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Peak systolic velocity of fetal middle cerebral artery to predict anemia in Red Cell Alloimmunization in un-transfused and transfused fetuses

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ABSTRACT

Abstract objective: To assess the accuracy of middle cerebral artery peak systolic velocity (MCA-PSV) in prediction of severe fetal anemia resulting from Red Cell Alloimmunization (Anti-D) in un-transfused and transfused fetuses. In addition to comparing the accuracy of MCA-PSV and the estimation of the daily decline of fetal hemoglobin (Hb), to determine the appropriate time of subsequent transfusions.

Study design: This was a retrospective study of a series of 84 anaemic fetuses due to Red Cell alloimmunization. During each in-utero transfusion session, measurements of (1)MCA-PSV, (2)pre- and (3)post-transfusion Hb levels were recorded. Receiveroperating characteristics (ROC) curves, negative and positive predictive values of MCA-PSV in predicting severe fetal anemia were calculated. Regression analysis assesses the correlation between fetal HB and MCA-PSV, and between observed and expected fetal hemoglobin levels.

Results: Eighty four anemic fetuses were included in the study and had an in-utero transfusion. The positive predictive value (PPV) of MCAPSV decreased sharply from 86.0 % at the first IUT, to 52.0 % and 52.1 % at the second and third IUTs respectively. According to the ROC curves, setting the cut-off at 1.70 MoM would provide the best performance of MCA-PSV with respect to the timing of the second and third IUT. Setting a higher threshold of 1.70 MoM for the 2nd and 3rd transfusions would increase the PPV from 52.0 % to 96.4 % at the second IUT, and from 52.1%–99.8 % at the third IUT.

Conclusion: In this study we suggest that a higher MCA-PSV (MoM 1.7 in compared to 1.5MOM) can accurately predict the recurrence of severe fetal anemia requiring serial IUTs. In transfused fetuses, MCAPSV accuracy to detect severe anemia decline slightly with increase number of IUT. In addition to that, the mean projected daily decrease in fetal hemoglobin has a similar accuracy to MCA-PSV in predicting moderate to severe fetal anemia.

Introduction

Red cell alloimmunization is still a serious pregnancy complication occurring at a rate of 0.6–0.9 per 1000 live births [1,2]. The severity of this disorder is attributed to being responsible for hemolytic fetal anemia, cardiac decompensation, subsequent fetal hydrops and eventually perinatal death [3]. If the fetus survives, persistent hemolysis may lead to severe neonatal jaundice and irreversible brain injury [4].

Despite the existence of effective prophylaxis through the use of anti-Rh immunoglobin, cases of alloimmunization continue to

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occur [5]; mainly because of unrecognized fetal-maternal hemorrhage, inadequate prophylaxis and the presence of more than 40 immunizing antigens for which there is not yet effective immune-prophylaxis [6–8]. Therefore, effective detection of the degree of anemia is essential because the prognosis of this condition has been completely modified and improved by intrauterine transfusion (IUT) procedures which is one of the most successful therapies in fetal medicine [9,10].

Initially, management involves invasive procedures including cordocentesis, to assess the degree of fetal anemia and determine the optimal timing of IUT [11–14]. These procedures may require repetitions with associated complications such as infection, feto-maternal hemorrhage which can increase antibody levels, fetal bradycardia, premature rupture of membrane, preterm labor and fetal loss [15–17].

In the last 15 years several studies have established the association of fetal anemia with increased blood flow velocities (hyperdynamic circulation) due to fetal compensations by hemodynamic adaptations. Subsequently, Mari et al. suggested that fetal middle cerebral artery peak systolic velocity (MCA-PSV) measurements could be used in management of red cell allo-immunized pregnancies to determine the proper time for intervention either through early delivery or fetal blood transfusion [18–20]. Doppler measurements of MCA-PSV higher than 1.5 multiples of the median (MoM) for the gestational age have the ability to predict moderate-to-severe fetal anemia requiring IUT with 100 % sensitivity and a relatively low false-positive rate (FPR) of 12 % [21]; thus invasive procedures could be avoided or postponed in more than 80 % of iso-immunized pregnancies [21,22].

This technique has both a high sensitivity and specificity for the first IUT, however the timing of subsequent transfusions remains difficult [23,24]. Since repeated transfusions are often required to prolong pregnancy, this results in a debate if MCA-PSV still remains a reliable tool in diagnosing anemia in fetuses receiving previous transfusions [21,25,26].

