26) to 6.6% (at GW 32), possibly due to repeat tests in cases with one positive test result. Fig. 1 shows MCA-PSV value plotted against GW at the time of the first positive test result for the 69 women with at least one positive test result (Fig. 1). The UCB-Hb was significantly lower and the number of cases with UCB-Hb < 14.0 g/dL was significantly greater in those with than without at least one positive MCA-PSV test result (Table 2). Neither the number of cases with LGA nor Rh blood type incompatibility/irregular antibodies differed significantly between the two groups with and without at least one positive MCA-PSV test result.

MCA-PSV MoM and UCB-Hb in cases with LGA and Rh blood type incompatibility/irregular antibodies

Median (range) MCA-PSV MoM was significantly lower (0.96 [0.64–1.78] vs. 1.06 [0.48–1.87], respectively, $P = 0.0016$) and

Table 2
UCB-Hb levels in two groups divided by MCA-PSV test results.

	At least one positive test result (MoM >1.5)		
	Yes (n = 69)	No (n = 630)	P-value
No. of tests given	336	1973	
No. of tests/case	4 (1–15)	3 (1–12)	<0.0001
No. of positive test result	102	0	
Positive on the first test	19 (27.5%)	0	
No. of positive test result/case	1 (1–10)	0	
Once	57 (82.6%)	0	
Twice	8 (11.6%)	0	
Three times	4 (5.8%)	0	
GW at delivery	38 (37–41)	38 (36–42)	0.0693
Light for gestational age (LGA)	9 (13.0%)	58 (9.2%)	0.2851
Rh blood type incompatibility[a]	3 (4.3%)	16 (2.5%)	0.4218
Infant birthweight (kg)	2.95 (1.49–4.20)	2.94 (1.59–4.44)	0.3766
<2.50 kg	12 (17.4%)	84 (13.3%)	0.3573
Apgar score (5 min)	9 (3–9)	9 (1–10)	0.6516
<8	2 (2.9%)	20 (3.2%)	1.0000
UCB-Hb (g/dL) at birth	14.0 (8.8–18.1)	14.9 (6.3–20.1)	0.0008
<14.0 g/dL	32 (46.3%)	201 (31.9%)	0.0216
<13.5 g/dL	23 (33.3%)	142 (22.5%)	0.0522
<12.5 g/dL	11 (15.9%)	70 (11.1%)	0.2354
<11.0 g/dL	3 (4.3%)	20 (3.2%)	0.4885
<10.0 g/dL (newborn anemia)	1 (1.4%)	6 (1.0%)	0.5185

Data are presented as the median (range). UCB-Hb, umbilical cord blood hemoglobin concentration.
[a] See footnote for Table 1.

median UCB-Hb was significantly higher (15.8 [8.8–19.4] vs. 14.7 [6.3–20.1], respectively, $P = 0.0002$) in the 67 LGA cases than in the 632 non-LGA cases. The number of cases with at least one positive test result did not differ between the two groups (13% [9/67] vs. 9.5% [60/632], $P = 0.2789$). Neither median MCA-PSV MoM (1.00 [0.64–1.29] vs. 1.06 [0.48–1.87], respectively, $P = 0.7681$), median UCB-Hb (14.1 [12.5–17.7] vs. 14.8 [6.3–20.1], respectively, $P = 0.3990$), nor number of cases with at least one positive test result (16% [3/19] vs. 9.7% [66/680], respectively, $P = 0.4218$) differed between the 19 cases with and the 680 cases without Rh blood type incompatibility/irregular antibodies.

