Original Article

Diagnostic Accuracy of Foetal Cardio-femoral index as a Predictor of Anemia in Rhesus Alloimmunized Foetuses

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Abstract

Objective: To calculate the diagnostic accuracy of the cardiofemoral index in prediction of neonatal anemia in rhesus alloimmunisation keeping neonatal hemoglobin estimation at birth as the gold standard.

Methodology: This cross sectional validation study was conducted in the department of Radiology, Shifa International Hospital, Islamabad from Jan 2016 to Dec, 2016. A total of 106 pregnant women near term between 32-35 weeks were included. Patients were subjected to Toshiba Nemio XG (Ta312) real time Doppler ultrasound. Using the 3.75 MHz sector transducer, the fetal biventricular outer dimension of heart was obtained. Then the foetal femur length was calculated. The cardiofemoral index was measured by the ratio between the biventricular outer dimension in diastole and femur length (both in centimeters). The neonatal blood was sent for hemoglobin estimation soon after birth to the hospital pathology laboratory. The results of the cardiofemoral index and neonatal hemoglobin were entered into the Performa.

Results: The average age of the patients was 25.93±5.97 years. Sensitivity, specificity, PPV, NPV and accuracy of the cardiofemoral index in detecting hemoglobin were 82.9, 92.3, 87.2, 89.5 and 88.7 % respectively.

Conclusion: Measurement of the cardiofemoral index in foetuses at risk for anemia due to Rhesus alloimmunization provides an accurate and noninvasive radiological test for the prediction of foetal anemia.

Keywords: Fetal Cardio-femoral index, Fetal Cardio-femoral index, foetal anemia

Cite this article as: Babar KS, Rafique MS, Pervez R, Kumar M, Mohsin K, Rafique A. Diagnostic Accuracy of Foetal Cardio-femoral index as a Predictor of Anemia in Rhesus Alloimmunized Foetuses. J Soc Obstet Gynaecol Pak. 2022; 12(3):230-234.

Introduction

The prevalence of alloimmunization is 23.6% among Rh (Rhesus) negative women. In developed nations, the prevalence of this disease has been reduced by the use of anti-D prophylaxis during pregnancy, after birth, and after an abortion. However, in developing and underdeveloped nations like Pakistan, where prophylactic programmes are lacking, 14% of affected pregnancies result in stillbirths, and 50% of newborns die or suffer brain trauma.[2] Fetal anaemia is the consequence of maternal alloimmunisation. The compensatory hyperdynamic responses of fetus to anemia include increasing cardiac output and changes in peripheral vascular resistance. In general, the foetus always tolerates mild to moderate anaemia well, but when the deficit of haemoglobin is extreme, fetal hydrops develops. In patients with isoimmunisation, a higher biventriclular outer dimension (BVOD) was associated with the relatively high likelihood of neonatal anaemia and need for transfusion.[3]

An inverse correlation was observed between fetal blood hemoglobin concentration and biventricular outer dimension measurement, regardless of gestational age, which opened up doors for its use as the fetal cardiofemoral index for prediction of anemia.[4] The cutoff of cardiofemoral index of 0.60 was the best to predict a level of fetal hemoglobin (Hb) below or equal to 10.0g/dl with 80.85% sensitivity, 83.13% specificity, 73.8% positive predictive value, and 88.46% negative predictive value, in the diagnosis of fetus anemia.[4] The

cardiofemoral index is obtained by the ratio between the ultrasonographic measurement of the biventricular outer dimension and femur length (both in centimeters). The cardiofemoral index may be a reliable noninvasive indicator of severe foetal anaemia in high-risk pregnancies, and its precision is the same for both transfusion-previous and non-transfusion-previous foetuses.[5]

A significant advance in the noninvasive identification of foetal anaemia is use of doppler ultrasonography examination to determine the peak systolic velocity of the foetal middle cerebral artery (MCA).[6] According to meta-analysis by Pretlove et al, tests other than MCA-PSV like cardio-femoral index have been discarded because of their lack of diagnostic accuracy.[7] Cabral et al, found that when CFI and MCA-PSV were combined, they were reliable indicators of severe foetal anemia.[8]

For the identification of severe foetal anaemia, Cabral et al, introduced the cardiofemoral index, a noninvasive technique that is still being investigated. This index serves as a direct indicator of heart size, and enlarged hearts are link to foetal anaemia. The CFI may also be used to predict severe recurring anaemia in foetuses and to check them frequently for anaemia whether or if they have received transfusions.[8] Red-cell immunization is a main factor of hemolytic foetal anemia and severe neonatal jaundice. Hence, the emphasis on the prevention of immunization in different situations of feto maternal bleeding by early intravenous injection of immunoglobulin is recommend depending on the term of pregnancy and the clinical circumstances.[9, 10] Since the literature has given controversial results about the accuracy of cardio-femoral index, we have planned to conduct a study to determine how accurate is cardio-femoral index is in the prediction of neonatal anemia locally. If found accurate, then this non-invasive method can be adopted in future for early diagnosis and to decrease morbidity in these patients.

