Doppler Diagnosis

10

Andrea Dall'Asta, Tullio Ghi, and Tiziana Frusca

Introduction

Fetal growth restriction (FGR) is a disorder affecting the fetal development and an acknowledged risk factor for poor neonatal condition at birth and impaired neurodevelopment and diseases such as hypertension, metabolic syndrome, and obesity in the adulthood [1–6].

FGR may be secondary to a number of other conditions which include congenital anomalies or genetic syndromes, intrauterine infections, and drug or substance misuse; however, most cases of FGR occur as a consequence of placental insufficiency leading to fetal hypoxia [7]. Currently, it is not possible to reverse the progressive nature of FGR; therefore, timed delivery remains the only effective intervention [7, 8].

FGR is currently subclassified into two entities, namely, early FGR and late FGR, which differ in terms of clinical manifestations, association with hypertension, Doppler features and patterns of deterioration, and severity of the placental dysfunction [7, 9–11] other than for the gestational age at diagnosis, which is conventionally set at or below 32 weeks for early FGR and beyond 32 weeks for late-onset FGR. As a general rule, early FGR is defined by fetal smallness and abnormal umbilical artery (UA) pulsatility index (PI) and shows a 60–70% association with hypertensive disorder or the pregnancy; on the other hand, late FGR is most commonly characterized by normal UA Doppler and only rarely co-existent with gestational hypertension or preeclampsia [7, 9].

Fetal adaptation to chronic placental insufficiency and hypoxia leads to the preferential diversion of the fetal cardiac output in favor of the left ventricle, which is ultimately responsible for the redirection of the fetal blood flow to the brain and the heart [12–14]. When fetal hypoxia worsens, adaptive mechanisms result in abnormal arterial and venous flow [15].

A. Dall'Asta · T. Ghi · T. Frusca (✉)
Department of Medicine and Surgery, Obstetrics and Gynecology Unit, University of Parma, Parma, Italy

L. M. M. Nardozza et al. (eds.), *Fetal Growth Restriction*,
https://doi.org/10.1007/978-3-030-00051-6_10

Fetal smallness is not a synonym of FGR as fetuses whose estimated fetal weight is below the 10th percentile for the given gestation may be constitutionally small but healthy and not necessarily growth restricted. These are defined as small for gestational age (SGA) fetuses. On the other hand, available evidence has suggested that an estimated fetal weight >10th percentile does not necessarily denote normal fetal growth, particularly at late gestation [16–19]. Therefore, FGR should be referred to fetuses with pathological smallness caused by an underlying functional problem, and hence a definition including not only a biometric cutoff but also Doppler indices of feto-placental function is currently agreed in most fetal medicine units [9, 16, 20, 21].

As stated by the Society for Maternal and Fetal Medicine, antenatal detection of FGR can improve outcomes by allowing selection of appropriate fetal surveillance and optimizing the timing of delivery [3].

Doppler ultrasound has become an essential tool in maternal and fetal medicine and particularly in the diagnosis and the surveillance of the growth-restricted fetus. Abnormalities of placental and fetal blood flows are a prominent feature of FGR caused by underlying placental dysfunction. In this chapter, we synthesize and assess the evidence-based role of the umbilical artery (UA), middle cerebral artery (MCA), ductus venosus (DV), and fetal cardiac Doppler in the diagnosis and monitoring of non-anomalous singleton fetuses with FGR of suspected placental origin.

Pathophysiology of Fetal Growth Restriction of Placental Origin

FGR is a complex process of adaptation of the growing fetus to the restricted metabolic supply of the placenta, unable to negotiate the full requirements of fetal genetic potential [20]. Each metabolic pathway, organ, and function reshapes a strategy to cope with this deprived environment [14].

