MULTI-VESSEL DOPPLER STUDIES IN INTRA-UTERINE GROWTH RESTRICTION

INTRODUCTION

The diagnosis and management of intrauterine growth restriction is difficult. Perinatal mortality and morbidity worsen as the fetal weight declines. The 10th percentile has been used to define "small for gestational age" at all gestational ages. This approach assumes that the risk of perinatal mortality is the same at all gestational ages. Boulet et al[1] have shown that this is, in fact, not the case. The risk of neonatal death at the 10th percentile has a bimodal distribution with peaks at 26 and 34 weeks' gestation. Hence, the 10th percentile is associated with an increased, but variable, risk of subsequent neonatal mortality. There is an acceleration in mortality and neonatal complications as the fetal weight falls below the 5th percentile[2].

The first step in the appropriate management of small-for-gestational age fetuses is to delineate those fetuses who are truly at risk. An individual fetus' growth potential may be compromised, resulting in any or all of the neonatal complications of intrauterine growth restriction (IUGR) above the arbitrary 10th percentile cut-off. Customized standards for fetal growth are better able to distinguish between "physiologically small" and "pathologically small" fetuses[3].

Serial abdominal circumference or fetal weight estimates are the best screening tests for IUGR[4]. Doppler studies are the mainstay for diagnosis and management. Complicated cases of early onset IUGR (< 30 weeks' gestation) may require a multi-vessel Doppler approach to evaluate pre-load, as well as after-load, affects of severe intrauterine growth restriction.

UMBILICAL ARTERY

Placental studies have shown that > 60% of the placental vascular bed is obliterated once impedance is increased in the umbilical artery[5]. When there is absent diastolic flow in the umbilical artery, the capillaries in placental terminal villi are decreased in number and they have fewer branches[6]. Blood gases obtained at cordocentesis have shown that 80% of fetuses with absent diastolic flow are hypoxic and 46% are acidemic[7]. Absent end-diastolic flow and reversed diastolic flow within in the umbilical artery have an associated 40% and 70% perinatal mortality, respectively[8].

A meta-analysis of nine randomized trials confirmed that perinatal mortality is significantly reduced when umbilical artery Doppler is used as an adjunct to fetal heart monitoring to manage IUGR[9,10]. The progressive waveform patterns associated with increasingly severe IUGR are illustrated in Figure 1a-d. Absent end-diastolic flow in the umbilical artery and middle cerebral artery pulsatility index < 5th percentile are considered "early" stage changes of IUGR. These Doppler alterations generally occur 14 days from delivery[11], but may persist for up to 26 days prior to delivery[12].

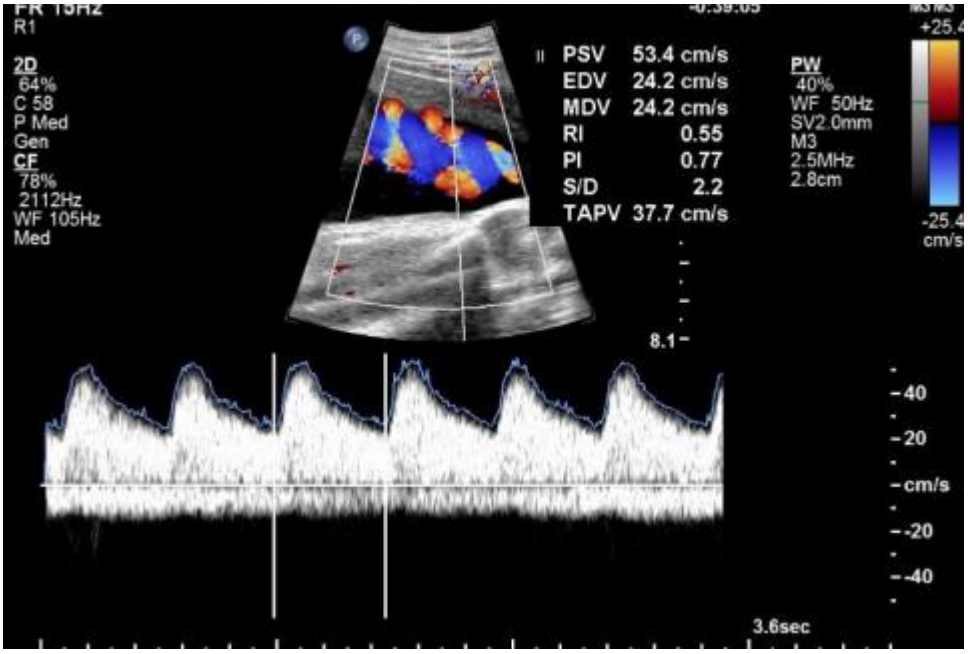

Fig 1a. Umbilical artery: normal S/D ratio. Click for larger image.

