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Fetal middle cerebral artery peak systolic velocity in the investigation of non-immune hydrops

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KEYWORDS: cordocentesis; Doppler ultrasonography; fetal anemia; middle cerebral artery; non-immune hydrops; parvovirus B19

ABSTRACT

Objective *In some cases of non-immune hydrops there is congenital or acquired fetal anemia. The aim of this study was to investigate the potential value of fetal middle cerebral artery peak systolic velocity (MCA-PSV) in the assessment and management of non-immune hydrops due to anemia.*

Methods *Fetal MCA-PSV and fetal hemoglobin concentration, in blood obtained by cordocentesis, were measured in 16 singleton pregnancies referred to our unit for further investigations because of a diagnosis of non-immune hydrops fetalis. In all cases a detailed ultrasound examination demonstrated moderate or severe ascites, with or without skin edema, and pericardial or pleural effusions. Furthermore, there were no obvious malformations to account for the hydrops. In each fetus the measured MCA-PSV and hemoglobin concentration were expressed as delta values (the difference in SD 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. In addition, we searched our database to identify the sonographic features and hemoglobin concentration of fetuses with congenital infection.*

Results *In the 16 cases of non-immune hydrops there were seven with parvovirus B19 infection, one each of α-thalassemia and primary cardiomyopathy and seven with no obvious explanation for the hydrops. There was a significant association between delta MCA-PSV and delta hemoglobin concentration (delta hemoglobin = (delta MCA-PSV + 0.1437)/−0.4154;* $R^2 = 0.7202$; $P < 0.0001$*). In 10 of the cases the fetal hemoglobin concentration was more than 4 SD below the normal mean for gestation and in all these cases the MCA-PSV was more than 2 SD above the normal mean for gestation. Our computer search identified an additional nine fetuses with parvovirus B19 infection and in all cases the predominant sonographic finding was ascites and the hemoglobin concentration was more than 4 SD below the normal mean. In contrast, only 3/14 fetuses with cytomegalovirus, toxoplasmosis, coxsackie B or* Treponema *infection had ascites and only 2/14 had a hemoglobin deficit of 4–6 SD.*

Conclusion *In the management of non-immune hydrops, measurement of fetal MCA-PSV can help identify the subgroup with fetal anemia. Copyright © 2004 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Hydrops fetalis, characterized by generalized skin edema and pericardial, pleural or ascitic effusions, is a non-specific finding in a wide variety of fetal and maternal disorders, including hematological, chromosomal, cardiovascular, renal, pulmonary, gastrointestinal, hepatic and metabolic abnormalities, congenital infection, neoplasms and malformations of the placenta or umbilical cord[1–3]. Fetal hydrops in red blood cell isoimmunization, which is characterized by severe ascites and lesser degrees of edema or pericardial and pleural effusions, develops when the fetal hemoglobin deficit is more than 6 SD[4]. In this condition the fetus compensates for anemia by hemodynamic adjustments, which can be assessed by Doppler ultrasound[5–8]. Measurement of the fetal middle cerebral artery peak systolic velocity (MCA-PSV) has been shown to provide sensitive prediction of the anemic fetus[9,10].

The aim of this study was to investigate the potential value of MCA-PSV in the assessment and management of non-immune hydrops presenting with the same sonographic features as immune hydrops.

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METHODS

This was a cross-sectional study of the fetal MCA-PSV in 16 pregnancies referred to our unit for further investigations because of a diagnosis of non-immune hydrops fetalis. In all cases a detailed scan, including fetal echocardiography, was carried out for the diagnosis of fetal malformations and the assessment of the severity of skin edema, ascites and pericardial or pleural effusions, which were subjectively classified as severe, moderate or mild. In all hydropic fetuses with no obvious markers of chromosomal defects or anatomical defects, such as cardiac or pulmonary abnormalities, to account for the hydrops, our policy is to perform cordocentesis for hematological investigations. In fetuses with moderate or severe ascites the fetal MCA-PSV is measured before cordocentesis and whenever the MCA-PSV is increased preparations are made for a fetal blood transfusion at the time of cordocentesis. Therefore, the entry criteria for this study were singleton pregnancies with a minimum of moderate fetal ascites in the absence of an obvious fetal defect.