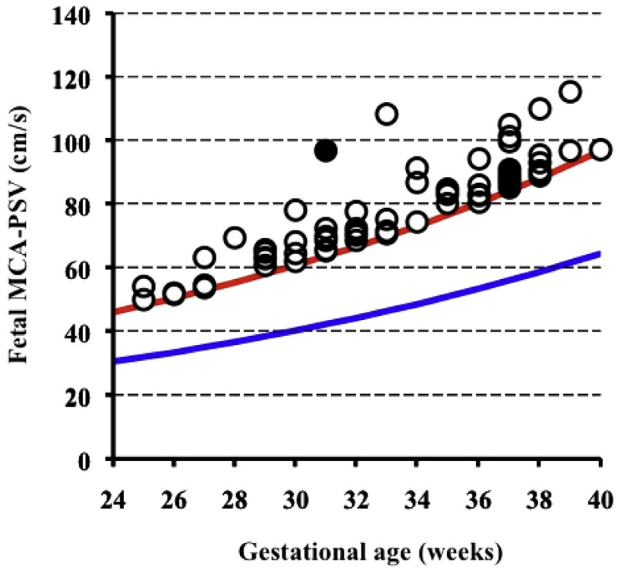

Fig. 1. MCA-PSA values in 69 women whose positive test result was noted for the first time. Closed and open circles indicate cases with and without newborn anemia, respectively. Red and blue lines indicate MCA-PSV MoMs of 1.50 and 1.00, respectively. The MCA test was given in 87, 121, 105, 129, 122, 129, 145, 152, 182, 209, 201, 267, 230, 137, 65, and 28 women at GW 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, and 40, respectively.

Relationship between values of fetal MCA-PSV MoM and UCB-Hb at birth

MCA-PSV MoM determined 4, 3, and 2 weeks prior to birth were significantly negatively correlated with UCB-Hb levels, but their correlations were weak (correlation coefficient [R], 0.2–0.4) (Fig. 2). R-value for the correlation between MCA-PSV MoM determined 1 week prior to birth and UCB-Hb was <2.0, and was therefore considered not to be significant.

Prevalence rates of newborns with UCB-Hb <12.5 g/dL in two groups divided by various MCA-PSV MoM cut-offs (Fig. 3)

The prevalence rate of newborns with UCB-Hb < 12.5 g/dL was consistently higher for the group with higher MCA-PSV MoM than the group with lower MCA-PSV MoM at all cut-off levels (Fig. 3): 17.0% (48/283) vs. 7.9% (33/416) with $P = 0.0004$, 17.9% (35/195) vs. 9.1% (46/504) with $P = 0.0022$, 19.0% (24/126) vs. 9.9% (57/573) with $P = 0.0056$, 17.0% (16/94) vs. 10.7% (65/605) with $P = 0.0838$, 18.6% (11/59) vs. 10.9% (70/640) with $P = 0.0880$, 22.0% (9/41) vs. 10.9% (72/658) with $P = 0.0428$, 16.7% (5/30) vs. 11.9% (76/639) with $P = 0.3939$, 26.3% (5/19) vs. 11.2% (76/680) with $P = 0.0580$, and 21.4% (3/14) vs. 11.5% (78/685) with $P = 0.2144$ for MCA-PSV MOM cut-off value of 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, and 1.50, respectively.

Changes in MCA-PSV MoM in seven cases with newborn anemia and three cases with both at least one positive MCA-PSV test result and Rh blood type incompatibility/irregular antibodies (Fig. 4)

Among the seven women giving birth to anemic newborns, only one (Case 1) exhibited a positive test result (Fig. 4A). It is interesting to note that three of seven cases with newborn anemia had anomalies, including thanatophoric dysplasia (Case 1) and congenital heart disease (Cases 2 and 4, respectively). The specific causes of newborn anemia were undetermined in all cases. Among 19 women with Rh blood type incompatibility/irregular antibodies, only three showed positive test results (Fig. 4B). None of these 19 women gave birth to anemic newborns.

