

Prediction of fetal anemia by measurement of the mean blood velocity in the fetal aorta

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In 68 red blood cell isoimmunized pregnancies the mean velocity of blood in the fetal aorta was measured by pulsed Doppler ultrasonography, and the fetal hemoglobin concentration was determined in blood samples obtained by cordocentesis. The values were compared to reference ranges of mean aortic velocity and hemoglobin for gestation, which were determined from 218 pregnancies that were not complicated by fetal hemolysis. In the red blood cell isoimmunized pregnancies there was a significant positive correlation between the aortic mean velocity and the hemoglobin deficit for the nonhydropic fetuses and a significant negative correlation between these two parameters for the hydropic fetuses. (*AM J OBSTET GYNECOL* 1990;162:209-12.)

Key words: Cordocentesis, red blood cell isoimmunization, pulsed Doppler, fetal aortic mean velocity, fetal anemia

In the management of red blood cell isoimmunized pregnancies the primary aim is to determine the degree of fetal anemia. Prediction of the severity of the disease has depended traditionally on the history of previous affected pregnancies, the type and level of hemolytic antibody in the maternal circulation, and the amniotic fluid optical density deviation at a wavelength of 450 nm, and more recently on ultrasonographic measurements of the fetus, umbilical vein, and placenta. However, fetal blood sampling and measurement of the hemoglobin concentration, which provide a direct assessment of the degree of fetal anemia, have demonstrated that these indirect parameters are not consistently reliable.¹⁻³

In a preliminary report, Rightmire et al.⁴ found a significant negative correlation between the hematocrit of fetal blood obtained at fetoscopy and the Doppler blood velocities in the fetal aorta. The aim of this study was to investigate further the relationship between aortic mean velocity and fetal anemia and to determine the clinical value of this Doppler measurement in the management of red blood cell isoimmunized pregnancies.

Patients and methods

The study included 68 red blood cell isoimmunized pregnant women who were referred to our unit at 17 to 38 (mean 25) weeks' gestation for fetal blood sampling and, if necessary, blood transfusion because they were considered to be severely affected on the basis of obstetric history and hemolytic antibody levels. The technique of cordocentesis and the indications for fetal blood sampling in a similar group of isoimmunized women have been described.⁵ The study was cross-sectional and the data were derived from fetuses that had not yet received transfusions. Gestational age was established from the history of the last menstrual period and from an ultrasonographic measurement of the fetal biparietal diameter at 16 to 18 weeks. The presence or absence of fetal hydrops (skin edema and ascites, pericardial or pleural effusions) was determined by ultrasonography at the time of fetal blood sampling.

Doppler examination of the fetal descending thoracic aorta was performed as previously described 1 to 2 hours before cordocentesis.⁶ A duplexed system, consisting of a 2 MHz pulsed Doppler probe attached (at a fixed angle of 53 degrees) to a 3 MHz linear array transducer (model 5000, ADR, Kranzbuhler, West Germany), was used. Doppler sonograms were recorded in the absence of fetal gross body and respiratory movements. The angle of insonation of the vessel was 45 to 55 degrees. The intensity-weighted, time-averaged mean velocity in two consecutive cardiac cycles was calculated automatically by a built-in computer from the Doppler shifted frequencies displayed in the sonogram. The coefficient of variation for this measurement is 5.9%.⁷ A reference range for aortic mean velocity be-

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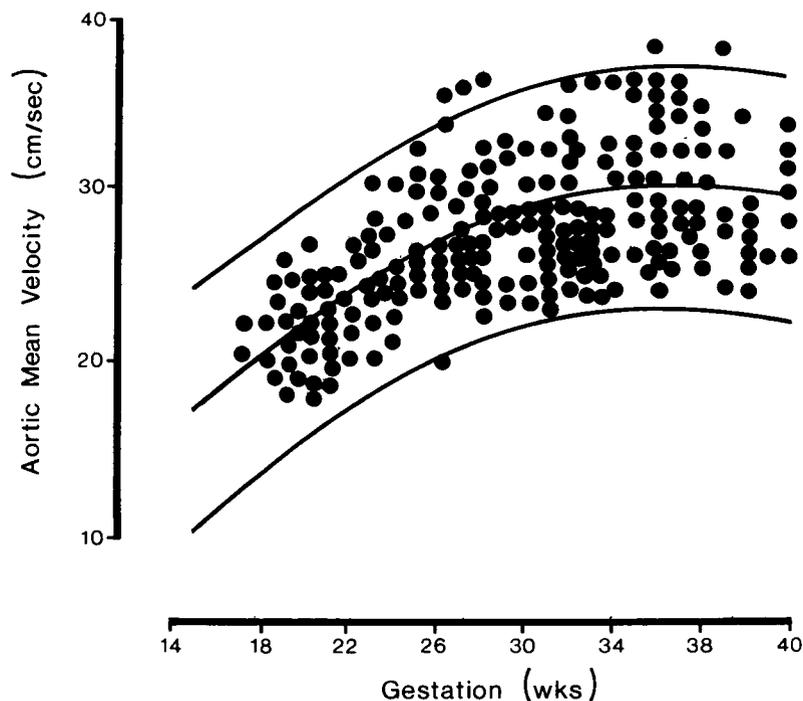


