Doppler and fetal growth retardation

Intrauterine growth retardation (IUGR) is multifactorial in origin but it is well recognised that disordered uteroplacental and fetoplacental haemodynamics may be a feature in some cases. Doppler ultrasound employs a beam of ultrasound which is reflected by moving blood cells to produce a characteristic flow velocity waveform in which the spectral frequency shift of the reflected waveform reflects the velocity of the blood cells in the insonnated vessel. This technique now allows the safe non-invasive assessment of human uterine, placental, and fetal haemodynamics in normal and complicated pregnancies.

Uteroplacental circulation

Normally the non-pregnant spiral arteries undergo trophoblast invasion in two phases with loss of the elastic and vasoactive muscle coats in the decidual portion initially (phase I) and then as far as the radial arteries (phase II). This leads to a marked increase in uteroplacental blood flow and subsequent protection from the effects of circulating pressor agents.

In pre-eclampsia there is failure of the second wave of invasion causing retention of the spiral artery muscle coat, reduced perfusion of the intervillus space, maternal hypertension, and persisting responsiveness to circulating pressors leading to subsequent acute necrotising atherosis and further vessel occlusion.1

Similar defective trophoblast invasion has been found in 50% of placental bed biopsies from normotensive pregnancies complicated by IUGR2 suggesting that these placental vascular abnormalities and uteroplacental under-perfusion constitute a significant but not a universal cause of IUGR.

Uteroplacental Doppler blood flow studies have shown significant reduction in the diastolic velocities from the uterine artery and its major branches in some compromised human pregnancies and are thought to be related to extent of failed trophoblast invasion, increased uteroplacental impedance, and uterine ischaemia.3 The shape of uteroplacental Doppler waveforms is different from that in the umbilical artery. The rate is much less, being equivalent to the maternal pulse rate, the systolic phase is usually more peaked and there is often a prognostically significant diastolic notch in abnormal waveforms (see figure).

Continuous wave uteroplacental screening studies are not reproducible and pulsed Doppler studies are expensive and time consuming such that a useful role in screening is unlikely. Bewley and her colleagues employed a dual technique with continuous wave Doppler initially followed by colour and pulsed wave Doppler for suspected abnormal waveforms.4 This allows exclusion of many normal cases quickly and inexpensively using continuous wave Doppler and reduces the number who require the more tedious and exacting pulsed wave studies which would not be practical on a larger scale. They found them to be useful as early as 20 weeks' gestation in identifying those mothers who will deliver a fetus small for gestational age (sensitivity 36–45%, specificity 87–97%) or develop pre-eclampsia and this compares well with other similar screening studies.

Umbilical artery circulation

Morrow et al performed successive placental embolisation on chronically catheterised pregnant ewes using 50 μm glass microspheres that became lodged in and occluded the arterioles of the placental tertiary villi.5 They found that the diastolic component of the umbilical artery Doppler flow velocity waveform became reduced, absent, and then reversed as embolisation proceeded, a pattern similar to that found in association with progressive IUGR and pre-eclampsia in humans. There was no association with increasing viscosity, hypoxia, hypoxia and acidosis, angiotensin II infusion (a proximal vessel constrictor), maternal hypertension, or reduced placental blood flow. The authors concluded that increased distal impedance was the likely cause of these abnormal waveforms as they were present in the embolisation experiments that increase the distal vascular resistance but could not be induced by any of the other listed factors.6 The mechanism of these waveform changes is thought to be a reflection of the forward propagated wave by the distal impedance which then reduces, cancels, or reverses the diastolic component of the waveform.

Umbilical artery waveforms are also influenced by cardiac contractility, vessel wall characteristics, and blood viscosity.7 Carunculectomy experiments, however, which reduce placental mass and blood flow leading to IUGR again suggest that the distal site of the vascular resistance is still the most important factor.

McCowan et al showed an inverse linear relationship between umbilical artery waveform indices and tertiary
villus vessel count,\textsuperscript{8} though it is not clear whether there is failure of the development of these vessels or whether there is obliteration due to uteroplacental hydropertension, vasoconstriction of the placental fetal vessels and subsequent hypoxic ischaemia of the intervillus space.\textsuperscript{9}

Some studies have even suggested that platelet-associated thromboxane (a potent vasoconstrictor) may be implicated in the pathogenesis of placental vascular obliteration.\textsuperscript{10} In any case it is clear that a reduction in patent small arterioles leads to increased peripheral resistance that is reflected in the abnormal flow velocity waveforms.