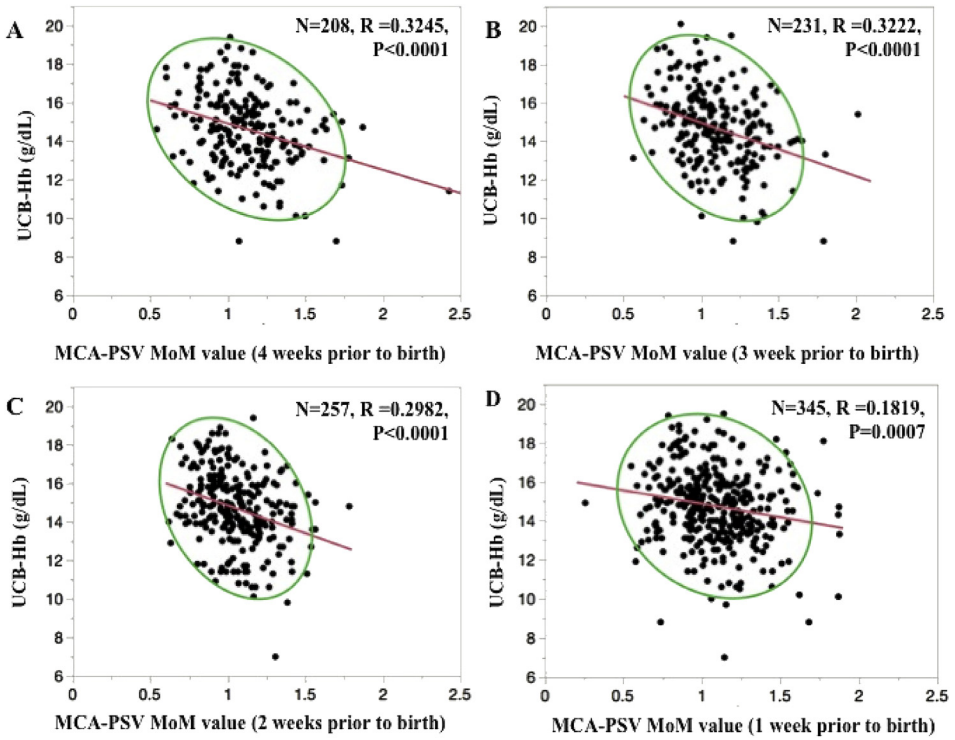

Fig. 2. Correlation between values of fetal MCA-PSV MoM and UCB-Hb. A, B, C, and D. Fetal MCA-PSV MoM values determined 4 weeks (22–28 days), 3 weeks (15–21 days), 2 weeks (8–14 days), and 1 week (0–7 days) prior to birth, respectively.

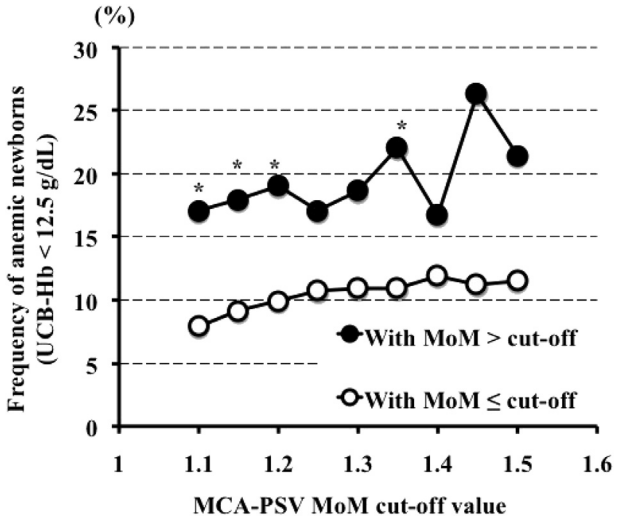

Fig. 3. Prevalence rates of newborns with UCB-Hb < 12.5 g/dL in two groups divided by various MCA-PSV MoM cut-offs. *, $P < 0.05$ between two groups. The total of 699 cases were divided into two groups by MCA-PSV MoM. Mean MCA-PSV MoM value was used as the datum for each case with multiple MCA-PSV test results. The number of newborns with UCB-Hb < 12.5 g/dL was consistently greater in the group with higher than lower MCA-PSV MoM value at any cut-off value; 17.0% (48/283) vs. 7.9% (33/416) with $P = 0.0004$, 17.9% (35/195) vs. 9.1% (46/504) with $P = 0.0022$, 19.0% (24/126) vs. 9.9% (57/573) with $P = 0.0056$, 17.0% (16/94) vs. 10.7% (65/605) with $P = 0.0838$, 18.6% (11/59) vs. 10.9% (70/640) with $P = 0.0880$, 22.0% (9/41) vs. 10.9% (72/658) with $P = 0.0428$, 16.7% (5/30) vs. 11.9% (76/639) with $P = 0.3939$, 26.3% (5/19) vs. 11.2% (76/680) with $P = 0.0580$, and 21.4% (3/14) vs. 11.5% (78/685) with $P = 0.2144$ for MCA-PSV MOM cut-off value of 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, and 1.50, respectively.

Discussion

The present study was performed in 699 unselected women examined for fetal MCA-PSV during the second and third trimesters at the attending physician's discretion and gave birth to singleton infants without proven chromosomal aberrations at or near term. MCA-PSV MoM determined 2–4 weeks before birth was significantly weakly negatively correlated with UCB-Hb at birth. A positive MCA-PSV test result defined as MCA-PSV MoM >1.5 occurred at least once in 9.9% (69/699) of women. Anemic infants were born to one (1.4%) of 69 women with at least one positive test result and to six (1.0%) of 630 women with negative test results. Thus, MCA-PSV test was unsatisfactory for prediction of newborn anemia.