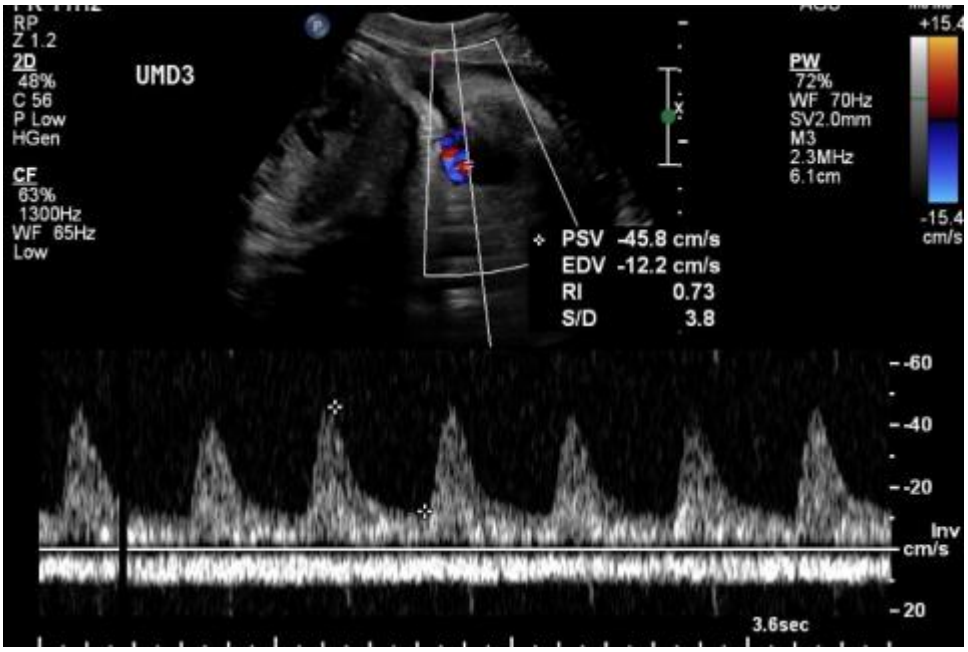

Fig 1b. Umbilical artery: elevated S/D ratio. Click for larger image.

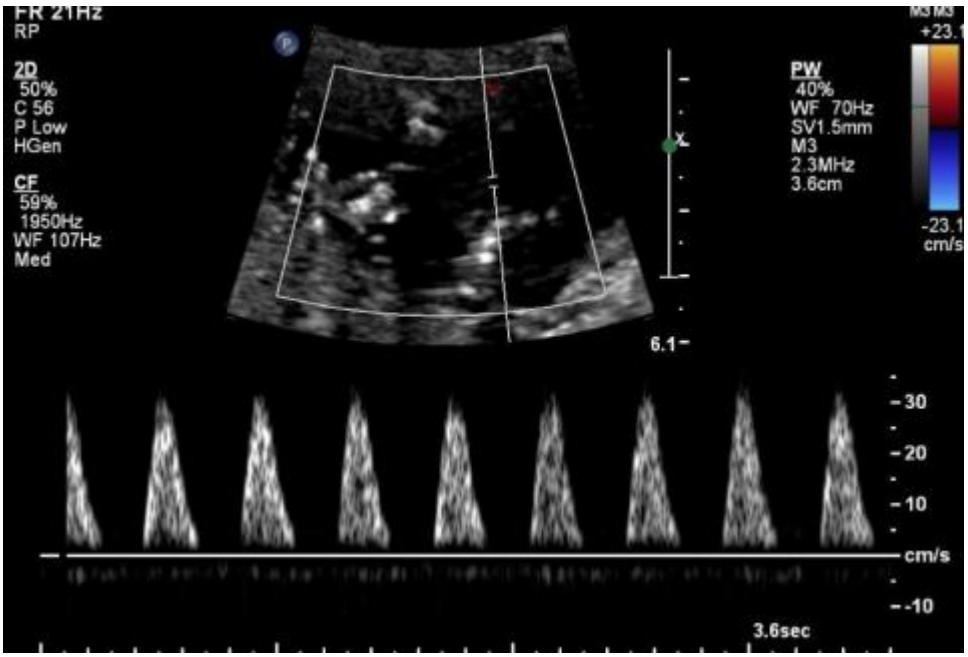

Fig 1c. Umbilical artery: absent diastolic flow. Click for larger image.

