

DIAGNOSTIC ACCURACY OF FETAL MIDDLE CEREBRAL ARTERY PEAK SYSTOLIC VELOCITY IN DETECTION OF NEONATAL ANEMIA IN RHESUS ALLOIMMUNIZATION

Shahzeb Mastoi,¹ Sumera Tabassum,¹ Mahnoor Panhwar,² Shahbaz Haider,³ Tabinda Urooj,¹ Madiha Asad¹

¹ Department of Radiology, Jinnah Post Graduate Medical Centre (JPMC), Karachi, Pakistan.

² Department of Pathology, Jinnah Sindh Medical University (JSMU), Karachi, Pakistan.

³ Department of Medicine, Jinnah Post Graduate Medical Centre (JPMC), Karachi, Pakistan.

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ABSTRACT

BACKGROUND: Maternal alloimmunization occurs when a pregnant woman has an immunologic response to a paternally derived red-cell antigen. Fetuses with anemia have a high cardiac output and decreased blood viscosity, resulting in high blood-flow velocities that could be used in prediction of fetal anemia. **OBJECTIVE:** To determine the diagnostic accuracy of fetal middle cerebral artery peak systolic velocity in detection of neonatal anemia in rhesus alloimmunisation keeping neonatal hemoglobin estimation at birth as the gold standard. **SETTING:** Department of Radiology, Jinnah Postgraduate Medical Center, Karachi. **MATERIALS AND METHOD:** Total 189 patients with Rhesus alloimmunization were included. Doppler examination of the middle cerebral artery was performed. Three measurements of peak systolic velocity at time of absent fetal body and breathing movements were taken, and the highest velocity level was recorded. A MCA-PSV of > 1.5 MoM was taken as positive. Sensitivity, specificity, and diagnostic accuracy were calculated. Stratification was done. P-value ≤ 0.05 was considered as significant. **RESULTS:** The overall mean mother's age was 29.29 ± 4.42 years. 55.6% neonates were male and 44.4% were female. 40.7% patients were diagnosed neonatal anemia by MCA-PSV and 40.2% by neonatal hemoglobin estimation at birth. Sensitivity, Specificity, PPV, NPV and diagnostic accuracy were 86.8%, 90.3%, 85.7%, 91.0%, and 88.8% respectively. **CONCLUSION:** The measurements of the peak velocity of blood flow provide an accurate and noninvasive means of determining the degree of anemia.

Keywords: Diagnostic Accuracy, Fetal Middle Cerebral Artery, Peak Systolic Velocity, Neonatal Anemia, Rhesus Alloimmunisation

Introduction

Maternal alloimmunization still affects a large number of pregnancies, particularly in developing countries. These pregnancies need specific follow-up at tertiary referral centers to carry out proper monitoring, in the view of a high risk of perinatal morbidity and mortality.¹

The antibodies produced new and old in response to a paternally derived red-cell antigen during previous pregnancies may cross the placenta, bind to antigens present on the fetal erythrocytes, and cause hemo-

lysis, and in severe cases hydrops fetalis, and fetal death.²

Survival rates can exceed 90 percent if anemia is diagnosed and treated with intrauterine blood transfusions.

In this high-risk context, assessment of the degree of fetal anemia is an essential strategy for managing these pregnancies. The most accurate test to assess the degree of fetal anemia, and thus the need for

Correspondence : Dr. Sumera Tabassum
Department of Radiology,
Jinnah Post Graduate Medical Centre (JPMC),
Karachi, Pakistan.
Email: sumert57f@yahoo.com

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transfusion, is the fetal hemoglobin (Hb) measurement by fetal blood sampling. Several non-invasive methods for the prediction of fetal anemia have been assessed, aiming to defer the use of invasive procedure.³

Fetuses with anemia have a high cardiac output and decreased blood viscosity, resulting in high blood-flow velocities, a feature that could be used in prediction of fetal anemia.⁴

This study is aimed to determine the diagnostic accuracy of "peak systolic velocity of fetal middle cerebral artery" in prediction of neonatal anemia in rhesus alloimmunisation keeping neonatal hemoglobin estimation at birth as the gold standard. Since the literature has shown controversial results about its sensitivity specificity and no such study has been conducted in Pakistan, our study and its results could be different due to different socioeconomic and educational status and it may add to contribution of nation's data to international research literature.

