Original Article

Prediction of Fetal Anemia by Different Thresholds of MCA-PSV and Delta-OD in First and Second Intrauterine Transfusions

Fatemeh Rahimi-Sharbaf MD•[1], Mamak Shariat MD[2], Fatemeh Mirzaie MD[1], Padideh Dehghan MD[2], Ebrahim Dastgardy MD[3], Khadijeh Adabi MD[1]

Abstract

Background: Our aim was to compare different thresholds of middle cerebral artery peak systolic velocity (MCA-PSV) and amniotic fluid delta optical density (Delta-OD) with fetal hemoglobin (Hb) during first and second intrauterine transfusions (IUT).

Methods: We determined serial MCA-PSV and Delta-OD in 27 red blood cell alloimmunized fetuses who needed IUT. Before the second IUT, MCA-PSV was measured. The sensitivity and specificity of MCA-PSV and Delta-OD were calculated and compared with fetal hemoglobin levels.

Results: From 27 fetuses, first time IUT MCA-PSV with a normal median value (MOM) cutoff of > 1.29 detected 60% of the moderate and 100% of the severe anemia cases. MCA-PSV of MOM > 1.5 detected none of the moderate and 93% of severe anemia cases. Delta-OD detected 50% of moderate anemic and 80% of severe anemic cases. At the second IUT, 91% of severe anemia cases were confirmed by MCA-PSV with MOM > 1.5 whereas MCA-PSV with MOM > 1.29 confirmed all cases. One case of moderate anemia was detected by MCA-PSV of MOM > 1.29 and none were detected by MCA-PSV with MOM > 1.5.

Conclusion: Different thresholds of MCA-PSV have higher sensitivity and specificity for detecting moderate and severe fetal anemia compared with Delta-OD. It also has a high sensitivity at the second IUT.

Keywords: Alloimmunization, amniocentesis, doppler ultrasonography, intrauterine transfusion, fetal anemia, middle cerebral artery

Cite this article as: Rahimi-Sharbaf F, Shariat M , Mirzaie F, Dehghan P, Dastgardy E, Adabi K. Prediction of Fetal Anemia by Different Thresholds of MCA-PSV and Delta-OD in First and Second Intrauterine Transfusions. *Arch Iran Med*. 2012; **15(3):** 162 – 165.

Introduction

Morbidity and mortality due to red blood cell alloimmunization have steadily declined because use of routine antenatal anti-Rh prophylaxis and the development of invasive and noninvasive investigations for monitoring alloimmunized pregnancies. However, red blood cell alloimmunization remains a major problem in several areas of the world.[1–5]

Amniocentesis and fetal blood sampling are used for screening and diagnosis of fetal anemia. Umbilical fetal blood sampling is the gold standard for diagnosis of fetal anemia. These procedures are invasive and associated with risks such as infection, fetal demise, worsening of maternal immunization, preterm labor, and abortion.[6–10] On the other hand; invasive procedures in all alloimmunized pregnant women expose 75% of the fetuses to unnecessary intervention. Thus, a noninvasive screening method would avoid the potential complications of such methods.[8,9]

Doppler ultrasound measurement of the human fetal middle cerebral artery peak systolic velocity (MCA-PSV) is a noninvasive diagnostic method. MCA-PSV has a predictable relationship with fetal hemoglobin (Hb) and hematocrit concentrations. Several studies have documented that Doppler MCA-PSV is useful in identifying severely anemic fetuses before the first intrauterine blood transfusion (IUT). However, MCA-PSV may be less accurate in the assessment of fetuses that have already been transfused, because in such fetuses the association between blood velocity and Hb concentration is weaker.[10, 11]

The purpose of our study is to compare the ability of the MCA-PSV in the prediction of moderate and severe anemia in red blood cell alloimmunized fetuses with the Delta-OD of amniotic fluid. We assess the validity of this technique at the time of subsequent transfusions, and whether there is a correlation between MCA-PSV normal median value (MOM) and fetal Hb.