The results of the present study did not suggest that MCA-PSV test had limited clinical value for prediction of fetal anemia. Only women giving birth at GW 36 or later were included and women giving birth to preterm infants before GW 36 were not included in this study. Although no cases were identified to have placental mesenchymal dysplasia (PMD) or fetomaternal hemorrhage (FMH) in this study population, MCA-PSV test played a significant role in the early intervention decision with early delivery before GW 36 for suspected fetal anemia due to PMD and FMH during the study period of our hospital [2,7]. In a review by Ishikawa et al. collecting 109 pregnancies complicated with PMD [13], intrauterine fetal death (IUFD) occurred in approximately one third (32/109) pregnancies with viable infants at GW 24 [13] and 91% (29/32) of IUFD occurred before GW 36. Although causes of IUFD were unclear in most reported cases with PMD, it was recently suggested that fetal anemia can explain adverse outcomes in some PMD pregnancies [2,13,14]. Therefore, we speculate that the MCA-PSV test would be especially useful in monitoring of pregnancies complicated with PMD. Clinical FMH occurring mostly at or near term would be detectable if MCA-PSV test was performed timely.

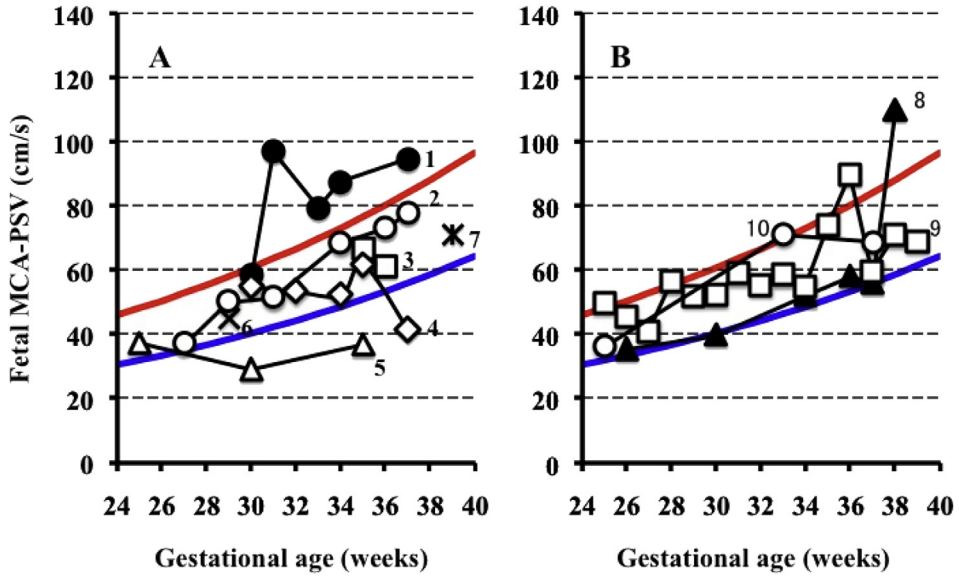

Fig. 4. Changes in MCA-PSV MoM in 10 cases. Numerals in the figure indicate case numbers. Red and blue lines indicate MCA-PSV MoMs of 1.50 and 1.00, respectively. A, Seven cases with newborn anemia: Case 1 had repeated positive test results, birthweight of 1488 g, thanatophoric dysplasia, and UCB-Hb of 8.8 g/dL, and died four hours after birth. Case 2 had a birthweight of 2620 g and congenital heart disease (single ventricle, double outlet right ventricle, and pulmonary stenosis) and UCB-Hb of 9.8 g/dL. Case 3 had a birthweight of 2915 g and UCB-Hb of 7.0 g/dL. Case 4 had a birthweight of 2894 g, congenital heart disease (double aortic arch), and UCB-Hb of 8.8 g/dL. Case 5 had a birthweight of 2920 g and UCB-Hb of 9.6 g/dL. Cases 6 and 7 underwent only one test and had birthweights of 3125 and 3175 g and UCB-Hb of 6.3 g/dL and 9.7 g/dL, respectively. Neither fetomaternal hemorrhage nor blood type incompatibility was confirmed in any of these cases. B, Three cases with both at least one positive MCA-PSV test result and Rh blood type incompatibility/irregular antibodies. Among 19 cases at high risk of fetal anemia with Rh blood type incompatibility or irregular antibodies, only three (Case 8, 9, and 10) exhibited positive MCA-PSV test results transiently, although MCA-PSV test was applied six times, 15 times, and three times in Case 8 (Rh blood type incompatibility), Case 9 (anti-Lea antibody), and Case 10 (Rh blood type incompatibility), respectively. UCB-Hb was 14.7, 13.4, and 13.7 g/dL in Case 8, Case 9, and Case 10, respectively.

