ORIGINAL RESEARCH

NONINVASIVE DOPPLER AND ULTRASOUND PARAMETERS TO PREDICT FETAL ANEMIA DUE TO RED BLOOD CELL ALLOIMMUNIZATION

Rıza Madazli

Kadın Hastalıkları ve Doğum Anabilim Dalı,Cerrahpaşa Tıp Fakültesi, İstanbul Üniversitesi, İstanbul, Türkiye

ABSTRACT

Objective: To evaluate the screening efficiency of ultrasound and Doppler measurements in the prediction of fetal anemia in alloimmunized pregnancies.

Materials and Method: In a prospective study, 24 nonhydropic fetuses with red blood cell alloimmunization were evaluated with ultrasound and Doppler imaging. Middle cerebral artery peak systolic velocity, intrahepatic umbilical venous maximum velocity, liver length, and spleen perimeter were measured. Results before first fetal blood sampling or delivery were analyzed.

Results: Eighteen fetuses were anemic and required intrauterine transfusion, and 6 were not severely anemic at birth. Middle cerebral artery Doppler imaging was the best predictor of fetal anemia (94.4%), followed by intrahepatic umbilical venous maximum velocity (72.2%). Sensitivity was low for spleen perimeter (55.5%) and liver length (50%). The areas under the curve equal to 0.972, 0.861, 0.667 and 0.528 for middle cerebral artery peak systolic velocity, intrahepatic umbilical venous maximum velocity, liver length, and spleen perimeter respectively were determined for the prediction of fetal anemia.

Conclusion: Middle cerebral artery peak systolic velocity is the best available noninvasive test in the prediction of fetal anemia.

Keywords: Rh alloimmunization, Fetal anemia, Doppler, Ultrasonography

RH UYUŞMAZLIĞINA BAĞLI FETAL ANEMİNİN BELİRLENMESİNDE DOPPLER VE ULTRASOUND PAREMETRELERİ

ÖZET

Amaç: Rh uyuşmazlığına bağlı fetal aneminin belirlenmesinde Doppler ve ultrason ölçümlerinin etkinliğinin değerlendirilmesi.

Materyal ve Metod: Rh izoimmünizasyonu olan nonhidropik 24 fetusa ultrason ve Doppler uygulandı. Orta serebral arter pik sistolik velositesi, intrahepatik umbilikal ven maksimum velositesi, karaciğer uzunluğu ve dalak çevresi ölçümleri yapıldı. Intrauterin kan transfüzyonu öncesi elde edilen son veriler değerlendirilmeye alındı.

Bulgular: 18 fetusda anemi tespit edilerek intrauterin kan transfüzyonu uygulandı, 6 fetus ise noninvaziv metodlar ile takip edilerek kan transfüzyonu uygulanmadan doğurtuldu. Orta serebral arter pik sistolik velosite ölçümü fetal anemi belirlenmesinde (%94.4) en etkili yöntem olarak tespit edildi.Intrahepatik umbilikal ven maksimum velosite, dalak çevresi ve karaciğer uzunluğunun fetal anemiyi belirlemedeki sensitiviteleri sırasıyla %72.2, %55.5 ve %50 olarak saptandı. Orta serebral arter pik sistolik velosite, intrahepatik umbilikal ven maksimum velosite, dalak çevresi ve karaciğer uzunluğunun fetal anemiyi belirlemedeki etkinlikleri ROC eğrisinin altında kalan alan olarak değerlendirildiğinde sırasıyla 0.972, 0.861, 0.667 ve 0.528 olarak tespit edildi.

Sonuç: Orta serebral arter pik sistolik velosite fetal aneminin belirlenmesinde en etkili noninvaziv yöntemdir.

Anahtar Kelimeler: Rh alloimmünizasyon, Fetal anemi, Doppler, Ultrasonografi

İletişim Bilgileri:
Prof. Dr. Rıza Madazli,
Kadın Hastalıkları ve Doğum Anabilim Dalı, Cerrahpaşa Tıp Fakültesi, İstanbul Üniversitesi, Cerrahpaşa, İstanbul, Türkiye
e-mail: madazli@superonline.com

Marmara Medical Journal 2007;20(3);172-178

INTRODUCTION

The aim of prenatal management of red blood cell alloimmunized pregnancies is to identify affected fetuses, correct their anemia by transfusion and deliver them at the optimal time. The correct timing of the first intrauterine blood transfusion (IUT) remains a challenge for the clinician. Transfusing a fetus too early, when only mild anemia is present, will unnecessarily increase the number of transfusions needed to reach a gestational age at which delivery can take place safely. By accurately predicting the need for transfusion, that is when the fetus is moderately-to-severely anemic, optimal timing of these procedures will lead to a minimum number of transfusions. Improved outcome can be expected by reducing the number of invasive procedures.