A transverse section of the fetal head was obtained by ultrasonography, color flow mapping was used to identify the circle of Willis and the MCA, and pulsed-wave Doppler was used to measure the PSV (cm/s)[7,9]. In each case the measured MCA-PSV value was expressed as a delta value (the difference in SD from the normal mean for gestation)[10]. Similarly, each measured hemoglobin concentration was expressed as a delta value of our previously published normal range for gestation[4]. Regression analysis was used to determine the significance of association between delta MCA-PSV and delta fetal hemoglobin concentration.

In addition to the assessment of the above cases, we searched our database to identify all pregnancies with congenital infection, which were not investigated by Doppler ultrasonography, to determine the sonographic features and hemoglobin concentration of such fetuses.

RESULTS

The ultrasound findings, MCA-PSV, hemoglobin concentration, diagnosis and outcome of the 16 fetuses with non-immune hydrops are summarized in Table 1. In the 16 cases of non-immune hydrops there were seven with parvovirus B19 infection, one each of α-thalassemia, primary cardiomyopathy and unexplained marrow suppression, and seven with no obvious explanation for the hydrops. The fetal hemoglobin concentration and MCA-PSV are plotted on the respective normal range for gestation in Figures 1 and 2. There was a significant association between delta MCA-PSV and delta hemoglobin concentration (delta hemoglobin = (delta MCA-PSV + 0.1437)/−0.4154; $R^2 = 0.7202$, $P < 0.0001$; Figure 3). In 10 of the cases the fetal hemoglobin concentration was more than 4 SD below the normal mean for gestation and in all these cases the MCA-PSV was more than 2 SD above the normal mean for gestation.

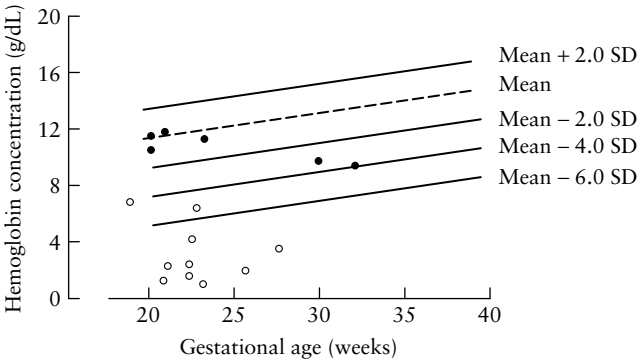

Figure 1 Hemoglobin concentration in the hydropic fetuses plotted on the normal range for gestation[4]. In the 10 fetuses with a hemoglobin deficit of more than 4 SD (○), the middle cerebral artery peak systolic velocity was more than 2 SD above the normal mean for gestation (see Figure 2).

Table 1 Ultrasound and Doppler findings, hemoglobin concentration, diagnosis and outcome of 16 fetuses with non-immune hydrops

GA	*Hb*	*MCA-PSV*	*Hydrops features*					
(weeks)	*(g/dL)*	*(cm/s)*	*Ascites*	*Pericardial*	*Pleural*	*Edema*	*Diagnosis*	*Outcome*
21	2.2	65	+++	+++	+	+++	Parvovirus B19	LB at 39 weeks
21	1.5	79	+++	+++	−	+++	Parvovirus B19	TOP at 23 weeks
22	4.1	58	++	+++	−	+	Parvovirus B19	IUD at 23 weeks
22	2.3	75	+++	+++	++	++	Parvovirus B19	LB at 40 weeks
22	1.8	40	+++	+	−	++	Parvovirus B19	LB at 39 weeks
25	1.9	91	+++	++	−	++	Parvovirus B19	IUD at 26 weeks
27	3.5	48	+++	++	−	+	Parvovirus B19	LB at 37 weeks
22	6.3	44	++	+	−	−	α-Thalassemia	TOP at 23 weeks
23	11.2	23	+++	+	−	+	Cardiomyopathy	Ongoing at 31 weeks
22	1.2	69	+++	+	−	+	Unexplained	LB at 37 weeks
30	9.7	47	++	−	−	−	Unexplained	LB at 36 weeks
17	7.6	48	++	+	−	+++	Unexplained	IUD at 18 weeks
32	9.3	61	+++	+++		+++	Unexplained	IUD at 33 weeks
20	10.5	20	++	++	−	+	Unexplained	TOP at 20 weeks
20	11.5	25	++	−	++	++	Unexplained	TOP at 20 weeks
21	11.8	28	++	++	++	+++	Unexplained	TOP at 21 weeks

+, mild; ++, moderate; +++, severe; GA, gestational age at presentation; Hb, fetal hemoglobin concentration; IUD, intrauterine death; LB, live birth; MCA-PSV middle cerebral artery peak systolic velocity; TOP, termination of pregnancy.

