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Determination of optimal timing of serial *in-utero* transfusions in red-cell alloimmunization

S. FRISZER*, E. MAISONNEUVE*†, G. MACÉ*, V. CASTAIGNE*†, A. CORTEY†, A. MAILLOUX†, F. PERNOT† and B. CARBONNE*†

**Department of Obstetrics and Gynecology, Hôpital Trousseau, Assistance Publique – Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France; †Centre National de Référence en Hémobiologie Périnatale, Hôpitaux Saint-Antoine et Trousseau, Assistance Publique – Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France*

KEYWORDS: fetal anemia; *in-utero* transfusion; middle cerebral artery peak velocity

ABSTRACT

Objectives *To assess the performance of middle cerebral artery peak systolic velocity (MCA-PSV) and of the expected daily decrease in fetal hemoglobin in determining the timing of serial* in-utero *transfusions (IUT) in red-cell alloimmunization.*

Methods *This was a retrospective study of a continuous series of suspected anemic fetuses undergoing IUT between June 2003 and December 2012. Doppler measurement of MCA-PSV and pre- and post-transfusion hemoglobin levels were recorded at the time of the first, second and third IUT. Receiver–operating characteristics (ROC) curves and negative and positive predictive values of MCA-PSV in the prediction of severe fetal anemia were calculated. The daily decrease of fetal hemoglobin (Hb) between IUTs was calculated. Regression analysis was used to assess the correlation between pretransfusion fetal hemoglobin and MCA-PSV, and between observed and expected (by projection of daily decreases) pretransfusion fetal hemoglobin levels.*

Results *One hundred and eleven fetuses required an IUT, of which 96 and 67 received a second and third IUT, respectively. The area under the ROC curve for MCA-PSV in the prediction of severe fetal anemia was not different for each rank of transfusion. The positive predictive value of MCA-PSV decreased from 75.3% at the first IUT, to 46.7% and 48.8% at the second and third IUTs, respectively, while the negative predictive value for a 1.5-MoM threshold remained high (88.9% at the second and 91.7% at the third IUT). The mean daily decrease in hemoglobin following each transfusion was 0.45, 0.35 and 0.32 g/dL, respectively. There was a persistent linear correlation between fetal hemoglobin and MCA-PSV and between observed and expected fetal hemoglobin levels.*

Conclusions *Both MCA-PSV and projection of daily decrease in hemoglobin are reliable means of diagnosing fetal anemia following previous IUTs. The high negative predictive value of MCA-PSV could allow subsequent IUTs to be postponed in selected cases.* Copyright © *2014 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Non-invasive Doppler measurement of middle cerebral artery peak systolic velocity (MCA-PSV) is used universally now to diagnose fetal anemia and decide when to perform an *in-utero* transfusion (IUT) in cases of severe red-cell alloimmunization[1,2]. An MCA-PSV greater than 1.5 multiples of the median (MoM) for gestational age predicts moderate-to-severe anemia with a sensitivity of 100% at a false positive rate of 12%[2]. However, serial transfusions are often needed to prolong pregnancy and there is debate as to whether MCA-PSV remains a reliable tool to diagnose anemia in previously transfused fetuses[3–5]. Several studies have observed a decreased sensitivity of MCA-PSV in serial transfusions, but these resulted in contradictory conclusions about the way to decide when to perform the next IUT[5,6]. The use of MCA-PSV with a higher cut-off was proposed by Mari *et al.*[5], whereas Scheier *et al.*[6] suggested a decision based on the hemoglobin level reached at the end of the previous IUT and the expected daily decline in hemoglobin. The aim of this study was to assess and compare the performance of measurement of MCA-PSV and the expected hemoglobin decline in the detection of severe anemia in fetuses previously transfused *in utero*. We also aimed to estimate the optimal time interval between two IUTs using the expected daily decline in fetal hemoglobin.

Correspondence to: Prof. B. Carbonne, Chef de Service de Gynécologie Obstétrique, Centre Hospitalier Princesse Grace, 98000 Monaco (e-mail: bruno.carbonne@chpg.mc)

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METHODS

We extracted from our database the records of 111 consecutive anemic fetuses that underwent intrauterine transfusions for red-cell alloimmunization from 1 June 2003 to 31 December 2012. Among these, 96 and 67 fetuses underwent a second and third IUT, respectively. Thirty-six fetuses received more than three transfusions but the data relating to the fourth transfusion onwards were not analyzed because of limited sample size.

