Prediction of fetal anemia by middle cerebral artery Doppler

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Abstract
Objectives: To assess the value of peak systolic velocity in the middle cerebral artery (MCA) in prediction of fetal anemia as a non invasive method in non hydropic fetuses.

Methods: The study included 30 pregnant women with non hydropic fetuses and with known red cell antibodies. Full ultrasound examination was done and peak velocity of systolic cerebral blood flow in MCA was measured. If severe anemia was suspected, fetal blood sampling by cordocentesis was performed.

Results: Thirty fetuses were examined, 22 were anemic and eight had a hemoglobin value within a normal range. The mean MCA peak systolic velocity for fetus with the normal hemoglobin (Hb) was 48.98 ± 13.94 while that for the anemic fetus was 64.79 ± 11.97 and \( P = 0.004 \).

Sensitivity of increased peak velocity of systolic blood flow in MCA for prediction of fetal anemia was 90.5% and specificity was 78.6%.

Conclusion: Doppler of peak velocity of systolic blood flow in MCA can be reliable in predicting anemia so delaying invasive methods until treatment (blood transfusion) is expected to be necessary.

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1. Introduction

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 (1). Women with rising red cell antibody levels, with or without a history of a previously affected pregnancy, are usually referred to fetal medicine units for specialized managements (2). Survival rates can exceed 90 percent if anemia is diagnosed and treated with intrauterine blood transfusions (3).

The most accurate test to assess the degree of fetal anemia, and thus the need for transfusion, is the fetal hemoglobin (Hb) measurement by fetal blood sampling (4). However, the standard test to evaluate the need for fetal transfusion is serial amniocentesis for the determination of bilirubin levels in amniotic fluid. Hemolysis leads to the accumulation of bilirubin in amniotic fluid, so its level correlates with the severity of hemolysis. The bilirubin level is quantified by spectrophotometry and expressed as the change in optical density at a wavelength...
of 450 nm (ΔOD₂₅₀); the ΔOD₂₅₀ values are then plotted on a Liley chart to estimate the severity of anemia (5). Both procedures have a significant rise of causing miscarriage, premature rupture of membrane, preterm delivery and increase antibody concentration (6).

Several non-invasive methods for the prediction of fetal anemia have been assessed, aiming to defer the use of invasive testing until transfusion is necessary (2,7,10). The association of increased blood flow velocity in the fetal middle cerebral artery (MCA) with fetal anemia is the most promising of these non-invasive tests as has subsequently been reported (9,8). Fetuses with anemia have a high cardiac output and decreased blood viscosity, resulting in high blood-flow velocities that could be used in prediction of fetal anemia (11,12). Brennan showed that in anemic fetus changes in cardiac output & blood-flow velocities are reflected by an increase in peak systolic velocity in the middle cerebral artery (13).

The objective of the current study is to assess the value of measuring peak systolic velocity in the middle cerebral artery (MCA) as a non invasive method in non hydromic fetuses for prediction of fetal anemia due to maternal red-cell alloimmunization.

2. Methods

2.1. Subjects’ studies

The study included 30 pregnant women with red cell antibodies referred for assessment and management. Patients were mainly referred if there was an increase in antibody levels in the maternal serum, or if there was a previous obstetric history of an anemic fetus or neonate. Assessment consisted of ultrasound examination for fetal biometry, exclusion of any structural abnormalities, liquor volume assessment, umbilical artery Doppler blood flow studies and Doppler blood flow velocity studies of the MCA. Hydrops was defined as fluid collection in body cavities or skin edema, and hydromic fetuses were excluded from the study. Cordocentesis was performed on 18 patients at their first visit and for the remaining, follow-up was arranged and those whose assessment was suggestive of worsening anemia underwent cordocentesis on the second visit.

2.2. Doppler studies

Doppler examination of the MCA 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. We have found that the systolic velocity decreases with distance from the point of origin of this vessel, so the angle between the ultrasound beam and the direction of blood flow was kept as close as possible to 0° and in all cases not to exceed 30°. The highest point of the wave from peak systolic velocity (PSV) was measured. Doppler images were recorded at a time when there was an absence of marked fetal body and respiratory movements, to avoid false elevation in PSV with fetal heart rate acceleration. At least three measurements were taken and the highest one is accepted as the final value. The reference test for the diagnosis of fetal anemia was measurement of peak systolic velocity of the MCA more than 1.5 multiple of median (MOM) using reference produced by Mari and his colleagues (9). Practical approach is to convert actual values into MOM to account for changes in gestational age, internet based calculator is available at www.perinatology.com.

2.3. Cordocentesis

Fetal blood sampling was performed by cordocentesis from the umbilical vein at the placental cord insertion with blood ready for fetal transfusion if necessary. Fetal blood was immediately examined for the determination of the full blood count and, if anemia was confirmed, intravascular transfusion was performed.

The reference test for the diagnosis of fetal anemia was measurement of the hemoglobin level in umbilical-cord blood. Fetal anemia is defined as Hb less than 0.65 times the median for gestational age, with the use of the published reference range (9).

