NONINVASIVE DIAGNOSIS BY DOPPLER ULTRASONOGRAPHY OF FETAL ANEMIA DUE TO MATERNAL RED-CELL ALLOIMMUNIZATION

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ABSTRACT

Background Invasive techniques such as amniocentesis and cordocentesis are used for diagnosis and treatment in fetuses at risk for anemia due to maternal red-cell alloimmunization. The purpose of our study was to determine the value of noninvasive measurements of the velocity of blood flow in the fetal middle cerebral artery for the diagnosis of fetal anemia.

Methods We measured the hemoglobin concentration in blood obtained by cordocentesis and also the peak velocity of systolic blood flow in the middle cerebral artery in 111 fetuses at risk for anemia due to maternal red-cell alloimmunization. Peak systolic velocity was measured by Doppler velocimetry. To identify the fetuses with anemia, the hemoglobin values of those at risk were compared with the values in 265 normal fetuses.

Results Fetal hemoglobin concentrations increased with increasing gestational age in the 265 normal fetuses. Among the 111 fetuses at risk for anemia, 41 fetuses did not have anemia; 35 had mild anemia; 4 had moderate anemia; and 31, including 12 with hydrops, had severe anemia. The sensitivity of an increased peak velocity of systolic blood flow in the middle cerebral artery for the prediction of moderate or severe anemia was 100 percent either in the presence or in the absence of hydrops (95 percent confidence interval, 86 to 100 percent for the 23 fetuses without hydrops), with a false positive rate of 12 percent.

Conclusions In fetuses without hydrops that are at risk because of maternal red-cell alloimmunization, moderate and severe anemia can be detected noninvasively by Doppler ultrasonography on the basis of an increase in the peak velocity of systolic blood flow in the middle cerebral artery. (N Engl J Med 2000; 342:9-14.)

MATERNAL alloimmunization occurs when a pregnant woman has an immunologic response to a paternally derived red-cell antigen that is foreign to the mother and inherited by the fetus. The antibodies may cross the placenta, bind to antigens present on the fetal erythrocytes, and cause hemolysis, hydrops fetalis, and fetal death. In the United States, the proportion of fetuses at risk for anemia because of maternal alloimmunization to red-cell antigens has been estimated to be 35 per 10,000 live births.[1] Among these at-risk fetuses, only 10 percent will require transfusion because of severe anemia[2] before 34 weeks of gestation. The remaining 90 percent are unaffected or have only mild anemia. Currently, invasive techniques such as amniocentesis and cordocentesis[3-5] are used to identify fetuses with severe anemia.

We previously reported that the peak velocity of systolic blood flow in the middle cerebral artery, as measured by Doppler ultrasonography, was increased in fetuses with anemia.[6] We selected the middle cerebral artery for these measurements because cerebral arteries respond quickly to hypoxemia, owing to the strong dependence of brain tissue on oxygen. Moreover, the middle cerebral artery is easily visualized with an angle of close to 0 degrees between the ultrasound beam and the direction of blood flow, and this measurement has low intraobserver and interobserver variability.[6]

Despite its theoretical advantages, the test has not gained widespread acceptance, primarily because of limited experience with its use. We conducted a multicenter, prospective study designed to determine the value of measurements of the peak velocity of systolic blood flow in the middle cerebral artery for the detection of fetal anemia due to maternal red-cell alloimmunization.

METHODS

Study Subjects

We studied 110 consecutive pregnant women carrying 112 fetuses. This total included one triplet pregnancy in which only two fetuses were at risk for anemia (one fetus was Rh-negative). The women were referred to one of the study centers at 15 to 36 weeks of gestation (mean [±SD], 25±5) for cordocentesis, and, if necessary, blood transfusion because there was an increased risk of fetal anemia on the basis of the obstetrical history (a previous pregnancy in which a fetus had anemia requiring transfusion), maternal serum red-cell antibody titers ≥1:16, or increasing bilirubin concentrations in amniotic fluid, as detected by serial spectrophotometric examinations indicating a change in optical density

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at 450 nm.[3] The gestational age was determined on the basis of the last menstrual period and was confirmed by ultrasonography. Fetal hydrops was defined as the presence of fluid in more than one body cavity and was diagnosed by ultrasonography at the time of blood sampling.

