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Research Article

Relationship between Cardiofemoral Index and Fetal Blood pH in Fetuses with Rh Alloimmunization

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Abstract

Introduction: Alloimmunization is the main cause of fetal and neonatal anemia. Unfortunately, in spite of the discovery of the anti-Rh immunoglobulin in the sixties, its incidence is still unacceptably high in Brazil. The Fetal Medicine Center of the Federal University of Minas Gerais (UFMG) is a referral center for alloimmunization. Fetal anemia is a common result of alloimunization and is an important cause of fetal congestive heart failure resulting in heart dilation. The increase in Cardiofemoral Index (CFI) reflects cardiac dilation in the process of worsening fetal anemia, which is demonstrated by the inverse correlation between this index and the concentration of fetal hemoglobin. Studies have also shown a correlation between fetal anemia and fetal gasometry: as fetal anemia worsens, fetal blood pH decreases. **Objective:** This study aims to determine the relationship between cardiofemoral index and fetal gasometry in fetuses with alloimmunization and, Bencke, to evaluate if a noninvasive method (CFI) can predict fetal acidemia. **Patients and Methods:** A cross-sectional study was carried out in 51 pregnant women with alloimmunization between 25 to 34 weeks of gestation, followed at the Fetal Medicine Center of the Federal University of Minas Gerais (UFMG). These patients, whose fetuses had clinical evidence of anemia, had formal indication for cordocentesis to determine the hemoglobin level in fetal blood. The 51 patients were submitted to a total of 68 cordocenteses. Before cordocentesis, cardiac measurements of Biventricular Outer Diameter (BVOD) were obtained in a four-chamber view at the end diastole using real time ultrasound and M-mode assessment. Afterwards, fetal femur length was obtained and CFI was calculated by dividing DVOD by femur length in each case. For the ultrasound scans, a SONOACE 8800 (Medsom) was used. Gasometry was determined in each blood sample obtained from cordocentesis. CFI was associated with fetal pH using linear regression ($p<0.05$). A ROC curve was used to determine the ideal cutoff point to compare CFI to fetal acidemia, defined as $pH<7.2$ ($p<0.05$). Results: an inverse relationship between CFI and fetal pH was observed ($p=0.001$); Using a ROC curve, the ideal cutoff point obtained to compare CFI to fetal pH was 0.64 ($p=0.0003$, sensitivity=100%, specificity=77%). **Conclusions:** We observed an inverse and significant relationship between CFI and fetal blood pH: as CFI increases, fetal pH decreases and fetal acidemia ($pH<7.2$) might happen; the ideal CFI cutoff point for the screening of fetal acidemia is 0.64. Fetuses with CFI below 0.64 are not acidemic, whereas fetuses with CFI equal or greater than 0.64 are at risk for acidemia.

Keywords: Isoimmunization; Fetal anemia; Cardiofemoral index; Fetal gasometry; Fetal acidemia

Introduction

In patients with alloimmunization, a fetal Biventricular Outer Dimension (BVOD) measurement of the fetal heart in the 95th percentile or greater was associated with a relatively high likelihood of neonatal anemia and need for transfusion [1]. An inverse correlation between fetal hemoglobin concentration and BVOD measurement has been shown, regardless of gestational age. [2].The Cardiofemoral Index (CFI) uses the ratio between the BVOD and the length of the femur to compose a parameter that is independent of gestational age. The increase in CFI reflects cardiac dilation in the process of worsening fetal anemia, which is demonstrated by the inverse correlation between this index and the concentration of fetal hemoglobin. ICF equal to or higher than 0.6 might has been associated (sensitivity: 80.9%; specificity: 83.1%; positive predictive value: 73.1% and negative predictive value: 88.5%) with the detection of fetal hemoglobin lower than 10 g/dl, a threshold for fetal transfusion [3,4]. Studies have also shown a correlation between fetal anemia and fetal gasometry: as fetal anemia worsens, fetal blood pH decreases. We studied the relationship between CFI and fetal acidemia in fetuses with alloimunization.

Methods

A cross-sectional study was conducted from January 2000 to January 2006 at the Fetal Medicine Center of the Federal University of Minas Gerais, Brazil, and included 51 alloimmunised pregnant women at high risk for fetal or neonatal anemia with 25-34 weeks' gestation age (mean 26.6 +- 2.5) and aged 19-41 years. This group of pregnant women was submitted to 68 cordocenteses. The study was aproved by the Ethics Committee and all participants were informed about the prenatal follow-up protocol. Fetuses requiring invasive testing were included in the study. Indication for cordocentesis was determined clinically based on previous history of erythroblastosis fetalis, indirect Coombs test (indirect anti- globulin test), spectrophotometric analysis, and Doppler examination of middle cerebral artery peak systolic velocity.