The standard procedure for management of severely alloimmunized pregnancies in our national referral center is based on weekly measurement of MCA-PSV. Doppler color flow mapping was used to identify the circle of Willis and MCA. The Doppler gate was placed at the proximal third of the MCA from its origin, with an angle of insonation of less than 15°. Peak systolic velocity was expressed as cm/s and the highest value out of two to three consecutive good quality measurements was recorded. Care was taken to avoid any pressure on the fetal head and the measurement was not performed when fetal body or breathing movements were noted. Two types of ultrasound equipment were used (GE Voluson Expert, Zipf, Austria and Nemio^{Tm} MX, Toshiba Medical Systems, Tokyo, Japan).

Severe immunization was defined as an anti-Rh antibody level > 5 IU/mL or anti-K1 antibody titer ≥ 16. Maternofetal incompatibility was assessed by non-invasive fetal RhD genotyping in cases of anti-D immunization (L'Institut de Biotechnologies Jacques Boy, Reims, France), and by amniocentesis or chorionic villus sampling in most cases of anti-K1 immunization. The decision to sample fetal blood, followed immediately by IUT in most cases, was based on observation of a sharp increase in MCA-PSV above 1.5 MoM, confirmed within 1 to 2 days. Severely anemic fetuses were transfused with adult donor packed red cells, cross-matched with the mother, with a hematocrit above 70–80%. The volume of blood to be transfused was determined by charts established in our referral center (unpubl. data), taking into account the estimated fetal weight, the initial fetal hemoglobin level, the target fetal hemoglobin level and the hematocrit of the packed red cells. Fetal hemoglobin was checked with a HemoCue® Analyzer (Fisher Scientific) when approximately half of the calculated volume had been transfused and, subsequently, by intermittent blood sampling until the end of the procedure to validate the progression of fetal hemoglobin. For the first IUT, the target hemoglobin level was less than four-fold the initial hemoglobin, as suggested by Radunovic *et al.*[7] and no more than 1 MoM of fetal hemoglobin level for gestational age. For subsequent IUTs, the target hemoglobin level was set higher, at *c.*1.2 MoM, to make subsequent transfusions less frequent[8].

Follow-up was based mainly on weekly ultrasound examinations, searching for early symptoms of fetal hydrops and measuring MCA-PSV. Indications for repeating IUT were any of the following: 1) MCA-PSV > 1.5 MoM; 2) possible fetal anemia based on the last post-transfusion hemoglobin value and on an expected daily decline of fetal hemoglobin (*c.* 0.45 g/dL after one IUT and 0.35 g/dL after two or more IUTs); 3) early signs of fetal hydrops. MCA-PSV, pre- and post-transfusion hemoglobin values were noted at each fetal transfusion and expressed as MoM to adjust for gestational age. Severe fetal anemia was defined as hemoglobin < 0.5 MoM for gestational age.

Statistical analysis

Statistical analysis was done using the R language for statistical computing (Version 2.11.0). We determined the detection rate, positive and negative predictive values and false-positive rate of MCA-PSV in the prediction of severe anemia for each rank of transfusion. Receiver–operating characteristics (ROC) curves were constructed and the areas under the curve (AUC) with 95% confidence intervals also were used to compare the performance of MCA-PSV in diagnosing anemia according to the number of previous transfusions (none, one or two) and to determine whether another cut-off of MCA-PSV could increase the performance of the test. Regression analysis was used to assess the correlation between MCA-PSV MoM values and hemoglobin MoM values at the time of each IUT.

The rate of mean daily decrease in fetal hemoglobin was calculated for each rank of transfusion by dividing the difference between the post- and pre-transfusion hemoglobin values of the following IUT by the number of days between transfusions. The 5th and 95th centiles were established in each case. Regression analysis was used to assess the correlation between observed and expected pretransfusion hemoglobin values for each rank of transfusion according to the previously determined rate of daily decrease in fetal hemoglobin. Continuous variables were compared using Student's *t*-test. Categorical variables were compared using chi-square analysis. A P value < 0.05 was considered statistically significant.