The gold standard test for the detection of fetal anemia remains fetal blood sampling (FBS), which allows accurate quantification of the degree of fetal anemia but carries with it a procedure related risk of fetal loss and fetomaternal hemorrhage, which can increase antibody levels[1,2]. Amniocentesis for amniotic fluid Δ optical density at 450 nm (OD450) measurement is still considered an essential management tool in rhesus disease. This test is also invasive, with inherent risks, and its predictive value has been questioned[3].

The diagnosis of intrauterine fetal anemia using non-invasive procedures has been the goal of many investigators. In the past decade, using two dimensional and Doppler ultrasound, many parameters have been evaluated for the detection of fetal anemia. Doppler assessment of blood flow velocities in the fetal middle cerebral artery (MCA), fetal aorta (Ao) and intrahepatic umbilical vein (IHUV), and ultrasound measurements of fetal liver length and spleen perimeter have been suggested as valuable noninvasive predictors of fetal anemia[4-9].

The aim of this study was to assess and compare the clinical use of peak systolic blood flow velocity measurements in the fetal middle cerebral artery (MCA-PSV), intrahepatic umbilical vein maximal flow velocity (IHUV), together with estimations of liver length and spleen perimeter in predicting fetal anemia in pregnancies complicated by red cell alloimmunization.

METHODS

The study was carried out in the Department of Obstetrics and Gynecology, Cerrahpaşa Faculty of Medicine. The study was approved by the Hospital's Ethics Committee, and all women who participated in the study gave informed consent. The study population consisted of 24 women with singleton non-hydropic fetuses referred to our unit for suspected fetal red cell anti-D alloimmunization. The maternal antibody titers ranged from 1: 16 to 1: 512. At the first visit, women referred with rhesus alloimmunization were grouped according to history as follows: mild (term delivery with phototherapy) (n = 2); moderate (previous neonatal exchange transfusion following delivery at term) (n = 9); or severe (previous fetal transfusion, fetal death due to hydrops or neonatal exchange transfusion at < 34 weeks) (n = 13). Patients with mild history of anemia were seen every 4 weeks before 28 weeks and every 2 weeks thereafter, provided the non-invasive tests were normal and the antibody titer was < 1:32. Visits were scheduled every 1–2 weeks in patients with a moderate or severe history or a rapidly rising antibody level. Abnormal noninvasive assessment and/or rising antibodies were indications for invasive procedures. All Doppler and ultrasonography results included in this study were obtained on the same day of fetal blood sampling for measurement of hemoglobin concentration. Fetal hemoglobin estimation was performed by cordocentesis from the umbilical vein at the placental cord insertion; blood was ready for intrauterine transfusion if necessary. The first 1 mL was discarded to avoid possible mixing with maternal blood, and then 1–2 mL fetal blood was taken for fetal hemoglobin determination. Intravascular transfusion was then performed if fetal anemia was confirmed. Significant fetal anemia was defined as a hemoglobin value of >4 SD below the mean for gestational age[10]. Hemoglobin deficit (D Hb = normal Hb (50th centile)–measured Hb) was estimated for each fetus. The normal Hb value for each

gestational age was obtained from Nicolaides[10], and the 50th centile was used as the normal reference range.

