Diagnostic Accuracy of Fetal Middle Cerebral Artery (MCA) Peak Systolic Velocity (PSV) In Prediction of Neonatal Anemia in Rhesus Alloimmunization

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Abstract

Objective: To assess the diagnostic accuracy of Middle Cerebral Artery (MCA) Peak Systolic Velocity (PSV) in Prediction of Neonatal Anemia keeping neonatal hemoglobin (Hb) at birth as gold standard.
Methods: A Cross sectional validation study conducted at Radiology department of PAF Hospital, Faisal Karachi affiliated with Fazaia Ruth Pfau Medical College (FRPMC) PAF Base Faisal Sharah-e-Faisal, Karachi from 26th November 2019 till 26th May 2020. A total of 125 pregnant women between 32-35 weeks were included through non probability consecutive sampling. The PSV was measured in the MCA closest to the transducer. An average of three readings was taken. An MCA-PSV of > 1.5 multiples of median (MoM) was taken as positive. The neonatal blood was sent for hemoglobin estimation soon after birth to the hospital pathology laboratory. The result of MoM was noted and compared with neonatal hemoglobin.
Results: Out of 125 pregnant women between 32-35 weeks, the mean age of the patients was 25.81 ± 5.82 years. Most of the women were multiparous that is 67 out of 125 (53.6%), and primiparous were 58 that constituted 46.4% of the total. 34.4% patients were anemic according to middle cerebral artery peak systolic velocity (MCA-PSV) while hematology laboratory reported 32.8% of neonates as anemic according to cut off hemoglobin of less than 13.5 gm/dl. Sensitivity, specificity, PPV, NPV and accuracy of the MCA-PSV in detecting the anemia was 90.2%, 92.9%, 86%, 95.1% and 92% respectively.
Conclusion: MCA- PSV Doppler is a useful modality for diagnosis of fetal anemia, although the primary means should be neonatal hemoglobin estimation at birth.
Keywords: Color Doppler ultrasound, MCA- PSV, Neonatal Hemoglobin
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Introduction

Maternal Alloimmunization is a pathological condition which occurs in women who are Rhesus negative (Rh-) and have been sensitized in a previous pregnancy. The resultant immune reaction causes the maternal iso-antibodies to destroy the fetal red blood cells (RBCs) of a Rhesus positive (Rh+) fetus. Despite the widespread implementation of anti-D gamma globulin prophylaxis, maternal alloimmunization is still the most common cause for fetal anemia. The hemolytic disease of new born affects around 2% of all births with about 0.03% having severe form of disease[1]. In RBCs of iso-immunized pregnancies, a trans-placental passage of maternal hemolytic antibodies occurs which causes fetal anemia[2]. The only accurate method of assessment of the severity of fetal anemia is by fetal blood sampling. Amniocentesis and cordocentesis used in past to diagnose fetal anemia secondary to red cell alloimmunization are invasive and associated with complications such as infection and pregnancy loss.

In the past three decades, many authors were interested in diagnosing fetal anemia with gray sca-

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le and Doppler ultrasonography. Noninvasive measures like Doppler assessment of blood flow velocities in the fetal middle cerebral artery (MCA), intrahepatic umbilical vein and fetal aorta, and ultrasound measurements of fetal liver length and spleen have been suggested as valuable predictors of fetal anemia[3,4]. The use of Doppler ultrasound evaluation to measure the peak systolic velocity (PSV) of the fetal MCA has been a breakthrough in the noninvasive detection of fetal anemia. It is based on the principle that the anemic fetus would increase cerebral flow of low viscosity blood to preserve oxygen delivery to the brain. An elevated peak MCA velocity of more than 1.5 times of the median is useful in the timing of intrauterine transfusion (IUT) in the red cell-alloimmunized pregnancies[5].

Doppler ultrasonography of the MCA has a sensitivity of 86.8% and specificity of 90.3% to detect fetal anemia[6]. However, this parameter is not considered the global standard of care for diagnosis of fetal anemia because incorrect use by an inexperienced operator may cause more harm than good. The MCA-PSV may not be useful in mild anemia. Moreover it has been found to be a reliable predictor only between 18 to 35 weeks of gestation. Healthy fetuses may have an unexpected rise in MCA-PSV that does not necessarily reflect state of anemia[7]. All these factors contribute to the reported false positive rate of MCA-PSV in detecting fetal anemia. Furthermore, studies in the past have given contradictory results[8]. The variation might be because of the difference in the definitions of fetal anemia used and because of different gold standard tests that were employed to detect fetal anemia. Since the literature has given controversial results about its accuracy, we conducted this study to determine how accurate MCA-PSV is in the prediction of neonatal anemia locally.