RESULTS

The maternal hemolytic antibodies responsible for fetal anemia were anti-D (isolated or together with anti-C and/or anti-E antibodies: 73.9%), anti-K1 (22.5%), anti-c (2.7%) and others (0.9%). The median gestational ages at the time of the first, second and third IUT were 26 + 6 (SD, 4.2; range, 17–35) weeks, 27 + 6 (SD, 3.9; range, 18–34) weeks and 29 + 3 (SD, 3.3; range, 19–34) weeks, respectively. Severe anemia (hemoglobin < 0.5 MoM) was confirmed in 81 (73.0%), 32 (33.3%) and 23 (34.3%) cases at the first, second and third IUT, respectively. Mean (± SD) hemoglobin level was 5.0 ± 1.9 g/dL at the first IUT, 7.2 ± 1.9 g/dL at the second IUT and 7.2 ± 1.6 g/dL at the third IUT. Among the 111 fetuses requiring a first IUT, 29 (26.1%) had sonographic signs of fetal hydrops, all of which had hemoglobin levels < 5.0 g/dL. The mean fetal hemoglobin level at the first IUT was 0.31 (± 0.09) g/dL and 0.57 (± 0.18) g/dL for fetuses with and without signs of hydrops ($P < 10^{-4}$), respectively.

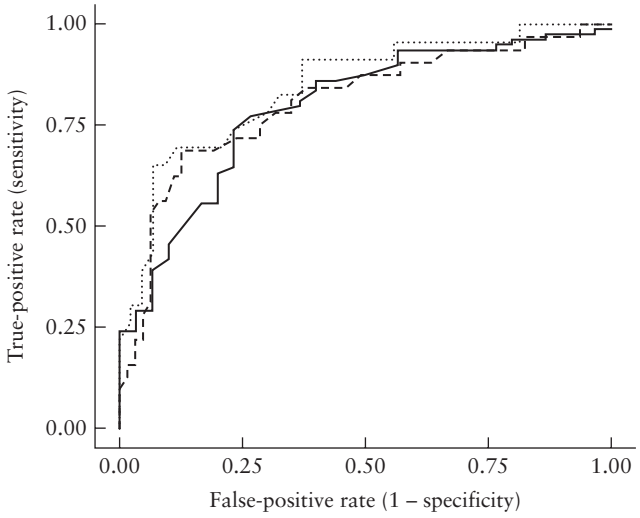

Figure 1 Receiver–operating characteristics (ROC) curves representing detection rates and false-positive rates of middle cerebral artery peak systolic velocity at first (——, AUC = 0.79 (95% CI, 0.70–0.89)), second (- - -, AUC = 0.81 (95% CI, 0.71–0.91)) and third (·····, AUC = 0.85 (95% CI, 0.74–0.95)) *in-utero* blood transfusions. Areas under ROC curves are not statistically significantly different.

Mean gestational age at delivery was 35 + 3 (SD, 2.0) weeks. Poor perinatal outcome was observed in three cases. Two pregnancies were terminated following the sonographic diagnosis of fetal anoxic cerebral lesions confirmed by *in-utero* magnetic resonance imaging[9]. One neonate died in the immediate postnatal period after an emergency Cesarean delivery at 27 weeks' gestation because of persistent fetal bradycardia during an IUT.

The ROC curves of MCA-PSV in the prediction of severe anemia are shown in Figure 1. The AUC was similar for each rank of transfusion: 0.79 (0.70–0.89) at the first IUT, 0.81 (0.71–0.91) at the second IUT and 0.85 (0.74–0.95) at the third IUT. The detection rate of MCA-PSV for a threshold of 1.5 MoM was 96.3%, 94.1% and 90.9% for the first, second and third IUT, respectively. Similarly, the negative predictive value (NPV) remained high, at 88.9% and 91.7%, respectively, after one and two previous IUTs. On the other hand, the PPV at a 1.5-MoM cut-off decreased sharply, from 75.3% to 46.7% and 48.8%, respectively, for the first, second and third IUT. According to the ROC curves, setting the cut-off at 1.73 MoM would afford the best performance of MCA-PSV at the time of the second and third IUT. Using a 1.73 cut-off would increase the PPV from 46.7% to 71% at the second IUT, and from 48.8% to 77.8% at the third IUT (Table 1).