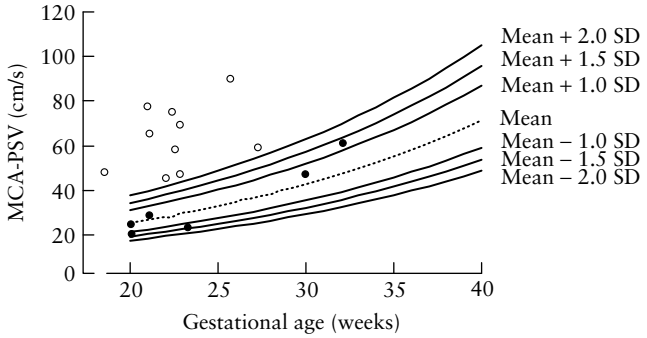

Figure 2 Middle cerebral artery peak systolic velocity (MCA-PSV) in the hydropic fetuses plotted on the normal range for gestation[6]. In the 10 fetuses with a hemoglobin deficit of more than 4 SD (○), the peak systolic velocity was more than 2 SD above the normal mean for gestation (see Figure 1).

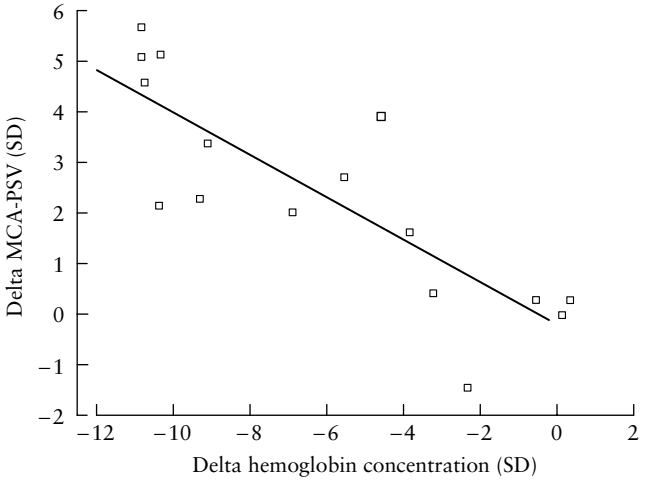

Figure 3 Fetal middle cerebral artery peak systolic velocity (MCA-PSV) plotted against fetal hemoglobin concentration (delta SD).

The most severely anemic fetuses were the seven with parvovirus B19 infection and in all cases one to three intrauterine blood transfusions were given. In four cases the hydrops resolved within 4 weeks of presentation and healthy babies were delivered at term. Two cases resulted in intrauterine death within 2 weeks of presentation and in one case hydrocephalus was diagnosed 2 weeks after the initial presentation and the pregnancy was terminated at the request of the parents. In one case the diagnosis of α-thalassemia was made and the pregnancy was terminated at the request of the parents. In seven cases the cause of non-immune hydrops remained unexplained. Two of these cases resulted in intrauterine deaths, in three cases the pregnancy was terminated, in one case there was spontaneous resolution of the hydrops and a healthy baby was born at 36 weeks and in another case with unexplained severe anemia the hydrops resolved after three intrauterine blood transfusions and a healthy baby was delivered at 37 weeks.

Our computer search identified 23 cases of congenital infection, which were not part of the MCA-PSV study (Table 2). There were nine fetuses with parvovirus B19 infection and in all cases the predominant sonographic finding was ascites and the hemoglobin concentration was more than 4 SD below the normal mean for gestation. In contrast, only 3/14 fetuses with cytomegalovirus, toxoplasmosis, coxsackie B or *Treponema* infection had

Table 2 Ultrasound findings and hemoglobin concentration in 23 cases with congenital infection