Materials and Methods

The Maternal-Fetal and Neonatal Research Center, Women Hospital, Tehran University of Medical Science, is a tertiary referral center for complicated pregnancies in Tehran, Iran. The study population consisted of 27 singletons, red blood cell alloimmunized pregnancies referred to our center from November 2006 through June 2010. The inclusion criteria were: obstetric history of red blood cell alloimmunization and increased indirect Coombs titers ≥ 1:16, past history of IUT, hydrops fetalis and having an infant that needed exchange transfusion after birth. Cases with evidence of hydrops (skin edema, pleural effusion, or ascites) were excluded from the study because these findings are a clear indication of severe anemia.

For anemia screening, we measured serial MCA-PSV levels at 7-day intervals and Delta-OD by amniocentesis every 1 – 3 weeks from 16 weeks of pregnancy. Cordocentesis was performed when either MCA-PSV, Delta-OD, or both showed the necessity for IUT. In all cases, fetal Hb concentrations were measured before the first IUT. In 17 cases, cordecentesis was done before the sec-

Authors' affiliations: [1]Department of Obstetrics and Gynecology, Women Hospital, Tehran University of Medical Sciences, Tehran, Iran, [2]Maternal-Fetal and Neonatal Research Center, Tehran University of Medical Sciences, Tehran, Iran, [3]Department of Pediatrics, Women Hospital, Tehran University of Medical Sciences, Tehran, Iraan.

•Corresponding author and reprints: Fatemeh Rahimi-Sharbaf MD, Department of Maternal-Fetal Medicine, Women Hospital, Nejatollahi St., Karim Khan Ave., Tehran 15978, Iran. Tel: +98-912-113-4105,
Fax: +98-218-891-5959, E-mail: rahimish@sina.tums.ac.ir; f_rahimis@yahoo.com
Accepted for publication: 15 March 2011

Table 1. Characteristic details of patients at first IUT.

Maternal age (mean ± SD)	33.66±4.49[years]
Gravidity (mean ± SD)	4.6 ± 2.4
Living Child (mean ± SD)	1.5 ± 1.3
History of IUT (N, %)	2, 6.5%
History of Hydrops (N, %)	19, 61.3%
History of IUFD (N, %)	16, 51.6%
History of neonatal Exchange (N, %)	6, 19.4%
Gestational age at 1st IUT weeks (mean ± SD)	21.54 ± 5.03 [weeks]
Fetal Hb before first IUT (mean ± SD)	6.36 ± 3.62 g/dl

Table 2. Characteristic details of patients at second IUT.

Gravidity (Mean ± SD)	5.22 ± 2.59
Living child (Mean ± SD)	1.81 ± 1.46
History of hydrops (N, %)	12, 68%
History of IUFD (N, %)	10, 59%
History of neonatal exchange (N, %)	4, 23%
Gestational age at second IUT (mean ± SD)	24.50 ± 4.02 [weeks]
Fetal Hb before second IUT (mean ± SD)	6.48 ± 3.39 g/dl

Table 3. Diagnostic values of MCA-PSV & Delta-OD to detect anemia in the first IUT.

Gold standard test	Sensitivity	Specificity	PPV	NPV	P value
MCA-PSV (MOM > 1.29)					
Severe anemia	100	50	71	100	0.015
Moderate anemia	60	60	50	50	0.015
MCA-PSV (MOM > 1.5)					
Severe anemia	93	90	93	90	< 0.0001
Moderate anemia	0	25	∞	0	< 0.0001
Delta –OD					
Severe anemia	80	65	72	30	0.04
Moderate anemia	50	75	70	40	0.04

Table 4. Diagnostic values of MCA-PSV to detect anemia in the second IUT.

Gold standard test	Sensitivity	Specificity	PPV	NPV	P value
MCA-PSV (MOM > 1.29)					
Severe anemia	100	80	84	100	0.006
Moderate anemia	33	50	50	100	0.006
MCA-PSV (MOM > 1.5)					
Severe anemia	91	100	100	100	< 0.001
Moderate anemia	0	100	∞	100	< 0.001

ond IUT.

Maternal medical records, as well as present and past obstetrical histories were collected. Gestational age was calculated according to the first day of the last menstrual period and matched with first trimester ultrasound.