A scatterplot with regression lines between MCA-PSV and pretransfusion fetal hemoglobin values is shown in Figure 2. There was a significant correlation at the time of the first ($r^2 = 0.28$; $P < 10^{-4}$), second ($r^2 = 0.29$; $P < 10^{-4}$) and third IUT ($r^2 = 0.13$; $P = 0.003$).

The mean daily rate of decrease in fetal hemoglobin (5^{th}–95^{th} centile) was 0.45 (0.14–0.78) g/dL/day after one IUT, 0.35 (0.22–0.47) g/dL/day after two IUTs and 0.32 (0.23–0.43) g/dL/day after three IUTs. The theoretical median period before recurrence of severe anemia at each rank of IUT is shown in Figure 3. This period was calculated for a post-IUT hemoglobin level of 1 MoM for the first IUT, and of 1.2 MoM for the following transfusions. In order to avoid any effect of gestational age, the values of hemoglobin decrease were expressed as MoM/day for this calculation. The median time (5^{th}–95^{th} centile) before relapse of severe anemia (< 0.5 MoM hemoglobin) increased progressively with the number of previous transfusions, from 13.2 (7.5–33.3) days after one IUT, to 25 (17.5–41.2) days and 26.9 (18.4–38.9) days after two and three IUTs, respectively. The range was highest after the first IUT and decreased after one and two more transfusions.

Table 1 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of middle cerebral artery peak systolic velocity (MCA-PSV) in the prediction of severe fetal anemia before first, second and third intrauterine blood transfusions

	MCA-PSV cut-off		
Parameter	*1.5 MoM*	*1.73 MoM*	P
First transfusion			
Sensitivity	96.2	74.7	0.0003
Specificity	21.9	75.0	< 0.0001
PPV	75.3	88.1	0.06
NPV	70.0	54.6	0.6
Second transfusion			
Sensitivity	87.5	68.8	0.13
Specificity	50.0	85.9	< 0.0001
PPV	46.7	71.0	0.047
NPV	88.9	84.6	0.77
Third transfusion			
Sensitivity	91.3	60.9	0.038
Specificity	50.0	90.9	< 0.0001
PPV	48.8	77.8	0.07
NPV	91.7	81.6	0.44

Data are given as %. MoM, multiples of the median.

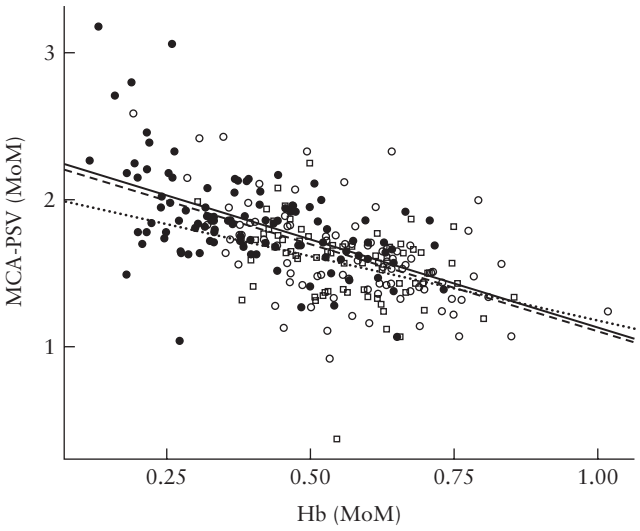

Figure 2 Scatterplot with regression lines of middle cerebral artery peak systolic velocity (MCA-PSV) against pretransfusion fetal hemoglobin (Hb) values, at first (●, ——, $r^2 = 0.28$), second (○, - - -, $r^2 = 0.29$) and third (□, ····· , $r^2 = 0.13$) *in-utero* blood transfusion. MoM, multiples of the median.