Recently, there have been several studies reporting a reduced sensitivity of MCA-PSV in fetuses receiving repeated transfusions. This has resulted in conflicting conclusions regarding the optimal method to decide the exact timing of the subsequent IUT procedure [27,28]. After an initial transfusion, using a cut-off for MCA-PSV higher than 1.5 MoM for diagnosing fetal anemia requiring subsequent IUT was proposed by several authors [18,25,26]. On the other hand, other authors including Scheier et al. recommend a decision of timing subsequent procedures based on the hemoglobin level at the end of the previous transfusion and on the expected daily decrease in fetal hemoglobin (Hb) [27]. Small number of studies have compared MCA-PSV to Hb decline rates in the determining the optimum procedure to be performed.

Materials and methods

Aim of the work

To assess the accuracy of middle cerebral artery peak systolic velocity (MCA-PSV) in prediction of severe fetal anemia resulting from Red Cell Alloimmunization in un-transfused and transfused fetuses. In addition to comparing the accuracy of MCA-PSV and the estimation of the daily decline of fetal hemoglobin (Hb), to determine the appropriate time of subsequent transfusions.

Study subjects

This single-center retrospective observational study was conducted from January 2015 to September 2019 and included all cases of patients with follow-ups or referrals to (Fetal Medicine Unit) Al-Kasr Al-Aini Maternity Hospital, Cairo University (Egypt) in which at least two IUTs were performed for severe fetal anemia as part of maternal red blood cell (RBC) alloimmunization. This study included 84 anemic fetuses, with gestational ages ranging from 20 to 34weeks gestation (calculated from the reported last menstrual period or adjusted to first-trimester crown–rump length measurements) that underwent intrauterine transfusions for red-cell alloimmunization. Among these, 82 and 57 fetuses underwent a second and third IUT, respectively. Twenty-three received more than three transfusions but the data relating to the fourth transfusion onwards were not analyzed because of limited sample size. We excluded fetuses with known chromosomal anomaly.

Doppler studies

The standard protocol for themanagement of severely allo-immunized pregnancies in our center was based on weekly measurements of MCA-PSV. The technique to measure MCA-PSV was performed as recommended by the International Society of Ultrasound in Obstetrics and Gynecology [29]. Recordings were obtained during the absence of fetal breathing, fetal body movements, and if necessary during temporary maternal breath hold. An axial section of the brain, including the thalami and the sphenoid bone wings, was obtained and magnified. Color flow mapping was used to identify the circle of Willis and the proximal MCA. The pulsed-wave Doppler gate was then be placed at the proximal third of the MCA, close to its origin in the internal carotid artery. The angle between the ultrasound beam and the direction of blood flow was kept as close as possible to 0 (less than 15 degrees). Care was taken to avoid any unnecessary pressure on the fetal head. At least three and fewer than 10 consecutive waveforms were recorded. The highest point of the waveform is considered as the PSV (cm/s). The MCA PSV was measured by autotrace. The mechanical and thermal indices were kept below 1.

Ultrasound equipments used were GE Vlouson E10, Zipf, Austria ultrasound machines with RM6C abdominal convex volume probe with active matrix array, 1–7 MHZ

The study was exclusive to women with a hemolytic antibody concentration of >15 IU/mL, as it has been previously demonstrated that lower levels are not associated with severe fetal anemia [30].

The decision to sample fetal blood, followed immediately by IUT was based on the detection of an increase in MCA-PSV above 1.5 MoM [22]. Severely anemic fetuses were transfused with O -ve packed red blood cells, cross-matched with the maternal blood, cytomegalovirus-negative (filtered) and irradiated with a hematocrit between 75–80 %. The IUT procedure was performed by AE (Professor of fetal medicine and has Diploma of Fetal medicine from Fetal medicine Foundation).

Ultrasound examinations were performed during weekly follow-ups, searching for early signs fetal anemia or fetal hydrops and measuring MCA-PSV. Indications for repeating IUT were based on an increase in MCA-PSV>1.5 MoM or de novo identification of ascites and/or hydrops regardless of the MCA-PSV value [34].