At every visit, Doppler measurements of MCA peak systolic velocity and IHUV maximum velocity, as well as ultrasound measurements of liver length and spleen perimeter were performed according to previously described methods[4-6,9] Briefly, color Doppler imaging was used to identify the circle of Willis and the MCAs in a cross-section through the fetal head. The pulsed Doppler sample volume was placed in the proximal part of the MCA, preferably with a 0-degree angle between the ultrasound beam and the vessel. If this could not be obtained, onscreen angle correction was applied, to ensure that the angle of insonation was less than 30 degrees. The gate size was adjusted to match the size of the vessel. When at least five identical consecutive waveforms were observed, the image was frozen and an on-screen calliper was used to measure the peak systolic velocity. The maximum velocity in the IHUV was measured in a cross-section of the fetal abdomen. The sample volume was placed at approximately one third of the distance between the abdominal wall and the portal vein, with the gate adjusted to the diameter of the vessel. A steady flow velocity pattern of 5 seconds was obtained before freezing the image. The maximum velocity was measured by placing a calliper with the horizontal lines on the edge of the Doppler signal. Maximum fetal liver length was measured in a parasagittal scan of the fetal abdomen from the diaphragm to the lower edge of the right liver. The fetal spleen perimeter was measured by the trace method in the same cross-sectional plane as used for the fetal stomach. All ultrasound and Doppler studies were performed by the author with an ATL 3000 machine with a 5-MHz curved array transducer. The results were plotted on previously published graphs[4-6,9]. For all measurements, values greater than the 95th percentile were considered abnormal, except for the MCA measurement, for which the cut-off value of 1.5 multiples of median was used.

The decision to perform FBS was given using all available information such as history, fetal movements, antibody titers, and included results of fetal ultrasound and Doppler findings. In all 18 cases in which FBS was performed, fetal anemia was confirmed and transfusion was carried out immediately.

The sensitivity, specificity, positive predictive value and negative predictive value were calculated from 2-2 tables. A receiver-operator characteristic (ROC) curve was constructed and the area under the curve (AUC) was used to compare the screening efficiency of various variables for predicting fetal anemia.

RESULTS

Of the 24 pregnancies, 6 cases were monitored by serial noninvasive assessments without any procedure. In all of these 6 cases antibody levels were stable and most of the noninvasive tests were within the reference range. The mean gestational age at delivery was 36, 8±1,7 weeks (range 34–39 weeks) and 2 were found to be RhD-negative postnatally. One of the neonates from this group required exchange transfusion after the delivery.

Eighteen fetuses underwent first fetal blood sampling/intravascular transfusion at a mean gestational age of 26±3,9 weeks. The hemoglobin values at the first procedure were 4–8 gr/dl (median 6 gr/dl) and Δ Hb was between 3-4 grams, 5-6 grams and >6 grams in 6, 9 and 3 of the cases respectively. The anemic fetuses received a median of two IUTs (range 1-4). The mean gestational age at delivery was 34, 2±2,7 weeks (range 32–38 weeks). All neonates are alive and well.

The results of the MCA peak velocity values at the time of first FBS or at delivery is shown in Figure 1. The test characteristics of the four noninvasive tests are given in the Table I. The sensitivities and false-positive rates (receiver operating characteristic curve - ROC) for the detection of fetal anemia by ultrasound and Doppler measurements are illustrated in Figure 2. The areas under the curve equal to 0.972, 0.861, 0.667 and 0.528 for MCA-PSV, IHUV, liver length, and spleen perimeter respectively were determined for the prediction of fetal anemia (Table II).

Table I. Test characteristics of ultrasound and Doppler measurements as predictors of fetal anemia in 24 red blood cell–alloimmunized pregnancies

Test	MCA	IHUV	Spleen	Liver
True positive	17	13	10	9
False positive	0	0	3	1
True negative	6	6	3	5
False negative	1	5	8	9
Sensitivity (%)	94.4	72.2	55.5	50
Specificity (%)	100	100	50	83.3
PPV (%)	100	100	76.9	90
NPV (%)	85.7	54.5	27.3	35.7

Table II. The screening efficiency of ultrasound and Doppler measurements as predictors of fetal anemia.

Parameters	AUC	SE	Significance
Middle cerebral artery peak systolic velocity	0.972	0.033	0.001
Umbilical vein maximal flow velocity	0.861	0.074	0.009
Liver length	0.667	0.123	0.230
Spleen perimeter	0.528	0.139	0.841