Fig. 1. Reference range (mean and 95% confidence intervals) of mean velocity of blood in fetal descending thoracic aorta with gestation ($n = 218$, $r = 0.64$, $p < 0.0001$, constant = -5.274 , linear constant = 1.925 , quadratic constant = -0.026 , residual SD = 3.327).

Table I. Accuracy of aortic mean velocity measurements in predicting fetal hemoglobin deficit

Cutoff value of deviation in aortic mean velocity	Fetal hemoglobin deficit gm/dl												
	-2	-1	0	1	2	3	4	5	6	7	8	9	10
$\geq +2$ SD	0%	0%	3%	5%	9%	14%	22%	31%	42%	53%	64%	81%	88%
$\geq +1$ SD	6%	10%	15%	23%	33%	44%	55%	66%	76%	84%	90%	94%	97%
≥ 0	32%	35%	54%	58%	68%	78%	85%	91%	95%	97%	100%	100%	100%
≥ -1 SD	60%	70%	79%	86%	92%	95%	98%	100%	100%	100%	100%	100%	100%
≥ -2 SD	88%	93%	96%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

tween 18 and 40 weeks' gestation was established from the study of 218 normal pregnancies.

Fetal blood samples (180 μ l) were collected into 20 μ l of isotonic edetic acid solution (0.5 mmol/L in 0.15 mmol/L sodium chloride), and the hemoglobin concentration (grams per deciliter) was determined with a Coulter S Plus counter. Results of direct Coombs' test were positive in all fetuses, and Kleihauer-Betke testing showed that all samples contained only fetal red blood cells. In normal fetuses the hemoglobin concentration rises linearly with gestation (hemoglobin = $7.9 + 0.19$ weeks' gestation) and 1 SD is approximately 1 gm/dl.*

In the control pregnancies regression analysis was

used to calculate individual 95% confidence intervals for aortic mean velocity with gestational age. In the red blood cell isoimmunized pregnancies the observed aortic mean velocity and hemoglobin in each fetus were subtracted from the corresponding normal mean for gestation, and subsequently regression analysis was used to calculate the individual 95% confidence intervals for the relation between the deviation in aortic mean velocity and fetal hemoglobin deficit.

Results

In the control pregnancies the aortic mean velocity increased with gestation and the best fit to the data was

provided by a quadratic equation (Fig. 1, $n = 218$, $r = 0.64$, $p < 0.0001$, constant = -5.274 , linear constant = 1.925 , quadratic constant = -0.026 , residual SD = 3.327).

In the red blood cell isoimmunized pregnancies there was an overall positive correlation between the fetal hemoglobin deficit and the deviation in aortic mean velocity ($n = 68$, $r = 0.464$, $p < 0.001$, constant = 0.151 , slope = 0.913 , residual SD = 5.952). However, separate analysis of the data from the hydropic and nonhydropic fetuses revealed a linear negative correlation for the hydropic fetuses ($n = 17$, $r = -0.540$, $p < 0.05$, constant = 59.1 , slope = -5.849 , residual SD = 8.511) and a linear positive correlation for the nonhydropic fetuses ($n = 51$, $r = 0.60$, $p < 0.0001$, constant = -0.368 , slope = 1.036 , residual SD = 3.621). The regression lines and individual values are shown in Fig. 2.