Doppler assessment of the FGR fetus relies on the evaluation of the fetal well-being by examining hypoxemia-triggered compensatory signs in the fetal circulation. Available data suggest that there are in fact various patterns of Doppler deterioration occurring in a truly sequential manner, meaning that an initial abnormal Doppler finding is followed by another and another over time [22, 23]. In 2008, Turan et al. described "mild placental dysfunction," "progressive placental dysfunction," and "severe early-onset placental dysfunction" as three different patterns of Doppler deterioration in FGR [23]. These presumed sequences and their potential to anticipate fetal deterioration form the basis for Doppler diagnosis and surveillance in FGR. According to the most common of them (i.e., "progressive placental dysfunction"), which occurred in almost 50% of all cases, placental insufficiency results in increased resistance of the feto-placental unit and in compensatory hemodynamic changes which include blood flow redistribution toward essential fetal organs (brain, heart, and adrenal glands) at the expense of other organ systems [14, 23, 24]. This phenomenon is attributed to a "brain sparing" adaptive response of the

cerebral blood vessels to the local effects of fetal hypoxemia with or without hypercapnia and is due to their autoregulatory capability to vasodilate in the event of reduced perfusion. As a result, decreased resistance to blood flow is found in the MCA.

These initial - "early" - changes are followed by elevations in venous Doppler indices. Abnormal DV Doppler waveforms either may be related to the vasodilatation of the isthmus of the DV, which is dependent on local mediators such as nitric oxide or prostaglandins [25], or may reflect an increased pressure in the right atrium as a result of the relative inability of the cardiac systolic function to overcome the increased peripheral resistance and the metabolic needs of the myocardium [26]. Therefore, DV flow abnormalities are regarded as "late" Doppler abnormalities which indicate that the adaptive mechanisms are overwhelmed and impending decompensation resulting in metabolic acidemia and cerebral hypoxia will shortly result in pathological fetal heart rate patterns and stillbirth [27–29].

It is important to note that the velocity of the Doppler deterioration as a sign of fetal adaptation to placental insufficiency varies depending on the gestational age [14]. This latter parameter is of paramount importance when considering the monitoring frequency, the administration of antenatal steroids and delivery [23].

Targets for Doppler Examination in the Fetus

Umbilical Artery

Umbilical artery Doppler allows the assessment of the resistance to blood perfusion of the feto-placental unit. Umbilical arteries are paired vessels carrying blood mostly pumped in the descending aorta by the right ventricle through the ductus arteriosus which obliterate after birth. The flow features of the umbilical artery can be assessed in a noninvasive qualitative manner using continuous or pulsed-wave Doppler ultrasound [30]. There is a significant difference in the impedance of the umbilical cord [31] – and therefore in the Doppler indices – at the fetal end, in the free loop, and at the placental end, being such impedance highest at the fetal end. Reference ranges for umbilical artery Doppler indices at these sites have been published [32, 33]. In clinical practice, Doppler waveforms of the umbilical artery can be obtained from any segment along the umbilical cord [3]; however, according to the International Guidelines, measurements of the Doppler indices of the umbilical artery should be made in a free cord loop in singletons [34]. Again, International Guidelines state that in multiple pregnancies and/or when comparing repeated measurements longitudinally, recordings from fixed sites, i.e., fetal end, placental end, or intra-abdominal portion, may be more reliable [34].

As a general rule for all Doppler measurements, the angle of correction is not necessary when measuring the PI; however, the angle of insonation should be <30 degrees, ideally as close to 0 degrees as possible. Additionally, Doppler indices should be obtained in the absence of fetal breathing and when the waveform is uniform [34].

Although there are other quantitative assessments of umbilical artery Doppler (e.g., resistance index) available, the systolic to diastolic (S/D) ratio and pulsatility index (PI) represent those most commonly used as they allow to manage most cases of suspected IUGR. Qualitatively, UA Doppler is assessed in terms of patterns of the end-diastolic flow (EDF), which is positive under normal circumstances; however, pathological increase of the vascular resistance caused by an obliteration of the placental vascular bed by over 50% progressively leads to absent EDF (AEDF) and reversed EDF (REDF) (Fig. 10.1).

Evaluation of placental function by UA Doppler has become a clinical standard to distinguish between SGA and FGR [7, 9, 16, 20]. Studies conducted on animal models and placental pathology have demonstrated that the obliteration of more than 50% of the placental vessels is required before absent or reversed end-diastolic velocities appear [35, 36]. On the other hand, small fetuses with normal UA Doppler are now considered as SGA or constitutionally small [16, 20, 21, 37, 38]. This may not be true for late-onset cases, in which a substantial proportion of cases with a normal UA have true FGR and are at risk of adverse perinatal outcome [39–42].

