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ABSTRACT

There have been recent major advances in obstetric ultrasound, regarding both improved technologies and sonographer expertise, which have resulted in changes in antenatal obstetric management. The placenta is routinely examined to some extent at the time of the second trimester fetal anomaly sonogram, timing of delivery in pregnancies complicated by intrauterine growth restriction is primarily dependent on Doppler sonographic assessment of umbilical and uterine artery blood flow, and an increasing number of specific placental lesions have been described. Many non-specialist diagnostic histopathologists may be unfamiliar with these obstetric advances, but they are an increasingly common indication for submission of placentas for histological examination. Since the aims of pathological examination of the placenta are to determine the pathological basis for the clinical findings and advance understanding of the pathophysiology of pregnancy complications, this review therefore provides an overview of the most common prenatal sonographic techniques and their clinical relevance to the diagnostic pathologist, primarily focusing on conditions with specific placental implications. These range from abnormalities of placental site and cord insertion, to obstetric complications such as antepartum haemorrhage, through sonographic placental parenchymal lesions such as subchorionic and intervillos thrombi, or chorioangiomata. In addition, the pathophysiological basis of abnormal maternal and fetal maternal Doppler indices and intrauterine growth restriction are now described, being associated with decidual vasculopathy and villous changes associated with reduced intervillous blood flow respectively. Finally, rare but characteristic, sonographic appearances of villous cystic or hydropic change, may be associated with intrinsic developmental placental abnormalities such as hydardiform mole and placental mesenchymal dysplasia, which require histological examination for their specific diagnosis.

There have been recent major advances in obstetric ultrasound, both regarding technologies and expertise, such that high-resolution antenatal structural imaging, determination of maternal and fetal blood flow parameters and 3D and 4D ultrasound, are part of routine practice. This has resulted in changes in the way antenatal and obstetric care is now delivered. For example, antenatal and obstetric management of pregnancies complicated by intrauterine growth restriction (IUGR) and pre-eclamptic toxaemia (PET) is now dependent on ultrasound, while specialist review, 90% being errors due to unrecognised lesions and 10% erroneous diagnoses, many of these differences possibly being related to pathologist unfamiliarity with current obstetric technologies. This review aims to provide an overview of relevant obstetric ultrasound techniques and their clinical relevance to the diagnostic pathologist, primarily focusing on conditions with specific placental implications. There are several detailed texts regarding histological findings and their implications of placental pathological lesions, and therefore this review will specifically discuss the pathological correlates of sonographic findings, with details of the specific histological entities being found elsewhere. The aim of pathological examination of the placenta is to determine the pathological basis for the clinical findings and advance understanding of the pathophysiology of pregnancy complications.

BASIC TECHNIQUES IN OBSTETRIC ULTRASOUND

Ultrasound examination is based on high-frequency, low-intensity sound waves being transmitted via an ultrasound transducer composed of a curved array of piezoelectric crystals. The ultrasound pulses are transmitted and the reflected signals received, the composite signal being visualised as an image representing differing echodensities. This image is rapidly updated, resulting in an apparent “real-time” display of a two-dimensional grey-scale image (B-mode ultrasound). Computer reconstruction of a series of these two-dimensional images captured in a specific way allows a “three-dimensional” representation of the object, either static (3D) or in “real time” (4D). Standard B-mode real-time imaging remains the standard technique for examination in obstetric sonography. Examination of blood flow requires use of techniques based on the Doppler frequency shift principle that for a moving structure, such as blood flowing through a vessel, the reflected wave will be at a different frequency from the transmitted wave depending on the direction and velocity of flow. The Doppler signals can be superimposed on the grey-scale image as coloured areas representing blood flow (colour Doppler imaging), while pulsed-wave Doppler of a specific vessel can determine its flow velocity waveform (FVW) from which both absolute velocities and impedance indices, such as the systolic to diastolic (S/D) ratio, resistance index (RI) and pulsatility index (PI), can be determined. In the present context, the main
vessels relevant are uterine (UtA) and umbilical artery (UA) FVWs, representing blood flow and resistance in the uteroplacental and fetoplacental circulations, respectively.6

