

Middle cerebral artery Doppler

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Introduction

In the last 50 years we have seen tremendous advances in the management of fetal haemolytic anaemia. What was once a disease of high perinatal mortality and morbidity has become a condition readily amenable to antenatal diagnosis and intrauterine fetal therapy. Prior to the 1960s, the management of severe fetal anaemia relied on preterm delivery and subsequent therapy in the neonatal period. In 1961, Liley¹ described the use of amniocentesis to predict the severity of fetal haemolytic anaemia. Amniotic fluid bilirubin concentrations, reflecting the degree of fetal haemolysis, gave indirect assessment of fetal anaemia.

The first therapeutic intervention for fetal anaemia was again described by Liley in 1963². He performed the first intrauterine transfusion via the intraperitoneal route. The introduction of real-time ultrasound facilitated needle-guided intraperitoneal transfusion in 1977³. The first intravascular transfusion, performed fetoscopically, was carried out by Rodeck in 1981⁴. Developments in imaging technology mean that intravascular transfusion is now routinely performed with the aid of ultrasound guidance, and success rates of 92–94% can be expected for the non-hydropsic anaemic fetus^{5,6}.

In the last twenty years we have witnessed another milestone in the management of fetal haemolytic disease. Prediction of fetal anaemia by the non-invasive method of middle cerebral artery Doppler has revolutionised the assessment of rhesus sensitised pregnancies, and provides the focus of discussion for this article.

Rationale for middle cerebral artery Doppler studies in fetal anaemia

The physiological response of a fetus to anaemia is an increase in stroke volume and hence an increase in cardiac output. As a result, the fetus develops a hyperdynamic circulation. Blood flow is redistributed to vital end organs, including brain, heart and adrenals, following changes in vascular resistance and a reduction in blood viscosity. The utility of Doppler studies in the assessment of fetal anaemia relies on the premise that provided the cross-sectional area of a blood vessel remains constant, blood velocity is directly proportional to blood flow. In addition, decreased blood viscosity results in increased blood flow^{7,8}. The increase in cardiac output, and reduced blood viscosity will both lead to an increase in blood flow, and hence blood velocity, in the anaemic fetus. In the middle cerebral artery this is reflected by an increase in peak systolic velocity.

The middle cerebral artery is the vessel of choice for assessment because it is accessible, and sensitive to the effects of hypoxia. The technique for middle cerebral artery peak systolic velocity measurement has been described in detail by Mari, *et al.*^{9,10}. An axial section through the fetal head that includes the thalami and cavum septum

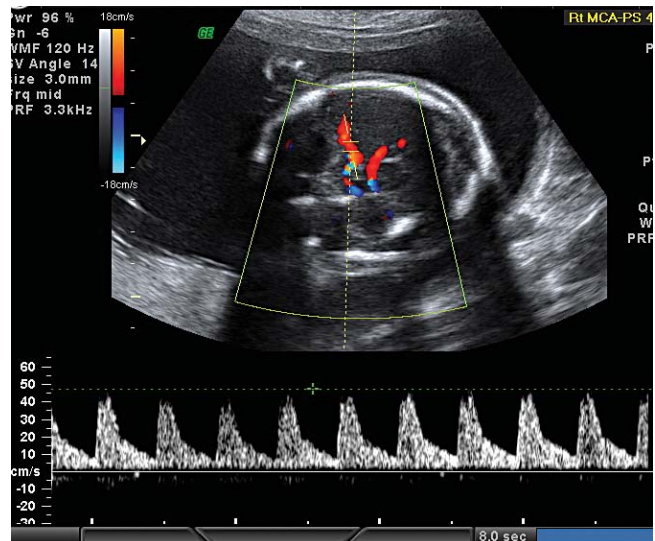


Fig. 1: Insonation of middle cerebral artery, with angle correction. Measurement of peak systolic velocity (cm/s).

pellucidum is obtained and the circle of Willis visualised with colour or power Doppler. The middle cerebral artery is examined close to its origin from the internal carotid artery. The sample volume should be placed in the centre of the vessel and the angle between the ultrasound beam and the direction of blood flow kept as close to 0° as possible. Angle correction can be used if required. The highest peak systolic waveform is measured, in the absence of fetal breathing movements.

Clinical investigations

Mari, *et al.*¹¹ reported their first comprehensive study of middle cerebral artery peak systolic velocity (MCA-PSV) in 1995. They demonstrated that they could diagnose fetal anaemia in all cases of rhesus sensitisation. However, the false positive rate was 50%.

In a study of 111 fetuses at risk of anaemia secondary to maternal alloimmunisation Mari, *et al.*⁹ measured MCA-PSV at the time of cordocentesis. These results were compared with a reference range for fetal haemoglobin established from normal, non-anaemic fetuses undergoing cordocentesis for prenatal diagnosis. Degrees of fetal anaemia were classified according to multiples of the median for gestational age. Multiples of the median (MoM) are calculated by dividing the measured value by the expected value for gestational age. Use of MoM allows appropriate interpretation of variables such as haemoglobin and MCA-PSV, which are known to change with gestational age.