Umbilical artery Doppler is related to fetal acidemia [43] and is the only measure that provides both diagnostic and prognostic information for the management of FGR [44]. A Cochrane systematic review reported that the use of UA Doppler was associated with a reduction in perinatal deaths, inductions of labor, and cesarean deliveries [45]. According to the Royal College of Obstetricians and Gynecologists,

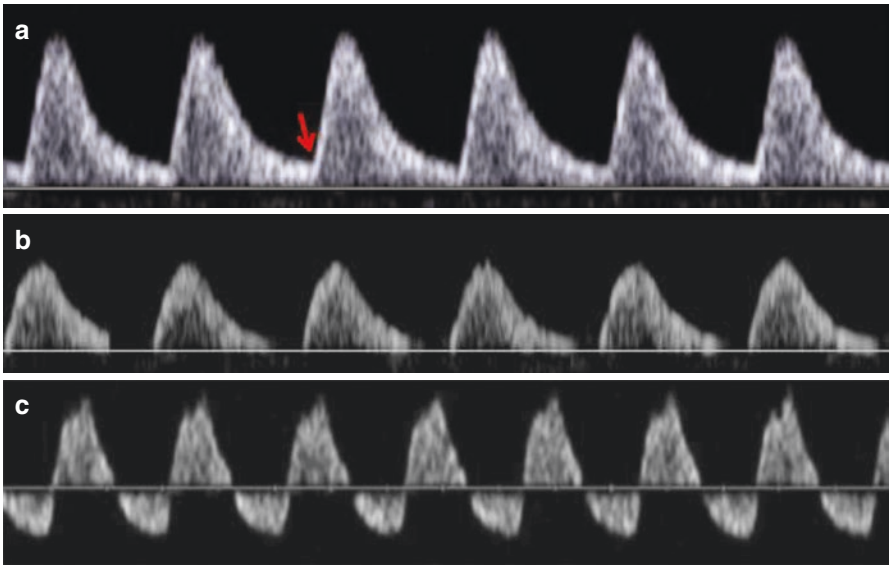

Fig. 10.1 Doppler assessment of the umbilical artery. (**a**) Umbilical artery Doppler showing high pulsatility index and positive end-diastolic flow (EDF, pointed by the arrow). (**b**) Umbilical artery Doppler with absent end-diastolic flow (AEDF). (**c**) Umbilical artery Doppler showing reverse end-diastolic flow (REDF)

the use of UA Doppler in a high-risk population reduces perinatal morbidity and mortality and should be the primary surveillance tool in the SGA fetus [46].

Umbilical artery flow identifies different degrees of impaired placental function. Absent end-diastolic flow (AEDF) and/or reversed end-diastolic flow (REDF), often considered a unique entity as absent/reversed end-diastolic flow (AREDF), indicate an important reduction of the function of the placenta. Longitudinal studies on high-risk pregnancies have shown that the transition from AEDF to REDF may be slow and gradual. AEDF can last for days and weeks before abnormal heart rate pattern or delivery [47], while REDF, which represents an extreme abnormality in waveform, has been related to a significant perinatal morbidity and mortality [47, 48] and to a higher incidence of long-term permanent neurologic damage compared to FGR fetuses with positive EDF [7, 49]. Absent or reversed EDF are mostly found in early FGR, and these patterns have been reported to be present on average 1 week before acute fetal deterioration. Up to 40% of fetuses with acidosis show this umbilical flow pattern [50]. Despite the fact that an association exists between the presence of REDF in the umbilical artery and adverse perinatal outcome (with a sensitivity and specificity of about 60%), it is not clear whether this association is confounded by prematurity [7]. Absent or reversed EDF in the umbilical artery is commonly associated with severe FGR with birthweight <3rd percentile for gestational age and oligohydramnios [3].

Middle Cerebral Artery

The middle cerebral arteries (MCAs) are two of the major branches of the circle of Willis and carry >80% of the cerebral circulation in the fetus [3, 34]. The MCAs are the most accessible cerebral vessels for ultrasound imaging in the fetus and can be sampled on an axial section of the brain including the thalami and the sphenoid bone wings [3, 34]. Color flow mapping should be used to identify the circle of Willis, and Doppler sampling should be performed at the proximal third of the MCA in order to obtain the best reproducibility [34, 51] (Fig. 10.2).

