Imaging and Assessment of Placental Function

ABSTRACT: The placenta is the vital support organ for the developing fetus. This article reviews current ultrasound methods of assessing placental function. The ability of ultrasound to detect placental pathology is discussed. Doppler technology to investigate the fetal, placental and maternal circulations in both high-risk and uncomplicated pregnancies is discussed and the current literature on the value of 3D Power Doppler studies to assess placental volume and vascularisation is also evaluated. The article highlights the need for further research into 3D ultrasound and alternative methods of placental evaluation if progress is to be made in optimising placental function assessment.

Keywords: placenta; infarcts; calcification; Doppler; 3D ultrasound.

Imaging and Assessment of Placental Function

The placenta is the vital support organ for the developing fetus. The fetal nutritional status is dependent on the ability of the mother to provide oxygenated blood to the uterine circulation and maternal surface of the placenta and the ability of the fetus to extract nutrients from the placenta and deliver them to the fetal tissues.[1] Therefore abnormal placental development and function may result in a wide range of pregnancy complications throughout the three trimesters. These include recurrent early miscarriage, mid trimester fetal death and preterm labour and the complications of pre-eclampsia, intrauterine growth restriction (IUGR), placental abruption and placenta praevia.[2,3,4] The results of a recent study showed that in 88% of stillbirths, the direct cause, or a major contributor to death was found in the placenta.[5] For a number of years ultrasound has been shown to offer an exclusive opportunity to examine the anatomy and development of the placenta in utero,[6] and whilst magnetic resonance imaging (MRI) is also now used ultrasound remains the main imaging method of choice. The advantage of ultrasound over other imaging methods is that it has a superb safety record,[7] is relatively inexpensive and allows real-time diagnosis.[8] Assessing placental function, particularly in the second trimester, has the advantage that it allows the identification of a high-risk fetus in the low-risk population, and therefore planning of subsequent monitoring of the pregnancy. This review will discuss the importance of optimal placental function and the current ultrasound methods used in its assessment.

ULTRASOUND FEATURES OF PLACENTA AND CORD

The ultrasound findings which denote the placenta in the early stage of pregnancy are increased echogenicity and thickening within the decidual reaction around the gestational sac. This hyperechoic rim of tissue around the sac may be discernible as early as 10 weeks gestation, a recent study reporting identification of the placenta, distinguished by its thickness, separate from the rest of the gestational sac lining as early as 5 weeks gestation.[9] The placenta is easily visible at approximately 15 weeks gestation when it demonstrates a uniformly granular echogenic pattern. Gradual sonographic changes occur from 20 weeks to term, which include development of septations, hyperechoic areas (representing areas of calcification), sonolucent areas and scalloping of the chorionic plate.[10] The normal placenta measures 15-20 cm at term, with placental thickness throughout pregnancy approximately equal to weeks of gestation, +/- 10mm. One study from which a normogram of placental thickness was developed, reliably demonstrated that placental thickness increases progressively between 8 and 20 weeks gestation.[11] However, the authors also concluded that variation at each week of gestation is somewhat high.

Current studies continue to support the correlation between first- or second-trimester measurements of placental size and a growth restricted fetus.[12,13] As placental thickness is difficult to determine accurately with two-dimensional (2D) ultrasound recent studies suggest the best estimation of size is the measurement of placental length (linear length), with placental size considered to be abnormally small when the maximum length is <10cm.[14] A thin placenta can also be indicative of chromosomal anomalies, severe intrauterine infection, and preconceptional diabetes mellitus, with a placental thickness < 1.5cm associated with stillbirth.[5] An enlarged placenta, on the other hand, can be the result of mesenchymal dysplasia,[6] a molar

pregnancy, aneuploidy, triploidy, placental hemorrhage, anemia, infection, (for example toxoplasmosis, cytomegalovirus and syphilis),[15] hydrops, and gestational diabetes. A large placenta can also be indicative of potential health problems in adult life with an increased risk of hypertension among both men and women at around 50 years of age found among those who had been born small for gestational age and had large placentas.[16]