At each transfusion MCA-PSV, pre- and post-transfusion hemoglobin values were noted and expressed as MoM to adjust for gestational age. The reference standard was the diagnosis of fetal anemia by blood sampling. The thresholds for assessing anemia were those of Mari and colleagues [22]: moderate anemia if less than 0.65 MoM and severe anemia if less than 0.55 MoM regardless of gestational age. The IUTs were conducted up to 34 gestational weeks; beyond this gestational age, labor was induced when MCA-PSV exceeded 1.5 MoM. If measurements remained approximately or less than 1 MoM, birth was scheduled at 36 weeks with induction of labor or cesarean delivery if vaginal birth

was not possible. At birth, the neonatal cord blood was sampled to determine Hb and/or Hct.

Statistical analysis

Statistical analysis was performed using the R language for statistical computing (Version 2.11.0). We determined positive predictive values (PPV), negative predictive values (NPV), false-positive rate and detection rates of MCA-PSV in predicting severe fetal anemia for each rank of transfusion. Receiver–operating characteristics (ROC) curves were constructed and the areas under the curve (AUC) with 95 % confidence intervals were utilized to compare the performance of MCA-PSV in detecting severe fetal anemia with respect to the number of previous transfusions (none, one or two) and to decide if another MCA-PSV cut-off value could increase the test performance. Regression analysis was utilized to evaluate the correlation between the values of MCA-PSV MoM and fetal hemoglobin MoM at the time of each IUT. The rate of mean daily decline in fetal hemoglobin was calculated for each rank of transfusion. This was done by dividing the difference between the post- and pre-transfusion hemoglobin values of the following IUT by the number of days between transfusions; additionally, the 5th and 95th centiles were established for every case.

Regression analysis was utilized to evaluate the correlation between observed and expected pre-transfusion fetal Hb values for each rank of transfusion according to the previously determined rate of daily decrease in fetal hemoglobin. Student's *t*-test was used to compare continuous variables; chi-square analysis was used to compare categorial variables. A P value<0.05 was considered statistically significant.

Results

Mean maternal age of the women was 28.25 ± 3.6 years; mean gestational ages at the time of the 1st, 2nd and 3rd transfusions were 24.3 ± 2.36 weeks, 28.22 ± 1.08 weeks and 30.24 ± 1.54 weeks respectively. The mean (± SD) Hb level was 5.92 ± 1.35 g/dL at the 1 st IUT, 8.79 ± 1.48 g/dL at the second IUT and 8.0 ± 1.22 at the third IUT. Severe fetal anemia (hemoglobin<0.55 MoM) was confirmed in 80/84 fetuses (95.2 %) during the first IUT, in 65/82 fetuses)(79.2 %) during the second IUT, and in 23/57 fetuses (40 %) during the third IUT. Sonographic signs of hydrops were present before the first IUT in 28 (29.5 %) of cases; hemoglobin levels in all cases with hydrops were <5.0 g/dL. The mean hemoglobin level in fetuses with hydrops at the time of 1st transfusion was significantly lower than in non-hydropic fetuses, 5.2 g/ dL versus 7.3 g/dL (p < 0.001), respectively.

Mean gestational age at the time of delivery was 35.78 (SD, 3.77) weeks. Adverse perinatal outcome was observed in four cases with hydrops complicated by IUFD occurring at 23, 26, 27, 29 weeks respectively. Moreover, three neonates died postnatally after an emergency Cesarean delivery at 30, 32, 33 weeks' gestation following persistent fetal bradycardia during the transfusion process; the complications of prematurity were compounded by sepsis and multi-organ failure.

ROC curves for the performance of MCA-PSV in predicting severe fetal anemia are demonstrated in Fig. 1. The areas under the ROC curve for MCA-PSV in predicting severe fetal anemia was almost similar for each rank of transfusion: 0.83 (0.76−0.90) at the 1st transfusion; 0.92 (0.85–0.97) at the second transfusion and 0.93 (0.87–0.99) at the third transfusion. MCA- PSV using a threshold of 1.5 MoM had a sensitivity of 96.8 %, 89.8 %, 92.5 % in detecting severe anemia for the first, second and third IUT, respectively. The negative predictive value (NPV) for the threshold of 1.5MoM remained high, at 91.0 % and 93.5 %, respectively, after one and two previous transfusions; on the other hand, the positive