Under normal conditions, the cerebral circulation is characterized by high impedance and shows high PI with continuous forward flow present throughout the cardiac cycle [52]. A reduction of the PI of the MCA identifies a process of adaptation by vasodilatation which is known as the “brain sparing effect” and has been associated with adverse fetal and perinatal outcome and suboptimal neurodevelopment at 2 years of age not only in early severe FGR flagged by an abnormal umbilical arterial PI but also in late and term FGR fetuses with normal UA PI [42, 53–55]. Despite these associations, available data have shown that cerebral Doppler is not useful for the diagnosis and the management in early FGR [56]. As regards late FGR, a potential role of MCA Doppler for the differential diagnosis between SGA and late FGR has been demonstrated [57–60]. Nevertheless, MCA Doppler testing of suspected late FGR fetuses has not been evaluated in randomized trials, and to date no specific intervention has been shown to improve outcomes based on abnormal findings [3].

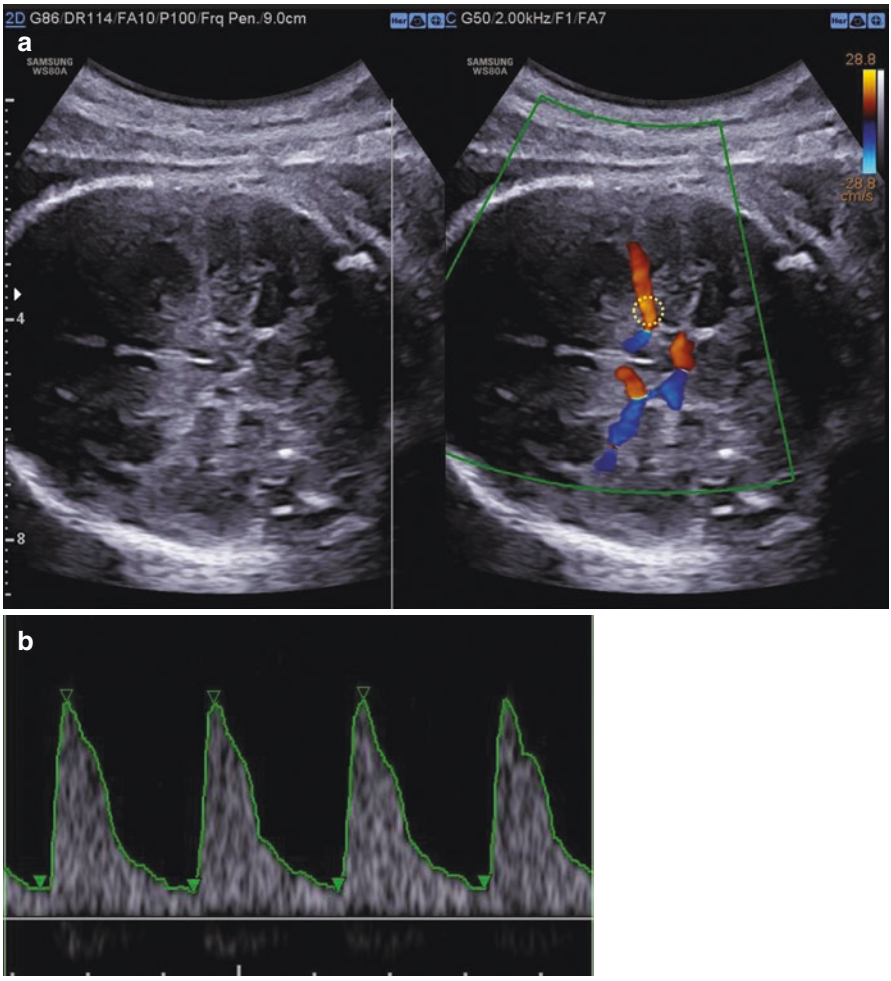

Fig. 10.2 Doppler assessment of the middle cerebral artery (MCA). (**a**) On gray-scale ultrasound, the MCA can be sampled on an axial section of the brain including the thalami and the sphenoid bone wings (left). Color flow mapping can identify the circle of Willis (right). Doppler sampling should be performed at the proximal third of the MCA (circled) in order to obtain the best reproducibility. (**b**) Normal MCA Doppler waveform showing low diastolic flow suggestive of high intracerebral resistance