**SONOGRAPHIC APPEARANCE OF THE NORMAL PLACENTA**

Standard B-mode examination reveals the placenta as a relatively homogeneous grey area adjacent to the uterine wall which, with advancing gestation, shows areas of differing echogenicity (fig 1A). In the third trimester, placental calcification may also be identified as echogenic “speckling”, most marked near the basal plate and occasionally scattered throughout the placental parenchyma (fig 1B). Placental localisation and examination of its gross anatomy should now be part of all routine obstetric ultrasound examinations.5

**SPECIFIC ENTITIES**

**Intrauterine growth restriction**

Most cases of IUGR are associated with uteroplacental vascular disease, a small number with other specific placental abnormalities such as maternal floor infarction or massive perivillous fibrin deposition, and a few are due to other conditions such as fetal infections or structural abnormalities. There is an association between an abnormal uteroplacental Doppler FVW and the presence of ischaemic-type changes in the placenta, such as infarction.7 8 Histological examination of the placental bed in such cases reveals that the extent of impaired trophoblast invasion correlates with the degree of abnormal uterine artery FVWs.9–12 Acute atherosis may also be present in the maternal vessels,13 14 and infant birth weight is most reduced in cases with acute atherosis in addition to other features of impaired trophoblast invasion.15 16

Placental infarction

Placental infarcts are a consequence of uteroplacental vascular disease, and are associated with IUGR and PET. Infarcts may be detected sonographically but the sensitivity is low, with only about 10% of all infarcts antenatally identified.17 The sonographic appearance varies with time such that most are initially hypoechoic, becoming more echogenic, sometimes with areas of calcification (fig 1E).15 17

Abnormal uterine artery Doppler waveforms

The underlying pathophysiological event in pregnancies complicated by IUGR or PET is defective trophoblast invasion of the placental bed and inadequate conversion of the spiral arteries into uteroplacental vessels. Identification of pregnancies at significantly increased risk for the development of these complications can now be performed using Doppler ultrasound examination of the UtAs at 20–24 weeks of gestation, with about 75% of women who subsequently develop severe PET and 30% of cases of severe IUGR being detected for a 5% screen positive rate.20 Pregnancies with abnormal trophoblast invasion show increased UtA flow resistance, manifest as a raised PI which progresses to absent, and finally reversed, end-diastolic flow (EDF) (fig 2A). Reversed EDF may be associated with fetal hypoxia and acidosis and is usually an indication for immediate delivery.22

Placentas affected by IUGR with abnormal UA Doppler indices usually show morphological abnormalities of terminal villi, including reduced terminal villous volume with small, straight villi, reduced villous vascularity and increased syncytial knot formation.23 In some rare cases it is possible that the primary abnormality is a defect in terminal villous tree development resulting in a reduced capillary bed size and hence increased vascular resistance.24 However, in the vast majority the primary event is reduced uteroplacental flow leading to secondary placent al fet al stem vessel vasocclusion and subsequent reduced fetoplacental villous flow with secondary changes in terminal villous morphology.25 However, there is conflicting data regarding the relationship between Doppler indices and stereological parameters of terminal villi.26 Several studies using both histopathological and morphometric methods, have reported stem artery wall thickening consistent with prolonged vasocostriction27–29 (fig 2B), and morphometric studies report that cases with absent EDF show significantly more stem vessels with medial hyperplasia and luminal obliteration, with a correlation between Doppler impedance indices and stem vessel wall thickness.30–33 These vasocostriction changes will, if sustained, lead to a progressive sclerosis and eventual obliteration of the more distal vasculature with diminished vascularisation of the terminal villi. Furthermore, placentas from IUGR pregnancies with abnormal UA Doppler indices are also associated with increased frequency of infarcts, the extent of these ischaemic-type changes also being related to the abnormal UA Doppler indices, confirming the association between impaired uteroplacental perfusion and subsequent reduced fetoplacental perfusion.34 Furthermore, experimental studies confirm the interrelationship between fetal and maternal circulations by demonstrating that reduced uteroplacental flow is followed by increased fetoplacental vascular resistance.35–37