The cordocenteses and measurements of peak systolic velocity were approved by the institutional review boards of the eight participating institutions, and all the pregnant women studied gave oral informed consent.

Doppler Studies

Doppler examination of the middle cerebral artery was performed before cordocentesis in all cases. An axial section of the brain, including the thalami and the cavitas septi pellucidi, was obtained. The circle of Willis was visualized and the middle cerebral artery of one side was examined close to its origin in the internal carotid artery, because we have found that the systolic velocity decreases with distance from the point of origin of this vessel. The angle between the ultrasound beam and the direction of blood flow was kept as close as possible to 0 degrees. The highest point of the wave form (peak systolic velocity) was measured.

Two-dimensional image-directed pulsed Doppler ultrasonography (GE PASS II, General Electric Medical Systems, Milwaukee) or color Doppler imaging (Acuson 128 XP or Acuson Sequoia, Acuson, Mountain View, Calif.; ATL Ultramark 9, HDI 3000 or HDI 5000, Advanced Technology Laboratories Ultrasound, Bothell, Wash.; or Phillips SD 800, Phillips Medical System, Irvine, Calif.) was used for the Doppler studies. Doppler images were recorded at a time when there was an absence of marked fetal body and respiratory movements. The spatial peak temporal average intensity was below 100 mW per square centimeter.

Reference Ranges for Fetal Hemoglobin and Peak Systolic Velocity

A reference range for hemoglobin concentrations in fetuses from 18 to 40 weeks of gestation was established from samples obtained by cordocentesis from 265 normal fetuses. These fetuses underwent cordocentesis for prenatal diagnosis (because of a suspicion of infection, chromosomal abnormalities, alloimmune thrombocytopenia, or immune thrombocytopenic purpura) and were subsequently found not to be affected by the condition under investigation.

To evaluate the measurements of peak systolic velocity in the middle cerebral artery, we used nomograms previously established for various gestational ages.[6] The expected values for peak systolic velocity were calculated with the following formula: $\text{MCA-PSV} = e^{(2.31+0.046\ \text{GA})}$, where MCA-PSV is the peak systolic velocity in the middle cerebral artery and GA is gestational age ($R^2 = 0.78$, $P < 0.001$).

Statistical Analysis

Regression analysis was used to calculate reference ranges for hemoglobin values during gestation according to the method described by Royston.[7] The values for hemoglobin and peak systolic velocity were expressed as multiples of the median in order to adjust for the effect of gestational age on the measurement.

Multiples of the median for the hemoglobin concentration were calculated by dividing the measured value by the expected hemoglobin value for gestational age as determined with the regression equation. The multiples of the median for the peak systolic velocity in the middle cerebral artery were calculated in a similar way.

The relation between the multiples of the median for the peak systolic velocity and the multiples of the median for the hemoglobin concentration was evaluated by regression analysis, and receiver-operating-characteristic curves[8] were used to determine whether the peak systolic velocity could be used to predict the risk of anemia.

Fetuses at risk for anemia may have hydrops, which can be diagnosed with Doppler ultrasonography. When hydrops is present in a fetus at risk for anemia, it is not necessary to perform any other test. We therefore analyzed the data from fetuses with and without hydrops to assess whether our test predicted anemia regardless of the presence or absence of hydrops.

Statistical analyses were performed with the SPSS statistical package (SPSS, Chicago). The area under the receiver-operating-characteristic curve was calculated with GraphROC computer program (GraphROC for Windows, Turku, Finland).

RESULTS

The hemoglobin concentrations in the normal fetuses followed a log-normal distribution ($P = 0.76$). The hemoglobin concentrations as a function of fetal age were best fitted by the following exponential function: $\text{hemoglobin concentration} = e^{(2.84 - 8.55/\text{GA})}$, where GA is gestational age ($R^2 = 0.34$, $P < 0.001$).

Hydrops is rare in fetuses with hemoglobin concentrations greater than 5 g per deciliter,[9] a value corresponding to a concentration 0.47 times the median at 18 weeks of gestation and 0.36 times the median at 37 weeks of gestation. Thus, we classified the degrees of anemia as follows: mild anemia (hemoglobin concentration from 0.84 to 0.65 times the median for gestational age), moderate anemia (hemoglobin concentration from less than 0.65 to 0.55 times the median), and severe anemia (hemoglobin concentration less than 0.55 times the median) (Fig. 1). The median hemoglobin concentrations and the concentrations at these cutoff points are shown in Table 1 as a function of gestational age.

