The usefulness of middle cerebral artery Doppler assessment in the treatment of the fetus at risk for anemia

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Search for the Holy Grail
One of the most longstanding and successful therapies in fetal medicine has been the intrauterine transfusion (IUT) of red cells to correct fetal anemia. Studies in animal models of anemia indicated that fetal blood velocities were increased as a result of increased cardiac output and reduced blood viscosity. Ultrasound measurements in the anemic human fetus have confirmed these findings.

Can Peak MCA Doppler Replace Amniocentesis for ΔOD_{450}?
Mari’s original report has led to a gradual abandonment of serial amniocenteses for ΔOD_{450} in favor of a noninvasive approach. Data would suggest that as many as 70% of invasive procedures can be eliminated through adoption of surveillance with serial middle cerebral artery (MCA) Doppler assessment. The technique has the potential to reduce complications such as preterm premature rupture of the membranes and enhanced maternal sensitization caused by transplacental amniocentesis.

Technique
For the clinician to obtain the MCA peak velocity, the fetal head should be in a transverse plane. The MCA vessels can be found with color or power Doppler ultrasound overlaying the anterior wing of the sphenoid bone near the base of the skull. An angle of insonation of <15 degrees should be used. Typically, the clinician can achieve an angle that approximates zero degrees by moving the transducer on the maternal abdomen. The use of angle correction software rarely should be necessary.

Although the fetal MCA closest to the anterior uterine wall is used usually, studies have revealed that the peak velocity in the contralateral MCA is valid. A 2-mm pulsed Doppler gate is placed over the vessel just as it bifurcates from the carotid siphon. More peripheral placement of the gate will result in a falsely low peak value. The peak systolic velocity should be measured during a period of fetal apnea and during absent fetal movement. This is especially important late in gestation, when a false elevation in the peak velocity can occur with fetal heart rate accelerations.

At least 3 measurements should be taken, and the highest measurement should be accepted as the final value. During the measurement, the Doppler baseline on the display should be adjusted close to zero; the pulse repetition frequency should then be adjusted in an effort to change the scale to the approximate peak velocity. These adjustments will optimize the appearance of the waveform and make the true peak velocity more readily discernible. Peak systolic measurements should be undertaken with the use of electronic calipers because automated measurement software that traces the waveform typically underestimates the true peak velocity.

MCA measurements, which should be performed weekly, can be initiated as early as 16-18 weeks of gestation. Recently, normal values for earlier gestational ages have been published. Previous authors have suggested that MCA values be plotted on a normal curve, much like the Liley curve. A more practical approach is to convert the actual values into multiples of the median to account for changes in gestational age. After 35 weeks of gestation, the false-positive rate for the prediction of anemia increases. However, in cases of a normal MCA peak velocity after 35 weeks of gestation, serial weekly measurements can be continued until the induction of labor is scheduled.

Timing Intrauterine Transfusions
Once a center has achieved a comfort level in the use of MCA Doppler assessment to detect anemia before the first
IUT, the natural tendency is to extend this technique to decide when to time the subsequent transfusions. Unfortunately, the data do not entirely support this practice.

The decreasing sensitivity of the peak MCA Doppler assessment to detect moderate-to-severe anemia after several IUTs probably has several explanations. By the third IUT, most of the circulating red cells in the fetal circulation are donor cells that contain adult hemoglobin. Fetal red cells have been shown to be less rigid than adult red cells, which is a rheologic property that contributes to an increased whole blood viscosity. In addition, correction of the fetal anemia through IUT raises the fetal hematocrit level, which substantially increases whole blood viscosity. Both of these will slow the speed at which blood moves through the fetal circulation. A shift from a principally fetal hemoglobin to an adult hemoglobin environment has the potential to decrease the delivery of oxygen at the tissue level because of differences in the oxygen dissociation curve of these 2 hemoglobins.

