Original Article

Assessment of the Correlation Between Hemoglobin Concentration and the Echographic Measurement of Biventricular Outer Diameter in Anemic Fetuses of Isoimmunized Women

Rosangela Lopes Miranda Rodrigues, Alamanda Kfoury Pereira, Marcos Roberto Taveira, Isabela Gomes de Melo, Gabriel Costa Osanan, Antônio Carlos Vieira Cabral
Belo Horizonte, MG - Brazil

Objective

To assess whether a significant correlation exists between the echographic measurement of biventricular outer diameter and the pretransfusional serum concentration of fetal hemoglobin and whether that echographic measurement can be used as a noninvasive marker of fetal anemia.

Methods

A prospective cross-sectional study was carried out comprising 65 cordocenteses performed in 36 anemic fetuses of mothers with isoimmunization to the Rh antigen. The biventricular outer diameter (BOD) was obtained by M-mode evaluation. Previous to the transfusion, a 0.5-mL fetal blood sample was obtained for hemoglobin measurement with spectrophotometry in the Hemocue device. The minimum square regression was used with $P < 0.05$ and multivariate analysis were used as statistical analysis.

Results

An inverse correlation was observed between the fetal hemoglobin concentration before transfusion and the BOD measurement, and a direct correlation was observed between the BOD measurement and gestational age. In addition, multivariate analysis showed that fetal hemoglobin concentration decreases as BOD increases, independently of the influence of gestational age on that parameter.

Conclusion

An inverse correlation exists between fetal hemoglobin concentration and BOD measurement, regardless of gestational age. The findings suggest that BOD may become an echographic predictor of the hemoglobin level of fetuses of isoimmunized pregnant women.

Key words

ecocardiography, fetal anemia, hemoglobin, isoimmunized pregnant women

Centro de Medicina Fetal of the Hospital das Clínicas of the UFMG
Mailing address - Rosangela Lopes Miranda Rodrigues
Rua Gonçalves Dias, 344/02 - Cep 30140-090 - Belo Horizonte, MG, Brazil - E-mail: rosalmr@terra.com.br
Received for publication: 02/05/2004
Accepted for publication: 08/13/2004
English version by Stela Maris Costalonga

Maternal isoimmunization to the Rh antigen is a potentially severe fetal disease characterized by transplacental transfer of fetal Rh-positive red blood cells to the circulation of Rh-negative mothers, triggering in the pregnant woman the production of antibodies that can cause hemolysis, and, consequently, fetal anemia [1].

Finn et al [2] discovered the effective maternal prophylaxis by using the anti-Rh immunoglobulin. Although immunoprophylaxis has greatly reduced the appearance of new cases of maternal immunization, its incidence is approximately 1.5 per 1000 life births. Considering our general population, one case of Rh isoimmunization occurs in each 200 to 300 pregnancies [1].

The fetal anemia consequent to hemolysis leads to a deficiency in red blood cells (whose major function is hemoglobin transportation), which causes a decrease in oxygen concentration in the tissues [3].

As a response to those alterations, stimulation of medullary erythropoietic foci occurs, resulting in exhaustion of the capacity of production, leading to stimulation of extramedullary foci, mainly in the liver and spleen [4], when the hemoglobin level reaches 7g/dL or less [5,6].

The fetus can support extremely low levels of hemoglobin, allowing the development of mechanisms of compensation, the major one being the increase in cardiac output responsible for maintenance of tissue oxygen supply [7, 8].

As the anemic process evolves, the mechanisms of fetal compensation disappear or become ineffective. A reduction in intravascular volume occurs with fluid loss to the extravascular compartment in the pleural, pericardial, peritoneal, and interstitial cavities, leading, in a terminal phase, to dilation in the cardiac chambers and inefficiency of the contractile myocardium, which result in fetal congestive heart failure [8].

Therefore, in severe fetal anemia, high output heart failure occurs, in which the fetal heart increases its output through an increase in heart rate or in stroke volume, or in both, to supply the peripheral oxygen needs. Consequently, the increase in heart workload leads to an increase in oxygen demand, which eventually exceeds the oxygen supply to the myocardium, culminating in dilated cardiomyopathy [9]. Based on these alterations, biventricular outer diameter (BOD) can be used as a highly accurate noninvasive method to detect cardiomegaly [3,10].