The umbilical cord is visible on ultrasound at 8 weeks gestation, is approximately equal in size to the crown rump length of the fetus, and is generally the same length of the fetus throughout pregnancy. The umbilical cord initially inserts centrally within the placenta. With placental development the cord grows preferentially in areas where there is optimal perfusion of the myometrium and it atrophies in the areas where the blood supply is suboptimal.[17] Seven percent of pregnancies have a battledore placenta, where the cord is inserted at the margin of the placenta. A recent study of 967 placentas assesses the effect on placental efficiency of the non-centrality of cord insertion. The authors concluded that a placenta with a non-central cord insertion, (even if the placenta has a normal shape), has a sparser chorionic vascular distribution, resulting in a vasculature that is metabolically less effective.[18] Ultrasound has been shown to have 86% sensitivity and a PPV of 71% ($p < 0.0001$) in the identification of lateral or marginal cords.[19]

PLACENTAL LESIONS

As highlighted in a recent review many different pathologies of the placenta can be detected by routine ultrasound, some of which may have a significant impact on clinical outcome.[15] A retrospective study found, at pathology, placental lesions in 87.2% of IUGR cases (as opposed to 74.5% of the controls).[20] The study used a

combination of placental lesions, including infarcts, intervillous thrombosis and maternal floor infarcts and the results indicated that the presence of $\geq$ 3 lesions was associated with an increased risk for IUGR and neonatal cranial ultrasound abnormalities. This study also reported that placental infarct is the one lesion more common in asymmetric IUGR, whereas the other lesions were more common in symmetric IUGR. A later study found placental lesions present in 93% of cases of 60 women with pregnancies complicated with early-onset IUGR.[18] In a study of 158 women with preeclampsia it was found that placental lesions were considerably more frequent in the women who had preterm deliveries.[21]

Placental lakes

Placental lakes are the most common placental abnormality seen on ultrasound and are defined as anechoic areas (> 2) surrounded by placental tissue of normal echogenicity. There are various opinions as to the exact measurement that defines these anechoic areas as lakes with one study suggesting a lake can be identified if the measurement is at least 1 cm in the largest diameter.[22] Whilst placental lakes have been reported as being associated with Rhesus incompatibility and high maternal serum α-fetoprotein levels[23] most studies however suggest that they are of little clinical significance.[22,24,25] Placental lakes can be visualized on ultrasound at any stage from the second trimester to term and their shape can be modified with uterine contractions or a change in maternal position.

Placental Infarcts

Placental infarcts are defined as localized areas of ischaemic villous necrosis and in the vast majority of cases are caused by thrombotic occlusion of an uteroplacental

artery. Occasionally infarcts can be the result of a hematoma behind the placenta (retroplacental) stripping the placenta away from its blood supply.[26] Uteroplacental ischemia and placental infarction can lead to poor maternal fetal gas exchange which ultimately contributes to progressive fetal hypoxia, with a strong association shown between the presence of infarcts and severe forms of IUGR and pre-eclampsia.[27,28]

The clinical significance of infarcts appears to depend on their size and position, with isolated peripheral infarcts, which are the most common, having no significance.[29,30] Large central infarcts are more serious as they may interrupt a significant proportion of placental function,[31] and central infarcts, involving more than 30% of the placenta, (and infarcts which occur early in pregnancy), are strongly associated with pregnancy-induced hypertension, intrauterine growth restriction, preterm delivery and fetal death.[26] The role of 2D ultrasound in the diagnosis of placental infarcts is questionable with one study finding that the presence of echogenic cystic lesions, i.e. cystic lesions with irregular echogenic borders, (Figure 1) on ultrasound had only 37% sensitivity and 63% PPV for villous infarcts that were confirmed on histology.[19]

Placental Calcification

The placenta normally matures and calcifies as the fetus approaches term and from 40 weeks gestation approximately 20% of placentas have extensive calcification.[15] Calcification occurring at an earlier stage, however, has been associated with pregnancy induced hypertension, fetal growth restriction, and intra-partum fetal distress. A large study of 1802 low-risk women confirmed that detection of a grade III placenta at 36 weeks gestation in a low-risk population assists in identifying the "at-risk" pregnancy.[32] Abnormal placental calcification is also thought to be

associated with diabetes and Rh incompatibility, with delayed placental maturation (DVM) occurring in these conditions.[33] Ultrasound assessment of placental calcification relies on Grannum grading. While clinical studies in the past have shown placental grading to hold promise, its role in clinical practice is now highly controversial. A recent study testing the experimental hypothesis that ultrasound appearances of early placental calcification reflects poor or reduced placental function suggests that grading as a means of monitoring placental function requires further investigation.[34] The authors conclude that the early appearance of a high-grade placenta is not a reliable predictor of pregnancy complications or pregnancy outcome. Perhaps this is due to the subjectivity of this method as while intra-observer agreement in grading placentas is generally good, agreement between observers has been shown to be only fair for all Grannum grades and poor for Grade III.[35] A more recent study, performed under strictly controlled viewing conditions, confirmed the lack of reproducibility associated with Grannum grading.[36]