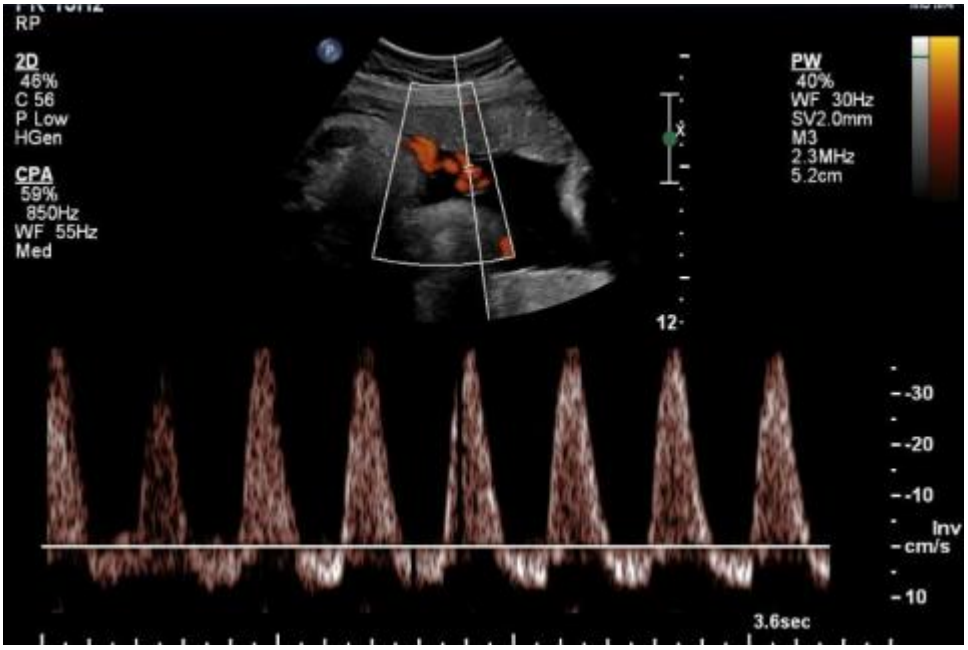

Fig 1d. Umbilical artery: reversed diastolic flow. Click for larger image.

Screening a low-risk population with umbilical artery Dopplers does not reduce perinatal morbidity and mortality[13] and is not recommended[14].

MIDDLE CEREBRAL ARTERY

With fetal hypoxemia, there is increased blood flow to vital organs (brain and myocardium) and reduced flow to the gastrointestinal tract and kidneys. Cerebral vasodilatation (Fig. 2a) is limited. The nadir of the middle cerebral artery PI is reached 14 days or more before fetal compromise[15]. With the onset of hypercapnia, vascular dilatation is suppressed by cerebral edema, resulting in a "normalization" of the middle cerebral artery pulsatility index (Fig. 2b)[16]. The reversal of adaptation in a growth restricted fetus is considered a poor prognostic sign. The middle cerebral artery peak systolic velocity becomes elevated (Fig. 2c) as a late finding in severe IUGR prior to a non-reassuring heart rate tracing, i.e. continuous late decelerations or a biophysical profile score < 4[17, 18]. The increase in the middle cerebral artery peak systolic velocity is due to an elevated left cardiac output associated with increased placental vascular resistance[18].

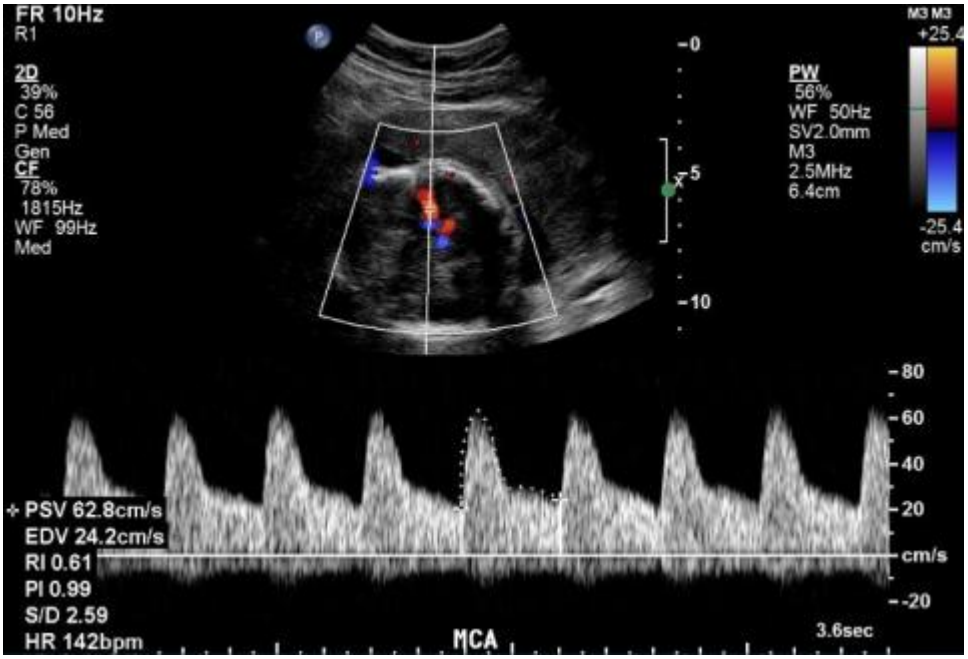

Fig 2a. Middle cerebral artery: pulsatility index < 5th percentile indicating brain-sparing. Click for larger

image.