MCA Doppler can be combined with the UA Doppler in the cerebroplacental ratio (CPR), also named as cerebro-umbilical (C-U) ratio; the umbilico-cerebral (U-C) ratio represents an inverted ratio of the same parameters and is suggested to be a better discriminator within the context of abnormal findings [56]. The cerebroplacental ratio (CPR) quantifies the redistribution of cardiac output by dividing the Doppler indices of the MCA with that of the UA. This ratio has been demonstrated to be more sensitive to hypoxia than its individual components on their own

and to better correlate with adverse outcome in SGA/FGR fetuses [61, 62] but also in apparently normally grown fetuses close to term [17–19, 63, 64]. Recent data suggest that reduced CPR together with uterine artery (UtA) Doppler represents the parameters which allow a differential diagnosis between SGA and late FGR fetuses with normal UA Doppler [42, 57–60].

Ongoing and planned trials are likely to provide further insights into the actual role of the cerebral Doppler – on its own or paired with UA within the context of the CPR or the U-C ratio – in the management of late FGR, particularly clarifying whether anticipating delivery based on abnormal CPR findings may improve the neurodevelopmental outcome in the infanthood (http://www.truffle-study.org/research/).

Ductus Venosus

The ductus venosus (DV) is one of the three arterial-to-venous shunts existing in fetal life and is responsible for the diversion of well-oxygenated blood from the umbilical vein to the inferior vena cava and the right atrium, thus bypassing the intrahepatic vascular system. Anatomically the DV consists in a narrow inlet whose diameter may vary depending upon local mediators such as nitric oxide and prostaglandins, thus determining a variation in the percentage of blood shunted through the DV. Under normal circumstances, the DV diverts a percentage of venous blood ranging between 30% at midgestation and 15% at term pregnancy; however, FGR is associated with increased ductus venosus (DV) shunting. Among the precordial vessels available for Doppler assessment in FGR fetuses (the others are represented by the inferior vena cava and the umbilical vein), the DV represents the most important one both for prognostic and diagnostic purposes in early FGR fetuses as demonstrated by the results of the TRUFFLE study [9, 65–69].

The DV can be visualized both with gray-scale ultrasound and with color or power Doppler either in a midsagittal or a transverse section of the fetal abdomen as a narrow vessel arising from the umbilical vein and a vertical oblique course to the inferior vena cava just below the diaphragm. Color flow mapping at its isthmic portion demonstrates the high velocity with "aliasing" at the narrow entrance of the DV and indicates the standard sampling site for Doppler measurements [3, 34].

Continuous forward flow throughout the cardiac cycle is seen in the normal fetus [3, 34, 72]. The correct sampling of the DV most commonly determines a biphasic waveform constituted by the "S" component, which represents the first increase in venous forward velocities as a result of the ventricular systole; the "D" component, which represents the second peak of velocity occurring during the passive ventricular filling of the ventricular diastole of the cardiac cycle; and finally the "A" component representing the late ventricular filling dependent on the atrial contraction which occurs in the late diastole of the cardiac cycle [3, 34] (Fig. 10.3). Rarely, non-pulsating recordings may be seen in healthy fetuses [34]. The DV Doppler can be assessed quantitatively by means of the DV PI, which is low under normal circumstances and increases as a result of the vasodilatation of the isthmus of the DV

