

Advances in Imaging in Prenatal Diagnosis and Fetal Therapy

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Abstract

Technological advances in ultrasound have contributed to improvements in prenatal diagnosis. Transvaginal scanning and harmonic imaging have allowed better resolution and improved structural characterisation. Doppler techniques have further been improved, which allow accurate flow studies of vessels in the placenta and fetus. These have contributed much to the management of intrauterine growth restriction, fetal anaemia and twin-twin transfusion syndrome (TTTS). Three-dimensional sonography and magnetic resonance imaging ultrafast sequences are useful adjuncts to conventional 2-dimensional sonography, increasing the confidence and diagnostic accuracy of prenatal diagnosis. Fetal therapy has seen major advances in recent years as well, secondary to improvements in endoscopic instruments and surgical techniques. Selective Nd:YAG laser photocoagulation of communicating vessels and cord occlusion have been used to treat complications of monochorionic twins like TTTS and twin-reversed arterial perfusion sequence.

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Introduction

Technology in sonography has advanced tremendously in recent years, contributing to improvements in clinical applications for prenatal diagnosis and fetal therapy. These include transvaginal scanning, harmonic imaging, Doppler imaging, 3-dimensional (3D) ultrasonography and magnetic resonance imaging (MRI) ultrafast sequences.¹

Transvaginal scanning allows closer approximation to the structures being examined, thus affording the application of higher frequencies and better resolution as a consequence. This complements transabdominal scanning in the structural survey of the fetus in the first trimester and allows the characterisation of the cervix in the second trimester for the prediction of preterm labour. In the third trimester, the transvaginal probe also allows the examination of the deeply impacted head in less conventional planes and accurate diagnosis of placenta praevia. The emergence of harmonic imaging has allowed better structural characterisation with better defined edges in the pregnant uterus.² These advantages are particularly useful when examining large patients and deep structures.

Further improvements in sonography and Doppler imaging techniques have allowed the accurate flow study

of various vessels in the uterus, placenta and fetus. This has resulted in improvements to the clinical management of intrauterine growth restriction (IUGR), fetal anaemia and twin-twin transfusion syndrome (TTTS).³ Three-dimensional sonography and MRI ultrafast sequences have been used as adjuncts to conventional ultrasound for prenatal diagnosis, improving the diagnostic accuracy in some difficult cases. Doppler imaging techniques, 3D sonography and MRI ultrafast sequences would be detailed further in this review.

Fetal therapy can be classified into medical, needling and surgical therapies. Fetal medical therapy has been described as early as 30 years ago for various inborn errors of metabolism (such as phenylketonuria, Wilson's disease, congenital adrenal hyperplasia, methylmalonic acidemia and multiple carboxylase deficiency), fetal hypothyroidism and fetal arrhythmias. Needling procedures for blood transfusion are established as treatments for fetal anaemia and fetal thrombocytopenia. Amnioreduction and septostomy have been used as palliative treatments of mild stages of TTTS. These will not be discussed further in this review.

Open fetal surgery has been performed by a few specialised

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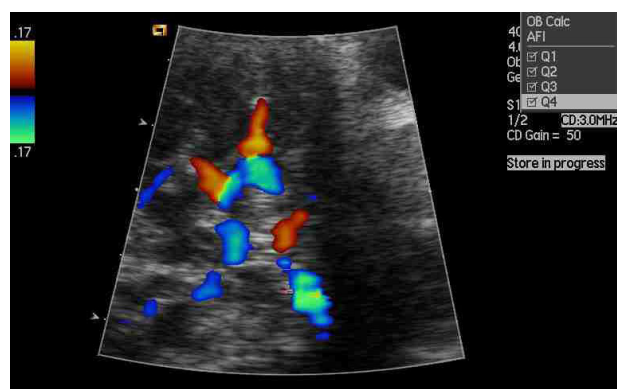


Fig. 1a.

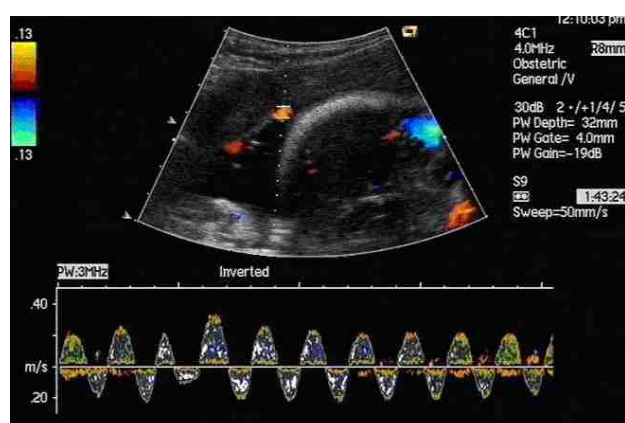


Fig. 2. Colour and power Doppler features of an arterio-arterial anastomosis. Note the setting to a low colour imaging frequency to demonstrate the aliasing effect, and the bidirectional flow and the cyclical fluctuating pattern due to difference in beat frequency.

centres in the world for a variety of lethal fetal conditions with largely disappointing results. It is the endoscopic surgical procedure for the treatment of TTTS, however, that has spearheaded successful efforts in the surgical treatments of fetal diseases.