Fig 2b. Brain, middle cerebral artery: reversed diastolic flow. Click for larger image.

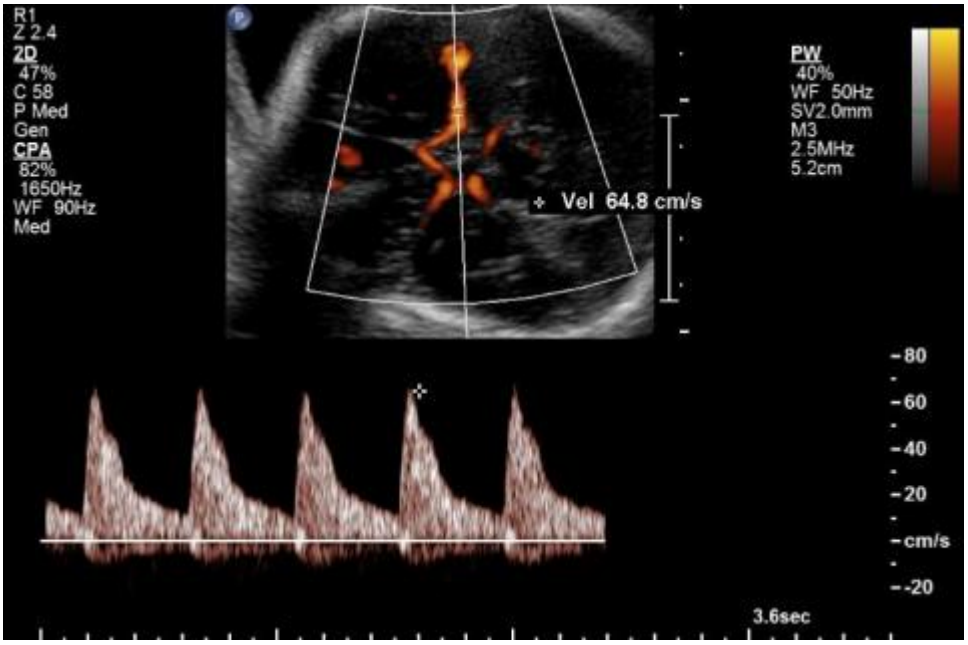

Fig 2c. Middle cerebral artery: elevated peak systolic velocity in growth restricted fetus at 26 weeks' gestation. Click for larger image.

Delivery should be considered when there is a 20-30% increase in the middle cerebral artery pulsatility index per day for 2 days (trend towards normalization)[19]. Since changes in the middle cerebral artery pulsatility index may occur daily, some of the changes noted above may be missed in an individual case. Because of the wide variability in middle cerebral artery indices, a single operator will have better and more consistent results[20].

INTRAUTERINE GROWTH RESTRICTION WITH NORMAL UMBILICAL ARTERY DOPPLERS

Small fetuses with normal umbilical artery Dopplers have traditionally been considered constitutionally small. More recent data indicates that this category contains some fetuses with true growth restriction and subsequent abnormal childhood neurodevelopmental testing[21]. While the causes for IUGR with normal umbilical artery Dopplers may be heterogeneous, uteroplacental insufficiency is the etiology in the majority of cases.

A decreased pulsatility index in the middle cerebral artery indicates fetal adaptation, even in the presence of a normal umbilical artery Doppler. Hence, an abnormal umbilical artery waveform pattern is not universally the first Doppler sign of intrauterine growth restriction[22]. Growth restricted fetuses with a normal umbilical artery Doppler may have microstructural and metabolic brain changes consistent with abnormal intrauterine brain development. The maturation and myelination of the frontal areas of the brain occur later in development and they are, therefore, more vulnerable to mild degrees of hypoxia[21]. The frontal lobes are the area of the brain most affected by adverse neurological outcome in growth restricted fetuses[23]. A subgroup of intrauterine growth restricted fetuses with normal umbilical artery and normal middle cerebral artery Dopplers have frontal lobe vasodilatation as manifested by changes in the anterior cerebral artery[24]. Long-term studies of growth restricted fetuses have documented a deficiency in general cognitive competence, suggesting frontal lobe dysfunction[25,26].

Once the pulsatility index in the middle cerebral artery is reduced, indicating increased diastolic flow, there is already a progressive reduction in blood flow to the frontal area. Perfusion of the basal ganglia continues to increase as the severity of intrauterine growth restriction increases. The regional redistribution of blood flow to the brain is dependent upon the severity and duration of the hypoxic insult[25]. Hence, "brain sparing" as documented by a middle cerebral artery pulsatility index < 5th percentile is not an entirely protective mechanism[27].