**Umbilical artery circulation and IUGR**

IUGR is the most common pregnancy complication associated with a reduction in the flow velocity waveform diastolic component and hence increased values for the umbilical artery waveform systolic to diastolic (S:D ratios) and other waveform indices implying that increased placental resistance is a major aetiological factor. The degree of waveform abnormality is directly related to the increase in the risk and severity of IUGR, hypoxia and acidosis,\textsuperscript{11} morbidity, and perinatal mortality.

Antenatal treatment with daily maternal administration of 75 mg oral aspirin has been shown to improve the outcome in pregnancies complicated by waveforms with reduced but present end diastolic velocities (AEDV) leading to a subsequent increase in birth weight, head circumference, and placental weight.\textsuperscript{11} The mechanism is not fully understood but its effect (reduction) on thromboxane A2; prostacyclin ratios has been cited.

In 189 high risk pregnancies Fleischer \textit{et al} found a 78\% sensitivity and 49\% positive predictive value for delivery of a small for gestational age fetus (birth weight <10th centile) but other similar umbilical artery Doppler studies have shown varied sensitivities from 40\% to 90\%.

To date there are only four published prospective blinded cohort studies that have examined the role of umbilical artery velocimetry as a screening tool in a normal (low risk) antenatal population and these have been extensively reviewed by the author.\textsuperscript{13} The studies assessed perinatal outcome in terms of perinatal morbidity, birth weight and nutrition status, hypoxia, acidosis, and death and all concluded that the Doppler technique was of no value for screening. Furthermore, an unpublished randomised control trial based on over 3000 pregnancies has shown a higher rate of induction for suspected IUGR with no improvement in perinatal outcome (M J Whittle, personal observation) suggesting that possible harm may result from unnecessary intervention prompted by abnormal Doppler studies.

**Fetal circulation and IUGR**

Fetal haemodynamic circulatory adaptation to hypoxia results in diversion of blood flow to brain, myocardium and adrenals such that cerebral flow velocity waveform diastolic velocities are increased and the waveform indices are reduced (implying increased flow), while diastolic velocities in the renal artery\textsuperscript{14} and descending aorta are reduced and waveform indices increased suggesting reduced blood flow to non-essential organs.\textsuperscript{15}

This 'centralisation' effect may have important implications for neurological outcome in terms of cerebral hyper-perfusion and haemorrhage and for effects on the non-essential organs such as gut (necrotising enterocolitis) and kidney (oligohydramnios, and renal failure) which may be underperfused.

\textit{Wladimiroff et al}\textsuperscript{16} were the first to describe pulsed Doppler examination of the intracranial vessels that demonstrated a fall in flow velocity waveform pulsatility implying reduced resistance and increased flow in IUGR.\textsuperscript{17} Significant correlations between both fetal acidosis and fetal asphyxia determined by fetal blood gas analysis and common carotid artery Doppler waveform indices\textsuperscript{18} suggests that cerebral Doppler studies can identify the extent of human fetal brain-sparing effect in IUGR. Vyas \textit{et al} suggest, however, that in extreme cases the waveform changes reach a plateau beyond which further degrees of acidosis and asphyxia are not associated with any further changes in waveform indices or implied cerebral blood flow, presumably due to maximal vasodilatation of the cerebral vascular bed.\textsuperscript{19}

Proportionate redistribution of cardiac output with increased aortic to pulmonary artery blood volume flow and velocities\textsuperscript{20} occurs in asymmetrical fetuses with IUGR with hypoxia. There is progressive loss of the aortic end diastolic velocities preceding abnormalities seen on cardiotocography by a median of three days (range of up to several weeks)\textsuperscript{18} and these changes are related to the degree of acidosis.\textsuperscript{22}

Aortic Doppler waveform analysis has a 63\% to 87\% sensitivity for prediction of intrapartum fetal distress but there is poor sensitivity in using aortic Doppler waveform analysis as a screening tool for delivery of a fetus small for gestational age (sensitivity 41\%–57\%) and aortic studies are therefore less predictive of outcome than those in the umbilical artery.\textsuperscript{21} It has also been observed that observation of aortic AEDV is predictive of significant neonatal morbidity (necrotising enterocolitis and haemorrhage) and death in the first year of life.\textsuperscript{23}

**Conclusion**

Doppler studies are useful in determining the aetiology in cases of IUGR and provide additional information about the uteroplacental and fetoplacental haemodynamics that appears to be predictive of outcome. While they are a useful adjunct to management in high risk pregnancies there is no evidence of any value in the low risk population or in timing obstetric intervention and thus there is great potential for harm if used indiscriminately.