All cases for the cardiofemoral index should submitted to B-mode and M-mode ultrasound. The biventricular outer dimension should be obtained according to a technique described by DeVore et al. 1985[11] The four-chamber echocardiographic image of the foetal heart is obtained in real time and the M-mode cursor is placed perpendicular to the interventricular septum in the plane of the atrioventricular valves. For biventricular outer dimension the image is frozen in cardiac diastole and the distance between the epicardiums of the right and left ventricles is measured. The length of the femur was measured along the diaphysis, excluding the distal epiphysis.[4,12] The cardio-femoral index is calculated by the ratio between biventricular outer dimension and femoral length.[4]

Methodology

A prospective cross-sectional validation study was conducted in the Department of Radiology, Shifa International Hospital over a period of one year from 01/01/2016 to 31/12/2016. Non-probability consecutive sampling was performed. In the Rh-isoimmunized pregnancies, anemia was present in 23/58 (39.6%) of the cases. [9] In the study by Cabral et al[4] the sensitivity was 80.85%. Using the similar formula for specificity, and keeping the specificity of 83.13% as reported by Cabral et al[4] and CI 95%, absolute precision 0.10, the sample size was calculated to be 106. Singleton pregnancies near term between 32-35 weeks and Rh-negative mothers with suspected fetal red cell anti-D alloimmunization on the basis of maternal anti-D titers >1:16 were included. Neonates with malformations and intrauterine growth restriction diagnosed on antenatal ultrasound as well as patients who had already received fetal blood transfusions in the current pregnancy were excluded.

Permission was taken from the hospital ethical review committee. Patients were scanned on Toshiba Nemio XG (Ta312). Using a 3.75 MHz sector transducer foetal biventricular outer dimension of heart was obtained. Then the fetal femur length was calculated. The cardiofemoral index was measured by the ratio between the biventricular outer dimension in diastole and femur length (both in centimeters). The neonatal blood was sent for hemoglobin estimation soon after birth to the hospital pathology laboratory. Data analysis was performed using SPSS 20.0. Gestational age was estimated using Naegle's rule. The EDD is calculated by counting nine months from the last menstrual period and adding seven days. Rhesus alloimmunization will be defined as pregnancies in whom mother have anti-D titers >1:16. The cardiofemoral index will be considered as positive if it is more than 0.60. Neonatal anemia will be defined as a hemoglobin level of 10.0g/dl or less.

Results

There were 106 pregnant women near term between 32-35 weeks in this study. The age of the patients is presented in table I. The average age of the patients was 25.93±5.97 years and mean gestational age, parity and hemoglobin are also shown in table I. Most of the

women had multiparity, i.e., 53.8%. 36.8% of patients were anemic according to the cardiofemoral index, while hematology hemoglobin of neonate was observed in 38.7% anemic according to cutoff Hb < 10 gm/dl. Sensitivity, specificity, PPV, NPV and accuracy of the cardiofemoral index in detecting the hemoglobin was 82.9%, 92.3%, 87.2%, 89.5% and 88.7% respectively as shown in table II.

Table I: Descriptive statistics of the patients (n=106)

	Age (Years)	Gestational Age (Weeks)	Parity	Hemoglobin (gm/dl)
Mean± SD	25.93±5.97	33.31±1.19	1.59±1.06	11.94±2.32
Min-Max	18-40	32-35	0-4	8.20-14.90
Median	26	33	2	12.05

Table II: Diagnostic Accuracy of Cardiofemoral Index (Cfi) In Prediction of Neonatal Anemia in Rhesus Alloimmunisation Keeping Neonatal Hemoglobin Estimation At Birth.

Cardiofemoral Index (CFI)	Diagnosis of Neonatal Anemia		Total
	Hb < 10 gm/dl (Anemia present)	Hb ≥ 10 gm/dl (Anemia present)	
Anemia Present (CFI > 0.60)	34 (TP)	5 (FP)	39 (36.8%)
Anemia Absent (CFI ≤ 0.60)	7 (FN)	60 (TN)	67 (63.2%)
Total	41 (38.7%)	65 (61.3%)	106
Sn 82.9%, Sp 92.3%, PPV 87.2%, NPV 89.5%, Accuracy 88.7%			

Table III: Comparison of Diagnostic Accuracy of Cardiofemoral Index (CFI) in Prediction of Neonatal Anemia in Rhesus Alloimmunisation Keeping Neonatal Hemoglobin Estimation at Birth between Gestational Age Groups.

