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Prediction of fetal anemia in rhesus disease by measurement of fetal middle cerebral artery peak systolic velocity

M. SCHEIER, E. HERNANDEZ-ANDRADE, A. CARMO, V. DEZEREGA and K. H. NICOLAIDES

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK

KEYWORDS: cordocentesis; Doppler ultrasonography; fetal anemia; middle cerebral artery; red blood cell isoimmunization

ABSTRACT

Objective *In red blood cell (RBC) isoimmunized pregnancies fetal anemia is associated with a hyperdynamic circulation. The aim of the present study was to examine further the possible value of fetal middle cerebral artery peak systolic velocity (MCA-PSV) in the management of affected pregnancies.*

Methods *A reference range of fetal MCA-PSV with gestation was constructed from the study of 813 normal singleton pregnancies at 20–40 weeks' gestation. Fetal MCA-PSV was also measured in 58 fetuses from RBC isoimmunized pregnancies, with maternal hemolytic antibody concentration of > 15 IU/mL at 19–38 weeks' gestation and within 10 days of measurement of fetal hemoglobin concentration in blood obtained either by cordocentesis (*n = *43) or at delivery (*n = *15). In the RBC isoimmunized pregnancies each of the measured MCA-PSV and hemoglobin concentrations was expressed as a delta value (difference in SDs from the normal mean for gestation). Regression analysis was used to determine the significance of the association between delta MCA-PSV and delta fetal hemoglobin concentration.*

Results *In the normal pregnancies there was a significant increase in fetal MCA-PSV with gestation (mean MCA-PSV =* $10^{0.0223 \times GA + 0.963}$*). In RBC isoimmunized pregnancies the fetal MCA-PSV was increased and there was a significant association between delta MCA-PSV and delta hemoglobin concentration (delta hemoglobin = (delta MCA-PSV + 0.093)/−0.356;* $R^2 = 0.638$*,* $P < 0.0001$*). An MCA-PSV of mean + 1.5 SDs detected 96% of severely anemic fetuses, with a hemoglobin deficit of at least 6 SDs, for a false-positive rate of 14%.*

Conclusion *Measurement of fetal MCA-PSV is a useful method of assessing fetal anemia. In the clinical management of isoimmunized pregnancies a cut-off in MCA-PSV of mean + 1.5 SDs can identify nearly all severely anemic fetuses with a low false-positive rate.* *Copyright © 2004 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

In red blood cell (RBC) isoimmunized pregnancies there is transplacental passage of maternal hemolytic antibodies that cause fetal anemia. The fetus compensates by hemodynamic adaptations that can be assessed by Doppler ultrasound. Several studies in the last 15 years have established that fetal anemia is associated with increased arterial and venous blood flow velocities[1–6]. Recently, Mari *et al.* suggested that measuring the fetal middle cerebral artery peak systolic velocity (MCA-PSV) could be used in the clinical management of isoimmunized pregnancies to identify the anemic fetus for timely intervention either through early delivery or intrauterine blood transfusion[7]. The aim of the present study was to examine further the possible value of fetal MCA-PSV in the management of affected pregnancies.

METHODS

This was a cross-sectional study of the fetal MCA-PSV in two groups of pregnant women. The first group comprised 813 normal singleton pregnancies attending for ultrasound examination at 20–40 weeks' gestation either at King's College Hospital, London, UK or at Sao Paulo University Hospital, St Paulo, Brazil. The data from this group were used to construct a reference range of MCA-PSV with gestation. The second group, which was examined in the authors' Fetal Medicine Unit at King's College Hospital, London, UK, comprised 58 fetuses from 56 women with RBC isoimmunization (54 with singleton

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, Denmark Hill, London SE5 8RX, UK (e-mail: fmf@fetalmedicine.com)

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pregnancies and two with dichorionic twins) who had not received previous fetal blood transfusions in the current pregnancy. We included only women with hemolytic antibody concentration of > 15 IU/mL because we have previously shown that lower levels are not associated with severe fetal anemia[8]. All Doppler results included in this study were obtained within 10 days (in 43 cases on the same day) of fetal blood sampling for measurement of hemoglobin concentration, either by cordocentesis ($n = 43$) or at delivery ($n = 15$). The median gestation at fetal assessment by Doppler was 29 (range, 19–38) weeks.