Red-cell alloimmunization was further investigated if the maternal serum titer of specific red-cell antibodies was 1:16 or more. The types and distribution of antibodies found in our study population are shown in Table 2.

Among the 111 fetuses at risk for anemia, 41 (37 percent) had normal hemoglobin concentrations, 35 (32 percent) had mild anemia, 4 (4 percent) had moderate anemia, and 19 (17 percent) had severe anemia without hydrops. Twelve fetuses (11 percent) had severe anemia with hydrops (Fig. 1). The mean (±SD) hemoglobin concentration among the fetuses with hydrops was 0.30±0.06 times the median, corresponding to a value of 3.8 g per deciliter.

In the analysis of receiver-operating-characteristic curves, we selected the strictest cutoff points (those allowing 100 percent detection of moderate and severe anemia), because we did not want to miss any fetuses with moderate or severe anemia that might be at risk for hydrops and death. The optimal threshold values for peak systolic velocity in the middle cerebral artery were 1.29 times the median for mild anemia, 1.50 times the median for moderate anemia, and 1.55 times the median for severe anemia (Fig. 2).

The threshold values for peak systolic velocity in the middle cerebral artery at different gestational ages are shown in Table 3. All of the fetuses with moderate or severe anemia had peak systolic velocity values above 1.50 times the median (Fig. 3).

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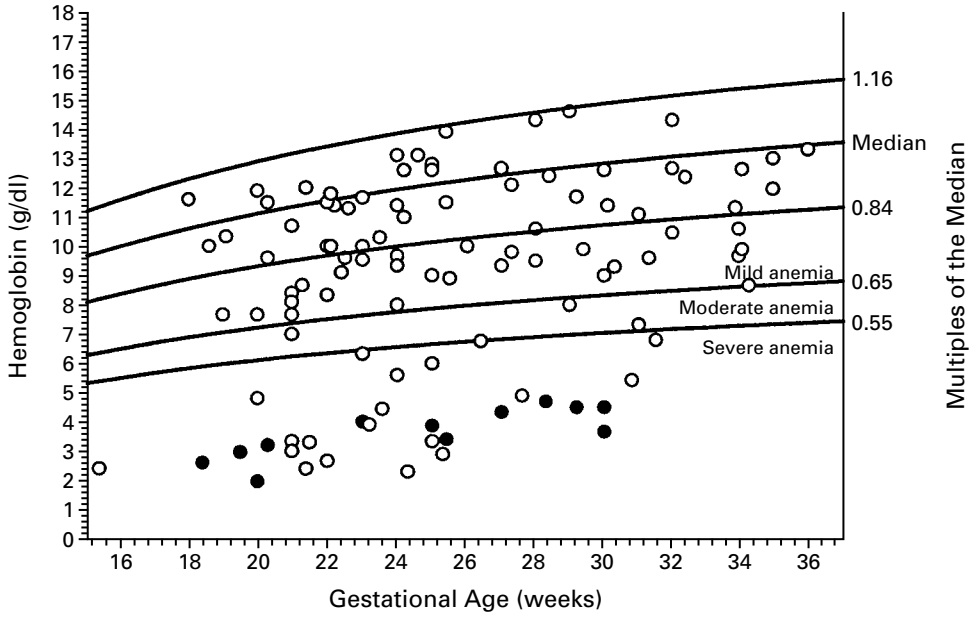

Figure 1. Hemoglobin Concentrations in 265 Normal Fetuses and 111 Fetuses That Underwent Cordocentesis.
The reference range in the normal fetuses was between 0.84 and 1.16 times the median (corresponding to the 5th and 95th percentiles). Values for the 111 fetuses that underwent cordocentesis are plotted individually. Solid circles indicate fetuses with hydrops.

median of the peak systolic velocity, as measured by the area under the receiver-operating-characteristic curve, was not significantly different when we compared all fetuses with anemia with fetuses with anemia but without hydrops ($P=0.93$). Similar results were obtained for a comparison of the peak systolic velocity measured in fetuses with severe anemia between those with and those without hydrops ($P=0.91$). This analysis confirmed that the multiple of the median of the peak systolic velocity is a strong predictor of anemia regardless of the presence or absence of hydrops.