The UA Doppler indices change rapidly following experimental occlusion of maternal uteroplacental flow, demonstrating that the mechanism must act rapidly and be reversible.38 Finally, perfusion of cotyledons from normal and IUGR pregnancies after delivery also shows that the high placental flow resistance is due to vasocostriction of stem vessels.39 This dynamic relationship between the two circulations has a physiological function, allowing matching of uteroplacental and fetoplacental flows, to minimise flow mismatch.39 40 The morphological changes of the terminal villi are therefore likely to be a consequence of reduced local fetoplacental flow following stem vessel vasocostriction rather than a primary event, further supported by similar changes following stem villous thrombosis. The mechanism of control of stem villous vascular tone is probably based on basal production of nitric oxide with superimposed hypoxic fetoplacental vasocostriction at the level of the small, intraplacental, stem vessels due to inhibition of vascular smooth muscle potassium channels.41
Antepartum haemorrhage

Significant frank vaginal bleeding in a potentially viable pregnancy may indicate either placenta praevia, vasa praevia or placental abruption. Clinical placental abruption occurs in 0.5–1% of pregnancies. Retropelacental bleeding/abruption is difficult to detect by ultrasound but may sometimes be identified as an echo-poor area between the placenta and uterine wall (fig 2C). Acute haematoma appears slightly hyperechoic, becoming hypoechoic and echolucent with time. In addition to direct visualisation of the retropelacental clot, in some cases, there may be thickening of the placenta overlying the area of separation. However, in women with a clinical history of abruption, retropelacental haematomas are detected pathologically in only about one third while, of those with a retropelacental haematoma present there is clinical evidence of abruption in only about 35% (fig 2D). In addition, since the introduction of routine ultrasound examinations in early pregnancy, the antenatal identification of early asymptomatic retropelacental haematomas has also been described in up to 3% of pregnancies.

Cervical cerclage/short cervix

Severe preterm delivery is the leading cause of neonatal mortality and antenatal prediction of patients at high risk remains a goal of antenatal care. The most effective method of screening for severe preterm delivery is by sonographic measurement of the cervical length at 22–24 weeks of gestation, those with a short cervix being at markedly increased risk. In women with a short cervix, cervical cerclage may be performed. Cerclage has not, however, been shown to be effective in improving outcome; it may be associated with iatrogenic complications such as membrane rupture and chorioamnionitis in addition to the risk of chorioamnionitis in relation to the short cervix.
Oligohydramnios/anhydramnios
Significant reduction, or absence, respectively, of amniotic fluid volume, using various sonographic measures such as the amniotic fluid index or depth of the largest pool of amniotic fluid are due to IUGR, premature membrane rupture or fetal anomaly such as renal agenesis. In monochorionic twin pregnancies, severe twin-to-twin transfusion syndrome (TTTS) results in oligohydramnios of the donor with polyhydramnios of the recipient sac.

Twin pregnancies
Chorionicity determination in early pregnancy is highly reliable by examination of the junction of the placenta with the intertwin membrane for the lambda or “T” signs. In monochorionic twins, TTTS is manifest as discordancies in fetal size and amniotic fluid volume with or without additional features, and chorionic plate vascular anastomoses may be identified on Doppler imaging. The relationship between clinical complications of TTTS and placental architecture has previously been reported. TRAP sequence can also be readily diagnosed by sonography from the first trimester.

Prenatally diagnosed fetal anomaly
Most structural fetal anomalies are not associated with specific morphological changes in the placenta. Some syndromes may, however, affect the placenta in addition to the fetus; examples include fetal triploidy (partial hydatidiform mole) and Beckwith–Wiedemann syndrome, the latter of which is associated with changes of placental mesenchymal dysplasia (PMD) where there is cystic change in stem villi, detectable sonographically in some cases (fig 2E,F). Overall, around a third of PMD are associated with Beckwith–Wiedemann syndrome. A wide range of other fetal aneuploidies, such as trisomies, are associated with villous dysmorphic changes.
including irregular outlines, trophoblastic pseudoinclusions, basement membrane mineralisation and peripheral trophoblast sprouting, although these changes are not specific for particular disorders. Most cases of fetal hydrops are associated with non-specific changes of placental villous oedema with or without apparent delayed villous maturation. The villous stroma is variably oedematous with stromal Hofbauer cells prominent, but changes are usually otherwise non-specific. A range of rare conditions such as inherited metabolic diseases may present with specific features, which will not be detailed further here.