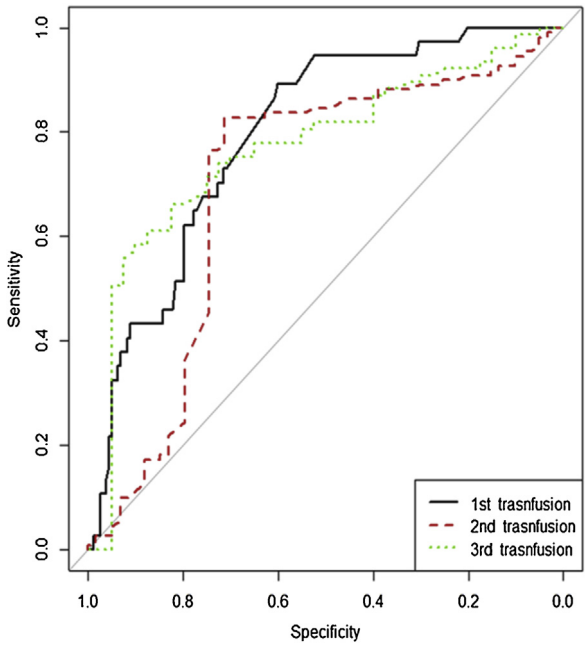

Fig. 1. (ROC) curves of the performance of MCA-PSV at 1st (AUC = 0.83 (95 % CI, 0.76–0.90), 2nd (AUC = 0.92 (95 % CI, 0.85–0.97) and 3rd (AUC = 0.93 (95 % CI, 0.87–0.99)) fetal blood transfusions. Areas under ROC curves are almost the same and are not statistically significantly different.

predictive value (PPV) decreased sharply from 86.0 % at the first IUT, to 52.0 % and 52.1 % at the second and third IUTs.

According to the ROC curves, setting the cut-off at 1.70 MoM would provide the best performance of MCA-PSV with respect to the timing of the second and third IUT. Setting a higher threshold of 1.70 MoM for the 2nd and 3rd transfusions would increase the PPV from 52.0 % to 96.4 % at the second IUT, and from 52.1%–99.8 % at the third IUT (Table 1). Consequently, the relationships between the MoM of MCA-PSV and the MoM of hemoglobin concentration were evaluated by the best fitting regression model.

A scatterplot with regression lines between the MCA-PSV and the values of pretransfusion fetal Hb is demonstrated in Fig. 2. It shows a significant correlation at the time of each rank of transfusion; at the first (r2 = 0.56; P < 0.001), second (r2 = 0.30; P < 0.001) and third IUT (r2 = 0.28; P = 0.001). With respect to the detection of severe fetal anemia through analysis of the Hb decrease levels; the actual mean daily rate of fetal hemoglobin decrease (5th–95th centile) was 0.42 (0.11–0.75) g/dL/day following one transfusion, 0.32 (0.19–0.44) g/dL/day following two

Table 1
MCA-PSV Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in predicting severe fetal anemia before 1st, 2nd and 3rd intrauterine fetal blood transfusions.

		MCA PSV MoM		
		1.5	1.7	P value
1st transfusion	Sensitivity	96.8 %	75.3 %	<0.001
	Specificity	32.4 %	75.7 %	<0.001
	PPV	86.0 %	93.0 %	0.054
	NPV	70.6 %	41.8 %	<0.001
2nd transfusion	Sensitivity	89.8 %	89.8 %	1
	Specificity	55.5 %	98.2 %	<0.001
	PPV	52.0 %	96.4 %	<0.001
	NPV	91.0 %	94.7 %	0.365
3rd transfusion	Sensitivity	92.5 %	87.5 %	0.712
	Specificity	55.8 %	99.6 %	<0.001
	PPV	52.1 %	99.8 %	<0.001
	NPV	93.5 %	93.9 %	1

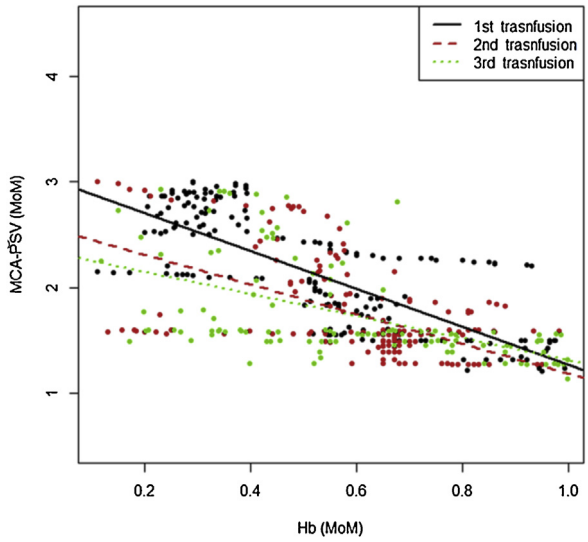

Fig. 2. Scatterplot with regression lines of (MCA-PSV) against pretransfusion fetal hemoglobin (Hb) values, at 1 st (*r*2 = 0.56), 2nd (r2 = 0.30) and 3rd (r2 = 0.28) fetal blood transfusion. MoM, multiples of the median.

transfusions and 0.29 (0.20–0.40) g/dL/day following three transfusions.