The sensitivity of the peak systolic velocity for the prediction of moderate anemia (a hemoglobin concentration of less than 0.65 times the median) and severe anemia (a hemoglobin concentration of less than 0.55 times the median) in the fetuses without hydrops was 100 percent (95 percent confidence interval, 86 to 100), with a false positive rate of 12 percent. The positive and negative predictive values were 65 percent and 100 percent, respectively.

The relation between the multiples of the median of the peak systolic velocity and the multiples of the median of the hemoglobin concentration was strong even in fetuses of mothers with Kell sensitization ($R^2=0.55$, $P<0.001$).

Table 1. Reference Ranges for Fetal Hemoglobin Concentrations as a Function of Gestational Age.*

Week of Gestation	Multiples of the Median				
	1.16	1.00 (median)	0.84	0.65	0.55
	grams per deciliter				
18	12.3	10.6	8.9	6.9	5.8
20	12.9	11.1	9.3	7.2	6.1
22	13.4	11.6	9.7	7.5	6.4
24	13.9	12.0	10.1	7.8	6.6
26	14.3	12.3	10.3	8.0	6.8
28	14.6	12.6	10.6	8.2	6.9
30	14.8	12.8	10.8	8.3	7.1
32	15.2	13.1	10.9	8.5	7.2
34	15.4	13.3	11.2	8.6	7.3
36	15.6	13.5	11.3	8.7	7.4
38	15.8	13.6	11.4	8.9	7.5
40	16.0	13.8	11.6	9.0	7.6

*The hemoglobin values at 0.65 and 0.55 multiples of the median (cutoff points for mild and moderate anemia, respectively) are also shown. The values at 1.16 and 0.84 multiples of the median correspond to the 95th and 5th percentiles, respectively (the normal range).

DISCUSSION

In this study, measurements of the peak velocity of systolic blood flow in the middle cerebral artery were found to predict the presence of moderate or severe

Table 2. Erythrocyte Antibodies in the 110 Mothers with Red-Cell Alloimmunization.*

Alloantibody Specificity	No. of Women
D	77
C	2
c	2
E	4
D and C	3
D and E	2
D and Kidd	1
D and Kell	1
Kell	14
Kell and M	1
Kell and E	1
Duffy	1
Kell, E, c	1

*One woman had triplet fetuses, of which two were at risk (the third was Rh-negative).

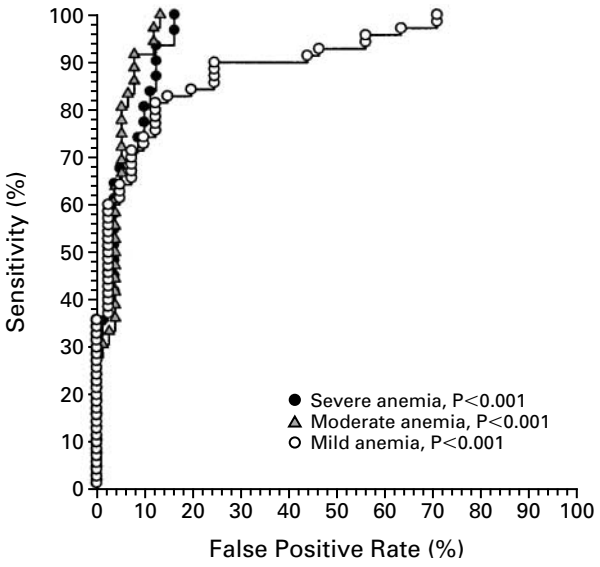

Figure 2. Receiver-Operating-Characteristic Curves for the Peak Velocity of Systolic Blood Flow in the Middle Cerebral Artery for the Prediction of Mild, Moderate, and Severe Fetal Anemia.

anemia in fetuses with a sensitivity of 100 percent and a false positive rate of 12 percent. A strength of the study is that the data were obtained by many operators in different medical centers using different ultrasound equipment; this consistency suggests that others should be able to obtain similar results.

Although other 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

Table 3. Expected Peak Velocity of Systolic Blood Flow in the Middle Cerebral Artery as a Function of Gestational Age.