This measurement was developed and perfected by Allan et al[11] and Kleinam et al [12], when they initiated a more complete cardio-

logical evaluation by using 2-dimensional echocardiography with direct visualization of the fetal heart. Later, that technique was associated with the M-mode technique, therefore allowing the obtainment of more precise measurements.

Wladimiroff et al [13] reported a normogram for the development of the fetal heart in several phases of pregnancy and were followed by Allan et al [14] and Silverman et al [15].

De Vore et al [10] carried out a study correlating the diameter of the ventricles with the biparietal diameter, as a parameter of fetal growth. Those authors reported the impossibility of using that measurement for assessing the growth of fetuses with intracranial diseases. Then, in a new study [16], they reported the efficacy of the femoral measurement for assessing fetal growth and correlated the former with the diameter of the ventricles.

In accordance with these studies and aiming at elucidating the fetal cardiac response to the anemic process, we carried out the present study, which aimed at assessing the following: whether a correlation exists between the echographic measure of the biventricular outer diameter and the pretransfusional concentration of fetal hemoglobin; and whether that echographic measure may be used as a noninvasive marker of fetal anemia.

Methods

Thirty-six isoimmunized pregnant women from the Fetal Medicine Center (CEMEFE) of the Hospital das Clínicas of the UFMG were followed up from July 1997 to February 2002. All had single pregnancies, and the 36 fetuses underwent 65 cordocenteses (mean of 1.8 transfusion per fetus). The gestational age ranged from 21 to 34 (28.5±3.2) weeks.

Fetal hemoglobin was obtained immediately before the intravascular transfusions. A 0.5-mL sample of umbilical cord blood was collected with an insulin syringe and analyzed in the Hemocue device, to measure the fetal hemoglobin concentration at the beginning of the invasive procedure.

Gestational age was corrected based on the ultrasound performed during the first gestational trimester.

The examinations for determining BOD were performed in the SONOACE 8800 (Medsom) or Sonoline Prima (Siemens) echographic devices always by an appropriate member of the CEMEFE, before the transfusional procedure.

Initially, a 4-chamber echographic image of the fetal heart was obtained through a transverse image of the fetal abdomen with slight cephalic angulation at an intermediate level between the transverse image of the abdomen and the skull roof. Then, with the interventricular septum perpendicular to the transducer and with the M-mode cursor placed at the level of the atrioventricular valves, the tracing of waves was detected and the image was frozen. Then, the biventricular outer diameter was measured between the right ventricular epicardium and the left ventricular epicardium during diastole, and the femur length was simultaneously measured along the diaphysis, excluding the distal epiphysis.

The measurement was considered normal or altered based on the comparison of the femur length with the biventricular outer diameter, according to the normality curve of De Vore et al [16], 1985 (fig. 1). The BOD values above the 95th percentile in regard to the femur length measurement were considered altered. This was a prospective cross-sectional study.

For statistical analysis, the minimum square regression was used aiming at assessing the relation of dependence between the continuous variables, pretransfusional concentration of fetal hemoglobin and gestational age, in regard to the BOD measure, and a P value < 0.05 was accepted.

The Mean T test was used to correlate hemoglobin levels and BOD.

Multivariate analysis was used to assess the persistence of the correlation between pretransfusional fetal hemoglobin and BOD, independently of the effect of other variables, such as gestational age.

Results

The study comprised 65 cordocenteses performed in 36 fetuses. The fetal conditions at the moment of intravascular transfusion, characterized by the level of pretransfusional hemoglobin, BOD, and femur measurements, are shown in table I.

Figure 2 shows the degree of dilation of the cardiac chambers assessed by use of the BOD measurement versus the femur length curve. Considering the 95th percentile, 17 (26%) fetuses had a BOD greater than the reference value for normality. All fetuses were anemic with a hemoglobin concentration below 10 g/dL.

An inverse correlation was observed between the pretransfusional hemoglobin concentration in fetal blood and BOD measurement (fig. 3). Therefore, as the intensity of fetal anemia increases, characterized in this study by the decrease in fetal hemoglobin concentration, the BOD measurement increases in size.