Mild, moderate and severe anaemia were categorised as haemoglobin concentrations of 0.84 to 0.65, 0.65 to 0.55 and <0.55 multiples of the median respectively. Regression analysis and receiver operating curves were employed to establish whether MCA-PSV could be used to predict the



risk of fetal anaemia. MCA-PSV had a sensitivity of 100% for the prediction of moderate or severe anaemia, and a false positive rate of 12%. The technique performed well, regardless of the absence or presence of hydrops. The test did not predict mild fetal anaemia. However, in clinical practice this is not a concern as these cases do not require antenatal fetal intervention. In this study, reliance upon MCA-PSV >1.5 MoM to diagnose moderate to severe anaemia would have avoided invasive testing in 70% of cases.

Having assessed the accuracy of MCA-PSV in the prediction of anaemia, Mari, *et al.*¹² conducted a subsequent study to establish the accuracy of MCA-PSV as a tool to predict actual fetal haemoglobin concentrations. Using a series of formulae they were able to quantify for each fetus ($n = 18$), the percentage difference between the expected and the observed haemoglobin levels. They found that the percentage difference between expected and observed haemoglobins decreased as the fetal haemoglobin MoM decreased. That is, MCA-PSV became more accurate at predicting haemoglobin levels with increasing severity of anaemia.

The majority of fetuses at risk of anaemia owing to red cell alloimmunisation will be unaffected or only mildly affected, and will not require intrauterine transfusion. MCA-PSV can predict fetal anaemia, but can it be used to identify those fetuses that will become anaemic? By performing a longitudinal assessment of MCA-PSV in healthy fetuses and those at risk of anaemia, Detti, *et al.*¹³ assessed the value of serial MCA-PSV measurements to predict fetuses that will become anaemic. They found that the rate of increase in MCA-PSV per week was greatest in those fetuses that subsequently developed moderate-to-severe anaemia. By performing MCA-PSV measurements over three consecutive weeks it would be possible to identify in advance those fetuses that are going to require in utero therapy and modify the frequency of fetal surveillance accordingly.

Effect of intrauterine transfusion on MCA-PSV

What is the utility of MCA-PSV for the fetus that has received an intrauterine transfusion? We know that following transfusion the properties of fetal blood are altered by the presence of adult red cells. Adult red cells are smaller than fetal red cells, have decreased cellular rigidity and increased erythrocyte aggregation^{14,15}. In addition, adult haemoglobin has a lower affinity for oxygen. It seems likely therefore that, owing to the changes in fetal blood viscosity following intrauterine transfusion, the ability of MCA-PSV to predict anaemia and time to the next transfusion will be affected. The mean rate of decline in fetal haemoglobin is 0.3 g/dL per day following intrauterine transfusion¹⁶, and on this basis subsequent transfusions would be estimated to occur at an interval of between 1 and 3 weeks. What is the evidence for MCA-PSV in the timing of further transfusions?

Detti, *et al.*¹⁷ addressed this question by studying 64 fetuses that had undergone a single intrauterine transfusion. They found that in order to reduce the false positive rate the cut-off for MCA-PSV had to be increased to 1.69 MoM for the prediction of severe anaemia. Other groups have confirmed the finding that the MoM cut-off for MCA-PSV has to be increased once intrauterine transfusion has taken place. Deren and Onderoglu¹⁸ increased their cut-off from 1.35 MoM to 1.4 MoM in order to reduce the false positive rate

for subsequent transfusion. However, they still found that the false positive rate for cases undergoing subsequent transfusion was double that of cases undergoing the first intrauterine transfusion (21.4% v 9.1%). Schieier, *et al.*¹⁹ examined the relation between MCA-PSV and fetal haemoglobin at the time of second and third transfusions. They found that for a 95% detection rate of severely anaemic fetuses the false positive rate for second and third transfusions was 37% and 90% respectively, compared with 14% for the first transfusion. By increasing their 1.5 SD cut-off to 1.7 SDs they were able to reduce the false positive rate from 47% to 37%. They concluded that MCA-PSV was useful in predicting the need for a second transfusion in severely anaemic fetuses, but with a substantial increase in false positive rate compared with the initial intrauterine transfusion. They did not find MCA-PSV useful in predicting severe anaemia in fetuses that had already undergone two transfusions. In contrast, Mari, *et al.*²⁰, in a study of 39 fetuses, found a linear correlation between MCA-PSV (MoM) and fetal haemoglobin (MoM) in fetuses that had previously undergone two intrauterine transfusions.