OBJECTIVE of the study is to determine the diagnostic accuracy of fetal middle cerebral artery peak systolic velocity in detection of neonatal anemia in rhesus alloimmunization keeping neonatal hemoglobin estimation at birth as the gold standard and to compare the results with international studies and contribute to literature by locally produced data in a public sector hospital of metropolitan city of Pakistan.

Materials & Methods

This cross sectional study was carried out in the Department of Radiology, Jinnah Postgraduate Medical Center, Karachi from 30th September 2017 to 25th March 2019.

As reported sensitivity and specificity of MCA-PSC in predicting the fetal anemia is 44% and 96%, and prevalence of fetal anemia in rhesus alloimmunization is 39.1%, margin of error for sensitivity = 10% and for specificity = 3%, then sample size taken was 189.

Non-probability consecutive sampling was used for the study.

All patients with Age between 20-45 years with parity 1-5, Singleton pregnancy, confirmed on ultra-

sound, Rhesus alloimmunization diagnosed as per operational definition. Pregnant women with gestational age between 32-36 weeks, confirmed on ultrasound were included in the study. Exclusion Criteria included neonates with malformations diagnosed on antenatal ultrasound, neonates with intrauterine growth retardation (Fetuses whose estimated weight is less than 10th percentile of its gestational age) diagnosed on antenatal ultrasound, patients who have received previous fetal blood transfusions in the current pregnancy, Ectopic pregnancies (Fetus who developed outside the uterus) confirmed on ultrasound.

OPERATIONAL DEFINITION:

Rhesus Alloimmunization:

It was defined as pregnancies in whom mother have anti-D titers >1:16.

Prediction Of Neonatal Anemia On MCA-PSV:

It was defined as positive in fetuses who have >1.5 MoM (from calculator downloaded from website: <http://www.perinatology.com/calculator/MCA.htm>)

Prediction Of Neonatal Anemia On Neonatal Hemoglobin:

It was defined as a hemoglobin level of 13.5 g/dL or less on neonatal blood sampling at the time of delivery.

DATA COLLECTION PROCEDURE:

Ethical committee approval was taken from institutional review board. Patients according to the inclusion/exclusion criteria were enrolled in the study. Informed consent was obtained from all the patients after explanation of the study protocol. Demographic details like mother's age, parity and gestational age were noted and Doppler examination of the middle cerebral artery was performed. An axial view of the brain, including the thalami and the cavitas septi pellucidi, were obtained. The circle of Willis was visualized using color Doppler and the middle cerebral artery (MCA) of one side was examined close to its origin from the internal carotid artery, with the angle between the ultrasound beam and the direction of blood flow being kept as close to zero as possible. Three measurements of peak systolic velocity (MCA-PSV) at time of absent fetal body and breathing movements were taken, and the highest velocity level

was recorded. Doppler examinations were performed by two radiologists of more than two years experience. It was converted into multiples of median with reference to gestational age from the calculator downloaded from the website <http://www.perinatology.com/calculators/MCA.htm>. A MCA-PSV of >1.5 MoM was taken as positive. The neonatal blood sent for hemoglobin estimation soon after birth to the hospital pathology laboratory and neonatal anemia was labeled as positive as per operational definition.

Results

Total 189 study subjects with age 20-45 years meeting inclusion criteria of study were included in the study to determine the diagnostic accuracy of fetal middle cerebral artery peak systolic velocity (MCA-PSV) in detection of neonatal anemia in rhesus alloimmunization keeping neonatal hemoglobin estimation at birth as the gold standard.