DOPPLER ULTRASOUND

Doppler technology has been used to investigate the fetal, placental and maternal circulations for a number of years and remains an ideal method of assessing placental function in both high-risk and apparently uncomplicated pregnancies.[37]

Umbilical artery Doppler

The normal umbilical artery (UA) circulation has low impedance, with continuing forward flow during diastole (Figure 2a) and an increase in the end-diastolic flow with advancing gestation. At term the umbilical blood flow represents approximately 20% of the biventricular fetal cardiac output.[38] Severe early-onset intrauterine growth

restriction (IUGR) is characterized by absent/reversed end-diastolic flow velocity in the umbilical arteries with reversed flow, which is associated with more than 70% of placental arterial obliteration, indicative of an advanced stage of fetal compromise (Figures 2b and 2c). Abnormal UA waveforms are demonstrated by a PI > 95th centile, (or RI / SDR > 95th centile). The resistance index will be raised when approximately 30% of the fetal villous vasculature is abnormal, and 60—70% damage to the villous vasculature is indicated when there is absent or reversed end-diastolic flow.[39] Over 40% of pregnancies with early onset IUGR are associated with pre-eclampsia.[19] Late onset IUGR, on the other hand, is more likely to be associated with normal UA Doppler waveforms.[29]

Umbilical Venous Doppler

Umbilical vein (UV) circulation has a waveform that is steady and without pulsations (Figure 2a) and can be assessed either within its entrance into the fetal abdomen or adjacent to the fetus within the amniotic fluid.[40] Fetal hypoxia is associated with a reduction in umbilical venous blood flow.[41] It has been demonstrated that single pulsations at the end of diastole, in association with severe bradycardia and absent or reversed end-diastolic flow in the umbilical artery (Figure 2b), may be a physiological pattern of a reduction in forward flow in the feteoplacental circulation. However this study also showed that umbilical venous pulsations appear to be a late finding in chronic fetal hypoxia.[42]

Middle Cerebral Artery Doppler

The middle cerebral artery (MCA) is the most accessible vessel of the fetal cerebral circulation for the performance of Doppler assessment. It is the main branch of the

circle of Willis and carries 80% of the blood flow to the ipsilateral cerebral hemisphere, which represents a constant 3%-7% of cardiac output throughout gestation.[43] The blood velocity in the MCA normally increases with advancing gestation, and therefore is of a high resistance pattern, with low end-diastolic flow velocities, which in turn is associated with a decrease in pulsatility index throughout gestation. In the early stages of uteroplacental insufficiency fetal adaptation mechanisms lead to increased left ventricular output and decreased cerebral resistance.When this occurs the MCA end-diastolic velocity is increased and S/D ratio decreases. An abnormal MCA is also indicated when the PI is less than the 5th centile.

While umbilical artery Doppler is superior to middle cerebral artery Doppler for monitoring IUGR, MCA Doppler velocimetry is of benefit for screening those fetuses who are small for gestational age (SGA) that are at risk of adverse outcome (ie growth restricted as opposed to genetically small).[44]

Uterine Artery Doppler

In a normal pregnancy there is a progressive decrease in impedance to blood flow at the level of the uterine vasculature which ensures a sustained increase in blood flow to the uterus with advancing gestation. In the non-pregnant state there is a rapid rise and fall in the uterine artery blood flow velocity during diastole and a ‘notch’ present in the waveform in the early diastolic phase. In pregnancy the progressive decrease in impedance to blood flow with gestation results in the loss of the ‘diastolic notch’ between 20 and 26 weeks (Figure 3). The Doppler indices (RI and PI) also decrease with advancing gestation.[45] As assessment of diastolic notching is quite subjective it is recommended that the PI value is a more reliable indicator of an abnormal

waveform.[46,47] A PI value above the 95th centile is considered abnormal. The results of a large multicenter study involving 8335 consecutive singleton pregnancies demonstrated that 5% of the population studied with a mean PI > 95th centile contained 69% of women who developed pre-eclampsia and IUGR, 24% of women who developed pre-eclampsia only and 13% of the women who went on to have growth restricted babies, in the absence of pre-eclampsia.[48]