GA (weeks)	*Infection*	*Ultrasound findings*	*Hb (g/dL)*
18	Parvovirus B19	Ascites (+++), edema (++)	4.4
16	Parvovirus B19	Ascites (+++), pericardial effusion (+++), edema (+)	5.7
25	Parvovirus B19	Ascites (++), pericardial effusion (+), edema (++)	7.0
19	Parvovirus B19	Ascites (++), pericardial effusion (++), edema (++)	2.0
24	Parvovirus B19	Ascites (+++), pericardial effusion (+), edema (++)	1.3
20	Parvovirus B19	Ascites (++), pericardial effusion (++)	5.4
20	Parvovirus B19	Ascites (+++), pericardial effusion (++), edema (+)	2.1
21	Parvovirus B19	Ascites (+++), pleural effusions (+)	2.6
21	Parvovirus B19	Ascites (+++)	5.9
22	Cytomegalovirus	Ventriculomegaly (+), echogenic bowel	11.6
22	Cytomegalovirus	Ventriculomegaly (+), echogenic bowel	6.9
20	Cytomegalovirus	IUGR	8.0
32	Cytomegalovirus	Liver calcifications	13.9
22	Cytomegalovirus	Microcephaly, echogenic bowel, IUGR	12.3
17	Cytomegalovirus	Ascites (+++), pleural effusions (++), edema (++)	9.2
20	Cytomegalovirus	Echogenic bowel	9.3
30	Coxsackie B	Ventriculomegaly (+++), IUGR	11.3
22	Toxoplasmosis	Ventriculomegaly (+)	9.5
30	Toxoplasmosis	Ventriculomegaly (+++)	12.7
24	Toxoplasmosis	Ventriculomegaly (+++)	8.6
28	Toxoplasmosis	Ascites (+++), pericardial effusion (++), edema (+)	13.3
31	Toxoplasmosis	Ventriculomegaly (+++), echogenic bowel	7.6
25	*Treponema pallidum*	Ascites (++), hepatomegaly	6.9

+, mild; ++, moderate; +++, severe; IUGR, intrauterine growth restriction; GA, gestational age at presentation; Hb, fetal hemoglobin concentration.

ascites and only 2/14 had a hemoglobin deficit of 4–6 SD.

DISCUSSION

The findings of the present study demonstrate that fetal anemia in non-immune hydrops is associated with a hyperdynamic circulation, manifested by increased fetal MCA-PSV. As in red blood cell isoimmunization, 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 all cases with hemoglobin deficit of 4 SD or more the MCA-PSV was at least 1.5 SD above the normal mean for gestation. Our findings are compatible with those of a previous report on 13 cases of non-immune hydrops, which demonstrated a high association between the fetal hemoglobin deficit and the MCA time-averaged mean velocity[11].

In our study we included only those fetuses with non-immune hydrops that did not have any obvious structural abnormalities to account for the hydrops. Furthermore, we selected cases with moderate or severe ascites, because this is the predominant sonographic finding in anemic hydrops in red blood cell isoimmunization. In the clinical management of such cases it is often necessary to undertake fetal blood sampling and in preparation for the cordocentesis it is useful to know if the fetus is likely to be anemic so that blood can be made available for fetal blood transfusion at the same time.

Parvovirus B19 infection is found in about 5% of all cases of non-immune hydrops but it accounts for about 25% of non-immune hydrops in anatomically normal fetuses[12,13]. In our series the incidence was even higher (44%), presumably because of the inclusion criteria of anatomically normal fetus with moderate to severe ascites. Non-immune hydrops due to parvovirus B19 infection is one of the very few causes of fetal hydrops that can be successfully treated antenatally[14,15]. In this respect, measurement of MCA-PSV is particularly useful in alerting the attending doctor of the presence of anemia and the need for fetal blood transfusion[16,17].

Parvovirus B19 is consistently associated with severe fetal anemia and tense ascites. Other congenital infections, such as cytomegalovirus, toxoplasmosis and *Treponema pallidum*, are also occasionally associated with anemia but this is usually milder than in the case of parvovirus. The commonest congenital infections with adverse effects on the fetus are cytomegalovirus and toxoplasmosis, and the commonest prenatal sonographic findings in these cases are ventriculomegaly or microcephaly and hyperechogenic bowel.

In non-immune hydrops with no obvious structural defects, measurement of MCA-PSV can help identify the subgroup with fetal anemia, where the predominant feature is tense ascites with dilated heart and the most common cause is parvovirus B19 infection. In some of these cases intrauterine blood transfusions can reverse the hydrops and result in healthy live births. In contrast, in hydropic fetuses with no associated anemia and normal MCA-PSV the prognosis is usually poor.

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