By using the Mean T test (table II), in which the fetuses were

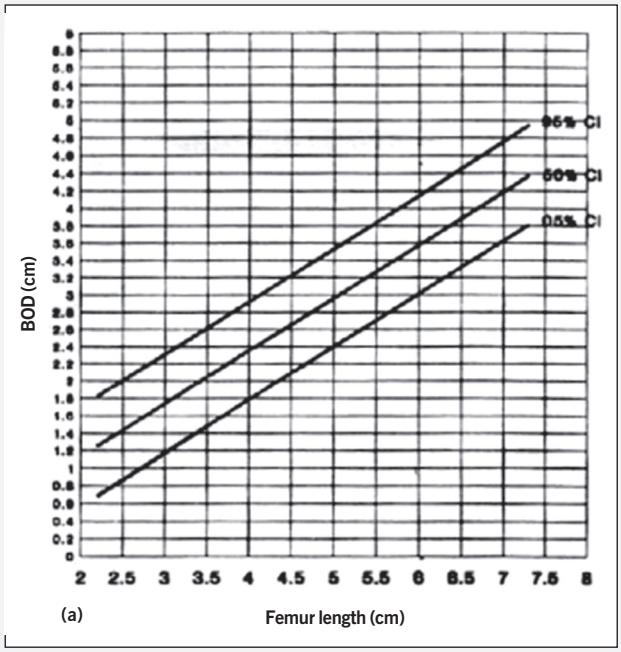

Fig. 1 - Normality curve of femur length X BOD.

Table I - Fetal conditions at the moment of intravascular transfusion

Characteristic	Minimum value	Maximum value	Mean ± SD value
Pretransfusional hemoglobin	2.90	17.10	10.93±3.47
BOD (cm)	2.10	4.80	3.27±0.59
Femur	3.20	6.50	5.41±0.77

selected according to their hemoglobin levels in regard to BOD, the following was observed: the group of fetuses with Hb=7 g/dL had a greater BOD than the groups of fetuses with Hb between 7 and 12 g/dL and =12g/dL. Therefore, the fetuses with hemoglobin below 7 g/dL had the greatest BOD measures.

A direct correlation was observed between BOD measurement and gestational age (fig. 4). Therefore, as pregnancy progresses, BOD increases in size.

Considering the interaction between the 2 factors triggering modifications in BOD (fetal hemoglobin concentration and gestational age) (tab. III), multivariate analysis shows that BOD increases as fetal hemoglobin concentration decreases (correlation coefficient, -0.06; P<0.0001; r^2, 51.6%), independently of the influence of gestational age on that parameter.

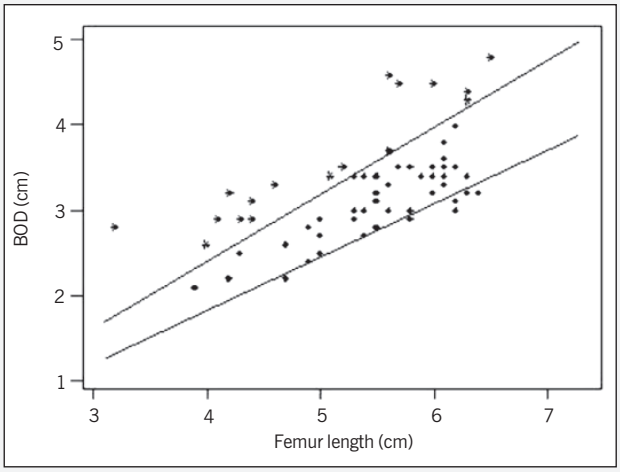

Fig. 2 - Normality curve by De Vore et al[16] showing the correlation between BOD and femur length.