A transverse section of the fetal head was obtained by ultrasonography (3–5-MHz curvilinear probe, Eccoccee SSA-340A, Toshiba Corporation, Tokyo, Japan and Acuson Aspen, Mountain View, CA, USA) and color flow mapping was used to identify the circle of Willis and the MCA. The pulsed-wave Doppler gate was then placed on the proximal one-third of the MCA and the angle of insonation was less than 20°. A 125-Hz high-pass filter was used to eliminate signals from slowly moving tissues. Attention was taken to avoid any unnecessary pressure on the fetal head[9] and the mechanical and thermal indices were always kept below 1. At least three consecutive waveforms, in the absence of fetal body or breathing movements, were recorded and the highest point of the Doppler envelope was considered as the PSV (cm/s).

Statistical analysis

In the normal pregnancies the data were normalized by logarithmic transformation and regression analysis was used to construct a reference range of MCA-PSV with gestation. In the RBC isoimmunized pregnancies each of the measured MCA-PSV values was expressed as a delta value (difference in SDs from the normal mean for gestation). Similarly, each measured hemoglobin concentration was expressed as a delta value of the authors' previously published normal range for gestation[10]. Regression analysis was used to determine the significance of association between delta MCA-PSV and delta fetal hemoglobin concentration. In order to test whether a linear regression model is suitable to describe the relationship between MCA-PSV and hemoglobin we performed *F*-tests for linear, quadratic and cubic relationships (SPSS for Windows Version 11, SPSS Inc., Chicago, IL, USA). The sensitivity, false-positive rate, positive predictive value, negative predictive value and likelihood ratio for different cut-offs in MCA-PSV in the prediction of fetal anemia (mild: delta values of between ≥ -2 SDs and < -4 SDs; moderate: between ≥ -4 SDs and < -6 SDs; severe: ≥ -6 SDs) were calculated.

RESULTS

In the normal pregnancies there was a significant association between fetal MCA-PSV and gestation (mean MCA-PSV $= 10^{0.0223 \times GA + 0.963}$; mean + 1 SD $= 10^{0.0223 \times GA + 1.045981}$; $R^2 = 0.697$; $P < 0.0001$; Figure 1), where GA is gestational age in weeks. The mean and mean + 1.5 SDs in this study are similar to the median and 1.5 multiples of the median of those reported by Mari *et al.*[7] (Table 1).

In the RBC isoimmunized pregnancies the median maternal hemolytic antibody (Table 2) concentration was 41 (range, 16–693) IU/mL. The fetal hemoglobin concentration was at least 6 SDs below the normal mean for gestation in 23/58 cases and in nine of these the fetuses were hydropic with tense ascites and dilated heart (Figure 2). The fetal MCA-PSV was increased (Figure 3) and there was a significant association between delta MCA-PSV and delta hemoglobin concentration (delta hemoglobin = (delta MCA-PSV + 0.093)/−0.356; $R^2 = 0.638$, $P < 0.0001$; Figure 4). The most appropriate description for this association was linear because it provided the highest value in the *F*-test (98.5, compared