DUCTUS VENOSUS

The average shunting of blood through the ductus venosus normally decreases from 30% at 18-20 weeks to 18% at 31-34 weeks gestation[28]. The normal ductus venosus waveform pattern has a peak systolic, a peak diastolic and peak atrial velocity (Fig. 3a). The ductus venosus is the only venous vessel with forward flow during all phases of the cardiac cycle. The S-wave reflects the pressure gradient between the peripheral venous system and the right atrium. The D-wave represents the opening of the atrial ventricular valves and passive early filling of the ventricles. Between the S and the D wave is a period of isovolumetric relaxation (IVR) when atrial pressure and waning systolic ejection pressure are comparable. With increasing myocardial hypoxia and acidosis, the cardiac muscle is less compliant and isovolumetric relaxation decreases, may become absent (Fig.3b), or even reversed. An evaluation of IVR and the A-wave is a more accurate predictor of fetal outcome then noting the absence or reversal of the A-wave[29].

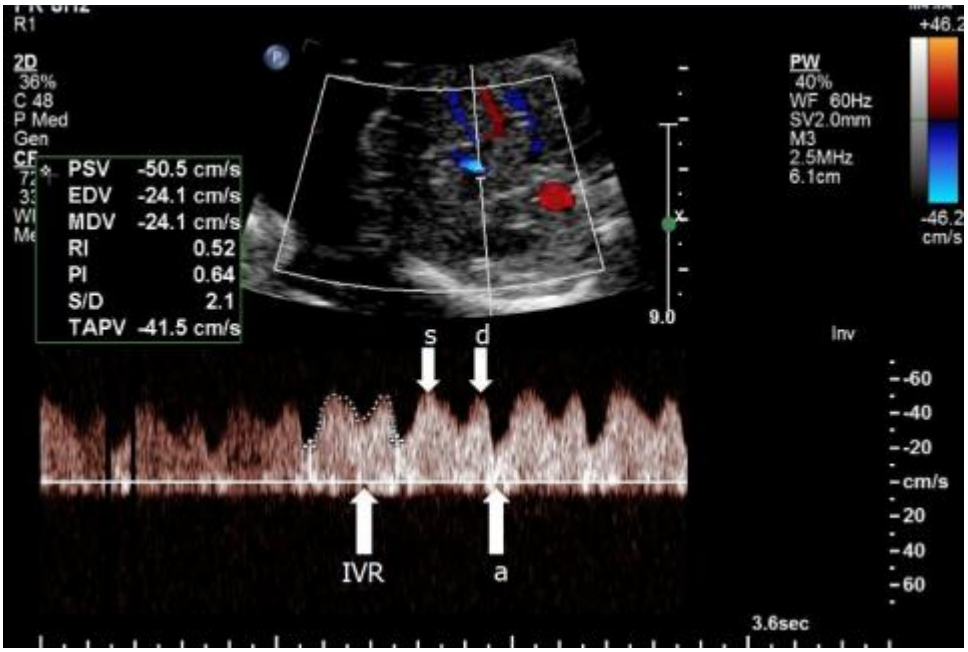

Fig 3a. Ductus venosus: normal pulsatility index (0.64). Click for larger image.