Measurements of Delta-OD were taken the day before cordocentesis and fetal Doppler MCA-PSV measured within six hours before cordocentesis. For measurement of MCA-PSV, color flow mapping was used to identify the MCA at the level of the circle of Willis, the pulsed wave Doppler gate was placed on the proximal one third of the MCA and the angle of insonation was kept at less than 20 degrees. Three consecutive wave forms in the absence of fetal body or breathing movements were then recorded, and the highest point of the Doppler envelope was considered as the PSV (cm/s). The measurement was repeated three times, with the maximum value considered for PSV. Attention was taken to avoid pressure on the fetal head. MCA-PSV expressed as multiples of the normal median (MOM) value were measured by the reference curve provided by Mari[11] and adjusted for gestational age. We used cutoff values of MCA-PSV above 1.29 and 1.5. For Delta-OD, the Queenan curve was used with the cutoff of the upper affected zone (zone 3) considered and adjusted for gestational age.[12]

In normal fetuses, Hb levels increase with gestational age, therefore a fixed Hb cutoff point cannot be used to define fetal anemia. The reference test for the diagnosis of fetal anemia was measurement of the Hb level in umbilical cord blood with the use of the reference range published by Nicolaides et al. in 1988.[13]Moderate anemia was defined as Hb between 2 SD-5 SD below the mean for gestational age and severe anemia was defined as an Hb level more than 5 SD below the mean (one SD is approximately 1g/dl).[13,14]

This study was approved by the Research and Ethics Committee of the Maternal, Fetal and Neonatal Research Center of Tehran University of Medical Sciences. Patients signed informed consents after being informed about the study.

Chi-square and Fisher exact tests were used. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated by standard formulas for a binominal proportion, generated for specific thresholds of MOM and Delta-OD. A *P* value < 0.05 was considered statistically significant.

Results

Past obstetric history and patient data are shown in Table 1. Demographic and characteristic details of patients at the time of the second IUT are shown in Table 2.

The study group consisted of 27 fetuses. At the first IUT, 5 of 27 cases (20%) were moderately anemic whereas 15 (60%) had severe anemia. The MCA-PSV threshold MOM of > 1.29 detected 60% of moderate and 100% of severe cases ($P < 0.015$), whereas the MCA-PSV with an MOM of > 1.5 detected none of the moderate cases and 93% of severe ones ($P < 0.0001$). In this group, Delta-OD was measured in 18 cases, of which 10 were severe and 4 were moderately anemic. Of these, Delta-OD detected 80% of the severe and 50% of the moderate cases ($P < 0.04$). Sensitivity, specificity, PPV and NPV are shown in Table 3.

In 17 cases that underwent a second IUT, 11 (65%) were severe and 3 (18%) moderately anemic. Of these, 91% of the severely anemic cases were confirmed by the MCA-PSV threshold MOM of > 1.5 and all were confirmed by the MCA-PSV cutoff MOM of > 1.29 ($P < 0.001$). One case of moderate anemia was detected by MCA-PSV with an MOM > 1.29 and none were detected by MCA-PSV with an MOM > 1.5. Sensitivity, specificity, PPV and NPV for the second IUT are shown in Table 4.

Discussion

Our data demonstrated that different thresholds of MCA-PSV had higher sensitivities and specificities for the detection of moderate and severe fetal anemia compared with Delta-OD. At the first IUT for the correlation between severe anemia and MCA-PSV with a cutoff MOM of > 1.5, there was a 93% sensitivity and 90% specificity, whereas Delta-OD showed 80% sensitivity and 65% specificity. For the detection of moderate anemia, the Delta-OD had 50% sensitivity and 75% specificity, whereas the MCA-PSV with an MOM of > 1.29 had 60% sensitivity and specificity. MCA-PSV with MOM > 1.5 showed 0% sensitivity and 25% specificity. Therefore, the MCA-PSV with a threshold MOM of > 1.29 was more accurate than the MCA-PSV MOM of > 1.5 and Delta-OD for the detection of moderate anemia. Additionally there was a high sensitivity at the second IUT for the detection of severe anemia.

Oepkes et al.[14] in a multicenter prospective study on 47 severe anemic fetuses compared MCA- PSV with amniocentesis and showed that the Doppler measurement was significantly more accurate than Delta-OD. They compared severe anemia with the MCA-PSV of MOM > 1.5, but moderate anemia was not considered.