AUC, Area under receiver-operator characteristic curve

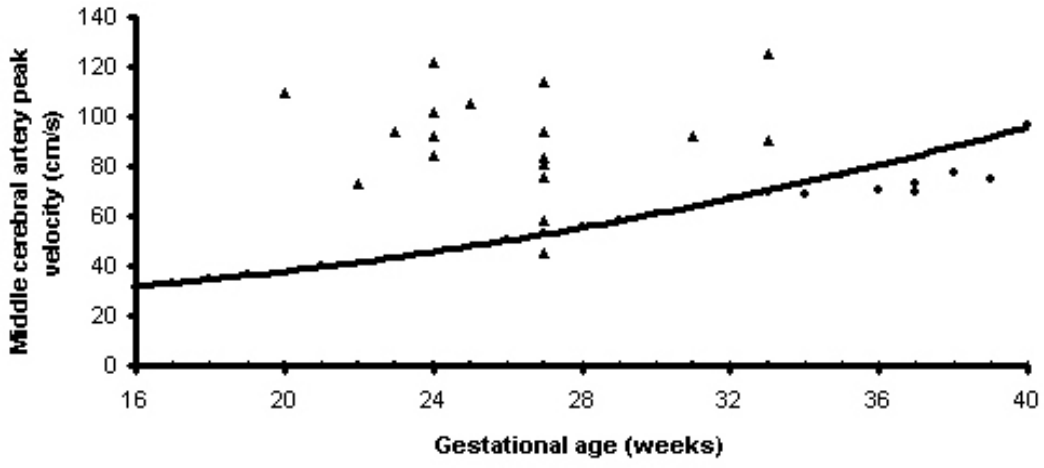

Figure 1: Middle cerebral artery peak velocity values at time of first FBS or at delivery. Triangles, anemic fetuses; circles, nonanemic fetuses. Line,1.5 multiples of median in normal pregnancies.

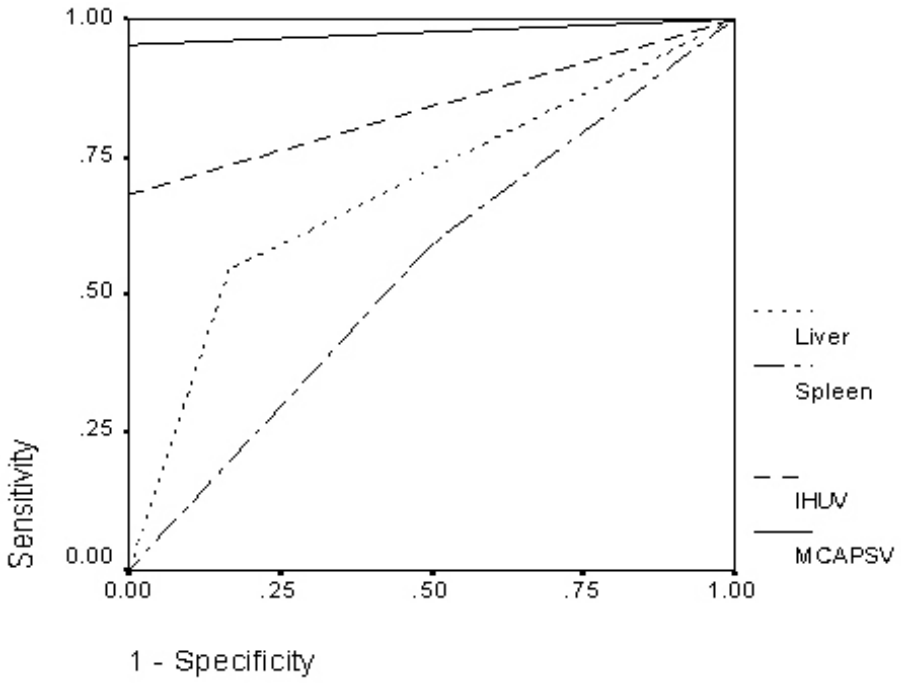

Figure 2: The receiver-operator characteristic curves showing the prediction performance of ultrasound and Doppler measurements for fetal anemia.

DISCUSSION

Theoretically, ultrasound scanning and Doppler technology to detect biophysical and hemodynamic changes associated with fetal anemia seem to have the potential for developing effective noninvasive testing. Such tests are needed because the current invasive strategies, namely serial amniocentesis to directly assess amniotic fluid bilirubin (D optical density 450) values or cordocentesis, are associated with fetal loss and maternal morbidity. Moreover, the reliability of amniocentesis has been questioned, especially in the early to mid-second trimester. The availability of the successful treatment of anemic fetuses, especially before hydrops develops, by intrauterine blood transfusions has further increased the importance of detecting at risk fetuses.