2.4. Statistics

Statistical presentation and analysis of the present study was conducted, using the mean by SPSS V.16.

Mean value X: the sum of all observations divided by the number of observations:

$$\bar{X} = \frac{\sum x}{n}$$

Where $\sum x = \sum & \text{n} = \text{number of observations}$. ROC-curve: Receiver Operating Characteristic curve analysis

Sensitivity: Probability that the test results will be positive when the disease is present (true positive rate, expressed as a percentage).

Specificity: Probability that the test results will be negative when the disease is present (true negative rate, expressed as a percentage).

3. Results

This study included 30 pregnant women with alloimmunization and non-hydromic fetuses. Twenty three cases had RhD antibodies. Other 5 cases were with Rh C antibodies and last 2 cases were with anti E antibodies.

Medium gestational age was 29.27 ± 3.54 (range 24–35 weeks). Medium maternal age was 31.1 ± 5.67 (range 22–44 years). All patients were multi gravid. Among the 30 fetuses at risk of anemia, 22 were anemic (Hb 8.07 ± 0.93) and 8 had normal Hb (Hb 10.08 ± 0.96).

Fetal blood was taken by cordocentesis for hemoglobin analysis in 22 cases, 18 at first visit and four at second visit. In the other 8 cases the MCA Doppler was within normal range (48.98 ± 13.94) and follow up antibodies titer remains stable and hemoglobin was determined in fetal cord blood obtained at birth and show normal Hb or mild anemia.

The mean MCA peak systolic velocity for fetuses with normal Hb was 48.98 ± 13.94 while that for anemic fetuses was 64.79 ± 11.97 ($P \leq 0.004$). The MOM of MCA for fetuses with normal Hb was 1.22 ± 0.21 while that for anemic fetuses was 1.62 ± 0.08 ($P \leq 0.001$).

There were non significant correlations between fetal Hb and maternal age with $P = 0.19$ (Fig. 1), while there were
Figure 1  Correlation between fetal Hb and maternal age in fetuses at risk of anemia due to red-cell alloimmunization. Open rectangle indicates fetuses with anemia & solid rectangle indicates fetuses with no or mild anemia.

Figure 2  Correlation between fetal peak systolic velocity of MCA and maternal age in fetuses at risk of anemia due to red-cell alloimmunization. Open rectangle indicates fetuses with anemia & solid rectangle indicates fetuses with no or mild anemia.

Figure 3  Correlation between MoM of fetal Hb and gestational age in fetuses at risk of anemia due to red-cell alloimmunization. Open rectangle indicates fetuses with anemia & solid rectangle indicates fetuses with no or mild anemia.
Figure 4  Correlation between MCA-PSV and gestational age in fetuses at risk of anemia due to red-cell alloimmunization. Open rectangle indicates fetuses with anemia & solid rectangle indicates fetuses with no or mild anemia.

Figure 5  Strong correlation between MoM of fetal Hb and MoM of MCA in fetuses at risk of anemia due to red-cell alloimmunization. Open rectangle indicates fetuses with anemia & solid rectangle indicates fetuses with no or mild anemia.

Figure 6  The distribution of MoM of MCA values in the anemic and non-anemic fetuses. Non anemic fetuses' median 1.19, range 1.53, maximum value 1.37, minimum value 1.03, anemic fetuses' median 1.62, range 1.53 maximum value 1.78, minimum value 1.52.
significant correlations between MCA and maternal age with $P = 0.001$ (Fig. 2).

On the other hand there was a strong negative correlation between gestational age and MOM of fetal Hb (correlation coefficient $r = -0.358$, $P \leq 0.028$) (Fig. 3). Also, there was a significant correlation between gestational age and MCA (correlation coefficient $r = -0.525$, $P \leq 0.014$) (Fig. 4).

The relation between the multiples of the median of the hemoglobin concentration and the multiples of the median of peak systolic velocity was strong (correlation coefficient $r = -0.574$, $P \leq 0.003$ for MOM of PSV) (Fig. 5).

ROC-curve: Characteristic curve analysis for sensitivity and specificity.

**Figure 7** Normal Doppler imaging of the middle cerebral artery peak systolic velocity (46.8) at 32 weeks 4 days’ gestation in a multi gravida 25 years with fetal Hb10.3.

Fig. 6 demonstrates the distribution of MOM of MCA values in the anemic and non-anemic fetuses, showing the median, range and maximum–minimum values for each group.

Sensitivity of increased PSV of MCA to predict fetal anemia in cases alloimmunized with red cell antibodies was 90.5% and specificity was 78.6% (ROC Curve).

Doppler imaging of the middle cerebral artery, peak systolic velocity shows a normal level in the non anemic fetus (where MCA was 46.8 at 32 weeks 4 days’ gestation in multi gravida 25 years with fetal Hb10.3) and was very high in cases of fetal anemia (where MCA was 68.8 at 30 weeks 6 days’
Figure 8  High Doppler imaging of the middle cerebral artery peak systolic velocity (68.5) in anemic fetus with fetal Hb 7.5 at 30 weeks 6 days' gestation of a multi gravida 29 years.