The clinical usefulness of MCA-PSV for prediction of fetal anemia is well established in cases complicated with maternal red cell alloimmunization [8]. Indeed, even in the 19 women at risk of fetal anemia with Rh blood type incompatibility or irregular antibodies, no invasive tests were given based on MCA-PSV results in this study. The strength of the study of Mari et al. [8] was simultaneous determination of both MCA-PSV and fetal hemoglobin concentration by cordocentesis among cases at risk of fetal anemia due to red cell alloimmunization. In their study [8], positive test results (defined similar to the present study) yielded very high sensitivity with a low false positive rate for prediction of fetal anemia. However, it was interesting to note that GW at the time of the test was exclusively less than 32 in all cases with fetal anemia predicted by MCA-PSV, suggesting that delivery occurred prematurely before GW 36 in most such cases in the study of Mari et al. [8]. In addition, cases with positive test results at more advanced stages of gestation did not have fetal anemia in the study of Mari et al. [8]. Taken together with our results, these observations suggested that among cases with a positive MCA-PSV test result, but not with indicated early termination of pregnancy, MCA-PSV test had limited clinical value for prediction of newborn anemia. Some backup tests, such as biophysical profile scoring by ultrasonography and non-stress testing by cardiotocography, may have suggested fetal well being in such cases. Thus, the results of the present study did not contradict those of Mari et al. [8].

The present study suggested that fetal MCA-PSV is not clinically useful for prediction of newborn anemia defined as UCB-Hb at birth <10.0 g/dL among women that would give birth at or near term. However, from the prospective viewpoint, we are not able to determine which women could continue their pregnancies in the presence of positive MCA-PSV test result unless other backup tests are given to determine fetal well-being.

In this study, as many as 2.7% (19/699) of women exhibited positive test results (MCA-PSV MoM > 1.5) on the first test. This rate of positive test results was reasonable based on a study by Kurmanavicius et al. [9], in which 5% of women showed MCA-PSV values, e.g., 53.1, 56.1, and 59.1 cm/s at GW 29, 30, and 31 corresponding to MCA-PSV MoMs of 1.30, 1.30, and 1.31, respectively, in the general pregnant population [9]. However, 22 physicians were involved in this study measuring MCA-PSV in 699 women. Pressure exerted on the maternal abdominal wall by the ultrasound probe during examination was suggested to be an important factor producing clinically significant measurable changes in fetal MCA-PSV [15,16]. It was possible that this factor influenced the MCA-PSV test results in this study.

Fetal MCA-PSV was high in cases of preterm FGR, defined as estimated fetal weight <3rd percentile, and such preterm FGR fetuses with MCA-PSV MoM >1.5 were more likely to die *in utero* compared to preterm FGR fetuses with MCA-PSV MoM ≤1.5 [10]. It was reasonable to speculate that LGA infants diagnosed at birth in this study may have suffered from preterm FGR. Unexpectedly, however, LGA infants did not have higher MCA-PSV MoM, but actually had lower MCA-PSV MoM and higher UCB-Hb in this study. We speculated that those surviving *in utero* to term or near term may have succeeded to compensate for the adverse *in utero* environment regarding blood oxygenation with increased hemoglobin concentrations, thus leading to no increase in MCA-PSV.

In conclusion, among unselected women giving birth at or near term, the MCA-PSV test was unsatisfactory for prediction of newborn anemia in this retrospective observational study. However, MCA-PSV MoM determined 2–4 weeks prior to birth showed a significant weak negative correlation with UCB-Hb at birth. The results of this study do not imply that MCA-PSV has limited clinical value from a prospective viewpoint, as in some cases preterm infants may have been born before GW 36 based on fetal anemia suggested by MCA-PSV together with compromised condition suggested by other tests, such as biophysical profile scoring by ultrasound and non-stress test by cardiotocography.

Conflict of interest

None declared.

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