Uterine artery Doppler performed between 11 and 14 weeks gestation identifies a significant percentage of women who develop severe pre-eclampsia and/or IUGR.[49] Whilst the presence of an early diastolic notch can be normal at this stage, results of recent studies suggest changing the indices used for screening purposes at this gestation. Some authors suggest using the lowest PI value (as opposed to the mean value),[50] whilst others suggest using the resistance index (RI) for first trimester Doppler studies as it has been shown to have better inter- and intra-observer reproducibility.[51,52]

A recent review of UtA Doppler studies concluded that whilst it is a useful screening tool for women known to be high-risk further research is required to support the possible benefits for screening low-risk women.[45] Current evidence also suggests that the UtA should be used in conjunction with the umbilical artery and middle cerebral artery to best predict adverse perinatal outcome in fetuses with late-onset IUGR, with more evidence required before its use as a stand-alone surveillance can be recommended.[53]

Colour/Power Doppler

Intervillous blood flow can be easily demonstrated as early as 12-13 weeks gestation by color or power Doppler (PD) ultrasound imaging. At 16-18 weeks small intraplacental arteries can be visualized at low flow settings and from 28 weeks (due to the fact that the placenta is now a highly vascular organ) both retroplacental and intraplacental arteries are easily visualized by colour or power Doppler (Figure 4). In a study of 66 normal and 63 high-risk pregnancies there was no relationship found between PD signals and placental vascular resistance, and the authors suggest that PD signals therefore are more reflective of organ volume blood flow.[54] Power Doppler is also currently being investigated as a method of detecting areas of placental infarction which manifest as areas of diminished blood flow.

3D ULTRASOUND ASSESSMENT

Three dimensional (3D) ultrasound allows the volumetric measurement of organs and spatial presentation of blood-flow information.[55] A significant advantage of current 3D volume imaging is the ability to save entire volumes, which contain all the relevant information from the scan. These volumes can be manipulated, interrogated and reconstructed into different displays at a later stage.[56] Measurements can be taken within the saved volume and measurement errors are minimised as multiplanar reconstruction of the captured 3D volume allows re-slicing in order to obtain the optimal plane for measuring.[57]

Placental volume

The results of research to date investigating first trimester 3D ultrasound assessment of placental volume are promising. A strong correlation has been found between the

volume of the placenta and crown rump length (CRL) measurement in healthy pregnancies studied between 7 and 10+6 weeks.[58] A large study of 2489 pregnancies found that placental volume/CRL, (termed as placental quotient or PQ), calculated at 12 weeks gestation has similar sensitivities for predicting pre-eclampsia and fetal growth restriction as Uterine artery Doppler at 22 weeks gestation. They also found UtA, however, to be marginally more sensitive for the prediction of pre-eclampsia.[59] A more recent study of 619 women found, among the known ultrasound and biochemical markers, only placental volume (PlaV) in the first trimester and PlaV plus Uterine artery Doppler PI measurement in the second trimester are independent predictors for SGA.[12]

Placental volume appears to be decreased in early gestation in pregnancies where there is a chromosomal abnormality, although one study found this to be the case for pregnancies affected by Trisomy 13 and Trisomy 18 only, which they suggest is most likely due to the early-onset fetal growth restriction associated with these conditions, as a result of impaired placental function.[60] The promising results of first trimester ultrasound assessment of placental volume suggest that if this method were used as standard practice it would have the advantage of ensuring close monitoring of pregnancies suspected to be at-risk and therefore further research at this stage of pregnancy is recommended.[61]

Placental blood flow

Initial studies have demonstrated that placental vessels viewed with 3D Power Doppler ultrasound correlate well with known anatomy, with a progressive increase in the number of intraplacental vessels and the number of vascular branches observed as gestation advances.[62] Power Doppler is the method of choice when assessing blood

flow during 3D imaging as it is less-angle dependent than frequency-based Doppler and therefore tends to produce a more complete 3D image. Power Doppler cannot determine direction of blood flow, however this is not relevant in the assessment of placental blood flow. Studies have shown reduced 3D Doppler vascular indices in clinical situations which are associated with reduced placental vascularization, for example early pregnancy loss, maternal smoking and intrauterine growth restriction. The indices used for quantifying vascularization and blood flow are:

VI *(Vascularization index)*, which assesses overall placental perfusion or vascularity (expressed as a percentage).