In a small, retrospective study by Pereira et al.[15] the researchers compared MCA-PSV with conventional management. In their study, there were five anemic fetuses, of which two were hydropic. They reported a Delta-OD with 80% sensitivity and 78% specificity for moderate to severe anemia. MCA-PSV of MOM > 1.5 had 100% sensitivity and 91% specificity for moderate to severe anemia. they considered Hb under 9 g/dL as both moderate and severe anemia. The researchers have concluded that MCA-PSV may have a better predictive accuracy for moderate to severe fetal anemia in red blood cell alloimmunization.

Our study revealed two separate thresholds for the diagnosis of moderate and severe anemia in fetuses at the first and second transfusions. MCA-PSV with an MOM > 1.5 cutoff could better detect severely anemic patients and for the detection of milder anemia, a lower cutoff (> 1.29) for MOM should be considered.

These results were comparable to a study by Mari et al.[10] that showed significant association between the degree of anemia and the mean velocity of blood flow in the middle cerebral artery. Moderate and severe anemia can be detected noninvasively by Doppler ultrasonography based on an increase in the peak velocity of systolic blood flow in the middle cerebral artery. Our findings show that for detection of moderate anemia the lower MCA-PSV of MOM > 1.29 should be used. These results have confirmed the results of other studies by Mari[16,17] that measured MCA-PSV in 18 fetuses before an initial cordocentesis. He demonstrated that the correlation between Hb and MCA-PSV was more accurate as the severity of anemia increased.

A study by Scheier et al.[3] has shown that in patients who received one previous IUT the prediction of fetal anemia provided by MCA-PSV was useful, but an increase in the cutoff was necessary. Our study also confirmed that at the second IUT for detection of severe anemia, the MCA-PSV of > 1.29 MOM had 100% sensitivity and 80% specificity. MCA-PSV with a > 1.5 MOM had 91% sensitivity and 100% specificity. Compared with the first IUT, a similar cut off had lower sensitivity.

Bartha et al.[18] have reported that the prediction of severe fetal anemia after one transfusion is less accurate than in non-transfused fetuses. The MCA-PSV is not useful in predicting severe anemia in fetuses that have previously undergone two transfusions. Our data suggest a good correlation between MCA-PSV and Hb in fetuses that have undergone one previous transfusion. In the second IUT the MCA-PSV cutoff MOM of > 1.5 could weakly detect true moderate cases but it detected severely anemic cases.

Maciuleviciene et al.[19] showed that the sensitivity of the MCA-PSV test decreased in less anemic fetuses from 77.3% in the subgroup with moderate anemia to 32% in the subgroup with mild anemia. This was in agreement with our study where the sensitivity of the MCA-PSV cutoff of > 1.29 was 60% for detection of moderate anemia. A study by Alshimmiri et al. in 2003 has shown that although MCA-PSV is highly specific, negative values do not rule out fetal anemia[20] and has emphasized the need for further research before it can be recommended in clinical practice. Another study performed by Rimon et al. proved that in the management of Kell isoimmunization, invasive procedures may be avoided by implementing MCA-PSV measurements.[21] Delineation of appropriate intervals between reassessments, the reliability of MCA-PSV following repeated IUTs and cutoff values for fetal blood sampling await further study.

In conclusion, MCA-PSV thresholds of MOM > 1.29 and > 1.5 in the diagnosis of severe anemia have a high sensitivity in first and second IUT. MCA-PSV is a non-invasive method for the detection of fetal anemia. We strongly recommend it as a screening test before the first and second IUT. Our results suggest that good correlation between MCA-PSV and fetal Hb remains following first IUT.

References

1. Seeds JW, Cheschеir NC, Bowes WA Jr, Owl-Smith FA. Fetal death as a complication of intrauterine intravascular transfusion. *Obstet Gynecol*. 1989; **74:** 1073 – 1075.
2. Liley AW. Liquor amnii analysis in the pregnancy complicated by rhesus isoimmunization. *Am J Obstet Gynecol*. 1961; **82:** 1359 – 1370.
3. Nicolaides KH, Rodeck CH, Millar DS, Mibashan RS. Fetal hematology in rhesus isoimmunisatin. *BMJ*. 1985; **1:** 661 – 663.
4. Scheir M, Hernandez-Andrade E, Carmo A, Dezerega V, Nicolaides KH. Prediction of fetal anemia in rhesus disease by measurement of fetal middle cerebral artery peak systolic velocity. *Ultrasound Obstet Gynecol*. 2004; **23:** 432 – 436.
5. Scheier M, Hernandez-Andrade E, Eduardo B, Fonseca EB, Nicolai-