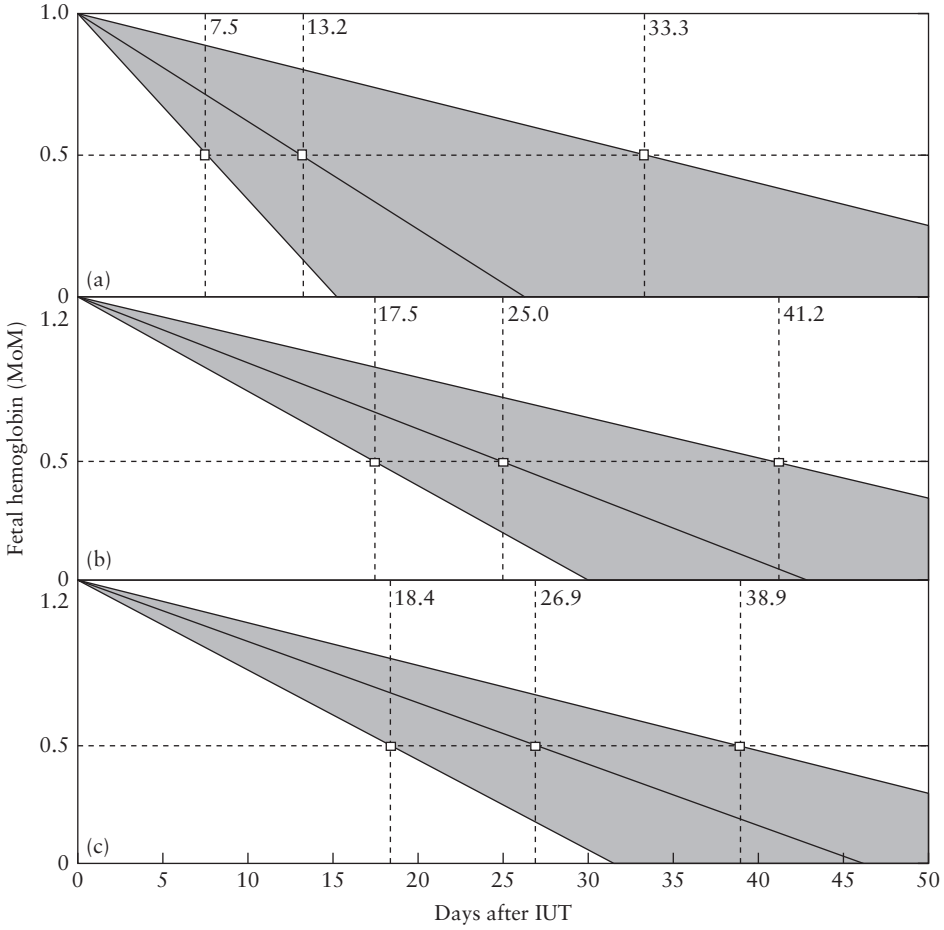

Figure 3 Theoretical projection of median and 5th and 95th centiles of period before recurrence of severe fetal anemia after first (a), second (b) and third (c) *in-utero* blood transfusions (IUT).

A scatterplot with regression lines between observed and expected (by projection of daily decreases) pretransfusion hemoglobin values after one or two previous transfusions is shown in Figure 4. There was a significant correlation at the second ($r^2 = 0.116$; $P = 0.0007$) and the third IUT ($r^2 = 0.106$; $P = 0.007$). Using Bland–Altman analysis (Figure 5), the bias of expected hemoglobin, compared with observed hemoglobin, was only −0.30 g/dL (95% CI, −0.74 to 0.14) at the second IUT and −0.25 g/dL (95% CI, −0.74 to 0.23) at the third IUT. However, the 95% limits of agreement between expected and observed values were large: −4.56 to 3.96 g/dL at the second IUT and −4.14 to 3.63 g/dL at the third IUT.

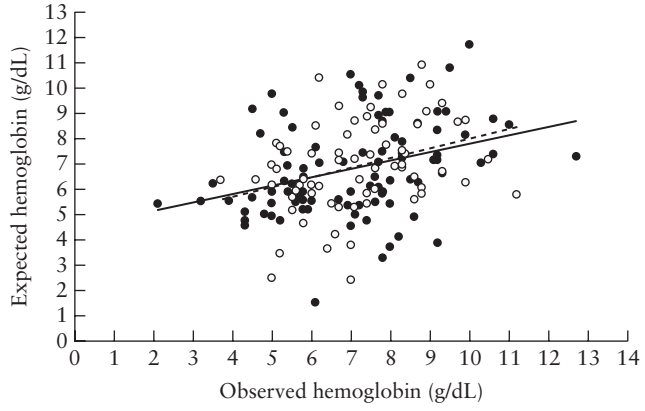

Figure 4 Scatterplot with regression lines of observed against expected (by projection of daily decreases) pretransfusion hemoglobin values after one (●, —; $R^2 = 0.116$) or two (○, - - -; $R^2 = 0.106$) previous transfusions.