FI *(Flow index)*, which assesses the intensity of placental blood flow (expressed as a number from 0-100)

VFI (*Vascularization-flow index*, which represents both vascularization and blood flow, and is also expressed as a number ranging from 0-100.[63,64]

All the flow indices have been shown to significantly increase over time with advancing gestation, with normative indices defined[65,66] The reproducibility of all indices (from 14-40 weeks) is good, with a correlation of greater than 0.85.[67] The latter study also showed FI and VFI to have the better intra-observer agreement. A study of 45 women ranging from 23-37 weeks gestation, found the flow index, which identifies the most severe cases of placental impairment, to have the lowest intraplacental variability of the three indices.[68] The authors recommend further larger studies in order to verify its accuracy in clinical diagnosis. In another recent study of 208 normal fetuses between 12 and 40 weeks and 13 with growth restriction (22-39 weeks) the authors found that, after 32 weeks, all the indices were significantly lower in 10 of the growth restricted pregnancies. Of the normal pregnancies 79 had lower values after 32 weeks.[69]

This real-time assessment of placental pathology will allow diagnosis and close monitoring of pregnancies deemed to be high-risk.[70] Studies have shown reduced 3D Doppler vascular indices in clinical situations which are associated with reduced placental vascularization, for example early pregnancy loss, maternal smoking and intrauterine growth restriction. 3DPD has not been found to be useful for screening for Trisomy 21 as the flow indices in affected pregnancies are not significantly different from normal pregnancies. However, as with placental volume, flow indices are significantly lower in pregnancies affected with trisomies 13 and 18.[71]

Due to the size of the placenta between 11 and 13+6 weeks it fits in easily within the volume box and therefore it is possible to obtain more accurate volume and vascularization information than at later gestations. Normal ranges of placental vascular indices for this gestation have been established.[71] A study of 84 pregnancies with low serum pregnancy-associated plasma protein A (PAPP-A) found an association with altered 3D placental Doppler indices related to subsequent development of growth restriction and adverse outcomes.[72] An interesting feature of this study is that in pregnancies with low PAPP-A levels where the neonate had a normal birth-weight, or was deemed to be healthy low birth-weight, there was no difference in placental vascularization during the first trimester. The authors also found a significant association between the degree of reduction in the 3D placental Doppler indices and the severity of growth restriction, and related problems, at birth. There is an association between maternal smoking and altered vascular indices in the first trimester, but not in placental volume.[73]

CONCLUSION

Placental volume and 3D blood flow assessment are not widely accepted as yet in routine practice.[26] Volume measurements are a more accurate assessment of placental villous mass than 2D linear measurements, however 3D measurements are more complex, time consuming and the equipment required is expensive.[73] It is evident that a more simple and objective method of assessing placental function is required. No one test alone can predict fetal health with absolute certainty, therefore it is important to optimize information gained through ultrasound. Further research into 3D ultrasound and alternative methods of placental evaluation is vital if progress is to be made in optimising placental function assessment.

REFERENCES

1. Sankaran S, Kyle PM. Aetiology and pathogenesis of IUGR. Best Pract Res Clin Obstet Gynaecol 2009;23:765.
2. Norwitz ER. Defective implantation and placentation: laying the blueprint for pregnancy complications. Reprod Biomed Online 2006;13:591.
3. Toal M, Chan C, Fallah S, et al. Usefullness of a placental profile in high-risk pregnancies. Am J Obstet Gynecol 2007;196:363.e1.
4. Abramowitz JS, Sheiner E. In Utero imaging of the placenta: Importance for diseases of pregnancy. Placenta 2007;21:S14
5. Kidron YM, Bernheim J, Aviram R. Placental findings contributing to fetal death, a study of 120 stillbirths between 23 and 40 weeks gestation. Placenta 2009; 30:700.
6. Jauniaux E, Nikolaides K, Hustin J. Perinatal features associated with placental mesenchymal dysplasia. Placenta 1997;18:701.
7. Salvesan KA, Lees C. Ultrasound is not unsound, but safety is an issue. Ultrasound Obstet Gynecol 2009;33:502.