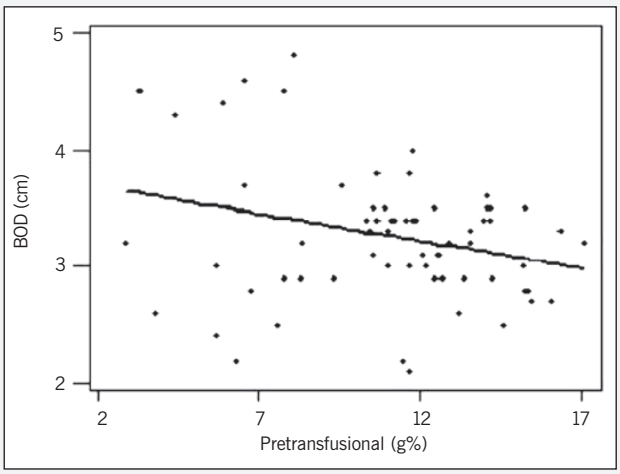

Fig. 3 - Correlation between the pretransfusional fetal hemoglobin concentration and BOD.

Table II - Correlation between fetal BOD and pretransfusional hemoglobin level

Hb (g/dL%)	N	BOD (cm)
12	12	3.09
>7<12	27	3.33
7	25	3.51
Mean T test.		

Discussion

Fetal anemia was recognized as a fetal disease more than 6 decades ago, and it accounts for elevated perinatal morbidity and mortality rates.

The evaluation of the degree of fetal anemia can only be established in an invasive manner as follows: 1) directly: by determining the hematimetric levels in fetal blood collected through cordocentesis; 2) indirectly: anemia can be diagnosed by the spectophotometric study of the amniotic fluid obtained through amniocentesis by determining the bilirubin level, considering the gestational age.

Although those invasive methods have low materno-fetal morbidity and mortality rates, they may increase the risk of feto-maternal hemorrhage, worsening the degree of sensitization, and even sensitization to other blood antigens, due to the increase in antibody production, aggravating the fetal condition [17,18].

The rates of fetal loss related to the procedure ranged from 1.5 to 5%, and they were related to the experience of the examiner[19].

For some time, a noninvasive method for determining the degree of fetal anemia has been sought. So far, however, we have not been able to establish a method that is effective in recognizing the level of fetal anemia, so as to consider invasive therapy.

After the 1980s, the increasing sophistication of ultrasound devices and the development of Doppler technology with color-flow mapping enabled the assessment of uterine perfusion, fetus-placenta unit, and different fetal vessels. Once again, the studies performed were not sufficient to predict, by using a single method, the impairment level of the anemic fetus.

Our study selected 36 fetuses of pregnant women isoimmunized

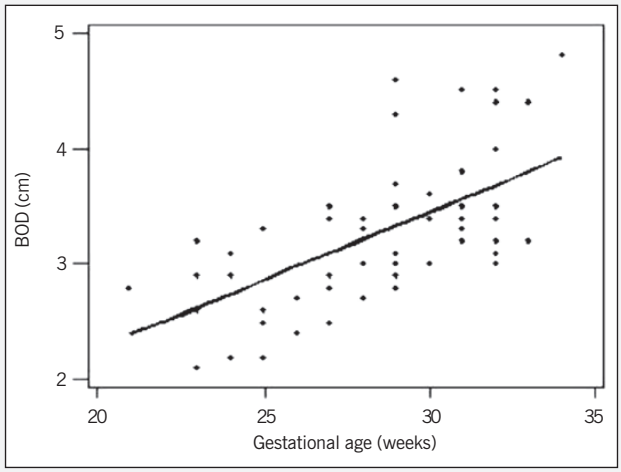

Fig. 4 - Correlation between gestational age and BOD.

Table III - Correlation between fetal BOD and pretransfusional hemoglobin level, considering the influence of gestational age

Parameter	Correlation coefficient	p	r^2
Pretransfusional hemoglobin	-0.06	<0.0001	51.6%
Gestational age (weeks)	0.12	<0.0001	
p of the regression <0.0001.			

to the Rh factor, who underwent 65 intravascular transfusions, with a mean of 1.8 transfusion per fetus. The gestational age ranged from 21 to 34 weeks (mean, 28.5 weeks).

The BOD measurement ranged from 2.1 to 4.8 cm (mean, 3.3 cm). Seventeen fetuses were above the 95th percentile, considering the normogram by De Vore et al [16] (fig. 1). That finding indicates that the fetal heart responds to the hyperdynamic circulatory state resulting from anemia with an increase in the BOD measurement.