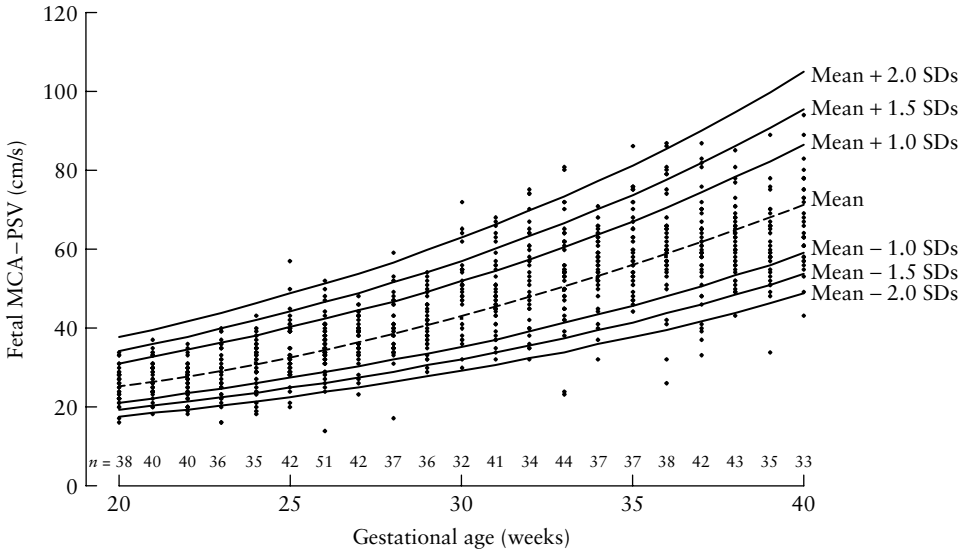

Figure 1 Reference range of fetal middle cerebral artery peak systolic velocity (MCA-PSV) with gestation from the study of 813 pregnancies.

Table 1 Fetal hemoglobin concentration and middle cerebral artery peak systolic velocity with gestation in the normal pregnancies. The values are compared to those of Mari *et al.*[7]

Gestation (weeks)	*Fetal hemoglobin concentration (g/dL)*				*Fetal MCA-PSV (cm/s)*			
	Present study		*Mari* et al.[7]		*Present study*		*Mari* et al.[7]	
	Mean	*−6 SDs*	*Median*	*0.55 MoM*	*Mean*	*1.5 SDs*	*Median*	*1.5 MoM*
18	11.0	5.3	10.6	5.8	23.1	30.8	23.2	34.8
20	11.3	5.6	11.1	6.1	25.6	34.2	25.5	38.2
22	11.6	5.9	11.6	6.4	28.4	37.9	27.9	41.9
24	11.9	6.3	12.0	6.6	31.5	41.9	30.7	46.0
26	12.2	6.6	12.3	6.8	34.9	46.5	33.6	50.4
28	12.5	6.9	12.6	6.9	38.6	51.5	36.9	55.4
30	12.8	7.2	12.8	7.1	42.8	57.1	40.5	60.7
32	13.1	7.5	13.1	7.2	47.4	63.3	44.4	66.6
34	13.5	7.8	13.3	7.3	52.6	70.1	48.7	73.1
36	13.8	8.1	13.5	7.4	58.3	77.7	53.5	80.2
38	14.1	8.4	13.6	7.5	64.6	86.1	58.7	88.0
40	14.4	8.8	13.8	7.6	71.5	95.4	64.4	96.6

MCA-PSV, middle cerebral artery peak systolic velocity; MoM, multiples of the median.

Table 2 Maternal hemolytic antibodies in the red blood cell isoimmunized pregnancies

Antibodies	n
Anti-D	27
Anti-D and -C	17
Anti-D and -E	1
Anti-D, -C and -e	1
Anti-D, -C and -Kell	1
Anti-D, -C, -E and -Fy	1
Anti-C	2
Anti-c	1
Anti-C and -Kell	1
Anti-E	1
Anti-Fy	2
Anti-Kell	1
Total	56

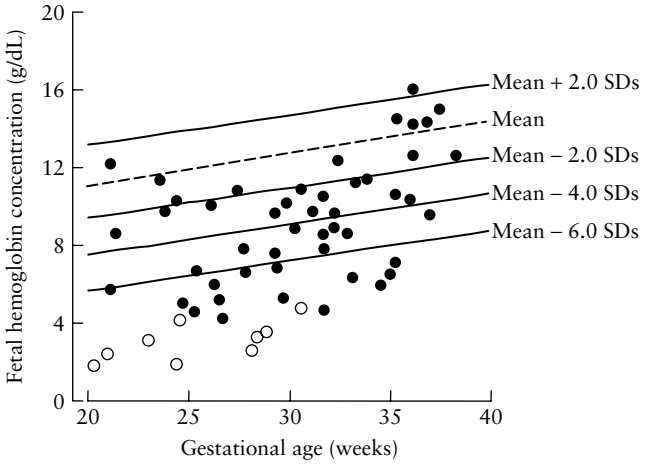

Figure 2 Fetal hemoglobin concentration in the red blood cell isoimmunized pregnancies plotted on the normal range for gestation[9]. Severe anemia is defined by fetal hemoglobin of > 6 SDs below the normal mean and nine fetuses in this group were hydropic (○).

to 61.5 and 40.3 for the quadratic and cubic fits, respectively). The screening characteristics of MCA-PSV in the prediction of fetal anemia are shown in Table 3.