**Abnormalities of placentation**

A low-lying placenta, in which some or all of the cervical os appears to be covered by placental parenchyma, is present in around 25% of pregnancies at 20 weeks, but placenta praevia at term only affects 1% due to expansion of the lower uterine segment. Circumvallate placentas show a peripheral rim of chorionic tissue which appears as an echodense ridge; however <10% of circumvallate placentas are detected prenatally. Succenturiate lobes are easily diagnosed by ultrasound (fig 3A), especially using colour Doppler to demonstrate communicating chorionic vessels (fig 3B,C). Colour Doppler may also allow identification of vasa praevia and velamentous cord insertion as vessels running across the cervical os and within the fetal membranes respectively. Abnormally invasive placentas (accreta, increta, percreta) may be diagnosed by prenatal sonography, although the sensitivity is low (<50%). Diagnosis is usually made in a patient with a history of previous lower segment caesarean sections and placenta praevia, in whom the normal hypoechoic region between placenta and myometrium is absent. In addition, there may be prominent vascularity on Doppler examination.

**Figure 3** (A) Sonographic appearance of a placenta (P) with a succenturiate lobe (L), connected via large chorionic vessels (B). (C) Macroscopic appearance of a placenta and succenturiate lobe with torn intramembranous vessels. (D) Sonographic appearance of a lobular well-circumscribed chorioangioma with vessels demonstrated on colour Doppler imaging. (E) and (F) Photomicrographs of placental chorioangioma.
Placental tumours

Placental chorioangiomas are easily detected antenatally as well-circumscribed hypoechoic lesions, usually protruding from the fetal surface of the placenta, with abnormal flow detectable with colour Doppler imaging (fig 3D-F).

“Jelly-like” placenta

In some cases of IUGR the placenta may sonographically appear thickened, with patchy areas of hypoechogenicity and abnormal texture, appearing to “wobble” in an abnormal fashion, termed “jelly-like placenta” (fig 4A). It has been suggested that it is associated with massive perivillous fibrin deposition and intervillous or subchorionic thrombosis in some cases.

Placental lakes

Echolucent areas within the placental parenchyma, with no blood flow on Doppler scanning, have been termed “placental lakes” and appear to represent areas of villous free intervillous space, due to intervillous thrombosis or subchorionic fibrin deposition, and possible association with IUGR (fig 4B,C).

Maternal floor infarction/massive perivillous fibrin deposition

In previously affected pregnancies sonographic prenatal diagnosis of recurrence has been reported with IUGR, oligohydramnios and diffuse increased placental echogenicity, but there are no large studies to examine the accuracy of prenatal diagnosis in an unselected population.

Intervillous thrombi

Intervillous thrombi can be identified antenatally as echo-poor placental “cavities” on ultrasonographic examination (fig 4D). Histologically they usually appear as laminated fibrin and erythrocytes; they mark a site of fetal bleeding into the intervillous space and hence into the maternal circulation.
although they have a poor sensitivity for identification of significant fetomaternal bleeding (fig 4E). 69

Calcification
Calcification predominantly affects the basal plate and septa, being a normal feature of placental maturity. Calcification may also affect old infarcts and in plaques of pervilleous or subchorial fibrin. There is an association between primigravidity and placental calcification. 70