This prospective study confirms the effectiveness of non-invasive management of red blood cell alloimmunization. As, in all cases in which FBS was performed according to history, antibody titers, and results of fetal ultrasound and Doppler findings, fetal anemia was confirmed and transfusion was carried out immediately. Those 6 cases in which pregnancy was followed without performing any invasive procedure all delivered non moderate-severe anemic fetuses that did not need IUT. Similar findings were also gained in the study performed by Dukler et al[11]. In their prospective study, 16 nonhydropic fetuses with red blood cell alloimmunization were evaluated with ultrasound and Doppler imaging. Non-invasive management correctly defined 6 severely anemic fetuses that required IUTs and 10 pregnancies that did not need any invasive procedure.

This study also demonstrates that Doppler measurements of fetal blood flow velocities are superior tests to liver and spleen measurements in the prediction of fetal anemia in red blood cell alloimmunization. MCA peak systolic velocity measurement with a sensitivity and specificity of 94.4% and 100% respectively, is the most accurate parameter and the best available noninvasive test in the management of pregnancies at risk for fetal anemia. In two other studies in which direct comparison of the diagnostic accuracy of the non-invasive tests have been performed; Iskaros et al[9] reported umbilical vein maximal flow velocity measurement to

be a better predictive test than liver length and spleen perimeter measurements in fetal anemia. Dukler et al[11] comparing the diagnostic accuracy of MCA peak systolic velocity, intrahepatic umbilical venous maximum velocity, liver length, and spleen perimeter demonstrated that Doppler measurements were superior tests to ultrasound measurements and MCA peak systolic velocity measurement with a 100% sensitivity and specificity was the most accurate parameter in the prediction of fetal anemia. They also stated that invasive diagnostic techniques could safely be avoided when normal MCA flow velocity was found.

Non-invasive Doppler ultrasound has shown impressive capabilities in the diagnosis of anemia. Velocity changes are thought to result from increased cardiac output and decreased viscosity of fetal blood (ie, a hyperdynamic circulation)[12]. Although flow velocities in all fetal vessels will be increased, the MCA is particularly suitable for assessment because of its easy visualization with color Doppler imaging and usually an angle of insonation close to 0 degrees can readily be obtained. In 1995, Mari et al[13] reported that MCA-PSV Doppler measurements could accurately predict fetal anemia in a prospective series of 16 pregnancies complicated by maternal red blood cell alloimmunization. Since that initial report, various other studies have strongly confirmed the efficacy of MCA peak systolic velocity in the prediction of fetal anemia with sensitivities ranging from 64 - 100%.[14-18]. MCA PSV can be used to detect degrees of fetal anemia justifying invasive fetal testing and intrauterine transfusion[11,14]. The MCA-PSV rises progressively as anemia worsens [16]. The use of the middle cerebral artery peak systolic velocity for the diagnosis of fetal anemia has led to a more than 70% reduction in the number of invasive tests, which often cause fetal death, in the assessment of red-cell alloimmunized pregnancies[14].

With measurement of the IHUV maximum flow velocity, we achieved 72.2% sensitivity, with no false-positive result. The sensitivity of 83 % was found by Iskarios et al (9) and Dukler et al[11] with false-positive rates of 0% and 20% respectively. This test seems less accurate than MCA velocities, but may still have a role as an additional tool in the evaluation of fetuses at risk for anemia.

Ultrasound measurements of spleen perimeter and liver length had sensitivities and false-positive rates of 55.5% and 50% and 50% and 16.6% respectively. These results may be explained by our understanding of the underlying pathophysiologic mechanisms. As the hemolytic disease progresses, the fetal liver and spleen may increase in size because of the increased production of red blood cells, at least temporarily. The fetus may, however, be able to compensate for the breakdown of red blood cells. In such cases, a fetus may have a large liver and spleen but would not necessarily be severely anemic. Conversely, more rapid breakdown of red blood cells may prevent the fetus from adapting to hemolysis, and anemia may develop without clear evidence of hepatosplenomegaly. The present and other studies which compare the role of spleen and liver measurements and Doppler parameters in the prediction of fetal anemia favor the use of Doppler[9,11].