Patients and Methods

This validation study was carried out in the Radiology department of PAF Hospital, Faisal Karachi affiliated with Fazaia Ruth Pfau Medical College (FRPMC) PAF Base Faisal Sharah-e-Faisal, Karachi from 26th November 2019 till 26th May 2020. A total of 125 pregnant women near term between 32-35 weeks were included through non probability consecutive sampling after approval of the study by the ethical review board of RMU. Inclusion criteria also included singleton pregnancies and Rh-negative mothers with suspected fetal red cell anti-D alloimmunization on the basis of maternal anti-D titers >1:16. Exclusions criteria were neonates with malformations diagnosed on antenatal ultrasound and neonates with intrauterine growth restriction diagnosed on antenatal ultrasound. Informed consent of the patients was obtained for conducting tests and using their data in research. The demographic data like name, age, address and telephone numbers were obtained. Confounding variables such as expertise of radiologist were controlled by having ultrasound performed by the single experienced radiologist. Patients were subjected to Toshiba Nemio XG (Ta312) real time ultrasound Doppler scanner. Doppler gate was placed in the center of MCA soon after its origin from internal carotid artery. An angle of insonation of zero degrees ensured the most accurate measurement of the PSV. The PSV was measured in the MCA closest to the transducer. Three consecutive waveforms, in the absence of fetal body or breathing movements, were recorded and the highest value was taken. It was converted into multiples of median with reference to gestational age with the help of a calculator as shown in figure I. A MCA-PSV of > 1.5 multiples of median (MoM) was taken as positive. The neonatal blood was sent for hemoglobin estimation soon after birth to the hospital pathology laboratory. The result of MoM was noted and compared with neonatal hemoglobin after birth.

Data was entered and analyzed through SPSS (version 23). Mean and standard deviation for numerical variables like age & parity were analyzed. The qualitative variables like placental thickness, liquor volume and fluid in body cavities, cardiac size and body wall thickness were presented as frequencies, percentages and proportions. A 2x2 table was generated to calculate sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of Doppler ultrasound, taking neonatal hemoglobin at birth as a gold standard. Stratification

was done with respect to age and parity to observe an accuracy of Doppler ultrasound.

Results

A total of 125 pregnant women near term between 32-35 weeks were included in this study. The mean age of the patients was 25.81 ± 5.82 years. Most of the women were multiparous that is 67 out of 125 subjects (53.6%), and primiparous were 58(46.4%). 34.4% patients were anemic according to middle cerebral artery peak systolic velocity (MCA-PSV) while hematology laboratory reported 32.8% of neonates as anemic according to cut off hemoglobin of less than 13.5gm/dl. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the MCA-PSV in detecting the anemia was 90.2%, 92.9%, 86%, 95.1% and 92% respectively as shown in Table 2.

Stratifications of age showed that accuracy of MCA-PSV in detecting the anemia was 93.3% in patients who were below 25 years of age and 90.7% for those older than 25 years of age. Sensitivity, specificity, PPV, NPV were 90.9%, 94.7%, 90.9% and 94.7% in patients who were below 25 years and were 89.5%, 91.3%, 81.0% and 95.5% respectively in patients who were above 25 years as shown in Table 3.

Stratification of parity showed that accuracy of MCA-PSV in detecting the anemia was 91.4% for primiparous and 92.5% for multiparous. Sensitivity, specificity, PPV and NPV were 88.9%, 92.5%, 84.2% and 94.9% in primiparous and were 91.3%, 93.2%, 87.5% and 95.3% respectively in multiparous as shown in table 4.

Table: Values of MCA-PSV (cm/s) based on MoM between the 23rd and 35th gestational weeks.