Up to 6 h prior to each of the 68 cordocenteses, scans were performed using a Sonoace 8800 ultrasound (Medison, Seoul, Korea) equipped with a 3.5 MHz probe. BVOD measurements were carried out according to the technique described [5]. The M-mode ultrasound cursor was set perpendicular to the inter-ventricular septum at the atrioventricular valves. Heart evaluation was performed by freezing an image during diastole and measuring the distance between the right- and left-side epicardia (Figure 1). Next, the femur length was measured from the greater trochanter to the distal metaphysis, excluding the distal epiphysis. Cardiofemoral Index (CFI) was calculated by dividing the BVOD by femur length. Results were not used for clinical purposes.

A small amount of blood, obtained from ultrasound-guided cordocentesis, was used to measure the fetal pH [6]. Samples were carried out at the Laboratory of the Hospital das Clínicas of UFMG, using a Copenhagen blood gases analyzer: 1.0 ml sample of umbilical cord blood was withdrawn with a syringe containing 0.1 ml of sodium heparin 5000 IU/ml; the syringe was sealed with a rubber placed on the tip of the needle; homogenization of the solution was obtained by rotating movements of the syringe; gasometric analysis was performed, measuring pH, using a microdosing blood gas analysis equipment.

To determine sample size, we considered an 80% study power (beta error of 20%) and a two- tailed alpha error of 5%. A minimum number of 50 cases was obtained, using the Statcalc function of the EPI-INFO® program, version 2002. This methodology was used, since there was no other similar study in the literature. Test characteristics (sensitivity, false positive ratio, negative prediction values, likelihood ratios for positive and negative test results) and Receiver- Operating Characteristic (ROC) curve was determined. The area under the curve (AUC) was calculated for comparisons and to determine the most accurate cutoff point for the diagnosis of fetal acidemia (pH<7.2). During the study period, 51 fetuses were submitted to a total of 68 cordocenteses: 36 fetuses were submitted to 1 cordocentesis; 11 fetuses were submitted to 2 cordocenteses; 2 fetuses were submitted to 3; and 1 fetus was submitted to 4 cordocentesis. The MINITAB Inc® program, version 11.12/1996, was used to create the database and perform statistical analysis. The relationship between the cardiofemoral index and fetal pH was estimated by linear regression. The significance level was $p<0.05$ (Figure 1).