In conclusion, this prospective study confirms the effectiveness of non-invasive management of red blood cell alloimmunization. Measurement of the PSV in the MCA in fetuses at risk for anemia due to maternal red cell alloimmunization provides an accurate, non-invasive and useful clinical test in the prediction of fetal anemia. Its use would prevent unnecessary invasive procedures and cordocentesis could be considered in those fetuses that develop ascites or a high MCA-PSV.

REFERENCES

1. Maxwell DJ, Johnson P, Hurley P, Neales K, Allan L, Knott P: Fetal blood sampling and pregnancy loss in relation to indication. Br J Obstet Gynaecol 1991; 98:892-897.
2. Bowman JM, Pollock JM, Peterson LE, Harman CR, Manning FA, Menticoglou SM: Fetomaternal hemorrhage following funipuncture: increase in severity of maternal red-cell alloimmunization. Obstet Gynecol 1994; 84:839-843.
3. Oepkes D. Invasive versus non-invasive testing in red-cell alloimmunized pregnancies. Eur J Obstet Gynecol Reprod Biol 2000; 92: 83-89.

4. Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ. Non-invasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. N Engl J Med 2000; 342:9-14.
5. Oepkes D, Meerman RH, Vandenbussche FP, Van Kamp IL, Kok FG, Kanhai HH. Ultrasonographic fetal spleen measurement in red blood cell alloimmunized pregnancies. Am J Obstet Gynecol 1993; 169:121-128.
6. Roberts AB, Mitchell JM, Pattison NS. Fetal liver length in normal and isoimmunized pregnancies. Am J Obstet Gynecol 1988; 161:42-46.
7. Steiner H, Schaffer H, Spitzer D, Batka M, Graf AH, Staudach A. The relationship between peak velocity in the fetal descending aorta and hematocrit in rhesus isoimmunization. Obstet Gynecol 1995; 85:659–662.
8. Kirkinen P, Jouppila P. Umbilical vein blood flow in rhesus-isoimmunization. Br J Obstet Gynaecol 1983; 90:640–643.
9. Iskaros J, Kingdom J, Morrison JJ, Rodeck CH. Prospective non-invasive monitoring of pregnancies complicated by red cell alloimmunization. Ultrasound Obstet Gynecol 1998; 11:432–437
10. Nicolaides KH, Soothill PW, Clewell WH, Rodeck CH, Mibashan RS, Campbell S. Fetal haemoglobin measurement in the assessment of red cell isoimmunisation. Lancet 1988; 1: 1073 -1075.
11. Dukler D, Oepkes D, Seaward G, Windrim R, Ryan G. Noninvasive tests to predict fetal anemia: A study comparing Doppler and ultrasound parameters. Am J Obstet Gynecol 2003; 188:1310-1314.
12. Rightmire DA, Nicolaides KH, Rodeck CH, Campbell S. Fetal blood velocities in Rh isoimmunization: relationship to gestational age and to fetal hematocrit. Obstet Gynecol 1986; 68:233-236.
13. Mari G, Adrignolo A, Ahuhamad AZ, P. et al. Diagnosis of fetal anemia with Doppler ultrasound in the pregnancy complicated by maternal blood group immunization. Ultrasound Obstet Gynecol 1995; 5:400-405
14. Mari G, Deter RL, Carpenter RL, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. N Engl J Med 2000; 342: 9–14.
15. Bullock R, Martin WL, Coomarasamy A, Kılby MD. Prediction of fetal anemia in pregnancies with red-cell alloimmunization: comparison of middle cerebral artery peak systolic velocity and amniotic fluid OD450. Ultrasound Obstet Gynecol 2005; 25: 331–334
16. Mari G, Detti L, Oz U, Zimmerman R, Duerig P, Stefos T. Accurate prediction of fetal hemoglobin by Doppler ultrasonography. Obstet Gynecol 2002; 99: 589–593.
17. Deren O, Onderoglu L. The value of middle cerebral artery systolic velocity for initial and subsequent management in fetal anaemia. Eur J Obstet Gynecol Reprod Biol 2002; 101: 26–30.
18. Scheier M, Andrade-Hernandez E, Carmo A, Dezerega V, Nicolaides KH. Prediction of fetal anemia in rhesus disease by measurement of fetal middle cerebral artery peak systolic velocity. Ultrasound Obstet Gynecol 2004; 23: 432–436.