DISCUSSION

The findings of this study confirm earlier observations that in RBC isoimmunization fetal anemia is associated with a hyperdynamic circulation[1–7] and fetal hydrops develops when the hemoglobin deficit is > 6 SDs[10]. In normal fetuses the mean hemoglobin concentration rises linearly with gestation from 11 g/dL at 18 weeks to 14.5 g/dL at 40 weeks; the 95% CIs are nearly parallel and 1 SD is approximately 1 g/dL[10]. In RBC isoimmunized pregnancies the lifespan of fetal erythrocytes is reduced because antibody-coated RBCs are destroyed in the reticuloendothelial system. The fetus compensates for anemia by hemodynamic adjustments but when the hemoglobin deficit exceeds 6 g/dL hydrops fetalis develops. The most likely explanation for the observed increase in MCA-PSV is that fetal anemia is associated with decreased blood viscosity leading to increased venous return and preload with consequent increase in cardiac output.

In the clinical management of isoimmunized pregnancies the aim is to predict whether the fetus is severely affected and to correct the fetal anemia by intrauterine blood transfusion. The only accurate method of assessing the severity of fetal anemia is by fetal blood sampling[10]. However, cordocentesis should only be undertaken if there is a strong suspicion that the fetus is severely affected because the procedure itself can cause miscarriage and it can also cause fetomaternal hemorrhage, thereby exacerbating the severity of the disease.

The findings of this and previous studies (Table 4) demonstrate that cordocentesis can safely be reserved only for those pregnancies demonstrating increased fetal

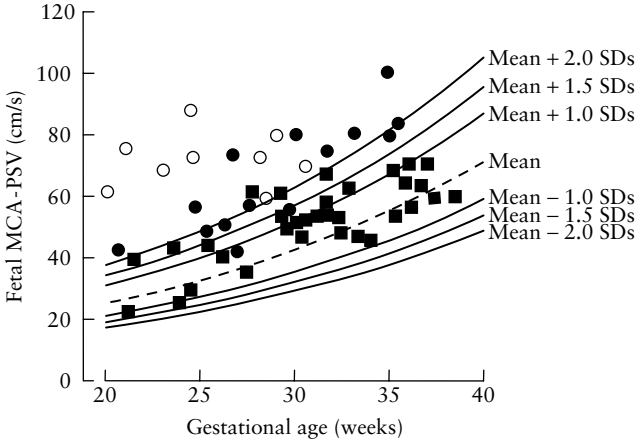

Figure 3 Fetal middle cerebral artery peak systolic velocity (MCA-PSV) in the red blood cell isoimmunized pregnancies plotted on the normal range for gestation according to fetal hemoglobin concentration of > 6 SDs below the mean (■) or < 6 SDs below the mean (●). The values from hydropic fetuses are indicated by open circles (○).

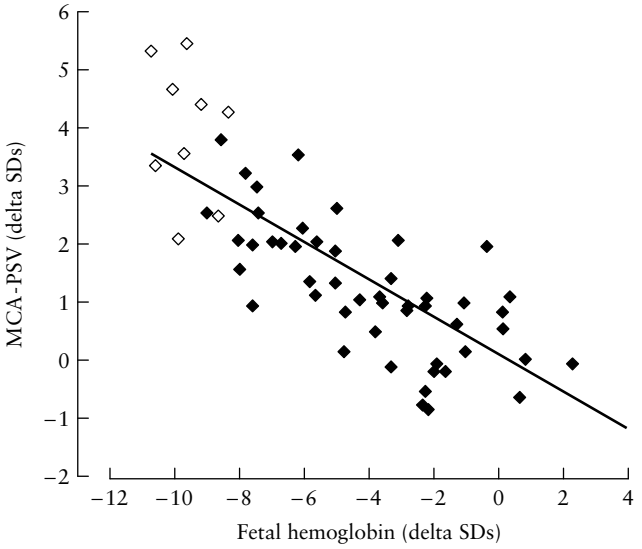

Figure 4 Fetal middle cerebral artery peak systolic velocity (MCA-PSV) plotted against fetal hemoglobin. The values from hydropic fetuses are indicated by open diamonds (◊).