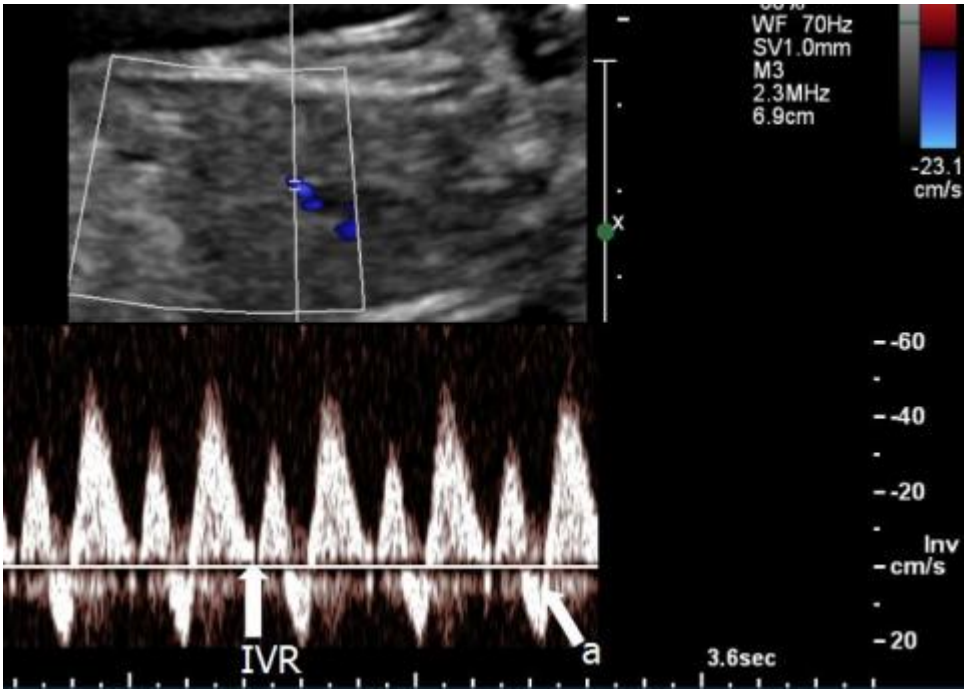

Fig 3b. Ductus venosus: elevated pulsatility index (1.02). Click for larger image.

The pulsatility index is utilized to quantitate ductus venosus flow. With advancing gestation cardiac compliance increases and placental resistance falls. As a result, the pulsatility index of the ductus venosus normally declines with advancing gestation[30]. An increase in cardiac after-load or decreased cardiac compliance will result in a decrease in forward flow and an increase in the pulsatility index (Fig. 3c).

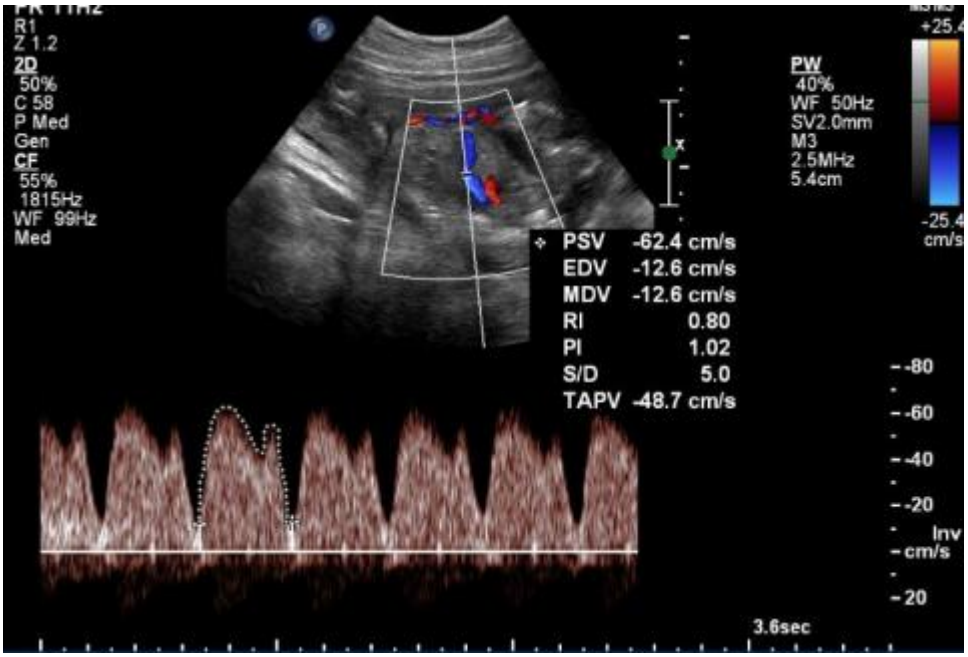

Fig 3c. Ductus venosus: absent IVR and reversed a-wave (a) flow. Click for larger image.

With hypoxemia there is an increase in umbilical venous flow through the ductus venosus and a reduction in hepatic blood flow[31]. Normal ductal flow suggests continued fetal compensation. Bellotti et al[32] have documented an 80% change in ductal diameter during prolonged observations of two growth restricted fetuses. With further fetal deterioration, there is reversed flow during the atrial contraction of the ductus venosus and a markedly increased pulsatility index (Fig. 3d). This indicates a failure of compensatory mechanisms and the onset of right heart failure. Fetuses with reverse flow in the A-wave

of the ductus venosus are not necessarily acidemic[33], and may survive for days to weeks in utero[34]. Hence, the main goal of antepartum surveillance, when the gestation age is < 30 weeks, is to differentiate fetuses with ductal venosus reversed flow who require intervention from those whose delivery can be delayed from days to weeks.