Advances in the Clinical Applications for Doppler Imaging

Improved techniques in sonography and Doppler imaging have improved the clinical management of IUGR, fetal anaemia and TTTS.

IUGR

The natural history of IUGR fetuses has been studied by many investigators. Abnormal changes in the umbilical arterial Doppler waveforms usually precede changes in cardiocardiographic recordings of the fetal heart rate.⁴ When fetal heart rate abnormalities and abnormal pulsatility index (PI) of the umbilical artery (UA) are both present, the likelihood of lactic acidosis, low pH and blood oxygen content is much increased.⁴ As placental insufficiency progresses, the UA's diastolic velocity decreases, becomes

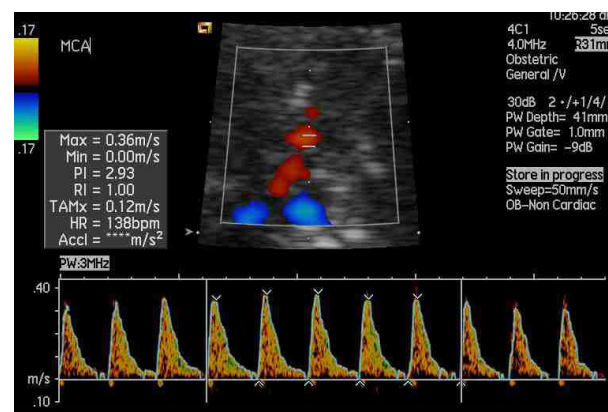


Fig. 1b.

Fig. 1a. The circle of Willis on colour Doppler. Fig. 1b. The middle cerebral artery peak systolic velocity. Zoom on the proximal part of the middle cerebral artery. The sample volume is placed between the origin of the middle cerebral artery from the internal cerebral artery and the middle of the artery such that the angle between the direction of blood flow and the ultrasound beam is close to zero. The angle corrector should not be used as this reduces the variability of the measurement.³

absent and eventually is reversed. Brain-sparing effect is observed as the blood flow to the brain is increased, as reflected by a decrease in the middle cerebral artery (MCA) PI. The MCA PI/UA PI ratio appears to be a more precise index than the UA or MCA alone in less severe IUGR fetuses, but its reliability decreases after 34 weeks' gestation.⁵

Early sonographic changes were a reduction in amniotic fluid index, a decrease in the UA PI and an increase in the MCA PI.⁶ Late changes included reversed UA flow and abnormal changes in the ductus venosus (DV), which were significantly associated with perinatal death.⁷

The timing of delivery of the preterm IUGR fetus remains unresolved by such knowledge of the natural history of IUGR fetuses though.³ The timing remains a consideration of the known gestation-specific mortality and morbidity rates associated with premature delivery versus the yet unknown morbidity and mortality associated with the sonographic and Doppler signs of IUGR.

Fetal Anaemia

The prediction of fetal anaemia from red cell alloimmunisation by the Doppler measurement of the MCA peak systolic velocity (PSV) has been a major evolution in the field of Doppler studies. It had been shown that MCA PSV was at least as good as the ΔOD_{450} for the prediction of fetal anaemia.⁸ An observational study, where measurement of the MCA PSV by a standardised method³ (Fig. 1) was performed just before cordocentesis in red blood cell alloimmunised pregnancies, predicts moderate and severe anaemia with sensitivity of 100% and a false positive rate of 12% at 1.5 MoM.⁹ A subsequent prospective

study with intention-to-treat showed a sensitivity of 88%.¹⁰ Weekly serial MCA PSV measurements up to 35 weeks have been recommended to reduce the false negative rate.³ This non-invasive method has reduced the need for invasive testing by 70%¹⁰ and has been used in routine clinical practice in many units.

While this application has been mainly studied in the areas of red cell alloimmunisation, it has also been used in the diagnosis of fetal anaemia from Parvovirus infection, fetomaternal haemorrhage and TTTS.³

Twin-twin Transfusion Syndrome (TTTS)

TTTS occurs in about 15% to 30% of all monochorionic (MC) twins. A major advance in the management of this disease must be the widespread practice of the determination of the chorionicity of multiple pregnancies, with the subsequent close monitoring for early detection of this disease in MC twins.