For the nonhydropic fetuses the accuracy of predicting the hemoglobin concentration deficit by measurement of the aortic mean velocity is shown in Table I. If the cutoff level for the aortic mean velocity is set at 2 SD above the normal mean for gestation, more than 53% of the severely anemic fetuses (hemoglobin deficit ≥ 7 gm/dl) will be detected and the false-negative rate (hemoglobin deficit ≤ 2 gm/dl) would be $< 9\%$.

Comment

In normal pregnancy the mean blood velocity in the fetal descending thoracic aorta increases with gestation, and this may reflect a progressive increase in cardiac output to fulfill the demands of the growing fetus.⁹ After 32 weeks' gestation the aortic velocity remains stable, in contrast to the velocity in the common carotid artery, which increases linearly with gestation. Furthermore, with advancing gestation there is a decrease in the impedance to flow in the common carotid artery.⁷ These findings led to the speculation that in the latter part of pregnancy a proportionally greater fraction of the cardiac output is directed to the fetal brain presumably to compensate for the progressive fall in fetal blood P_{O_2} and increase in P_{CO_2} .¹⁰

In the nonhydropic fetuses from red blood cell isoimmunized pregnancies there is an inverse correlation between the hemoglobin concentration and the velocity of blood in the descending aorta. If it is assumed that in anemia the cross-sectional area of the aorta does not change, the increased velocity would reflect an increase in blood flow. This finding confirms the prediction, from a mathematical model, that in fetal anemia the cardiac output is increased to maintain an adequate oxygen delivery to the tissues.¹¹ As in postnatal life the correlation between anemia and cardiac output may be mediated by an increase in stroke volume caused by (1) decreased viscosity leading to increased venous return,

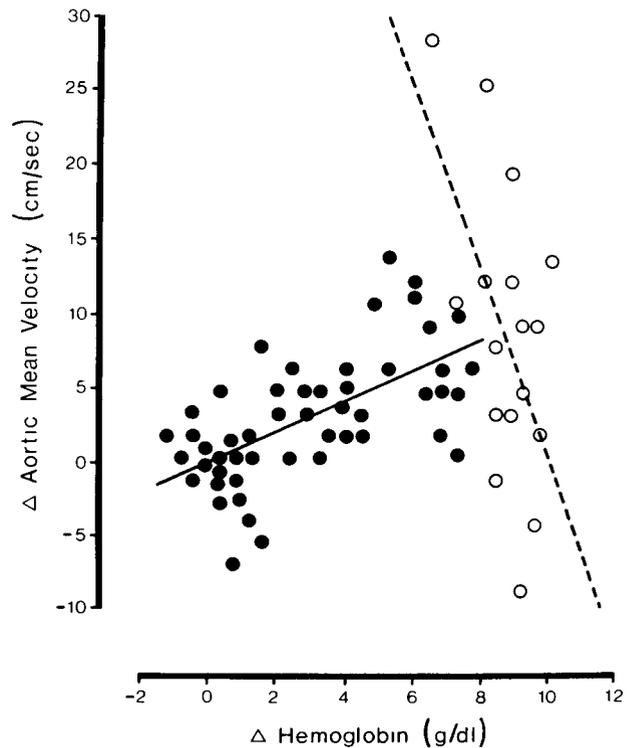


Fig. 2. Relation between deviation (Δ) in aortic mean velocity ($\Delta =$ observed aortic mean velocity minus normal mean for gestation) and hemoglobin deficit ($\Delta =$ normal mean hemoglobin concentration for gestational age minus observed value) in 51 nonhydropic (\bullet) and 17 hydropic (\circ) fetuses from red blood cell isoimmunized pregnancies.

(2) hypoxic peripheral vasodilation and therefore decreased peripheral resistance, and (3) hypoxic stimulation of chemoreceptors leading to improved myocardial contractility.^{12, 13}

In hydropic fetuses the hemoglobin concentration deficit was ≥ 7 gm/dl and the aortic mean velocity decreased with worsening anemia. These findings suggest that in severe anemia there is cardiac decompensation, presumably caused by the associated hypoxia and lactic acidemia.¹¹ Alternatively, as with fetal lambs, in the severely anemic human fetus there may be a compensatory redistribution in blood flow to the most vital organs, such as the brain and heart, and the supply to the rest of the body falls.¹⁵ Another possible mechanism for the association of reduced aortic blood flow and severe anemia is increased peripheral resistance, which results from clogging of placental capillaries with large immature red blood cells; when the fetal hemoglobin concentration deficit is ≥ 7 gm/dl, there is recruitment of extramedullary erythropoiesis and an increase in circulating erythroblasts.¹⁶