Gestational age (weeks)	Multiples of the median for MCA-PSV			
	1.0	1.29	1.50	1.55
23	35.44	45.72	53.16	54.93
24	35.48	45.77	53.22	55.00
25	35.81	46.20	53.72	55.51
26	36.45	47.03	54.68	56.50
27	37.43	48.29	56.15	58.02
28	38.77	50.01	58.15	60.09
29	40.49	52.23	60.73	62.75
30	42.61	54.97	63.91	66.04
31	45.16	58.26	67.74	70.00
32	48.17	62.13	72.25	74.66
33	51.65	66.62	77.47	80.05
34	55.63	71.76	83.44	86.22
35	60.13	77.56	90.19	93.20

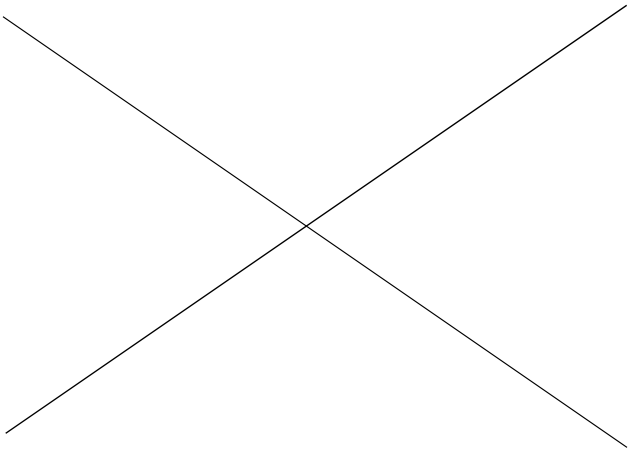

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Table 2. Diagnostic accuracy of MCA PSV in detecting fetal anemia

MCA-PSVDoppler Findings	HAEMOTOLOGY Diagnosis of neonatal anemia		Total
	Hb < 13.5 gm/dl (Anemia present)	Hb e" 13.5 gm/dl (Anemia present)	
Anemia Present(e"1.5 MoM)	37 (TP)	6 (FP)	43 (34.4%)
Anemia Absent(<1.5 MoM)	4 (FN)	78 (TN)	82 (65.6%)
Total	41 (32.8%)	84 (67.2%)	125
Sensitivity	37/41	90.2%	
Specificity	78/84	92.9%	
PPV	37/43	86.0%	
NPV	78/82	95.1%	
Accuracy	(37+78)/125	92.0%	

Table 3. Diagnostic accuracy of MCA PSV in detecting fetal anemia by age groups

Age Groups (Years)	MCA-PSV Doppler Findings	HAEMOTOLOGY Diagnosis of neonatal anemia		Total
		Hb < 13.5 gm/dl (Anemia present)	Hb e" 13.5 gm/dl (Anemia present)	
< 25 years	Total (AP+AA)	20 (TP)	2 (FP)	22
		2 (FN)	36 (TN)	38
		22	38	60
> 25 years	Total (AP+AA)	17 (TP)	4 (FP)	21
		2 (FN)	42 (TN)	44
		19	46	65

For Age < 25 Years			For Age > 25 Years		
Sensitivity	20/22	90.9 %	Sensitivity	17/19	89.5 %
Specificity	36/38	94.7 %	Specificity	42/46	91.3 %
PPV	20/22	90.9 %	PPV	17/21	81.0 %
NPV	36/38	94.7 %	NPV	42/44	95.5 %
Accuracy	20+36/60	93.3 %	Accuracy	17+42/65	90.7 %

Table 4. Diagnostic accuracy of MCA PSV in detecting fetal anemia by Parity

Parity	MCA-PSV Doppler Findings	HAEMOTOLOGY Diagnosis of neonatal anemia		Total
		Hb < 13.5 gm/dl (Anemia present)	Hb e" 13.5 gm/dl (Anemia present)	
Primiparous	Total (AP+AA)	16 (TP)	3 (FP)	19
		2 (FN)	37 (TN)	39
		18	40	58
Multiparous	Total (AP+AA)	21 (TP)	3 (FP)	24
		2 (FN)	41 (TN)	43
		23	44	67

For Primiparous For multiparous

Sensitivity	16/18	88.9 %	Sensitivity	21/23	91.3 %
Specificity	37/40	92.5 %	Specificity	41/44	93.2 %
PPV	16/19	84.2 %	PPV	21/24	87.5 %
NPV	37/39	94.9 %	NPV	41/43	95.3 %
Accuracy	16+37/58	91.4 %	Accuracy	21+41/67	92.5 %