Gestational Age (Weeks)			Diagnosis of Neonatal Anemia		Total
			Hb ≤ 10 gm/dl	Hb ≥ 10 gm/dl	
31-33	CFI Diagnosis of fetal Anemia	CFI > 0.60	14	2	16
		CFI ≤ 0.60	5	36	41
	Total		19	38	57
>33	CFI Diagnosis of fetal Anemia	CFI > 0.60	20	3	23
		CFI ≤ 0.60	2	24	26
	Total		22	27	49
Total	CFI Diagnosis of fetal Anemia	CFI > 0.60	34	5	39
		CFI ≤ 0.60	7	60	67
	Total		41	65	106
Sn 73.68%,Sp 94.74%, PPV 87.50%, NPV 87.80%, Accuracy 87.70% Sn 90.91%, Sp 88.89%, PPV 86.96%, NPV 92.31%, Accuracy 89.79%					

Stratification of data was done according to gestational age of female at the time of scan with results in table III. The sensitivity and specificity for cardiofemoral index in diagnosing neonatal anemia is 73.6 and 94.7% for gestational age from 31 to 33 weeks. The sensitivity and specificity for cardiofemoral index in diagnosing neonatal anemia is 90.9 and 88.8 % for gestational age above 33 weeks. These calculations of data described in table III.

Discussion

The causes of foetal anaemia are numerous. But one of the most frequent causes is still red cell alloimmunization. The issue of foetal anaemia will persist, so it's critical to be aware of the techniques available for diagnosing it, particularly non-invasive methods.[13] For many years, red cell alloimmunization-related foetal anaemia has been diagnosed using amniocentesis and cordocentesis. But the procedures are invasive and come with risks like infection, haemorrhage, and even foetal death. [14,15]

The first study to suggest that ultrasonography can be helpful in cases of foetal anaemia, conducted by Campogrande et al.[16] According to Hobbins[17] in 1980, hydramnios, increased placental thickness, enlargement of the fetus's liver, and hydrops were all indications of foetal anaemia. He also recommended that a diagnosis of the condition could be made with the help of ultrasound. Following this research, other researchers examined for an ultrasonographic technique that could accurately diagnose foetal anaemia. According to DeVore et al.[18], anaemic foetuses had a larger umbilical vein diameter. The visibility of both sides of the foetal bowel was described by Benacerraf and Frigoletto[19] as a sign of foetal anaemia. Nicolaides et al. [20] investigated six ultrasonographic measurements but reached the conclusion that they were not good parameerst of foetal anaemia. Hydramnios and placental thickness were found to be useful indicators of foetal anaemia, study conducted by Chitkara et al.[21] According to Oepkes et al.[22], splenic circumference is increased in anaemic foetuses and may help in the identification of the condition. The findings of Vintzileos et al.[23] that anaemic foetuses have larger foetal livers were validated by Roberts et al. [24]

Doppler imaging parameters have been suggested by other researchers for the identification of foetal anaemia.; Rightmire et al. [26] discovered that anaemic babies had higher umbilical artery resistance index and aortic and inferior vena cava blood velocities; and Copel

et al.[27,28] carried out a retrospective research and reported that the evaluation of maternal circulation and the foetal aorta might diagnose foetal anaemia, although these authors were unable to prove the findings when they prospectively used the formula acquired in the retrospective analysis. The MCA peak systolic velocity (PSV) method, introduced by Mari G et al[29], has shown encouraging results in the detection of foetal anaemia.

It is important to note that BVOD is easy to obtain, since the four-chambered view of the fetal heart is essential component of the general obstetric ultrasound examination and can be done by the ultrasonographer in primary care services. Beforehand indecisive studies have tried to predict foetal anemia by cardiac measurements; it was demonstrated that, irrespective of the physiological factor of fetal growth causing simultaneous increase of the cardiac chambers, the reduction of hemoglobin levels associate with the increase of the BVOD measurement.[30] Ventricular remodelling with dilatation of the cardiac chambers is largely accountable for the increase in cardiac output detected in the anemic fetuses, and probably responsible for the good results of the suggested cardio-femoral index. The cardio femoral index uses the ratio between BVOD and femoral length to compose a parameter independent of gestational age.

Thus, elevation of the cardiac-femoral index reflects cardiac dilatation in the course of deteriorating foetal anemia, which is demonstrated by the inverse association between the index and the concentration of foetal hemoglobin found in the study. However, it is essential to rule out the causes of shortening of bones that could falsely compromise the index, such as skeletal dysplasias and chromosomal disorders.[3,4,5]

We observed that when the value of the cardiac-femoral index is equal to or more than 0.6, the results of our study are comparable with that done by Cabral et al[4] for the detection of foetuses with hemoglobin less than 10 g / dl, perfect level for the performance of intrauterine treatment. Therefore, it is thought that this index will be very valuable for the diagnosis of foetal anemia alone or in association with other non-invasive methods, with the great advantage of being a simple, easy to perform and affordable methodology.

Conclusion

Measurement of the cardiofemoral index in foetuses at risk for anemia due to Rhesus alloimmunization provides an accurate, noninvasive, simple, and affordable radiological test for the prediction of foetal anaemia.

Disclosure: This article is retrieved from a CPSP approved dissertation.

Acknowledgement: Special thanks to statistician 'Mr.Aamir Afzal' (B.Sc Stats, M.Sc Stats, MS HME, analysis222@gmail.com). We acknowledged his consultancy services in statistical analysis/design of the data and guidance.

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