Published data and anecdotal clinical experience do not support the use of MCA Doppler assessment to time serial IUTs beyond the first transfusion interval. What then is the clinician to do? Many experienced clinicians use empiric intervals between procedures. In cases of severe anemia at <24 weeks of gestation, the fetal hematocrit level should be only partially corrected to allow for physiologic adjustment to the acute change in viscosity. Radunovic et al suggested that no more than a 4-fold increase in hematocrit level or a target value of 25% be used in these cases. Such a practice will reduce perinatal mortality rates immediately after the procedure. A repeat procedure is undertaken after 48 hours to correct the hematocrit level into the normal range.

In gestational ages of >24 weeks, intervals of 7-10 days are used typically between the first and second IUTs; an interval of 2 weeks can be used between the second and third procedures. Subsequent procedures can be timed every 3 weeks once fetal erythropoiesis has been suppressed, as evidenced by Kleihauer–Betke stain or flow cytometry. Alternatively, a calculated decline in hemoglobin level of 0.4, 0.3, and 0.2 g/dL/d for the first, second, and third transfusion intervals, respectively, can be used to decide when to perform the next IUT.

**DETECTING FETAL ANEMIA IN OTHER DISEASE STATES**

A prospective evaluation of at-risk fetuses because of maternal Kell alloimmunization with the peak MCA velocity has revealed a sensitivity and specificity of 89% for the detection of fetal anemia. Although this series consisted of only 30 fetuses, the sensitivity appears similar to the detection of fetal anemia found in Rhesus alloimmunization in the recently published large multicenter trial.

In utero parvovirus infection can result in transient suppression of red cell precursors from the fetal bone marrow. MCA Doppler assessment has been used to detect the resulting anemia. A threshold of 1.29 multiples of the median (MoM) has been proposed; however, this will lead to the detection of cases of mild anemia. Because frank hydrops has been reported to resolve spontaneously in as many as 30% of cases, it would appear prudent to use a threshold value of the MCA velocity of 1.5 MoM if one is contemplating IUT as a therapeutic option. Experience with MCA Doppler assessment to detect fetal anemia caused by Bart’s hemoglobin in cases of homozygous alphathalassemia has been limited. MCA peak velocity appears useful in the detection of the anemic fetus with alphathalassemia; however, its utility in these cases must be questioned because of a lack of therapeutic options.

In cases of severe twin-twin transfusion syndrome (TTTS) that is treated with laser therapy, anastomotic placental vessels may be missed in as many as one-third of cases. In approximately 13% of laser cases, a reversed TTTS situation (called the twin anemia-polyhydramnios sequence) may develop, whereby the recipient becomes anemic and the donor becomes plethoric. In this scenario, the recipient twin will exhibit an elevated peak MCA systolic velocity of >1.5 MoM, although a decreased velocity will be noted in the donor (usually <1.0 MoM). Treatment by IUT of the recipient has proved successful in prolonging these pregnancies in some cases. It would appear prudent therefore that weekly MCA Doppler scans be assessed for at least 4 weeks after laser therapy has been undertaken for severe TTTS.

In 1 series of 73 early intrauterine growth restricted fetuses, neonatal anemia was detected in 29% of cases. When absent end-diastolic velocity was noted in the umbilical artery by Doppler assessment, 43% of these fetuses exhibited anemia at birth. The peak MCA Doppler assessment has been studied to predict fetal anemia in intrauterine growth restriction. Unfortunately, although a linear relationship was found between MCA Z scores and neonatal hemoglobin, no specific threshold value could be determined to predict fetal anemia.

Finally, acute fetomaternal hemorrhage with resulting fetal anemia has been detected with the peak MCA velocity.

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**CLINICAL IMPLICATIONS**

- The peak systolic velocity in the fetal middle cerebral artery (MCA) can replace serial amniocentesis for the detection of fetal anemia in cases of red cell alloimmunization.
- Experience with this technique must be acquired before reliable results can be obtained.
- The peak MCA velocity may aid in the timing of the second in a series of intrauterine transfusions; published data to date do not support its use thereafter.
- MCA Doppler assessment has proved effective in the detection of fetal anemia in other disease states, such as fetal parvovirus infection, alphathalassemia, twin anemia-polyhydramnios sequence after laser therapy, and fetomaternal hemorrhage.