Discussion

Middle cerebral artery peak systolic velocity Doppler for diagnosing and managing cases of fetal anemia was initially utilized in cases of red cell alloimmunization and was later expanded to other types of anemia. Red blood cell alloimmunization, twin-twin transfusion syndrome, parvovirus B-19 infection and feto-maternal hemorrhage are the prevalent causes of fetal anemia.[9] ABO Rh incompatibility results in severe hemolytic disease of newborn often requiring multiple exchange transfusions especially in developing countries[10]. There was a dire requirement for newer noninvasive methods for diagnosing fetal anemia. Apart from 3 parameters like intrahepatic umbilical venous maximum velocity, liver length, and spleen perimeter, fetal MCA-PSV was also analyzed. Doppler ultrasound analysis of MCA-PSV analysis is highly sensitive and more specific non-invasive test than the others[11]. It is also seen to be more useful and reliable than the umbilical arteries[12]. Fetal MCA-PSV is inversely related to hemoglobin value and results from increased cardiac output due to hyper-dynamic circulation and a reduction in blood viscosity, both leading to increased blood flow velocity[13].

As a consequence of entry of fetal cells into the maternal circulation at delivery, subsequent pregnancies will involve a greater severity of fetal/neonatal hemolytic disease due to an anamnestic maternal antibody response. Therefore, if the patient has had a prior pregnancy with a significant affected pregnancy (fetal hydrops, intrauterine fetal transfusion, neonatal exchange transfusion, preterm delivery because of fetal anemia), there is a high certainty of severe fetal anemia in subsequent pregnancies with an Rh+ fetus. For this reason, the severity of fetal anemia is assessed beginning at 16 to 18 weeks of gestation but maternal antibody titers are not routinely evaluated, as they do not reliably predict the severity of fetal anemia.

In present study sensitivity, specificity, and accuracy of the MCA-PSV in detecting the hemoglobin was 90.2%, 92.9%, and 92% respectively. Similar results were also reported from our neighboring country in another study[14]. In one study, MCA-PSV with a normal median value (MOM) cutoff of >1.29 detected 60% of the moderate and 100% of the severe anemia cases while MCA-PSV of MOM>1.5 detected none of the moderate and 93% of severe anemia cases[15]. Therefore, different thresholds of MCA-PSV have varying sensitivity and specificity for detecting fetal anemia. In our study MCA-PSV of >1.5 multiples of median (MoM) was taken as positive. But the literature clearly denotes that the sensitivity and accuracy of the middle cerebral artery Doppler is substantially greater than amniocentesis for the detection of anemia[16].

In this study accuracy of MCA-PSV Doppler in detecting hemoglobin was 93.3% in patients with below and equal to 25 years of age and 90.7% for >25 years of age. The hemodynamic adaptations by fetus for compensation can be assessed by Doppler ultrasound[17]. The noninvasive prediction of fetal anemia in fetuses at risk due to maternal Rhesus alloimmunization can be greatly enhanced by measuring the peak systolic velocity in the fetal middle cerebral artery (MCA-PSV). The fetal MCA-PSV correlates well with hemoglobin concentration and hematocrit[18]. Measurement of MCA PSV is now become the standard methods for fetal anemia diagnosis in a diverse fetal disease[19]. This modality is based on the fact that fetuses with anemia have an increased blood flow velocity (hyper dynamic circulation). The advantages of studying the MCA rather than other vessels is that it allows measurements of velocity without angle correction because the angle of insonation in the axial plane of the MCA is close to 0°, which improves reproducibility[20].

Conclusion

Measurement of the MCA-PSV in fetuses at risk for anemia due to Rhesus alloimmunization provided an accurate, noninvasive clinical test for the prediction of fetal anemia, although the primary means should be fetal hemoglobin estimation at birth. Clearly, the widespread use of MCA Doppler assessment to detect fetal anemia in other fetal diseases is on the near horizon in future.

Ethical approval was obtained from the Institutional Review Board Committee of Fazaia Ruth Pfau Medical College (FRPMC) PAF Base Faisal Sharah e Faisal, Karachi. Ref App IRB/26. Written informed consent was taken from all participants.

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Conflict of Interest

Authors have no conflict of interest and no grant/funding from any organization.

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