Umbilical cord lesions
The umbilical cord is easily visualised by ultrasound, including assessment of the number of vessels. 71 72 In cases with a single umbilical artery, only two vascular profiles are seen, including the larger vein and the artery, which is larger than normal. 73 The cord insertion site is also easily documented with reliable identification of marginal or velamentous cord insertion. 74 More recently, the antenatal umbilical cord vessel coiling pattern can be determined, the generally accepted method being the umbilical coiling index (UCI; the number of complete coils per centimetre length). Several studies have now documented the normal UCI, which is around 0.2 in the delivered (postnatal) placenta (pUCI) and 0.4 when determined antenatally by sonography (aUCI). This apparent discrepancy is probably due to the fact that in utero the umbilical vessels are distended with fetal blood, with resulting tighter apparent coiling of the helical vessels. Although an association between the aUCI and pUCI is normal UCI, which is around 0.2 in the delivered (postnatal) placenta (pUCI) and 0.4 when determined antenatally by sonography (aUCI). This apparent discrepancy is probably due to the fact that in utero the umbilical vessels are distended with fetal blood, with resulting tighter apparent coiling of the helical vessels. Although an association between the aUCI and pUCI is present (as expected since both are a measure of the same entity), antenatal sonographic determination of UCI has a low sensitivity (40%) to predict undercoiling or overcoiling as determined postnatally, indicating that aUCI and pUCI may not represent measurements of exactly the same phenomenon; some cases overcoiled or undercoiled on antenatal examination are within the normal range after delivery and vice versa. 75 A range of adverse outcomes have been reported in association with antenatal and postdelivery abnormal cord coiling. Hypocoiled cords are associated with increased frequency of intrauterine death, congenital abnormalities such as trisomies, and abnormalities of placental development. Hypercoiled cords are associated with fetal abnormalities, intrauterine growth restriction, fetal acidosis and asphyxia. It is currently uncertain whether these are simply associations with no pathophysiological significance or whether the cord coiling pattern can directly cause adverse pregnancy outcome, but pathological assessment of coiling may become of clinical importance. 76
Cord cysts are easily detectable, with allantoic cysts close to the fetal insertion, centrally located between the vessels. Cystic umbilical cord lesions are identified more frequently in the first trimester, most of which resolve spontaneously during the pregnancy and appear to be of no clinical significance, although a range of adverse outcomes have been reported in association with cord cysts, including intrauterine demise and chromosomal defects. 77 78 Prenatally detected mass lesions in the cord appear as hyperechogenic, solid and cystic lesions, usually representing aneurysms, haemangiomas, angiomyxomas or, rarely, teratomas. 79 80

Molar placenta
Classically, second-trimester complete hydatidiform mole (HM) has a characteristic sonographic appearance, with the uterine cavity filled by variably sized cystic structures which replace the normal products of conception. 81 In partial HM the degree of cystic change is less marked and a fetus may be identifiable, although fetal abnormalities will be present. However, in current clinical practice, with routine early pregnancy ultrasound examinations and sonographic assessment of vaginal bleeding in pregnancy, most HM now present as early pregnancy failure rather than the traditional appearance of villous vesicular change. 82 Both complete and partial HM exhibit distinctive histological characteristics, even in the first trimester (fig 4F). 83 84 characterised by abnormal proliferation of villous trophoblast, villous hydropic change and numerous specific other features. In the UK, most HM are now evacuated around 10 weeks of gestation. 85 About half are entirely asymptomatic, detected as pregnancy failure following routine sonographic examination; the remainder present with vaginal bleeding. 86 Analogous to the changing clinical and pathological aspects of HM, traditional sonographic presentations are also rarely seen. Several large studies have now reported on the use of ultrasound in the detection of HM in early pregnancy, indicating that pre-evacuation identification of hydatidiform moles by ultrasound in the first and early second trimester is achieved in only 40–60% of cases in routine clinical practice, 87 88 including about 80% of complete HM and 50% of partial HM; the remainder appear sonographically as a simple missed miscarriage. Additionally, >10% of the cases identified as “molar” on ultrasound examination were in fact non-molar hydropic miscarriages on histological review. Although improvements in expertise and ultrasound technology will occur, a proportion of early HM have simply not yet developed sufficient villous hydrops to be detectable by ultrasound examination. 89

Invasive procedures
Invasive intrauterine procedures, such as amniocentesis, cordocentesis and chorionic villus sampling, should be carried out under direct, continuous ultrasound guidance, the needle being highly echogenic, to minimise procedure-related complications. Death may still occur secondary to complications, including inadvertent puncture of chorionic plate vessels or introduction of amniotic fluid.

Take-home messages
► Prenatal ultrasound can identify a range of features which are related to specific placental pathologies.
► Specific pathological correlation of prenatal features should be provided where possible.
► Pathological correlates of Doppler abnormalities of blood flow are now determined.
► Many sonographic features are non-specific and may be due to a range of different underlying pathologies.

Competing interests: None declared.

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