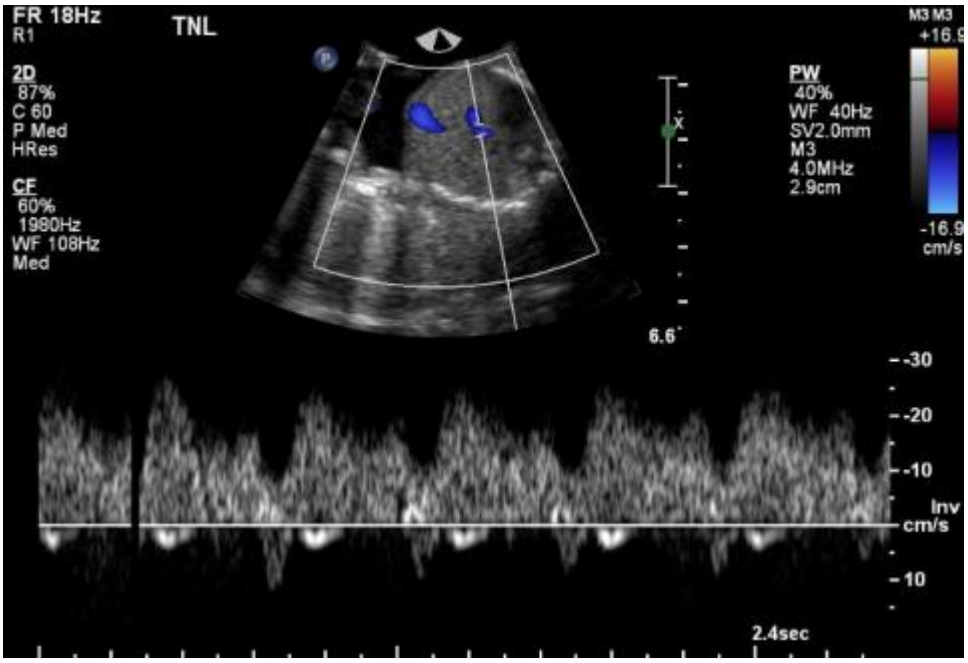

Fig 3d. Ductus venosus: reversed a-wave. Click for larger image.

As with all Doppler waveform patterns, there is a transitional phase of ductus venosus reversed flow. Intermittent reversed flow in the ductus venosus may occur from 2 to 57 days. Once reverse flow is constant, it may persist from 1 to 23 days before delivery is mandated by non-reassuring fetal testing[35].

UMBILICAL VEIN

Umbilical vein pulsations have been defined as a diastolic decrease in velocity of = 15% of baseline (Fig. 4).

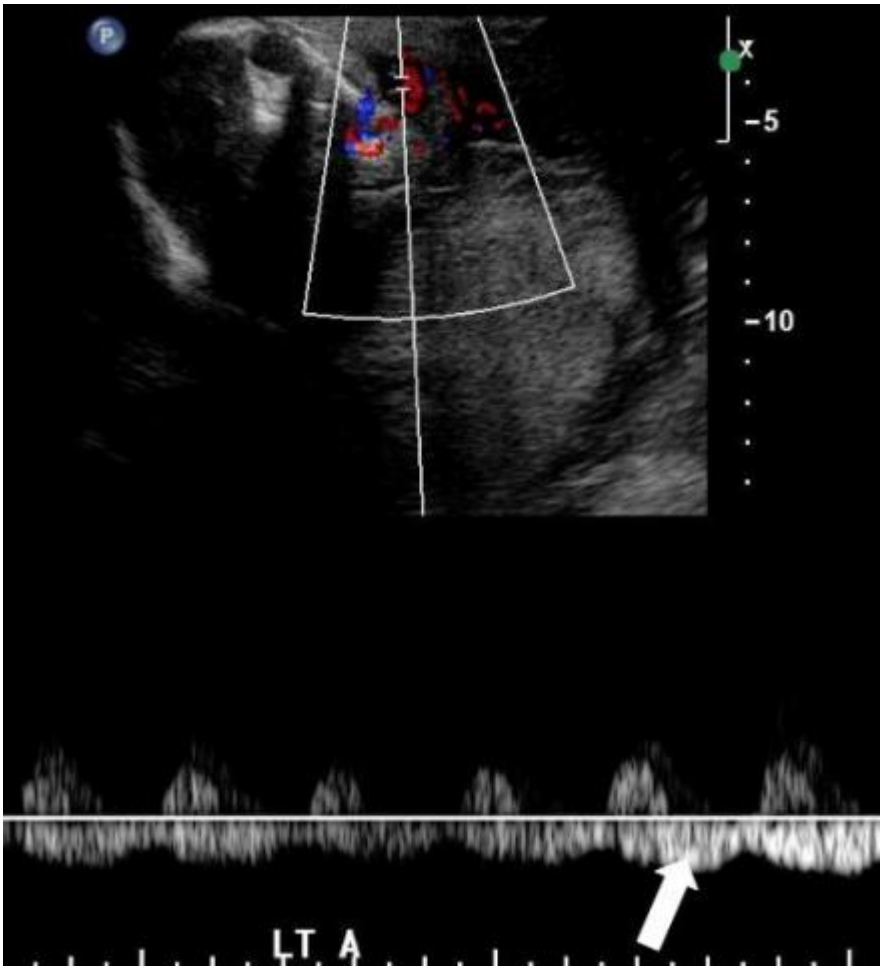

Fig 4. Umbilical vein pulsation (arrow). Click for larger image.