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Role of erythropoietin in the newborn

Since the isolation of the human erythropoietin gene in 1985,1 there has been interest in the possible use of recombinant human erythropoietin (r-HuEpo) as an alternative treatment to blood transfusion in preterm infants. Several studies have now been published reporting varying degrees of response but as yet no conclusive evidence has been presented to support the routine use of r-HuEpo in the preterm infant.

Current need for transfusion

The requirement for blood transfusion for preterm infants of less than 1500 g birth weight is well recognised.2 There are two main groups of preterm infants who require blood transfusion: the first being those who require early transfusion during the first few weeks after birth and the second those who develop anaemia at around six weeks after birth. The so called (early) anaemia of prematurity. A late anaemia of prematurity occurring after several months is almost entirely due to iron deficiency and will not be addressed further here.

The first group of sick, often ventilated, preterm infants requiring intensive care receive the majority of blood transfusions. These preterm infants are one of the most frequently transfused groups of patients receiving a mean of four (range 0–10) transfusions during the first 28 days of life.3 Although there are many causes for the development of this early anaemia, the main aetiological factor is the need for multiple blood tests for intensive care management. It has been shown that up to 67 ml/kg of blood may be removed during the first four weeks of a preterm infant’s life.3–5 These early transfusions accounting for the majority of the blood transfusions given to preterm infants, and are very unlikely to be ameliorated by r-HuEpo.

The second group of infants require blood transfusion at around 6 weeks of age because of the anaemia of prematurity but are often otherwise healthy. The anaemia of prematurity is an exaggeration of the fall in haemoglobin that all infants undergo during the first months of life.6

With infants of earlier gestation the anaemia of prematurity is more profound. These infants often develop signs of anaemia and require transfusion. The aetiology of the anaemia of prematurity is in part related to the universally low serum erythropoietin concentration (with associated low reticulocyte counts) found even in the presence of anaemia.7,8 It is the anaemia of prematurity that has been the target of the currently published clinical studies into the role of erythropoietin in preterm infants.

Risks associated with blood transfusion

Whether given in the first few weeks after birth or later for the anaemia of prematurity, the use of blood products in preterm infants continues to be of concern due to the risks associated with transfusions. The main anxiety is the significant risk of transmission of viral agents through blood products. Until recently the most frequent viral infection transmitted was cytomegalovirus and, along with hepatitis B and C, transmission of cytomegalovirus continues to be a small but significant risk.5 Before the routine use of cytomegalovirus negative blood products for preterm infants there was a significant infection rate of 25–30% associated with cytomegalovirus positive blood, with a mortality of around 25% of those infected.11 This has been substantially reduced by the use of cytomegalovirus negative blood in preterm infants.

The risk of HIV transmission by blood transfusion in the UK is currently estimated to be less than one in a million transfusions,12 although up to 20/million in parts of the USA and considerably higher in other parts of the world.13 One of the earliest reports of transfusion associated HIV infection arose in an 18 month child who was repeatedly transfused at birth.15 There continues to be concern that there could be another yet unknown transfusion agent with the devastating effects of HIV around the corner. The risks are increased by multiple transfusions from many different donors and can be lessened by the repeated use of blood from a single donor unit for an individual infant.

Many parents of preterm infants express natural concerns over the safety of transfusions, and the specific religious objections from Jehovah’s Witnesses and other groups also pose difficult problems.10 With this background, several studies have now been published that seek to address the question of the efficacy of r-HuEpo in the preterm infant.

Evidence for a biological response to r-HuEpo

Several in vitro studies using cell culture techniques have demonstrated that preterm infants with the anaemia of prematurity born between 27–33 weeks’ gestation have adequate numbers of erythroid progenitors.17–19 The progenitors from both peripheral blood17,18 and bone marrow19 are responsive to r-HuEpo in vitro.

A wide range of doses of r-HuEpo has been tried in the limited number of clinical studies so far published, ranging from 70 U/kg/week20 to 1200 U/kg/week.21 Some of these
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