It is now well accepted that almost all MC placentae contain vascular anastomoses resulting in inter-twin transfusion. The placental vascular morphology that is most commonly associated with TTTS is the occurrence of one or more deep unidirectional arteriovenous anastomoses (AVAs) and absence of superficial bidirectional arterio-arterial anastomoses (AAA).¹¹

Doppler studies of placental vascular anastomoses in MC twins have been used to predict the occurrence of the TTTS. Presence of the AAA has been associated with a milder form of TTTS and better outcomes if TTTS occurs.¹² AAAs can be detected on the chorionic plate between the 2 cord insertions by the characteristic spectral appearance caused by aliasing on colour Doppler imaging, the characteristic bidirectional flow on power Doppler¹³ and the cyclical fluctuation in waveform due to difference in beat frequency (Fig. 2). AAA detection has been used in a few specialised twin clinics, where its *in vivo* predictive value for TTTS has been confirmed.¹³

Abnormal Doppler studies of UA, umbilical vein (UV) and DV are important in characterising Quintero stage 3 of TTTS,¹⁴ where more invasive treatments like cord occlusion or selective laser ablation of the placental vascular anastomosis may be considered.

MCA PSV may also be useful to predict fetal anaemia in the donor in TTTS, as well as in the surviving co-twin in the event of a single intrauterine death in MC twins.

New Adjuncts to Conventional Ultrasound for Prenatal Diagnosis

3D Sonography

Three-dimensional volume sonography involves the acquisition of a volume which is saved and stored for future

use. The major advantage of 3D sonography is the ability to display a volume in planes in which direct image acquisition is not possible.¹ Other advantages of 3D scanning are the ability to render an image of the fetal surface [hence its usefulness in evaluation for craniosynostosis, facial clefts and ease of recognition by patients and doctors not trained in 2D sonography], the ability to save volumes and to send them remotely for another ultrasound specialist to review as well as the ability to measure dimensions of an organ in a reconstructed plane (hence allowing volume measurements).¹ Its value in promoting bonding between the parents and the fetus when the image is more easily recognisable is not questioned. Such “entertainment” as the primary indication for this 3D scan, however, is deplored by most specialists.

Most fetal malformations identifiable sonographically can be visualised with standard 2D sonography. Three-dimensional sonography cannot be used as a screening technique currently and is used as an adjunct in fetuses with abnormalities detected on 2D sonography. It increases the time that the patient is in the ultrasound examination room and the time that the practitioner needs to manipulate the images into readable slices.¹ There is also a definite and important learning curve for the sonographer in obtaining a good readable volume and the practitioner to manipulate that volume into interpretable displays. The image resolution of the reconstructed planes is inferior to that of the acquisition planes. This, however, is likely to improve as technology progresses.

MRI Ultrafast Sequences

The recent advances in the development of ultrafast MRI sequences have allowed high-resolution and high-quality imaging of the moving fetus. True fast imaging steady precession and half-Fourier acquired single-shot turbo spin-echo sequences have been used successfully as an adjunct for the diagnosis of fetal anomalies in clinical practice.¹⁵ It has been used for the evaluation of suspected abnormalities of the fetal brain (such as ventriculomegaly, Dandy Walker malformation and absent corpus callosum), head and neck (such as fetal goiter and cystic hygroma), chest (such as congenital diaphragmatic hernia, congenital cystic adenomatoid malformation), abdomen (such as abdominal wall defects and renal anomalies) and spine (such as myelomeningocele and sacrococcygeal teratoma).¹⁵

The major advantages include those associated with 3D volume acquisition (as detailed above), improved diagnostic accuracy and its acceptability as a modality for post-mortem examination by parents who would otherwise not agree to conventional post-mortem examination.

The main disadvantages include the non-availability of this modality in many centres and the learning curve