The theoretical median time before the repeated occurrence of severe anemia at each rank of IUT was calculated for a post-transfusion Hb level of 1 MoM for the initial IUT, and of 1.2 MoM for subsequent IUT. The values of Hb decline were expressed as MoM for this calculation in order to eliminate the impact of gestational age. The median time (5th–95th centile) before the recurrence of severe anemia increased with respect to the number of previous transfusions, from 11.2 (6.5–31.2) days after one IUT, to 22.1 (15.4–39.3) days and 25.6 (16.2–35.7) days after two and three IUTs, respectively. The highest range was reported following the 1st transfusion; and decreased after one and two more transfusions. A scatterplot with regression lines between the observed and the expected (by an estimate of daily decreases) pretransfusion fetal Hb levels after one or two previous IUT is demonstrated in Fig. 3; there was a significant correlation present at both the second ($r2$ = 0.751; $P \leq 0.0001$) and the third IUT ($r2$ = 0.824 ; $P \leq 0.001$).

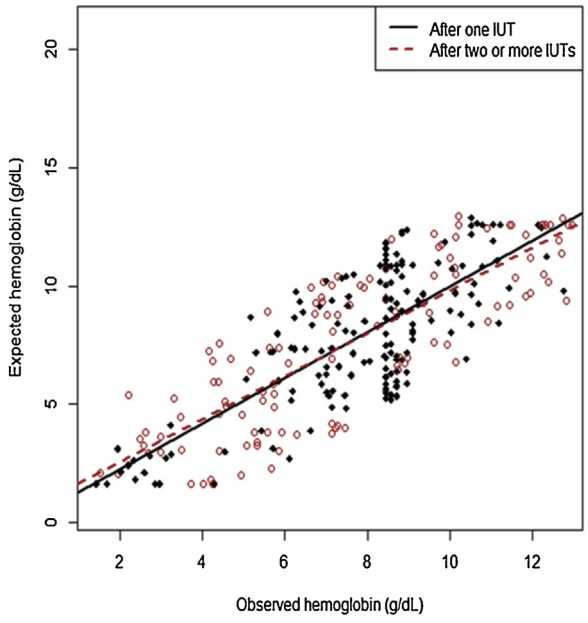

Fig. 3. Scatterplot with regression lines of observed against expected pretransfusion hemoglobin values after one (*R*2 = 0.75) or two (R2 = 0.82) previous transfusions.

Discussion

Principal findings of the study

This is a large series of IUT cases. Our results, suggested that MCA-PSV with a threshold higher than 1.5MoM is a reliable method for the prediction of severe anemia in RH isoimmunization fetuses. Additionally, the study shows a decline in PPV of MCA_PSV after repeated IUT.

The expected daily decline method to predict fetal anemia showed no statistical significance when compared to MCA-PSV. The high NPV of MCA-PSV could allow the avoidance of invasive interventions in cases falsely expected as having severe anemia by the expected daily decrease in hemoglobin. However, regardless of the tool utilized in scheduling subsequent transfusions, at the time of both a 2nd and 3rd IUTs; almost half of the fetuses will not have severe anemia.

Comparison with previous studies

The detection of anemia by MCA-PSV measurements differs according to the number of the previous IUTs performed. In our series, the sensitivity of PSV is 96.8 % with a positive predictive value of 86.0 % prior to any IUT. These results on un-transfused fetuses are in resemblance to those described by Mari et al. [18] who described a MCA-PSV sensitivity of 100 % and PPV of 88 % in the prediction of fetal anemia. More recently, Friszer et al. [26]; Ghesquie`re and colleagues [34] described similarly high values of sensitivity and PPV.

