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REVIEW ARTICLE

Noninvasive Diagnostics of Fetal Anemia

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ABSTRACT

Even though the use of anti-D immunoglobulin has dramatically decreased the incidence of hemolytic disease of fetus and newborn, it still remains a significant cause of fetal and neonatal morbidity and mortality. The main challenge facing fetal medicine specialists today is not the skill required for invasive therapy, but rather the noninvasive monitoring of the disease so that its progress can be predicted to guide the need and timing of intrauterine transfusions to minimize unnecessary invasive testing. In previous years many different diagnostic tests were proposed but the assessment of middle cerebral artery peak systolic velocity still stands as a gold standard for noninvasive assessment of fetal anemia.

Keywords: Fetal anemia, Rh-isoimmunization, Ultrasound, Doppler, Middle cerebral artery peak, Systolic velocity.

INTRODUCTION

Hemolytic disease of the fetus and neonate (HDFN) is caused by fetal red cell hemolysis that occurs after placental transfer of maternal immunoglobulin G. There are more than 50 red cell antibodies that can potentially cause HDFN, most common are anti-RhD, anti-Rhc and anti-Kell.[1] It has to be mentioned that with the established antenatal and postnatal use of anti-D prophylaxis for rhesus D negative women, the incidence of HDFN has dramatically fallen.[2] However, this condition still affects a large number of pregnancies with significant health and financial implications. The main challenge facing fetal medicine specialists today is to minimize unnecessary invasive testing by using noninvasive monitoring of the disease to guide the need and timing of intrauterine transfusions (IUT).

Maternal antibody levels, used for screening of HDFN, are usually measured as titer or quantification. It is generally accepted that a cut-off value for titer is 1:32 and a value of anti-D between 4 and 15 IU/ml.[1,3] These cut-off values should indicate further fetal surveillance techniques.

Fetal blood sampling is the gold standard for diagnosis of fetal anemia. The procedure loss rate is about 1 to 2%.[4] Therefore, this intervention should be reserved only for the fetuses that will require IUT. Amniocentesis and spectral analysis of bilirubin for prediction of fetal anemia were first introduced by Liley in 1961.[5] The results are plotted on gestational age dependent Liley chart and all results falling in zone 3 or the upper part of zone 2 indicate the need for IUT. The Liley chart can be used for prediction of fetal anemia from 27th gestational week onward. The procedure loss associated with amniocentesis is between 0.25 and 1% per procedure.[6] In addition to procedure loss, the invasive testing is associated with fetomaternal hemorrhage as well, which in turn may increase antibody levels, and thus exacerbate the disease.

In past two decades several ultrasound-based diagnostic tests for detection of fetal anemia were proposed with aim to defer the invasive testing until IUT is expected to be necessary. The proposed tests were as follows: Umbilical vein dilatation, measurement of fetal spleen and liver, measurement of placental thickness and Doppler assessment of various vessels.[7] At present moment, the vessel of choice for assessment of fetal anemia is middle cerebral artery.[7]

Mari et al were the first to report the increase of middle cerebral artery peak systolic velocity (MCA-PSV).[8] The test performed well in moderate to severely anemic fetuses, with reported sensitivity of 100% and a false-positive rate of 12%. Other authors have confirmed their findings with sensitivity ranging from 88 to 100%.[9-11]

The Assessment of MCA-PSV

Anemic fetuses have a hyperdynamic circulation as a result of increased cardiac output and reduced blood viscosity.[12] These hemodynamic changes cause the increase in fetal blood velocity.[12] Although blood velocities in all fetal vessels will be increased, the MCA is particularly suitable for assessment, as the brain circulation is known to respond quickly to hypoxemia.[12] Since the diameter of MCA stays the same, the increased MCA-PSV is directly proportional to the increased blood flow of the brain.[10]

The proper image for MCA-PSV assessment is just below the image for biparietal measurement. Color Doppler mode should be turned on and circle of Willis identified. The MCA is located laterally from the circle Willis, coursing above the greater wing of sphenoid bone (Fig. 1). The MCA-PSV should be measured close to its origin from internal carotid artery. As peak systolic velocity is a measurement that is angle dependent, the volume sample caliper has to be placed as close as possible