TABLE I: FETAL ANOMALIES AMENABLE TO FETAL SURGICAL TREATMENT, THEIR INDICATIONS FOR TREATMENT AND SURGICAL OPTIONS

Disease	Indications	Surgery
Congenital diaphragmatic hernia (CDH)	- Isolated CDH (normal karyotype and no other major structural anomaly) - Gestational age at diagnosis <26 weeks - Right lung to head circumference ratio <0.9 - Liver herniated into the chest	Tracheal occlusion with a clip or balloon catheter - open - fetoscopic
Congenital cystic adenomatoid malformation or bronchopulmonary sequestration	- Hydrops - Gestational age <32 weeks - Open fetal lobectomy	Thoracoamniotic shunt (for lesions with a macrocyst)
Sacroccygeal teratoma	- Signs of high output cardiac failure — polyhydramnios and hydrops - Gestational age <30 weeks - Fetal cardiac status is not severely compromised	- Open resection of fetal sacroccygeal teratoma - Ablation of vascular supply in sacroccygeal teratoma - Percutaneous aspiration of a dominant large cystic component
Lower urinary tract obstruction	- Normal 46XY karyotype - Oligohydramnios with bladder distension and bilateral hydronephrosis (with no other structural anomalies) - Consecutive 3 successive fetal urine sampling with favourable urine electrolytes, osmolality and protein	Vesicoamniotic shunt, fetal cystoscopic ablation of urethral valves
Myelomeningocele	- Gestational age 20 to 25 weeks - Good leg movement - Absence of clubbed feet and other anomalies - Presence of Arnold Chiari malformation	Open fetal myelomeningocele repair
Fetal hydrothorax	- Unilateral pleural effusion - With or without hydrops	- Percutaneous aspiration - Percutaneous thoracoamniotic shunt
Twin-twin transfusion syndrome	- Oligohydramnio and polyhydramnio sequence with absent bladder in the donor and: - Absent or reversed flow in umbilical artery, reversed flow in ductus venosus or pulsatile flow in the umbilical vein (Quintero's stage 3) - Hydrops in either twin (Quintero's stage 4)	Selective Nd:YAG laser photocoagulation of communicating vessels or cord occlusion
Twin reversed arterial perfusion sequence	- Size ratio of acardiac twin to pump twin >70% - Polyhydramnios and hydrops	Intrafetal ablation or cord occlusion

required in interpreting the MR images as fetal images are different from paediatric images.

Fetal Therapy

The indications for fetal surgical therapy are limited¹⁶ (Table I). Improvements in the accuracy of prenatal diagnoses and better understanding of the natural histories of fetal diseases (both with and without treatments) have allowed accurate prognostication and appropriate selection of cases that might benefit from fetal therapy.

Open fetal surgery has been performed for various lethal fetal conditions, largely with disappointing results. Introduction of such treatment has been preceded by much work on experimental animal models. It is still considered experimental and is currently performed in only a few centres by teams trained in multidisciplinary techniques

required for complete care of both mother and fetus.

Minimally invasive surgery is establishing its role in the field of fetal therapy, just like in other surgical fields. Endoscopic surgery has been employed mainly in the treatment of TTTS. This has become a reality with improvements in fiberoptic technology and modifications in the paediatric endoscopic instruments.

TTTS

The aetiology of TTTS is related to the nature, number and size of placental anastomoses and their haemodynamic function. A primary vascular aetiology of the presence of at least one deep unidirectional AVA associated with a paucity of superficial bidirectional anastomoses has been proposed and is well-accepted.¹¹ Its management should be individualised according to the severity of the disease.

For mild stages of TTTS (Quintero stages 1 and 2),¹⁴ expectant management with close surveillance or delivery if gestation has reached 34 weeks may be pursued, with amnioreduction reserved for those with severe polyhydramnios. More severe stages of TTTS (Quintero stages 3 and 4) are associated with poorer perinatal outcomes and may benefit from a treatment that aims at interrupting the placental vascular anastomoses that cause the disease.

Nd:YAG laser for the selective photocoagulation of the communicating vessels on the chorionic plate is the most logical treatment for TTTS. It can be done between 16 and 26 weeks of gestation. This technique has now evolved into one of selective ablation of properly identified superficial and deep AVAs at the vascular equator.¹⁷

A rigid 1.9- to 2.0-mm paediatric cystoscope can be inserted under continuous ultrasound guidance. The chief technical problem is access to the chorionic plate in anteriorly sited placentas. This can be overcome with a flexible fetoscope through a single port or a side firing laser fibre through a second port under the guidance of a rigid angled fetoscope.¹⁸ This technique requires a learning curve - both achieving the dexterity of laparoscopic procedures and the correct identification of vascular anastomoses. The major disadvantages of this procedure are the immediate loss of one twin in about 25% and 5% to 10% iatrogenic premature rupture of membranes.¹⁹

Selective cord occlusion of one twin is reserved for severe or refractory TTTS. This can be performed by bipolar diathermy and has been associated with about 90% survival of the co-twin in stages 3 and 4 TTTS, and is associated with a 20% risk of post-procedure amniorrhexis.¹⁹

Conclusion

The at-risk or abnormal fetus can now be assessed by a variety of modern imaging tools and various invasive investigations. This has contributed to major advances in prenatal diagnosis and the study of fetal sonoembryology, physiology and pathophysiology of diseases. In turn, this expanded knowledge and improved surgical instruments have allowed major advances in fetal therapy. The clinician involved in the care of the obstetric patient should stay regularly updated in this field.

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