DISCUSSION

The timing of repeat *in-utero* transfusions is important because each procedure bears a 1.5–3% risk of fetal morbidity and mortality[10,11]. The overall risk is particularly high in cases of anemia occurring at early gestational ages, for which some five or six serial IUTs may be required during a single pregnancy[12]. Our results, from a large series of serial *in-utero* transfusions, suggest that both MCA-PSV and the mean projected daily decrease in fetal hemoglobin are reliable means of predicting severe anemia following previous IUTs. Yet, regardless of the method used to schedule subsequent IUTs, half of the fetuses will not be severely anemic at the time of a second or third transfusion. The high NPV of MCA-PSV (*c.* 90% in previously transfused fetuses) could allow premature interventions to be avoided in cases erroneously predicted

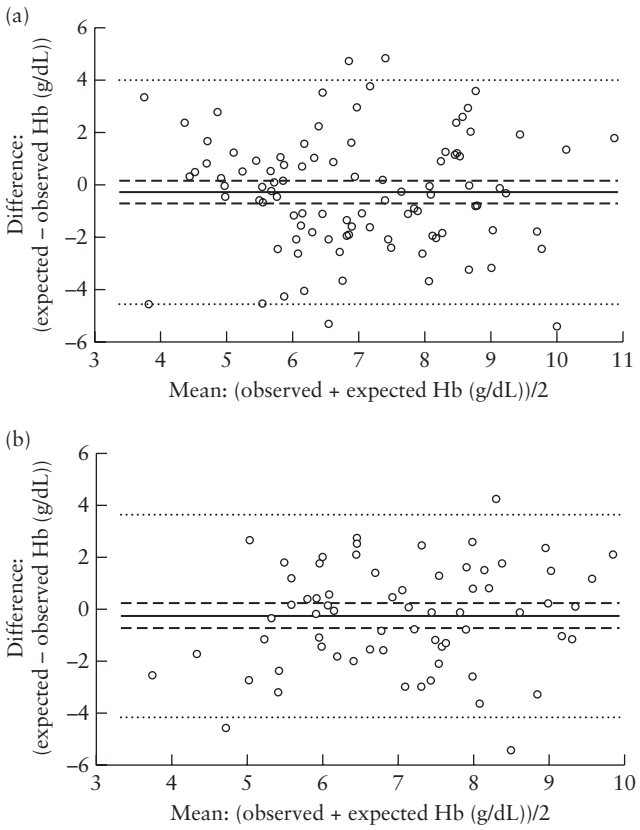

Figure 5 Bland–Altman plots comparing fetal hemoglobin level observed at fetal blood sampling with that expected from daily decrease in fetal hemoglobin at time of second (a) or third (b) *in-utero* blood transfusion. ——, bias; - - -, 95% CI of bias; ·····, 95% limits of agreement.

as severely anemic by the expected daily decrease in hemoglobin.

Among the few studies that have evaluated the timing of repeat IUTs, that by Detti *et al.*[4] concluded that Doppler assessment of MCA-PSV allows detection of severely anemic fetuses after one previous IUT, with 100% sensitivity if the cut-off point is adjusted to 1.69 MoM. In a series of 39 fetuses, Mari *et al.*[5] measured MCA-PSV before a third IUT and found a linear correlation between fetal hemoglobin and MCA-PSV. They observed that, had they used a cut-off greater than 1.5 MoM for timing of the transfusion, five cases of moderate-to-severe anemia would have been missed. Scheier *et al.*[6] determined that MCA-PSV was predictive of severe anemia at a second IUT (detection rate, 95%; false-positive rate, 37%), but not at a third. For fetuses previously transfused twice, they suggested that timing of the subsequent IUT be based on the last post-transfusion hemoglobin value and an expected rate of fetal hemoglobin decrease of 0.3 g/dL/day. One of our aims being a reduction in the number of invasive procedures, we believe that evaluating the PPV of MCA-PSV rather than its detection rate is a more pertinent approach to assessing the performance of this test.