8. Levine D. The role of computed tomography and magnetic resonance imaging in obststrics. In: Callen PW, ed. Ultrasonography in Obstetrics and Gynecology. 5th edition. Philadelphia: WB Saunders; 2008. p 808.
9. Wong HS, Cheung YK, Taits J. Sonographic study of the decidua basalis in the first trimester of pregnancy. Ultrasound Obstet Gynecol 2009;33:634.
10. Kulhmann RS, Warsoff S. Ultrasound of the Placenta. Clin Obstet Gyecol 1996;39:519.
11. Tongsong T, Boonanurak P. Placental thickness in the first half of pregnancy. J Clin Ultrasound 2004;32:231.
12. Law L, Leung TY, Sahota DS, et al. Which ultrasound or biochemical markers are independent predictors of small-for-gestational age? Ultrasound in Obstet Gynecol 2009;34:283.
13. Proctor LK, Toal M, Keating S, et al. Placental size and the prediction of severe early-onset intrauterine growth restriction in women with low pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 2009;34:274.
14. Toal M, Keating S, Machin G, et al. Determinants of adverse perinatal outcome in high-risk women with abnormal uterine artery Doppler images. Am J Obstet Gynecol 2008;198:330e1.
15. Abramowicz JS, Sheiner E. Ultrasound of the placenta: A systematic approach. Part 1 Imaging. Placenta 2008;29:225.
16. Barker DJ. Fetal origins of coronary heart disease. BMJ 1995;311:171.
17. Benirschke K, Kaufmann P. Placental shape aberrations. In: Benirschke K, Kaufmann P, eds. Pathology of the human placenta. 4th edition. New York: Springer-Verlag; 2000. p 335.
18. Yampolsky M, Salafia CM, Shlakhter O, et al. Centrality of the umbilical cord insertion in a human placenta influences the placental efficiency. Placenta 2009;30;1058
19. Viero S, Chadda V, Alkazaleh F, et al. Prognostic value of placental ultrasound in pregnancies complicated by end-diastolic flow velocity in the umbilical arteries. Placenta;2004:25:735
20. Vascardi RM, Sun CJ. Placental lesion multiplicity: risk factor for IUGR and neonatal cranial ultrasound abnormalities. Early Hum Dev. 2001;62:1.
21. Moldenhaeur JS, Stanek J, Warshak C, et al. The frequency and severity of placental findings in women with preeclampsia are gestational age dependent. Am J Obstet Gynecol 2003;189:1173.
22. Reis NS, Brizot ML, Schultz R, et al. Placental lakes on sonographic examination: Correlation with obstetric outcome and pathologic findings. J Clin Ultrasound 2005;33:67.

23. Jauniaux E, Nicolaides K. Placental lakes, absent umbilical artery flow and poor fetal growth in early pregnancy. Ultrasound Obstet Gynecol 1996;7:141.

24. Jauniaux E, Ramsey B, Campbell S. Ultrasonographic investigation of placental morphologic characteristics and size during the second trimester of pregnancy. Am J Obstet Gynecol 1994;170:130.

25. Thompson M, Vines S, Aquilina J, et al. Are placental lakes of any clinical significance. Placenta 2002;23:685.

26. Feldstein VA, Harris RD, Machin GA. Ultrasound evaluation of the placenta and umbilical cord. In: Callen PW, ed. Ultrasonography in Obstetrics and Gynecology. 5th edition. Philadelphia: WB Saunders; 2008. p 721.

27. Salafia CM, Pezzullo JC, Ghidini A, et al. Clinical correlations of patterns of placental pathology in preterm pre-eclampsia. Placenta 1998;19:67.

28. Ferrazzi E, Bulfamante G, Mezzopane R, et al. Uterine doppler velocimentry and placental hypoxic-ischemic lesion in pregnancies with fetal intrauterine growth restriction. Placenta 1999;20:389.

29. Kingdom J, Huppertz B, Seaward G, et al. Development of the placental villous tree and its consequences for fetal growth. Eur J Obstet Gynecol Reprod Biol 2000;92:35.

30. Fox H. The development and structure of the placenta. In: Fox H, ed. Pathology of the placenta. 2nd edition. Philadelphia: WB Saunders; 1997. p 1.

31. Alkazelah F, Viero S, Kingdom JC. Sonographic evaluation of the placenta. In: Rumack CM, Wilson SR, Charboneau et al, eds. Diagnostic ultrasound. 3rd edition. St Louis: Elsevier Mosby; 2005. p. 1557.

32. McKenna D, Tharmaratnam S, Mahsud S, et al. A randomised tria; using ultrasound to identify the high-risk fetus in a low-risk population. Obstet Gynecol 2003;101:626.

33. Clair M, Rosenberg E, Temkin D, et al. Placental grading in the complicated or high-risk pregnancy. J Ultrasound Med 1983;2:297.

34. Yin TT, Lounhna SS, Padfield J, et al. No correlation between ultrasound placental grading at 31-34 weeks of gestation and a surrogate estimate of organ function at term obtained by stereological analysis. Placenta 2009;30:726.