Week of Gestation	Multiples of the Median			
	1.00 (median)	1.29	1.50	1.55
	cm/sec			
18	23.2	29.9	34.8	36.0
20	25.5	32.8	38.2	39.5
22	27.9	36.0	41.9	43.3
24	30.7	39.5	46.0	47.5
26	33.6	43.3	50.4	52.1
28	36.9	47.6	55.4	57.2
30	40.5	52.2	60.7	62.8
32	44.4	57.3	66.6	68.9
34	48.7	62.9	73.1	75.6
36	53.5	69.0	80.2	82.9
38	58.7	75.7	88.0	91.0
40	64.4	83.0	96.6	99.8

anemia.[10-13] This lack of correlation 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, we found in a preliminary study that the peak systolic velocity in the middle cerebral artery was higher in fetuses with anemia than in normal fetuses.[14] Similar results were reported by Vyas and coworkers.[15] However, this group did not find a significant association between the degree of anemia and the mean velocity of blood flow in the middle cerebral artery.[12]

On the basis of our results, the previously reported observation that hydrops may develop in a fetus in which the hemoglobin concentration is 7 g per deciliter lower than the mean[9] needs to be modified. The use of a hemoglobin value of less than 0.55 times the median seems more appropriate, because the hemoglobin concentration increases exponentially with advancing gestation. Therefore, a hemoglobin deficit of 7 g per deciliter may not have the same meaning at 20 weeks as at 34 weeks.

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.[16] Similar results were subsequently found in studies in humans.[17,18] Furthermore, the peak systolic velocity in the middle cerebral artery decreases when the fetal hematocrit rises.[19] These findings indicate that there is a reciprocal relation between the hemoglobin concentration and the velocity of cerebral blood flow.

We found that the risk of anemia was high in fe-

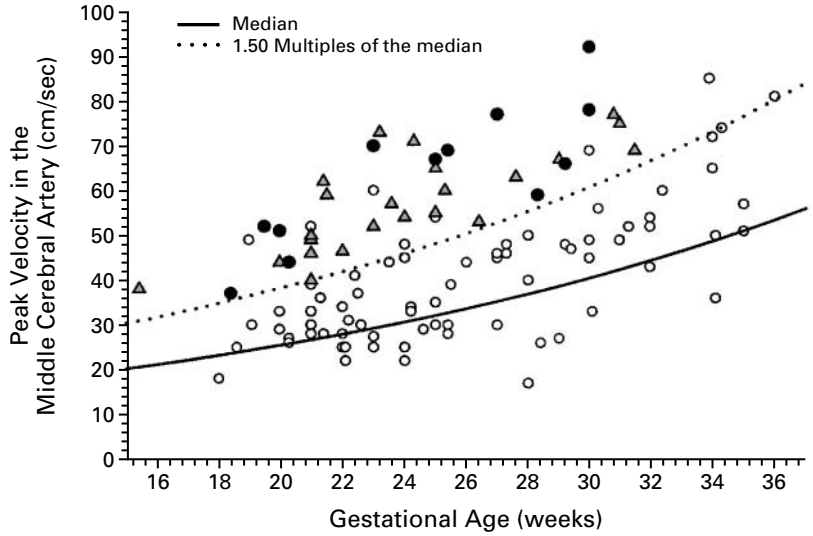

Figure 3. Peak Velocity of Systolic Blood Flow in the Middle Cerebral Artery in 111 Fetuses at Risk for Anemia Due to Maternal Red-Cell Alloimmunization.

Open circles indicate fetuses with either no anemia or mild anemia (≥0.65 multiples of the median hemoglobin concentration). Triangles indicate fetuses with moderate or severe anemia (<0.65 multiples of the median hemoglobin concentration). The solid circles indicate the fetuses with hydrops. The solid curve indicates the median peak systolic velocity in the middle cerebral artery, and the dotted curve indicates 1.5 multiples of the median.

tuses 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.[2]

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. 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,[4,20] and a procedure-related pregnancy loss of 1 percent.[4] If each fetus at risk for anemia were to undergo one cordocentesis procedure, we estimate 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.[21,22] For both amniocentesis and cordocentesis, there are no data concerning the optimal frequency of repeated sampling. Furthermore, these procedures may be associated with a worsening of maternal alloimmunization.[23-25] 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.[26] The use of measurements of peak systolic velocity as described here would decrease the number of fetuses subjected to amniocentesis and cordocentesis.

In conclusion, 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.

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