Wave propagation from the ductus venosus to the umbilical vein is significantly reduced due to reflection at the inlet of the ductus. With distension of the ductus venosus due to hypoxia, the close approximation of the diameters between the ductus venosus and umbilical vein leads to less wave reflection, the transmission of the ductal wave to the umbilical vein, and umbilical venous pulsations[36].

Pulsations in the umbilical vein are more common at the abdominal inlet than in a free-loop of umbilical cord or intra-abdominally. The constriction at the umbilical ring reduces the compliance of the vessel and, therefore, permits transmission of a pulse. The umbilical artery at the abdominal inlet may also transmit a pulse to the umbilical vein[37].

The significance of umbilical vein pulsations relates primarily to its presence or absence in a free-loop of umbilical cord[38]. A single, double or triphasic umbilical vein pattern has been described. A single umbilical venous pulsation, possibly secondary to high resistance within the umbilical artery, is associated with a 15.8% perinatal mortality[38]. With increased hypoxia/hypercapnia, the ductal S and D wave may be reflected in the umbilical vein. An umbilical venous double pulsation is associated with a 61.5% perinatal mortality[38]. Finally, reversed flow in the A-wave may give rise to a triphasic umbilical venous pattern with systolic and diastolic antegrade flow and atrial reversed flow. This latter, rare umbilical venous pattern indicates right-sided cardiac compromise and a worsening fetal condition that results in fetal demise within 2-7 days and a high perinatal mortality even with expeditious delivery[39,40].

TIMING OF DELIVERY

Until 26 weeks' gestation the primary contributor to neonatal outcome is gestational age[20]. After 27 weeks' gestation fetal acidemia and the risk of stillbirth must also taken into consideration when timing delivery.

A growth restricted fetus in the late 2nd and early 3rd trimester who has undergone chronic starvation may be able to tolerate continued stress better than a 3rd trimester fetus with a high metabolic demand who suddenly has a significant reduction in placental function.

When Doppler abnormalities develop at an early gestational age, it generally progresses more rapidly. With mild Doppler abnormalities, only the umbilical artery and middle cerebral artery are affected. If these initial Doppler abnormalities do not worsen within 7-10 days, they are unlikely to do so. Progressive placental dysfunction typically follows a sequence (Table I). The progression in severity of Doppler abnormalities within 2 weeks of detection indicate significant disease with early intervention likely[41]. In cases of pre-eclampsia, the Doppler changes are unpredictable[34].

TABLE I. TYPICAL PROGRESSION OF MULTI-VESSEL DOPPLER STUDIES WITH PROGRESSIVE PLACENTAL DYSFUNCTION

1. Elevated umbilical artery S/D ratio
2. Middle cerebral artery PI < 5th percentile (brain-sparing)
3. Umbilical artery - absent diastolic flow
4. Umbilical artery - reversed diastolic flow
5. Ductus venosus - elevated pulsatility index
6. Ductus venosus - reversed a-wave
7. Ductus venosus - decreased IVR, reversed a-wave
8. Umbilical vein double pulsations
9. Umbilical vein triple pulsation with reversed a-wave flow

The combination of a multi-vessel Doppler study and biophysical profile are complimentary tests to assess acid base status and the timing of delivery[42].

The American College of Obstetricians and Gynecologists recommends weekly fetal assessment (biophysical profile score, modified biophysical profile [non-stress test and amniotic fluid index] and umbilical Doppler velocimetry) in cases of intrauterine growth restriction[43].

These recommendations must be modified depending upon gestational age and the severity of growth restriction.

The further a compromised vein is from the heart, the higher the perinatal mortality risk. For example, perinatal mortality is 8 times greater with an abnormal ductus venosus waveform pattern and 18 times greater with pulsations in the umbilical vein[44]. In fetuses with a gestational age < 30 weeks and an increased pulsatility in the ductus venosus, daily testing is appropriate. Absent or reversed ductus venosus A-wave, a reduced ductus venosus IVR, and a double pulsation in the umbilical vein of a free-loop of umbilical cord indicate fetal decompensation and mandates delivery at a tertiary center[45].

In 70% of cases Doppler deterioration occurs 24 hours before a decline in the biophysical profile score. When both a multi-vessel Doppler study and the biophysical profile score are abnormal, an expeditious delivery is mandatory[44].

CONCLUSION

Serial fetal biometry and multi-vessel Doppler studies are currently employed in an attempt to optimize neonatal survival. The complexity of the interaction between gestational age, fetal reserve, Doppler studies, and long-term neurobehavioral outcome, mandates that each case be assessed individually.

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