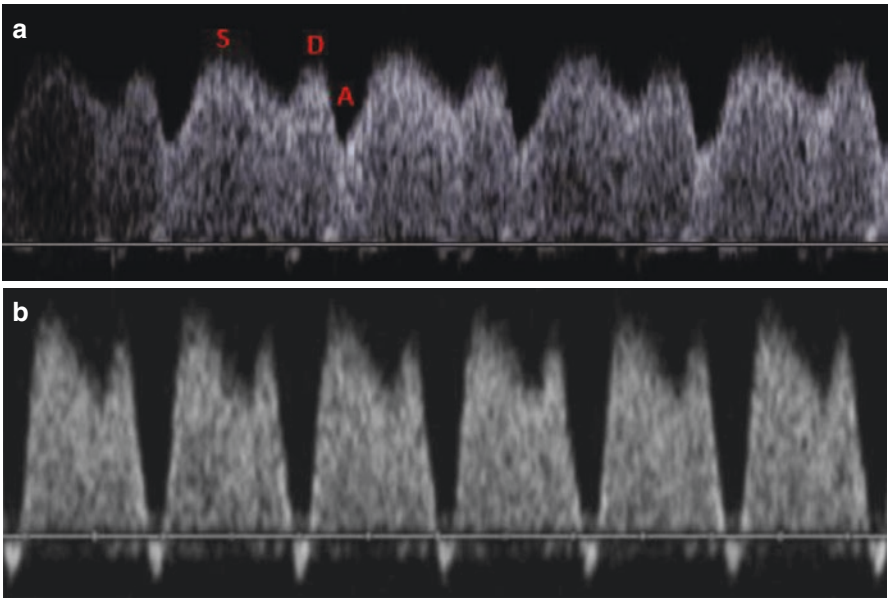

Fig. 10.3 Doppler assessment of the ductus venosus (DV). (**a**) DV showing biphasic waveform characterized by an "S" component, which corresponds to the ventricular systole; a "D" component, which represents the second peak of velocity occurring during the passive ventricular filling of the ventricular diastole of the cardiac cycle; and a late diastole "A" component corresponding to the late ventricular filling dependent on the atrial contraction. In (**b**) reversed "A-" wave at 30 weeks

and of cardiac dysfunction both in terms of increased preload and afterload resistance. Qualitative evaluation of the DV Doppler includes the assessment of the "A" component of the waveform which in the case of decreased, absent, or reversed flow represents myocardial impairment and increased ventricular end-diastolic pressure resulting from an increase in right ventricular afterload. This abnormal waveform in the ductus venosus has been documented in FGR fetuses and linked to increased neonatal mortality rate [71, 72]. A semiquantitative evaluation of the DV Doppler has also been suggested; however, there is no evidence-based data supporting its usefulness for the management of early or late FGR fetuses [73].

There is no available data on DV Doppler in late FGR fetuses. As regards early FGR, evidence from the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE study) has shown the crucial role of DV Doppler for the management of preterm growth-restricted fetuses before 32 weeks of gestation [9, 65–69]. In contrast to the alterations of the UA and the MCA Doppler, which represent early signs of impaired placental function, DV flow waveforms become abnormal only in advanced stages of fetal compromise [27, 74, 75]. It has been shown that the PI of the DV is related to acidemia at cordocentesis [28] and low pH at birth, being the DV PI inversely related to the UA pH at birth [76]. Absence or reversal of the DV "A-wave" represent signs of late adaptation to chronic hypoxia and impending decompensation similar to the REDF in the umbilical artery. In 2001, Hecher et al.

described the time sequence of changes in fetal monitoring variables in early FGR and demonstrated that DV Doppler and short-term variation (STV) of fetal heart rate, which can be measured by means of computerized cardiotocography (cCTG), are important indicators for the optimal timing of delivery before 32 weeks of gestation [27]. More recent data have shown high specificity of the absence or reversal of the DV A-wave for the prediction of low UA pH at birth [24] and significant association with perinatal death regardless of the gestational age at delivery [76]. These findings were confirmed by the results of the TRUFFLE study [9, 65–69].

Cardiac Function in Fetal Growth Restriction: Rationale for the Doppler Investigation of the Fetal Heart

During fetal life, the right and the left ventricles work in parallel and have independent outputs, with a right ventricular dominance [13]. As a result of the "early" changes described by the most common pattern of Doppler deterioration occurring in FGR fetuses, which we have detailed, increased umbilical resistance leads to an increase in the right ventricular afterload. Conversely, the onset of the "brain sparing" effect leads to a reduction in left ventricular afterload leading to a preferential shift of the cardiac output to the left ventricle and hence to the brain and to the coronary vessels arising from the ascending aorta.