des KH. Prediction of severe anemia in red blood cell alloimmunization after previous intrauterine transfusions. *Am J Obstet Gynecol*. 2006; **195:** 1550 – 1556.
6. MacGregor SN, Silver RK, Sholl JS. Enhanced sensitization after cordocentesis in a rhesus-isoimmunized pregnancy. *Am J Obstet Gynecol*. 1991; **165:** 382 – 383.
7. Deren O, Onderoglu L. The value of middle cerebral artery systolic velocity for initial and subsequent management in fetal anemia. *Eu J Obstet Gynecol*. 2002; **101:** 26 – 30.
8. Ghidini A, Sepulveda W, Lockwood CJ, Romero R. Complications of fetal blood sampling. *Am J Obstet Gynecol*. 1993; **168:** 1339 – 1344.
9. Tongsong T, Wanapirak C, Kunavikatikul C, Sirirchotiyakul S, Piyamongkol W, Chanprapaph P. Fetal loss rate associated with cordocentesis at midgestation. *Am J Obstet Gynecol*. 2001; **184:** 719 – 723.
10. Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. *N Eng J Med*. 2000; **342:** 9 – 14.
11. Teixeira J, Duncan K, Letsky E, Fisk NM. Middle cerebral artery peak systolic velocity in the prediction of fetal anemia. *Ultrasound Obstet Gynecol*. 2000; **15:** 205 – 208.
12. Queenan JT, Tomai TP, Ural SH, King JC. Deviation in amniotic fluid optical density at a wavelength of 450 nm in Rh-immunized pregnancies from 14 to 40 weeks' gestation: a proposal for clinical management. *Am J Obstet Gyncol*. 1993; **168:** 1370 – 1376.
13. Nicolaides KH, Soothill PW, Clewell WH, Rodeck CH, Mibashan RS, Campbell S. Fetal haemoglobin measurement in the assessment of red cell isoimmunisation. *Lancet*. 1988; **1:** 1073 – 1075.
14. Oepkes D, Seaward G, Vandenbussche F, Windrim R, Kingdom J, Beyene J, et al. Doppler ultrasonography vs. amniocentesis to predict fetal anemia. *N Eng J Med*. 2006; **355:** 156 – 164.
15. Pereira L, Jenkins T, Berghella V. Conventional management of maternal red cell alloimmunization compared with management by Doppler assessment of middle cerebral artery peak systolic velocity. *Am J Obstet Gyn*. 2003; **189:** 1002 – 1006.
16. Mari G, Detti L, Utku Oz, Zimmerman R, Duerig P, Stefos T. Accurate prediction of fetal hemoglobin by Doppler ultrasonography. *Obstet & Gyncol*. 2002; **99:** 589 – 593.
17. Mari G, Zimmermann R, Morise KJ, Deter RL. Correlation between middle cerebral artery peak systolic velocity and fetal hemoglobin after 2 previous intrauterine transfusions. *Am J Obestet Gynecol*. 2005; **193:** 1117 – 1120.
18. Bartha JL, Abdel-Fattah SA, Hunter A, Denbow M, Kyle P, Soothill PW. Optimal interval between middle cerebral artery velocity measurements when monitoring pregnancies complicated by red cell alloimmunization. *Fetal Diag Ther*. 2006; **21:** 22 – 25.
19. Maciuleviciene R, Gaurilcikas A, Simanaviciute D, Nadisauskiene RJ, Gintautas V, Vaitkiene D, et al. Fetal middle cerebral artery Doppler velocimetry in cases of rhesus alloimmunization. J Matern Fetal Neonatal Med. 2008; 21: 361 – 365.
20. Alshimmiri MM, Hamoud MS, Al-Saleh EA, Mujaibel KY, Al-Harmi JA, Thalib L. Prediction of fetal anemia by middle cerebral artery peak systolic velocity in pregnancies complicated by rhesus isoimmunization. *J Perinatol*. 2003; **23:** 536 – 540.
21. Rimon E, Peltz R, Gamzu R, Yagel S, Feldman B, Chayen B, et al. Management of kell isoimmunization–evaluation of a Doppler-guided approach. *Ultrasound Obstet Gynecol*. 2006; **28:** 814 – 820.