In this study, we observed that following the first transfusion there is still high sensitivity of MCA-PSV but a reduced PPV, down to 52.0 % following the 1st IUT and 52.1 % following the 2nd IUT. Similarly, in the study performed by Friszer et al. [26] there was still a good remaining sensitivity (96.2, 87.5, and 91.3 % for the 1st, 2nd and 3rd IUTs) but sharply declined PPV following the 1st IUT (75.3, 46.7, and 48.8 % for the 1st, 2nd and 3rd IUTs). This decline of the PPV is attributed to the decrease in the number of anemic fetuses.

In our study, we confirmed severe fetal anemia in 79.2 % during the second IUT, and in 40 % during the third IUT. Similarly, in the study performed by Ghesquie`re et al. [34], 78.9 % and 40 % of fetuses had anemia at the time of the 2nd IUT and 3rd IUT respectively. Additionally, Friszer et al. [26] described that 33.3 % and 34.3 % of fetuses in their study were truly anemic during the second and 3rd IUT respectively. This means that depending only on MCA-PSV measurements at a threshold of 1.5 MoM for timing the 2nd and 3rd IUT will increase the risk of transfusing non-anemic fetuses with its associated complications [14,32,35–37].

Few studies have evaluated the role of doppler assessment of MCA in the timing of repeat IUTs. Initially, Mari et al. [22] measured MCA-PSV in a series of 39 fetuses before the third IUT; in their study, although a linear correlation was found between fetal hemoglobin and MCA-PSV; a threshold value of 1.5 MoM failed to detect 5 of 12 cases of moderate to- severe anemia. however, they did not have a sufficient sample size to determine a new threshold for detecting all cases of anemia that required a third transfusion. Deren and Onderoglu [23] reported that the detection of all cases with severe anemia by Doppler measurements of MCA-PSV is achieved with a false-positive rate (FPR) of 9.1 % in fetuses that had not been previously transfused, compared with 21.4 % in fetuses that had previously received between 1 and 4 intrauterine transfusions.

Detti et al. [25] suggested that a higher threshold of MCA-PSV>1.69 MoM would correctly detect all fetuses with severe anemia following a single IUT, with a 100 % sensitivity and low FPR of 6%. Similarly, the Society for Maternal- Fetal Medicine recommended higher threshold (MoM > 1.69) after an initial transfusion for the diagnosis of severe fetal anemia necessitating a second transfusion [16]. Additionally, with a threshold at 1.73 MoM, Friszer et al. [26] detected an improvement in the PPV of MCA-PSV doppler measurements (71 % in the 2nd IUT and 77.8 % in the 3rd IUT).

A meta analysis by MARTINEZ-PORTILLA et al. in 2019, concluded that MCA-PSV shows moderate accuracy for the prediction of moderate–severe anemia in untransfused fetuses (86 % sensitivity and 71 % specificity), and that accuracy declines with increasing number of intrauterine transfusions. This correlates with our results. The metaanalysis included 695 fetuses over the duration of 10 years [38].

The authors concluded that using MVA-PSV of 1.5 MOM means that about 30 % of non-anemic fetuses would undergo unnecessary IUT, and about 20 % of anemic fetuses would be missed. This supports our recomendation of using MCA-PSV 1.7MOM and weekly measurements. Also, this prompts researchers to try to incorporate other methods of predicting fetal anemia especially after IUT [38].

On the other hand, in the study by Scheier et al. [27] it was found that both Doppler measurements of MCA-PSV and the estimated Hb concentration (from the measured post-transfusion Hb level after the first transfusion with the assumption that the rate of decrease in fetal Hb is 0.4 g/dL per day) has similar performance in the prediction of fetal anemia in patients receiving one previous IUT. Meanwhile, patients who had already received 2 IUTs, logistic regression analysis revealed that MCA-PSV is not a significant predictor of moderate and/or severe fetal anemia. The only significant prediction of fetal anemia is achieved from the estimation of the fetal Hb concentration through measurement of post-transfusion Hb level after the second transfusion with the assumption that the rate of decrease in fetal Hb is 0.3 g/dL per day. Moreover, a recent study by Ghesqui`ere L et al. [34] has indicated that, particularly after second IUTs, several formulae to estimate red-cell destruction are more accurate than MCA- PSV. They also concluded that among the various Hb decrease rate calculation formulae, the formula described by Garabedian et al. [32] with an expected daily decline of fetal hemoglobin of 0.40 g/dL after one IUT and 0.34 g/dL after two or more IUTs seems to be the best, with values that are nearly identical to the actual Hb decrease levels as observed in their series.