Figure 9  High Doppler imaging of the middle cerebral artery peak systolic velocity (74.0) in anemic fetus with fetal Hb 8.5 at 32 weeks 3 days' gestation in a multi gravida 44 years.
gestation in multi gravida 29 years with fetal Hb 7.5 & MCA was 79.2 at 32 weeks 3 days’ gestation in multi gravida 44 years with fetal Hb 8.5) (Figs. 7–9).

4. Discussion

Doppler velocimetry in the middle cerebral artery (MCA) has played a major role in the fetal medicine for the last 23 years, both in intrauterine growth-restricted (IUGR) and anemic fetuses. Its utility in the diagnosis and management of cases of fetal anemia was initially demonstrated in the cases of red cell alloimmunization and later extended to other types of anemia (16,15).

Data of the present findings confirm that MCA peak systolic velocity compared with hemoglobin levels at either fetal blood sampling, or cord sampling at delivery if antenatal intervention had not been indicated is significantly increased in the cases of fetal anemia owing to red cell antibodies. The most likely physiological explanation for this is that anemia is associated with both increased cardiac output, due to the hyperdynamic circulation, and a reduction in blood viscosity, both leading to increased blood flow velocity.

The association between increased MCA blood flow velocity and fetal anemia has been previously demonstrated using peak systolic velocity (9,10,17). The use of published, generally agreed, reference range was preferred for this study.

The peak systolic velocity in the middle cerebral artery decreases when the fetal hematocrit rises (20). These findings indicate that there is a reciprocal relation between the hemoglobin concentration and hematocrit values and the velocity of cerebral blood flow (18). We found that the risk of anemia was high in fetuses with a peak systolic velocity of 1.50 times the median or higher. Such findings support the previous work of Moise who found that an elevated peak MCA velocity of >1.5 multiples of the median is useful in the timing of the initial intrauterine transfusion (IUT) in the red cell-alloimmunized pregnancies (19). Fetuses with values below 1.50 either did not have anemia nor 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 as had been previously reported by (1).

Although cordocentesis allows direct measurement of fetal hemoglobin, it is associated with infection, bleeding, fetal bradycardia, premature rupture of the membranes and pregnancy loss (21). However, anemia is less invasive than cordocentesis but the reliability of measurements of bilirubin in amniotic fluid before 27 weeks of gestation is questionable. Yet for both procedures there are no data concerning optimal accuracy (22,23). Opakes and his colleagues showed through comparing Doppler ultrasonography versus amniocentesis that measurements of the peak velocity of systolic blood flow in MCA can safely replace invasive testing of Rh-alloimmunized pregnancies (24).

Therefore, the use of measurements of peak systolic velocity as described here would be beneficial and decrease the number of fetuses subjected to cordocentesis and amniocentesis. These findings coincided with the work of Alshimmiri and his colleagues who have shown that fetal MCA-PSV weakly correlates with the degree of fetal anemia in groups with or without previous intrauterine transfusion; however, velocity threshold levels were sensitive enough to predict most fetuses with moderate to severe anemia (25).

Our findings coincided with the work of previous researchers who demonstrated that MCA-PSV measurement is essential in the diagnosis, evaluation, and management of the cases of fetal anemia (26,27). The use of this modality lessens the need for invasive procedures. Also, Kenneth and Moise showed that the peak systolic velocity of the MCA was effective in the detection of fetal anemia in a variety of pathologic states (28). They showed that addition of this noninvasive method to detect the anemic fetus has enabled the maternal-fetal specialist to intervene earlier in the course of such diseases as hemolytic disease of the fetus/newborn infant and fetal parvovirus infection. Although the middle cerebral artery peak systolic velocity Doppler has limited diagnostic accuracy, it remains the gold standard for noninvasive screening of fetal anemia (29).

Our results were compared with hemoglobin levels at either fetal blood sampling in 22 cases, or cord sampling at delivery in 8 cases where antenatal intervention had not been indicated. MCA-PSV had a sensitivity of 90.5% and a specificity of 78.6% for the detection of severe anemia. Brennand showed by comparing hemoglobin levels in 165 fetuses at either fetal blood sampling, or cord sampling at delivery that the sensitivity and accuracy of the middle cerebral artery Doppler (sensitivity of 88%, specificity of 82%) were substantially greater than anioncoentesis (sensitivity of 76%, specificity of 77%) for the detection of anemia (13).

Hydropic fetuses were excluded from this study. This is because we wished to assess how effective the measurement of MCA Doppler velocity is at predicting fetal anemia in borderline cases, in which the decision to sample the fetal blood is not clear.

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. Clearly, the widespread use of MCA Doppler assessment to detect fetal anemia in other fetal diseases is on the near horizon. However, no non-invasive test is 100% accurate in all cases, and so the assessment of patients with red cell antibodies should be comprehensive and include all possible relevant information, including obstetric history and rate of change of antibody levels.

References