35. Sau A, Seed P, Langford K. Intraobserver and interobserver variation in the sonographic grading of placenta maturity. Ultrasound Obstet Gynecol 2003;23:374.

36. Moran M, Ryan J, Brennan PC, Higgins M, McAuliffe FM. Is Grannum Grading of the Placenta Reproducible? In: Sahiner B, Manning DJ, eds. Medical Imaging 2009: Image Perception, Observer Performance, and Technology Assessment, 2009. p W1-W6.

37. Abramowicz JS, Sheiner E. Ultrasound of the placenta: A systematic approach. Part II Functional Assessment (Doppler). Placenta 2008;29:921.

38. Poston L. The control of blood flow to the placenta. Exp Physiol 1997;82:377.

39. Bashatt AA. Fetal growth disorders. In: James DK, Steer PJ, Weiner CP, eds. High risk pregnancy management options. 3rd edition. Philadelphia: Saunders; 2006. p 240.

40. Abuhamad AZ. The role of Doppler ultrasound in obstetrics. In: Callen PW, ed. Ultrasonography in obstetrics and gynecology. 5th edition. Philadelphia: Saunders; 2000. p 800.

41. Nicolaides KH, Rizzo G, Hecher K. Doppler studies in fetal hypoxemic hypoxia. In: Nicolaides KH, ed. Placental and fetal Doppler. 1st edition. London: The Parthenon Publishing Group; 2000. p 80

42. Hofstaetter C, Dubeil M, Gudmundsson S. Two types of umbilical venous pulsations and outcomes of high-risk pregnancy. Early Hum Dev 2001;61:111.

43. Veille JC, Hanson R, Tatum K. Longitudinal quantitation of middle cerebral artery blood flow in normal human fetuses. Am J Obstet Gynecol 1993;169:1393.

44. Fong KW, Ohlsson A, Hannah ME. Prediction of perinatal outcome in fetuses suspected to have intrauterine growth restriction: Doppler US study of fetal cerebral, renal and umbilical arteries. Radiology 1999;213:681.

45. Sciscione AC, Hayes EJ. Uterine artery Doppler flow studies in obstetric practice. Am J Obstet Gynecol 2009; 201:121.

46. Lees C. Uterine artery Doppler: time to establish the ground rules. Ultrasound Obstet Gynecol 2000;16:607.

47. Alkazaleh F, Viero S, Simchen M. Ultrasound diagnosis of severe thrombotic placental damage in the second trimester: an observational study. Ultrasound Obstet Gynecol 2004;23:472.

48. Papageorghiou AT, Yu CK, Bindra R, et al. Multicenter screening for pre-eclampsia and fetal grpwth restriction by transvaginal uterine artery Doppler at 23 weeks gestation. Ultrasound Obstet Gynecol 2001;18:441.
49. Martin AM, Bindra R, Curcio R, et al. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11-14 weeks of gestation. Ultrasound Obstet Gynecol 2001;583.
50. Poon LC, Karagiannia G, Leal A, et al. Hypertensive disorders in pregnancy: screening by uterine artery Doppler imaging and blood pressure at 11-13 weeks. Ultrasound Obstet Gynecol 2009;34:497.
51. Melchiorre k, Leslie K, Perfuma F, et al. First-trimester uterine artery Doppler indices in the prediction of small-for-gestational age pregnancy and intrauterine growth restriction. Ultrasound Obstet Gynecol 2009;33:524.
52. Hollis B, Mavrides E, Campbell S, et al. Reproducibility and reliability of transabdominal uterine artery Doppler velocimetry between 10 and 14 weeks of gestation. Ultrasound Obstet Gynecol 2001;18:593.
53. Cruz-Martinez R, Figueras F. The role of Doppler and placental screening. Best Pract Res Clin Obstet Gynaecol 2009;23:845.
54. Dubiel M, Kozber H, Debniak B, et al. Fetal and placental power Doppler imaging in normal and high-risk pregnancy. Eur J Ultrasound 1999;9:223.
55. Kurjak A, Kupesic S, Kos M. Ultrasound of the placenta. Clin Obstet Gynecol 1996;39:519.
56. Benacerraf BR. The role of three-dimensional ultrasound in the evaluation of the fetus. In: Callen PW, ed. Ultrasonography in obstetrics and gynecology. 5th edition. Philadelphia: Saunders; 2000. p 831.
57. Chan LW, Leung TY, Sahota DS, et al. Volumetric (3D) imaging reduces inter- and intraobserver variation of fetal biometry measurements. Ultrasound Obstet Gynecol 2009;33:447.
58. Nardozza LM, Nowak PM, Araujo EJ, et al. Evaluation of placental volume at 7-10+6 weeks of pregnancy by 3D-Sonography. Placenta 2009;30:585.
59. Hafner E, Metzenbauer M, Hofinger D, et al. Comparison between three-dimensional placental volume at 12 weeks and uterine artery impedance/notching at 22 weeks in screening for pregnancy-induced hypertension, pre-eclampsia and fetal growth restriction in a low-risk population. Ultrasound Obstet Gynecol 2006;27:652.