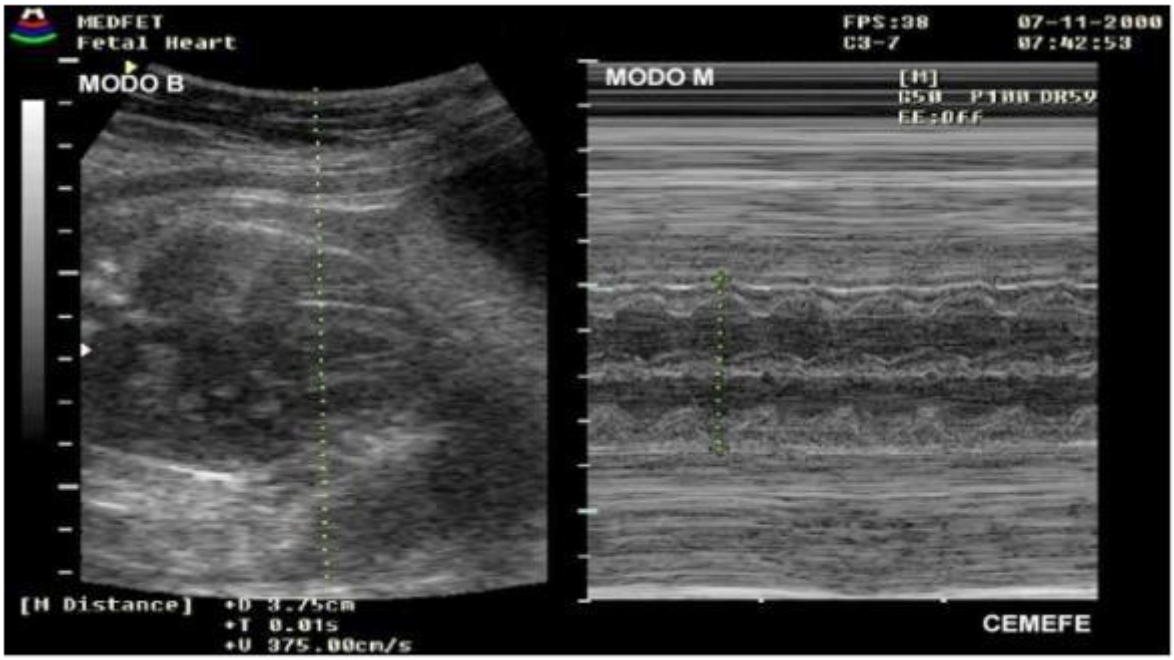


Figure 1: Ultrasound of the fetal biventricular outer dimension (BVOD).

Results

A total of 51 fetuses from 25 to 34 weeks of gestational age were submitted to 68 cordocenteses (median 1.33 procedures per fetus). Maternal characteristics of the study population (n=51) and fetal parameters before each cordocentesis (number of total cordocenteses=68) are shown in Table 1. In the 68 cases, the cardiofemoral index obtained was associated with the fetal blood pH obtained under ultrasound guidance.

Characteristics	n	Mean±SD	Median	Range
Maternal characteristics				
Maternal age, y	51	26.6±2.5	-	19-41
Parity	51	-	2	1-8
Gestational age at first care, weeks	51	27.3±4.3	-	13-34
Gestational age at first cordocentesis, weeks	51	28.0±3.7	-	25-34
Numbers of Rh antigens	51	-	1	1-6
Fetal parameters				
Hydrops at first cordocentesis	16 (31.3%)	-	-	-
Number of cordocentesis	68	-	2	1-4
Fetal hemoglobin before cordocentesis, g/dL	68	9.15±3.07	-	4.5-15.7
Femur length, cm	68	5.1±0.9	-	3.2-6.3
Biventricular outer dimension, cm	68	3.3±0.8	-	2.0-5.9

Cardiofemoral index (CFI)	68	0.65±0.15	-	0.43-0.86

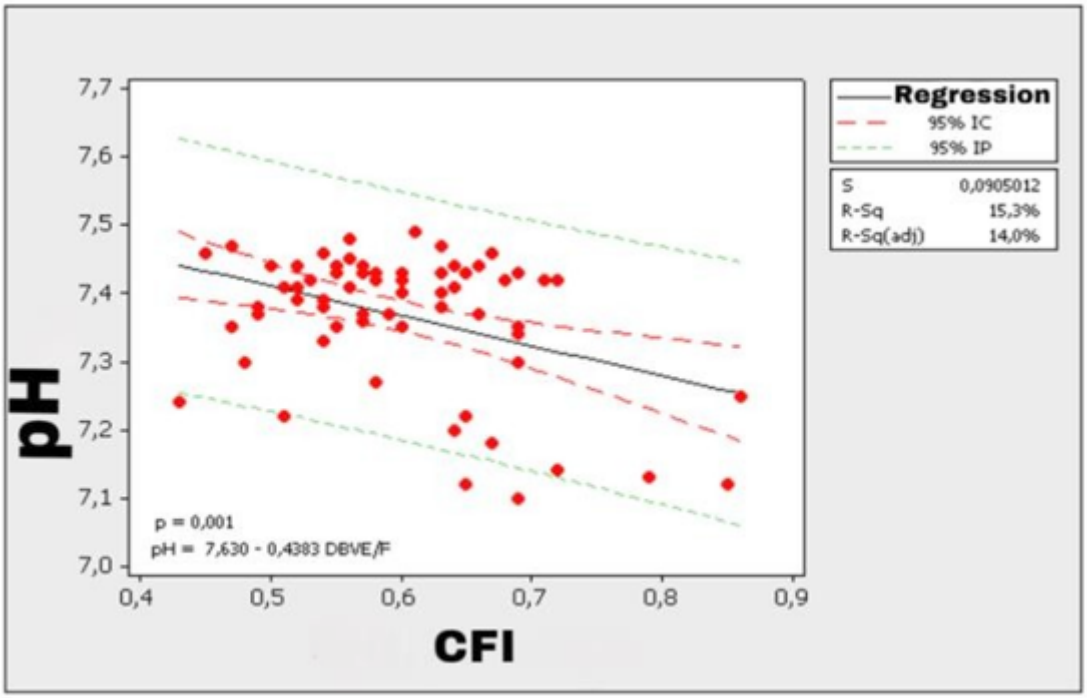
Table 1: Maternal characteristics of the study population (n=51) and fetal parameters before cordocentesis (total of 68 cordocentesis).