Statistical package for social sciences (SPSS 21) was used for data compilation and analysis. The overall mean mother's age was 29.29 ± 4.42 years. The overall mean gestational age was 34.02 ± 1.16 weeks. The overall mean parity of study subjects was 3.01 ± 1.01 . Among all study neonates, 55.6% were male and 44.4% were female.

Among study subjects, 39.7% had family income $\leq 20,000$ PKR, 54.5% had family income between 21,000 to 50,000 PKR and only 5.8% had monthly family income more than 50,000 PKR.

In our study, 40.7% patients were diagnosed neonatal anemia by MCA-PSV and 40.2% by neonatal hemoglobin estimation at birth as presented in (Tab. 1) and (Tab. 2) respectively.

Sensitivity, Specificity, Predictive values and diagnostic accuracy of MCA-PSV for neonatal anemia by taking neonatal hemoglobin estimation at birth as gold standard were calculated.

The results showed that there were 66 patients true positive, correctly diagnosed and 102 patients were true negative, also correctly concluded. Sensitivity, Specificity, PPV, NPV and diagnostic accuracy were 86.8%, 90.3%, 85.7%, 91.0%, and 88.8% respectively. These results are presented in (Tab. 3).

The stratification according to age of mother, gestational age, gender of baby, educational status,

	Frequency (n)	%
Yes	77	40.7%
No	112	59.3%
Total	189	

Table 1: Frequency distribution of neonatal anemia on MCA-PSV (n=189)

	Frequency (n)	%
Yes	76	40.2%
No	113	59.8%
Total	189	

Table 2: Frequency distribution of neonatal anemia on neonatal hemoglobin estimation at birth (n=189)

MCA-PSV	Neonatal hemoglobin estimation at birth			P-value
	Yes (n=76)	No (n=113)	TOTAL	
Yes (n=77)	66	11	77	0.000*
No (n=112)	10	102	112	
TOTAL	76	113	189	
Sensitivity	Specificity	PPV	NPV	Accuracy
86.8%	90.3%	85.7%	91.0%	88.8%

Chi square test was applied.
P-Value ≤ 0.05 considered as significant.

* Significant at 0.05.

Table 3: Diagnostic accuracy of MCA-PSV for diagnosis of neonatal anemia neonatal hemoglobin estimation at birth as gold standard (n=189)

parity, ethnicity and socioeconomic status was done and sensitivity, specificity, and diagnostic accuracy were also calculated. Post stratification with these modifiers was calculated using chi square test considered $p \leq 0.05$ as significant. All calculations concluded similar results and no significant difference found among the groups made considering age of mother, gestational age, gender of baby, educational status, parity, ethnicity and socioeconomic status.

Discussion

Since the literature has shown controversial results about diagnostic accuracy and sensitivity and specificity of noninvasive measurements and ultrasound findings in detecting fetal anemia in rhesus alloimmunization, and no such study has been known to be conducted in Pakistan and it is thought that our results could be different due to the presentation of

multiple ethnicity and different socioeconomic and educational status. So, this study was aimed to determine the diagnostic accuracy of fetal middle cerebral artery peak systolic velocity in prediction of neonatal anemia in rhesus alloimmunisation keeping neonatal hemoglobin estimation at birth as the gold standard in public sector hospital of metropolitan city Karachi.

While reviewing literature, in one study by Alshimmiri, it is stated that sensitivity and specificity of MCA-PSV in predicting the fetal anemia is 44% and 96%.⁵ Another study by Ochoa-Torres showed that Doppler ultrasonography of the middle cerebral artery has a sensitivity of 91.7% and specificity of 90.9%⁶ to detect fetal anemia.

In our study 40.7% patients were diagnosed neonatal anemia by MCA-PSV and 40.2% by neonatal hemoglobin estimation at birth. The results showed that there were 66 patients were true positive, correctly diagnosed and 102 patients were true negative, correctly diagnosed. Sensitivity, Specificity, PPV (Positive Predictability Value), NPV (Negative predictability value) and diagnostic accuracy were 86.8%, 90.3%, 85.7%, 91.0%, and 88.8% respectively.