In the prediction of fetal anemia the diagnosis of hydrops fetalis by real-time ultrasonography identifies a group of fetuses with a hemoglobin deficit of ≥ 7

gm/dl. In the absence of hydrops the finding of an aortic mean velocity above the normal range suggests that the fetus is probably anemic, whereas if the aortic mean velocity is at or below the normal mean for gestation, the fetus is unlikely to be anemic (Table I). However, there is a large overlap in values, therefore in the clinical management of red blood cell isoimmunized pregnancies Doppler measurements of the fetal aortic mean velocity cannot predict accurately the degree of fetal anemia.

REFERENCES

1. Nicolaidis KH, Rodeck CH, Mibashan RS, Kemp JR. Have Liley charts outlived their usefulness? *AM J OBSTET GYNECOL* 1986;155:90-4.
2. Nicolaidis KH, Fontanarosa M, Gabbe SG, Rodeck CH. Failure of ultrasonographic parameters to predict the severity of fetal anemia in rhesus isoimmunization. *AM J OBSTET GYNECOL* 1988;158:920-6.
3. Nicolaidis KH, Rodeck CH, Mibashan RS. Obstetric management and diagnosis of haematological disease in the fetus. *Clin Haematol* 1985;14:775-805.
4. Rightmire DA, Nicolaidis KH, Rodeck CH, Campbell S. Midtrimester fetal blood flow velocities in rhesus isoimmunization: relationship to gestational age and to fetal hematocrit in the untransfused patient. *Obstet Gynecol* 1986;68:233-6.
5. Nicolaidis KH, Soothill PW, Rodeck CH, Clewell W. Rh disease: intravascular fetal blood transfusion by cordocentesis. *Fetal Ther* 1986;1:185-92.
6. Griffin D, Cohen-Overbeek T, Campbell S. Fetal and uteroplacental blood flow. *Clin Obstet Gynecol* 1983;10:565-602.
7. Bilardo CM, Campbell S, Nicolaidis KH. Mean blood velocities and flow impedance in the fetal descending thoracic aorta and common carotid artery in normal pregnancy. *Early Hum Dev* 1988;18:213-21.
8. Nicolaidis KH, Soothill PW, Clewell WH, Rodeck CH, Mibashan RS, Campbell S. Fetal haemoglobin measurement in the assessment of red cell isoimmunization. *Lancet* 1988;1:1073-5.
9. De Smedt MCH, Visser GHA, Meijboom EJ. Fetal cardiac output estimated by Doppler echocardiography during mid and late gestation. *Am J Cardiol* 1987;60:338-42.
10. Soothill PW, Nicolaidis KH, Rodeck CH, Campbell S. Effect of gestational age on fetal and intervillous blood gas and acid-base values in human pregnancy. *Fetal Ther* 1986;1:168-75.
11. Huikeshoven FJ, Hope ID, Power GG, Gilbert RD, Longo LD. A comparison of sheep and human fetal oxygen delivery systems with use of a mathematical model. *AM J OBSTET GYNECOL* 1985;151:449-55.
12. Daniel MK, Bennett B, Dawson AA, Rawles JM. Haemoglobin concentration and linear cardiac output, peripheral resistance, and oxygen transport. *Br Med J* 1986;292:923-6.
13. Guyton AC, Jones CE, Coleman TG. *Circulatory physiology: cardiac output and its regulation*. Philadelphia: WB Saunders, 1973:396-8.
14. Soothill PW, Nicolaidis KH, Rodeck CH, Clewell WH, Lindridge J. Relationship of fetal hemoglobin and oxygen content to lactate concentration in Rh isoimmunized pregnancies. *Obstet Gynecol* 1987;69:268-70.
15. Peeters LLH, Sheldon RF, Jones MD, Makowski EL, Meschia G. Blood flow to fetal organs as a function of arterial oxygen content. *AM J OBSTET GYNECOL* 1979;135:637-46.
16. Nicolaidis KH, Thilaganathan B, Mibashan RS, Rodeck CH. Erythroblastosis and reticulocytosis in anemic fetuses. *AM J OBSTET GYNECOL* 1988;159:1063-6.