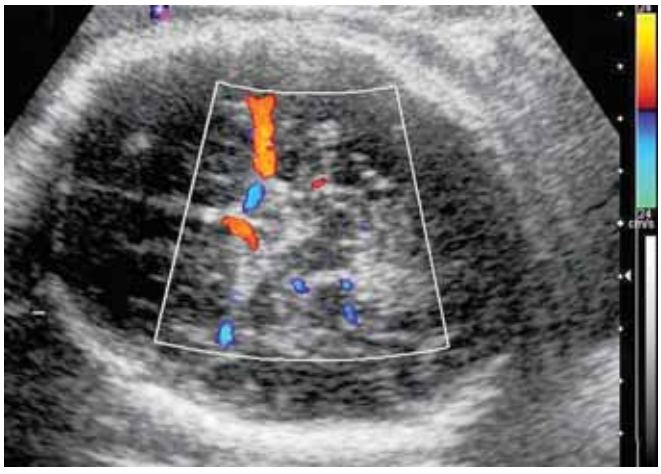

Fig. 1: The proper transverse section of fetal head is presented and MCA is identified with Doppler mode

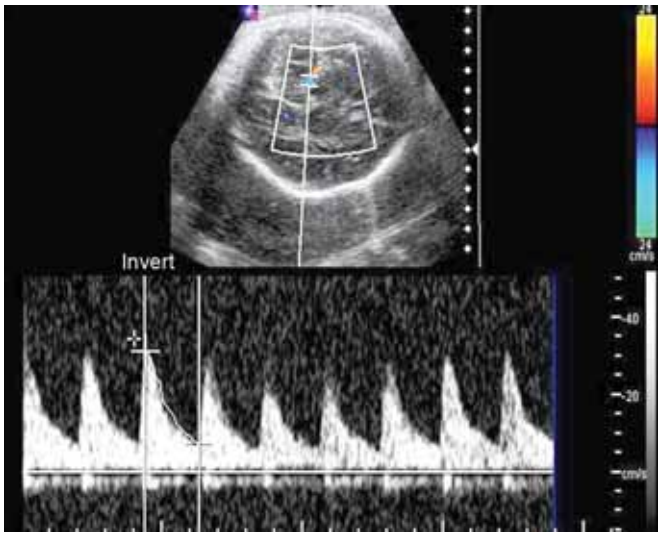

Fig. 2: The wave signals are of similar appearance and the MCA-PSV is presented

to 0° angle, if needed angle correction tool can be used as well. During the measurement, the fetus should be at rest, minimal pressure should be applied to mother's abdomen and wave signals should be similar (Fig. 2). The most commonly used cut-off MCA-PSV value is 1.5 multiples of the median (MoM) for gestational age.[10]

DISCUSSION

A recent meta-analysis of all available noninvasive methods for detection of fetal anemia found MCA-PSV to be the most reliable when sensitivity and specificity are determined against the gold standards of fetal blood sampling or neonatal hemoglobin.[7] The sensitivity and specificity of MCA-PSV are markedly similar to that of OD450 from amniocentesis.[7] Other Doppler measurements, such as resistance index and pulsatility index did not show a good correlation with fetal anemia, mainly because they are not angle-dependent measurements.[7]

Spleen and liver are hematopoietic organs that increase in size due to stimulated hematopoesis. The idea that measurement of these organs would correlate with fetal anemia has some merit, but these measurements are not easily obtained and are not widely used. The mentioned meta-analysis showed that their sensitivity and specificity do not justify their use as screening test.[7] Assessment of umbilical vein dilatation and measurement of placental thickness do not appear to be useful screening test for fetal anemia.[7]

There are several other studies on noninvasive tests, such as cardiofemoral index, splenic artery peak systolic velocity and middle cerebral artery deceleration angle, that have shown promising results but this data is from small cohort studies.[13-15]

CONCLUSION

Doppler assessment of MCA is a widely used diagnostic test in fetomaternal units for assessment of growth-restricted fetuses for 'brain-sparing' effects. This everyday use and good intra-observer and interobserver variability make it an excellent tool for noninvasive follow-up of fetal anemia.[16] Further research should be done on test combinations to improve diagnostic accuracy and post-IUT follow-up.

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