Through multivariate analysis, we observed that, independently of the physiological factor of fetal growth leading to the concomitant growth of the cardiac chambers, the drop in fetal hemoglobin leads to an increase in BOD measurements, indicating a statistically significant association, which allows us to state that the greater the degree of fetal anemia, the greater the diameter of its cardiac chambers.

Based on the findings of this study, we observed that BOD measurement is a promising noninvasive investigational method for detecting fetal anemia and for following up the fetuses as gestation evolves, because the correlation between that parameter and fetal hemoglobin was not influenced by gestational age. We can, therefore, emphasize that BOD can be an echographic predictor of the hemoglobin level in fetuses of isoimmunized pregnant women.

References

1. Correa Junior MD, Correa, MD. Isoimunização pelo fator Rh- incompatibilidade sangüínea no sistema ABO. In: Noções Práticas de Obstetrícia 1999; 33: 437-6.
2. Finn R, Clarke CN, Donohoet WT et al. Experimental studies on the prevention of Rh haemolytic disease. Brit Med 1961; 5238:1486-90.
3. Rizzo G, Arduini D, Romanini C et al. Fetal cardiac function. The Pathernon Publishing Group 1995; 131p.
4. Bowman JM. Hemolytic disease. In: Creasy, R.K., Resnik, R. Maternal-fetal medicine. 4.ed. Saunders 1999; 8: 711-3.
5. Nicolaides KH, Thilaganathan B, Rodeck CH. Erytroblasts and reticulocytesis in anemic fetuses. Am J Obstet Gynecol 1989;159:1063-5.
6. Nicolaides KH. The relationship of fetal plasma protein and hemoglobin level to the development of hydrops in rhesus isoimmunization. Am J Obstet Gynecol 1985; 152:341-2.
7. Manning FA. Gravidez aloimune: diagnóstico e conduta. In: Medicina Fetal: Perfil Biofísico, Princípios e Aplicabilidade Clínica. Rio de Janeiro: Revinter 2000; c.8: 395-5.
8. Davis LE, Hohimer RA, Giraund GD, Reller MD et al. Right ventricular function in chronically anemic fetal lambs. Am J Obstet Gynecol 1996; 174:1289-4.
9. Shaw SL. Cardiomiopatias fetais. In: Drose, J.H. Ecocardiografia fetal. Rio de Janeiro: Revinter 2001; 20: 249-2.
10. De Vore GR, Siassi B, Platt LD. IV. M-mode assessment of ventricular size and contractility during the second and third trimesters of pregnancy in the normal fetus. Am J Obstet Gynecol 1984; 150: 981-8.
11. Allan LD, Sahn DJ, Lange LW et al. Quantitative real-time cross-sectional echocardiography in the developing normal human fetus and new born. Circulation 1980; 62: 588-7.
12. Kleinman CS, Donnerstein RL, Jaffe CC et al. Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. Pediatrics 1980;65:1059-7.
13. Wladimiroff JW, Mcgie JS. M-mode ultrasonic assessment of fetal cardiovascular dynamcis. Br J. Obstet. Gynecol 1981;88: 1241.
14. Allan LD, Joseph MC, Boyd EGCA et al. M-mode echocardiography in the developing human fetus. Br Heart J 1982; 47: 573-3.
15. Silverman NH, Tan J, Holffman JLE et al. Cardiac dimensions determined by cross-sectinal echocardiography in the normal human fetus from 18 weeks to term. Am J Cardiol 1992; 70: 1459-7.
16. De Vore GR, Siassi B, Platt LD. Use of femur length as a means of assessing M-mode ventricular dimensions during second and third trimesters of pregnancy in normal fetus. J Clin Ultrasound 1985; 13: 619-5.
17. Spinatto, J.A. Hemolytic disease of the fetus a plea for restrain. Obstet Gynecol 1992; 80: 873-7.
18. Cabral ACV, Diniz SSA. Isoimunização materna. In: Obstetrícia. Imprensa Oficial 1998. c.28, 277-3.
19. Daffos F. A new procedure for fetal blood sampling in utero: preliminary results of 53 cases. Am J Obstet Gynecol 1983; 168: 985-9.