60. Wegrzyn P, Faro C, Falcon O, et al. Placental volume measured by three-dimensional ultrasound at 11 to 13+6 weeks of gestation: relation to chromosomal defects. Ultrasound Obstet Gynecol 2005;26:28.
61. Campbell S. Is placental size a good predictor of obstetric complications? Ultrasound Obstet Gynecol 2009;34:247.
62. Pretorius DH, Nelson TR, Baergen RN, et al. Imaging of placental vasculature using three-dimensional ultrasound and color power Doppler: a preliminary study. Ultrasound Obstet Gynecol 1998;12:45.
63. Merce LT, Barco M, Alcazar JL, et al. Intervillous and uteroplacental circulation in normal early pregnancy loss assessed by 3-deimensional power Doppler angiography. Am J Obstet Gynecol 2009;315:e1.
64. Alcazar JL. Three-dimensional power Doppler devised vascular indices: what are we measuring and how are we doing it? Ultrasound Obstet Gynecol 2008;32:485.
65. Yu CH, Chang CH, Ko HC, et al. Assessment of placental fractional moving blood volume using quantitative three-dimensional power Doppler ultrasound. Ultrasound Obstet Gynecol 2003;29:19.
66. Lee W. Quantitative approaches for volume sonography during pregnancy. Ultrasound Clin 2007;2:203.
67. Merce LT, Barco MJ, Bau S. Reproducibility of the study of placental vascularisation by three-dimensional power Doppler. J Perinatal Med 2004;32:228.
68. Guiot C, Gaglioti P, Oberto M, et al. Is three-dimensional power Doppler ultrasound useful in the assessment of placental perfusion in normal and growth-restricted pregnancies? Ultrasound Obstet Gynecol 2008;31:171.
69. Noguchi J, Hata K, Tanaka H, et al. Placental Vascular Sonobiopsy using three-dimensional power Doppler ultrasound in normal and growth restricted fetuses. Placenta 2009;30:391.
70. Konje JC, Huppertz B, Bell SC, et al. 3-dimensional colour power angiography for staging human placental development. Lancet 2003;362:1199.
71. Rizzo G, Capponi A, Cavicchioni O, et al. Placental vascularisation measured by three-dimensional power Doppler ultrasound at 11 to 13=6 weeks' gestation in normal and aneuploid fetuses. Ultrasound Obstet Gynecol 2007;30:259.

72. Rizzo G, Capponi A, Pietrolucci ME, et al. First-trimester placental volume and vascularisation measured by 3-dimensional power Doppler sonography in pregnancies with low serum pregnancy-associated plasma protein A levels. J Ultrasound Med 2009;28:1615.
73. Rizzo G, Capponi A, Pietrolucci ME, et al. Effects of maternal cigarette smoking on placental volume an dvascularization by 3-dimensional power Doppler ultrasonography at 11+0 to 13+6 weeks of gestation. Am J Obstet Gynecol 2009;415.e1.

FIGURE LEGENDS

Figure 1. Echogenic cystic lesions (indicated by arrows).

Figure 2a. Normal umbilical artery blood flow velocity waveform demonstrating continuing forward flow during diastole, i.e. positive diastolic velocity. The uninterrupted tracing of the flow in the umbilical vein below the baseline demonstrates the lack of movement and breathing during acquisition of the waveform.

Figure 2b. Absent end-diastolic velocity in the umbilical artery, with notched venous flow in the umbilical vein.

Figure 2c. Reversed umbilical artery end-diastolic velocity.

Figure 3. Uterine artery blood flow velocity waveform with normal blood flow pattern. The sample gate is placed over the uterine artery, which crosses over the internal iliac vessels.

Figure 4. Power Doppler mapping of placenta at 28 weeks gestation.