MCA-PSV; in more than 95% of the severely anemic fetuses the MCA-PSV was > 1.5 SDs above the normal mean for gestation. This high sensitivity can be achieved with a relatively low false-positive rate and therefore invasive testing can be avoided or delayed in more than 80% of isoimmunized pregnancies with high maternal serum antibody concentration.

We propose that assessment of the severity of fetal hemolysis should be based on (1) the history of previous affected pregnancies[14,15], (2) the levels of maternal hemolytic antibodies[8] and (3) ultrasonographic examination for the detection of ascites[10] and Doppler studies for diagnosis of a hyperdynamic circulation[1–7,9,11–13]. For patients with a previous RBC isoimmunization-affected pregnancy the objective should be to perform the first ultrasound scan and Doppler studies at approximately 10 weeks before the time of the earliest previous fetal or neonatal death, fetal transfusion or birth of a severely affected baby, but not before 17–18 weeks. Fetal death or the development of hydrops do not occur before this gestation, presumably because the fetal reticuloendothelial system is too immature to result in destruction of

Table 3 Screening characteristics of fetal middle cerebral artery peak systolic velocity in the prediction of fetal anemia: sensitivity, specificity, positive predictive value and negative predictive value for fetal hemoglobin concentrations > 2 SDs, > 4 SDs and > 6 SDs below the normal mean for gestation

MCA-PSV cut-off	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Mean + 0.5 SDs				
Hemoglobin deficit 6 SDs	100	31	49	100
Hemoglobin deficit 4 SDs	97	38	66	91
Hemoglobin deficit 2 SDs	86	54	82	53
Mean + 1.0 SDs				
Hemoglobin deficit 6 SDs	96	60	61	95
Hemoglobin deficit 4 SDs	91	73	81	86
Hemoglobin deficit 2 SDs	71	84	94	48
Mean + 1.5 SDs				
Hemoglobin deficit 6 SDs	96	86	81	97
Hemoglobin deficit 4 SDs	78	92	93	77
Hemoglobin deficit 2 SDs	55	92	96	39
Mean + 2.0 SDs				
Hemoglobin deficit 6 SDs	83	91	82	91
Hemoglobin deficit 4 SDs	95	71	69	95
Hemoglobin deficit 2 SDs	49	100	51	100

MCA-PSV, middle cerebral artery peak systolic velocity; NPV, negative predictive value; PPV, positive predictive value.

Table 4 Doppler studies reporting on the prediction of severe fetal anemia in previously untransfused fetuses by measurement of the fetal middle cerebral artery peak systolic velocity

Reference	*Gestation (weeks (range))*	n	*Fetal anemia*		*Increased MCA-PSV*		
			Cut-off	n *(%)*	*Cut-off*	*Sensitivity (%)*	*FPR (%)*
Mari *et al.* (2000)[7]	25 (15–36)	111	0.55 MoM	31 (28)	1.5 MoM	100	16
Teixeira *et al.* (2000)[11]	— (15–35)	26	−4.0 SDs	5 (19)	1.0 SD	83	20
Zimmermann *et al.* (2002)[12]	25 (16–37)	125	0.55 MoM	9 (7)	1.5 MoM	89	23
Deren and Önderoglu (2002)[13]	28 (24–33)	44	0.6 MoM	22 (50)	1.35 MoM	100	9
Present study	29 (19–38)	58	−6.0 SDs	23 (40)	1.5 SD	96	14

FPR, false-positive rate; MCA-PSV, middle cerebral peak systolic velocity; MoM, multiples of the median.

antibody-coated erythrocytes. Assessment should be carried out at intervals of 1–2 weeks and cordocentesis need only be performed if there is fetal ascites or the fetal MCA-PSV is > 1.5 SDs above the normal mean for gestation. In patients that had no or mildly affected previous pregnancies the maternal hemolytic antibody levels should be measured at 2–3-weekly intervals from 17 weeks' gestation onwards. When the antibody concentrations are persistently < 15 IU/mL, the degree of fetal hemolysis is insignificant or mild and delivery can be delayed until term. If the antibody levels are > 15 IU/mL the disease may be severe and the fetus should be assessed by ultrasound and Doppler examinations at weekly intervals and cordocentesis should be considered in those fetuses that develop ascites or a high MCA-PSV.

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