Role of MCA-PSV in fetal anaemia of different aetiologies

What is the role for MCA-PSV in the management of pregnancies complicated by anaemia that, in contrast to rhesus alloimmunisation, is not due solely to red cell haemolysis? Although haemolysis is a contributor to the anaemia associated with Kell alloimmunisation, erythroid suppression plays a large role. Van Dongen, *et al.*²¹ prospectively studied 27 fetuses at risk of anaemia secondary to Kell alloimmunisation. Again, MCA-PSV was expressed as a multiple of the median and defined as abnormal if greater than 1.5 MoM. The decision to perform cordocentesis was made by the attending clinician on the basis of available clinical information. Results of MCA-PSV were compared with fetal haemoglobin values obtained either at intrauterine transfusion, or delivery if antenatal intervention had not been necessary. The sensitivity and specificity of MCA-PSV for predicting fetal anaemia in these Kell-alloimmunised pregnancies was 89%. The results did not differ when non-hydrops fetuses were analysed separately. They compared MCA-PSV with other ultrasound measurements – splenic perimeter and liver length and confirmed that the sensitivity for these latter parameters was poor. The authors concluded that MCA-PSV was a reliable predictor of fetal anaemia in Kell alloimmunised pregnancies and facilitated timely intervention with intrauterine therapy.

Erythrovirus B19 infection during pregnancy can, if transmitted to the fetus, result in severe anaemia and non-immune hydrops. The virus binds to the blood group P antigen cellular receptor present on haemopoietic precursors, endothelial cells, fetal myocytes and placental trophoblast. Its action on the haemopoietic system results in the profound anaemia. In Delle Chiaie, *et al.*'s study²² confirming the relationship between MCA-PSV and fetal anaemia, 10 cases of parvovirus infection were included. The group demonstrated that a threshold of 1.29 MoM for MCA-PSV had a sensitivity of 100% for predicting any degree of fetal anaemia, and a specificity of 100%. Cosmi, *et al.*²³ also confirmed that MCA-PSV is a valid tool for monitoring parvovirus-induced anaemia, and a cut-off of >1.5 MoM had a sensitivity and specificity for the prediction of anaemia of 94.1% and 93.3% respectively.

There are other clinical scenarios in which MCA-PSV may be useful for the diagnosis of anaemia. It has been shown to be diagnostic in anaemia due to massive fetomaternal haemorrhage²⁴. There is evidence to support its use in cases of twin-to-twin transfusion syndrome where there has been an intrauterine death of one twin²⁵. Other applications include anaemia secondary to placental chorioangioma²⁶ and homozygous alpha thalassaemia²⁷.

What are the potential advantages of non-invasive testing?

Amniocentesis and spectral analysis of amniotic fluid was in its day a major breakthrough in the management of alloimmunised pregnancies. It has been used with great success to reduce the perinatal morbidity and mortality associated with haemolytic disease. However, there are a number of limiting/complicating factors associated with its use:

- Prediction of fetal anaemia relies on the presence of haemolysis which may not be the main pathological process resulting in anaemia. As discussed previously erythroid suppression plays a major role in anaemia due to Kell alloimmunisation^{28,29}.
- The timing of amniocentesis is determined by antibody titres and past obstetric history, both of which are unreliable in Kell affected pregnancies^{30,31}.
- Extrapolation of the Liley data has limited reliability for the prediction of anaemia prior to 27 weeks gestation³².
- The procedure-related loss rate for amniocentesis is 0.25–1% per procedure, and serial testing is generally required^{33,34}.
- Fetomaternal haemorrhage occurs in 2.3–17% of procedures, potentially increasing the severity of sensitisation and hence fetal anaemia^{35,36}.

MCA-PSV compared with amniocentesis

The important question as to whether non-invasive testing with MCA Doppler is as good as the traditional method of invasive testing by amniocentesis was addressed by Oepkes and the DIAMOND Study Group³⁷. A prospective, international, multicentre study was carried out to compare MCA-PSV with amniocentesis, using Liley charts, for detection of severe fetal anaemia. Women with RhD, Rhc, RhE or Fya alloimmunised pregnancies were recruited and managed according to their hospital's own protocol. When testing was clinically indicated to assess the need for intrauterine transfusion, both amniocentesis and middle cerebral artery Doppler were performed. These investigations were repeated serially as required. A total of 165 fetuses were analysed. The results were compared with haemoglobin levels at either fetal blood sampling, or cord sampling at delivery if antenatal intervention had not been indicated. MCA-PSV had a sensitivity of 88%, specificity of 82% and accuracy of 85% for the detection of severe anaemia. In comparison, amniocentesis had a sensitivity, specificity and accuracy of 76%, 77% and 76% respectively. The sensitivity and accuracy of middle cerebral artery Doppler was substantially greater than amniocentesis.

Conclusion

Doppler assessment of the peak systolic velocity of MCA blood flow is a reliable and effective, non-invasive, method of monitoring alloimmunised pregnancies at risk of fetal

anaemia. Studies have demonstrated that it is applicable to a variety of antibodies – D, c, E, Kell, Fya and Jka. Its role can also be extended to fetal anaemia of different aetiologies. The multicentre nature of many of the reported studies confirms that consistency can be attained within different units and with different ultrasound equipment. Appropriate training is obviously essential for the success of the technique, and this is clearly achievable. The fact that 50–70%^{9,37} of invasive procedures can be avoided by relying on MCA-PSV has transformed the management of “at risk” pregnancies for both clinicians and patients, and as such MCA-PSV must be considered the latest significant advance in the management of fetal anaemia.

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