The reasons for a decreased predictive value of MCA-PSV following IUT are not well established. It has been suggested that blood viscosity following transfusion of adult red cells could be lower than that of fetal blood. Indeed, adult red cells are smaller and show lower deformability compared to fetal red cells[13–15]. Other factors such as fetal hemoglobin content and pCO_2 may directly affect cerebral vascular regulation and account for increases in MCA-PSV[16].

In our experience, the overall performance of MCA-PSV in predicting severe anemia, as assessed by AUCs, was almost unchanged from the first to the third IUT, suggesting that MCA-PSV could be used for subsequent transfusions in the same way it was used for the first. However, the PPV for a threshold of 1.5 MoM decreased dramatically from the first IUT (75.3%) to the second (46.7%) and third IUT (48.8%). This means that, if the decision to perform a second or a third IUT were based solely on MCA-PSV, fewer than half of these fetuses would be found to be severely anemic. This rather low PPV may be explained, at least in part, by the 0.5-MoM cut-off used to define severe anemia in our study. This cut-off, lower than that in previous studies, was chosen for the following reasons. First, fetal hydrops is rarely observed at hemoglobin levels > 5.0 g/dL, which, according to the original data of Mari *et al.*[2], corresponds to hemoglobin concentrations of 0.47 MoM at 18 weeks and 0.36 MoM at 37 weeks. A threshold of 0.5 MoM thus allowed us to identify correctly fetuses at risk of severe complications, without observing any case or recurrence of fetal hydrops. Second, the definition of severe anemia as a hemoglobin deficit ≥ 6.0 g/dL, used by Scheier *et al.*[6], does not take into account the physiological evolution of hemoglobin levels during pregnancy and corresponds to fetal hemoglobin levels > 5.0 g/dL after 20 weeks' gestation. Based on ROC curves, we determined that a cut-off of 1.73 MoM would be the best compromise at the time of the second and third IUT, with a PPV reaching up to 71% and 77.8%, respectively. Yet, as did Mari *et al.*[5], we found that, based only on MCA-PSV with this increased cut-off, 11 cases of severe anemia would have been missed.

The optimal timing for the second, third or fourth IUT can also be anticipated from the hemoglobin concentration reached at the end of the previous transfusion and from the expected daily decrease in hemoglobin level. We determined that the median time before the fetus becomes severely anemic again (< 0.5 MoM) increases with the rank of IUT, from 13 to 25 and 27 days, respectively, after one, two and three IUTs. There are two reasons for the lower time interval following the first IUT. First, there is a higher daily decrease in hemoglobin following one IUT (0.45 g/dL) than that following two (0.35 g/dL) or three IUTs (0.32 g/dL). The higher decrease in hemoglobin following the first transfusion is thought to be related to remaining fetal red cells and thus persistent hemolysis. The second reason is the fact that the target hemoglobin rate for the first IUT (1 MoM) is lower than that for the next IUTs (1.2 MoM) in order to avoid a dangerously large increase in fetal hematocrit, which is associated with a risk of fetal death, especially in cases of fetal hydrops[7]. At subsequent IUTs, it has been shown previously that the

post-transfusion hemoglobin concentration can be safely increased above normal values for gestational age (1.2 MoM) to reduce the number of IUTs to be performed[8].

Whatever combination of the two methods is used, weekly or twice-weekly ultrasound assessment should be maintained to detect early signs of fetal hydrops, especially when an early rise in MCA-PSV is observed following IUT. Using this algorithm, even though a limited number of fetuses had hemoglobin levels < 0.5 MoM at the time of IUT, no case of severe hydrops or anemia-related fetal death occurred in the interval between two IUTs.

In conclusion, we suggest that severe fetal anemia can be monitored using both MCA-PSV and the mean projected daily decrease in fetal hemoglobin in cases of serial transfusions. However, MCA-PSV should be monitored systematically before cordocentesis and the transfusion can be safely postponed if the value is < 1.5 MoM. Indeed, for the many women living in places remote from referral centers, this approach has the pragmatic advantage of allowing subsequent IUTs to be scheduled with the patient's awareness that the procedure may be postponed safely.

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