The descriptive analysis of the study group according to the variables cardiofemoral index and fetal pH is show in Table 2.

Variables	Mean	Min-Max	Median	Standard deviation
BVOD/Femur length (CFI)	0.59	0.43 - 0.86	0.58	0.086
pH	7.36	7.1-7.49	7.4	0.097

Table 2: Descriptive analysis of the study group according to the variables cardiofemoral index and fetal pH.

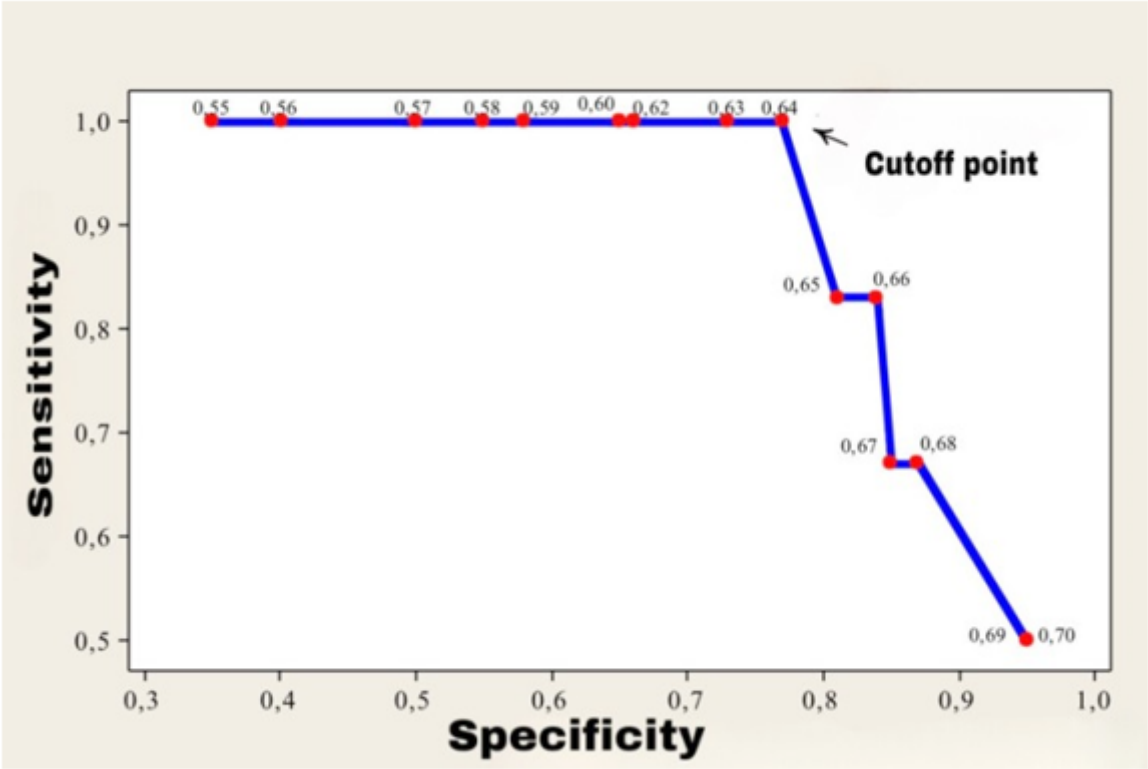
An inverse relationship between the cardiofemoral index and fetal blood pH (p=0.001) was observed. Thus, as the cardiofemoral index increases, the pH in fetal blood decreases (Graphic 1). The regression equation found was pH=7.63-0.438 BVOD/Femur length.



Graphic 1: Relationship between Cardiofemoral Index (CFI) and fetal blood pH.

The Area Under the Curve (AUC) was calculated for comparisons and to determine the most accurate cutoff point for the diagnosis of fetal acidemia (pH<7.2).

The value 0.64 was considered the best cutoff point for the index under study, with a sensitivity of 100% and a specificity of 77% (Graphic 2).