As one of the aims is a reduction in the number of invasive procedures, it is clearly evident through the assessment of the performance of MCA-PSV, that the evaluation of PPV is a more relevant approach than its detection rate. The decreasing predictive values of MCA-PSV in detecting severe fetal anemia following IUTs can be described by changes in fetal blood viscosity due to the presence of different amounts of adult blood in the fetal circulation. Adult red cells as compared to fetal blood cells are smaller and less rigid, but have increased erythrocyte aggregation resulting in lower viscosity [10,39–42]. Other contributing factors, such as fetal hemoglobin content and pCO2 may have a direct effect on cerebral vascular regulation with a possible increase in MCA-PSV. The shift from fetal to adult hemoglobin results in decreasing the delivery of oxygen at the tissue level due to the variations in the oxygen disassociation curves of these 2 hemoglobins [16,19,41]. This is supported by recent findings indicating that the peak MSA-PSV is related to both fetal Hb and oxygen content [17,21].

In this study, the PPV for MCA-PSV threshold of 1.5 MoM decreased significantly from 86.0 % at the 1st IUT to 52.0 % and 52.1 at the 2nd and 3rd IUT respectively. Similarly, in the study by Friszer et al. [26] the positive predictive value for a threshold of 1.5 MoM decreased from the 1st (75.3 %) to the 2nd (46.7 %) and 3rd (48.8 %) IUTs. Subsequently, depending only on MCA-PSV to perform a second or a third transfusion, less than half of these fetuses would be found to have severe anemia. This observed relatively low PPV may be described, by the 0.5-MoM cut-off used in the definition of severe anemia in the present study. In this study a lower cut-off than previous studies was chosen because of the extremely rare detection of fetal hydrops at hemoglobin levels>5.0 g/dL, which, according to Mari et al. [18] is correspondent to hemoglobin concentrations of 0.47 MoM at 18 weeks and 0.36 MoM at 37 weeks. Therefore, a threshold of 0.5MoM would allow the correct detection of anemic fetuses without observing the occurrence or recurrence of hydrops. Additionally, the dependence on the definition of severe anemia as a hemoglobin deficit≥6.0 g/dL described by Scheier et al. [27] doesn't take into account the physiological changes of Hb levels throughout gestation that corresponds to fetal Hb levels>5.0 g/dL after 20 weeks' gestation. In this study, based on ROC curves, it was discovered that a cut-off of 1.70 MoM would be the best threshold at the time of the 2nd and 3rd transfusions, with a positive predictive value reaching 96.4 % and 99.8 %, respectively.

The proper timing for the both the 2nd and 3rd transfusions can also be anticipated from the concentration of fetal Hb reached at the end of the previous IUT in addition to the expected daily decline in Hb levels [24]. In our study, it was found that the median time prior to the recurrence of severe fetal anemia increases with the rank of transfusion, from 11 to 22 and 25 days following 1st, 2nd and 3rd intrauterine transfusions respectively. One possible explanation for declining time intervals following the first IUT, is that it may be attributed to a higher daily decline in fetal Hb levels after one IUT (0.45 g/dL) than that following two (0.35 g/dL) or three IUTs (0.32 g/dL); which may be attributed to the persistent hemolysis of the remaining fetal red cells [43,26].

Strengths and limitations

The strengths of our study include: Firstly, a relatively large case series of women undergoing intrauterine blood transfusion. Secondly, all scans were performed by trained sonographers who carried out the measurements according to a standardized protocol.

The limitation of our study is that it was a retrospective study.

In conclusion: In this study we suggest that MCA-PSV with a higher recommended threshold for the diagnosis of fetal anemia (MoM > 1.7) can accurately predict the recurrence of severe fetal anemia requiring serial IUTs and give an accurate assessment of when to re-sample the fetus. In addition to this, the mean projected daily decrease in fetal hemoglobin has a similar accuracy to predict moderate to severe fetal anemia.

Recommendations

More research is needed to examine new techniques to predict severe anemia in transfused fetuses or using different thresholds of MCA-PSV to predict severe anemia in transfused fetuses.

In transfused fetuses, the accuracy of MCA-PSV to predict severe anemia is declining and this has to be put in consideration when considering repeat IUT.

Close monitoring of anemic fetuses should be performed through weekly or twice-weekly ultrasound assessment to detect the early signs of fetal hydrops. This will subsequently prevent the occurrence of cases of severe hydrops or anemia-related fetal death in the interval between two IUTs.

Declaration of Competing Interest

The authors report no declarations of interest.

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