Although studies have evaluated the efficacy of noninvasive measurements in detecting fetal anemia, most have failed to find a good correlation between ultrasound findings and the presence of fetal anemia.⁷⁻¹⁰ Among these studies, study by Copel,⁸ pulsed doppler waveform was focused and Bahado-Singh¹⁰ focused fetal spleen by ultrasound.

This lack of correlation in others could be attributed to the use of angle-independent indexes, such as the pulsatility index and the resistance index, which are independent of blood velocity. In contrast, in a preliminary study, Mari G¹¹ found that the peak systolic velocity in the middle cerebral artery was higher in fetuses with anemia than in normal fetuses. Similar results were reported by Vyas and coworkers.¹² However, Hecher K group did not find a significant association between the degree of anemia and the mean velocity of blood flow in the middle cerebral artery.⁹

A precedent for an increased velocity of blood flow in the cerebral arteries of fetuses with anemia can be found in data indicating that the velocity of blood flow in several circulatory beds, including the brain, is increased in fetal animals with anemia because of

an increased cardiac output and a decline in blood viscosity.¹³ Similar results were subsequently found in other studies.¹⁴⁻¹⁵

Furthermore, the peak systolic velocity in the middle cerebral artery decreases when the fetal hematocrit rises.¹⁶ These findings indicate that there is a reciprocal relation between the hemoglobin concentration and the velocity of cerebral blood flow. In a study they found that the risk of anemia was high in fetuses with a peak systolic velocity of 1.50 times the median or higher. Fetuses with values below 1.50 either did not have anemia or had only mild anemia. The fact that this test does not predict mild anemia well is not clinically important, because no intervention is indicated in fetuses with mild anemia, as defined in our study, whereas those with moderate or severe anemia should undergo cordocentesis and may need transfusion.¹⁷

In the United States, on the assumption that 4 million infants are born each year, approximately 4000 pregnancies are complicated by Rh alloimmunization, but only 10 percent of those require intrauterine transfusion before 34 weeks of gestation. More than 10,000 pregnancies are complicated by alloimmunization against other blood-group antigens, and less than 10 percent of those require intrauterine transfusion. Therefore, approximately 1400 fetuses each year require intrauterine transfusion.¹⁷

To detect the fetuses at risk for hydrops before 34 weeks of gestation (10 percent of the entire population at risk), either serial cordocentesis or serial amniocentesis is currently performed. Although cordocentesis allows direct measurement of fetal hemoglobin, it is associated with infection, bleeding, fetal bradycardia, premature rupture of the membranes,^{18,19} and a procedure-related pregnancy loss of 1 percent.¹⁷ If each fetus at risk for anemia were to undergo one cordocentesis procedure, they estimated that there would be at least 140 fetal losses every year. Amniocentesis is less invasive than cordocentesis, but the reliability of measurements of bilirubin in amniotic fluid before 27 weeks of gestation is questionable.^{20,21} For both amniocentesis and cordocentesis, there are no data concerning the optimal frequency of repeated sampling.²²⁻²⁴ Furthermore, these procedures may be associated with a worsening of maternal alloimmunization. Finally, the results of the analysis of amniotic fluid in cases in which there is sensitization to Kell

antigens correlate poorly with the severity of fetal anemia.²⁵

Study Limitations

The main limitations of the present study include a single-center experience. It was conducted with small sample size therefore, the results might not be generalizable to larger populations.

Conclusion

The study findings concluded that with 86.8% sensitivity, 90.3% specificity and 88.8% diagnostic accuracy, the measurements of the peak velocity of blood flow in the middle cerebral artery in fetuses at risk for anemia due to maternal red-cell alloimmunization provide an accurate and noninvasive means of determining the degree of anemia.

Conflict of Interest: Authors declared none

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