Graphic 2: ROC curve to determine the ideal cardiofemoral index cutoff point for the prediction of fetal acidemia.

Table 3 shows the comparison between the Cardiofemoral Index (CFI) and fetal acidemia in the study group, considering the value of 0.64 as the CFI cutoff point. Fetuses with pH<7.2 were considered acidemic.

Índice cardiofemoral	pH<7.2	pH≥7.2	Total
≥0.64	6	14	20
<0.64	0	48	48
TOTAL	6	62	68
P=0.0003			

Table 3: Relationship between cardiofemoral and fetal acidemia fetal in the study group, considering cutoff of 0.64.

Positive predictive value=30%; negative predictive value=100%; percentage of false positives=70%; percentage of false negatives=0%; Accuracy=79.4%.

Discussion

Fetal echocardiography is used to diagnose fetal heart and evaluate the prognosis of anatomic cardiac lesions. Fetal anemia can cause fetal congestive heart failure and subsequent hydrops. The BVOD is the widest measurement of the ventricles at the atrioventricular valve plane, and it is an important method for the diagnosis of fetal cardiomegaly [7]. BVOD was first described to diagnose feta anemia by Ouzounian, et al. [1]. CFI is a direct marker of the size of the fetal heart size and its enlargement, and has also been associated with fetal anemia [3,4]. It is known that fetuses with severe anemia might evolve with a decrease in fetal blood pH [8].

Fetal pH might be influenced by maternal diseases presenting with metabolic acidosis, such as chronic hypertension, preeclampsia, nephropathy, diabetes mellitus [9]. In our study, alloimunized pregnant women with such diseases were excluded.

The fetal blood gasometry also depends on the studied population. Therefore, we decided to use to consider fetal acidemia as the presenter of fetal pH<7.2, according to what Riley and Johnson (1993) proposed in the largest study of the literature, which evaluated the gasometric parameters of 3.522 fetuses at various gestational ages [10].

Our study aimed to determine whether CFI has the potential to predict fetal acidemia (pH<7.2). The receiver–operating characteristics showed that CFI performs well for predicting fetal acidemia. We observed an inverse and significant relationship between cardiofemoral index and fetal pH: while cardiofemoral index increases, fetal pH decreases and acidemia (pH<7.2) might happen. The ideal set point of cardiofemoral index for screening of fetal acidemia is 0.64: fetuses with cardiofemoral index below 0.64 are not acidemic whereas fetuses with cardiofemoral index higher than 0.64 are at risk for acidemia (with 100% sensitivity, 77% specificity and 79.4% accuracy (p<0.0003).

The positive predictive value found in this study was low (30%), resulting in a high false-positive rate (70%). The low value found can be explained through statistical concepts. It is known that the positive predictive value of a test is influenced by the prevalence of the disease. In this study, only six fetuses were acidemic (pH<7.2) and, therefore, despite the high sensitivity found, it was not possible to conclude that the cardiofemoral index greater than or equal to 0.64 can predict acidemia. However, the high specificity and high negative predictive value found (100%) allow the use of the cutoff point of 0.64 to screen fetuses at risk of acidemia: fetuses with a cardiofemoral index lower than 0.64 have no acidemia. On the other hand, fetuses with CFI equal to or higher than 0.64 are at risk of acidemia.

Limitations of CFI measurement include the quality of the ultrasound equipment, fetal positioning, maternal obesity, excessive fetal movement and the experience of the examiner. However, all examinations were performed by a single examiner, duly trained, using a high-resolution ultrasound scanner.

The most relevant finding of this study was its clinical applicability, as it shows that, with the use of an ultrasound measurement, CFI, it is possible to identify fetuses with alloimmunization at risk of acidemia, as well as identify alloimmunized fetuses in which acidemia can be rule out. It is important to study fetal acidemia in pregnancies complicated by alloimmunization due to the risk of brain injury secondary to this acid-base disorder [11].

Trials correlating other non-invasive methods with blood pH in pregnancies complicated by alloimmunization are essential in order to better understand the impact of fetal acidemia in such patients. Prospective studies that assess the cognitive and neuropsychomotor development of newborns with alloimmunization are also extremely important in order to understand the real clinical impact of our results.

The present study reports preliminary data on the usefulness of the CFI to predict fetal acidemia in pregnancies complicated by alloimmunization. Our results suggest that further studies, with a larger number of acidemic fetuses, may show cardiofemoral index values with a higher positive predictive value for fetal acidemia.

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