Other than the "brain sparing effect," additional evidence has shown an increase in the coronary flow in FGR fetuses which was called the "heart-sparing effect" [77]. Such increased blood supply, together with the intrinsic mechanisms responsible for the autoregulation of the coronary flow - which are dependent upon the relative concentrations of oxygen and carbon dioxide, hydrogen ions, potassium, lactate, adenosine, and other metabolites and are activated in cases of chronic hypoxia such as FGR [77] - seem to explain why the coronary vessels can be imaged at earlier gestation in FGR fetuses compared to normally grown ones [78]. Nevertheless, no quantitative comparisons of the coronary flow between FGR and normal fetuses have been undertaken, and no prospective evaluation of the coronary flow in FGR and its correlation with Doppler and infant outcomes has been performed.

Following cerebral – and cardiac – redistribution, no further blood shifting occurs; however, a longitudinal reduction in the cardiac output occurs as a result of worsening hypoxia which leads to a progressive increase both of the left and the right ventricular afterload as well as an increased venous return from the superior vena cava secondary to the "brain sparing" process. These ultimately increase the filling pressure of the right atrium and lead to the Doppler abnormalities of the DV [25, 26]. Such scenario of progressive systolic and diastolic overload in fact represents a continuum of abnormal filling and emptying pressures which need to be overcome by the fetal heart of the growth-restricted fetus, and it seems reasonable to hypothesize that different steps of cardiac overload are responsible for the three different phenotypes of morphological remodeling of the fetal heart in FGR which have been very recently described [79].

Based on these assumptions, the analysis of fetal cardiac function in FGR might provide important information on the hemodynamic status and the cardiovascular adaptation of the fetus and help in the differential diagnosis between FGR and SGA [80]. A broad range of US techniques have been applied for evaluation of fetal cardiac function, and several fetal myocardial functional parameters have been evaluated and suggested as potentially useful within the context of fetal smallness. Nevertheless, their use in early and late FGR is not supported by any clinical evidence, and today none of them leads to changes in the perinatal management compared to the "conventional" assessment of peripheral arteries and the venous system [81].

Doppler of the Aortic Isthmus

The aortic isthmus (AoI) is the segment of the aorta located between the origin of the left subclavian artery and the connection of the ductus arteriosus to the descending aorta. The AoI is the only arterial connection between the right ventricle, which supplies mainly the systemic and placental circulations, and the left ventricle, which supplies essentially the cerebral vascular network [8, 82]; therefore, its blood flow pattern reflects the balance between ventricular outputs and the relative difference in vascular impedance in either vascular system. The rationale for the Doppler assessment of the AoI is represented by the fact that during diastole, when the aortic and pulmonary valves are closed, the direction of blood flow in the AoI solely reflects the differences between the downstream impedances of the right (mainly placental vascular resistance) and left (mainly cerebral vascular resistance) ventricles [8].

The AoI can be visualized using gray-scale (B-mode) ultrasound either on the longitudinal view of the aortic arch or on the cross-sectional view of the upper thorax at the level of the three-vessel/trachea views [83, 84] (Fig. 10.4). Once the vascular segment is identified, pulsed-wave Doppler velocimetry can be performed after the adjustment of the size of the sample gate according to the size of the AoI, which is dependent upon gestational age [85].

Antenatal Doppler study of the AoI includes the quantitative assessment of the peak systolic (PSV), end-diastolic (EDV), and time-averaged maximum (TAMXV) velocities through the AoI itself; the semiquantitative evaluation of the PI and/or of the isthmic flow index (IFI), which was devised in order to include the amount and direction of blood flow and is computed as (PSV + EDV)/PSV [86]; and the qualitative description of antegrade or retrograde flow [87–90]. Under normal conditions, AoI velocity waveforms show antegrade flow during systole and diastole because the placental resistances are lower than those present in the fetal upper body. The normal waveform of the AoI is characterized by a quick systolic upstroke (short acceleration time) with mean peak systolic velocities ranging between 30 and 100 cm/s followed by a more gradual deceleration of the velocity and a narrow incisura at the end of systole, which is usually absent before 20 weeks of gestation. Retrograde flow during diastole or net blood flow

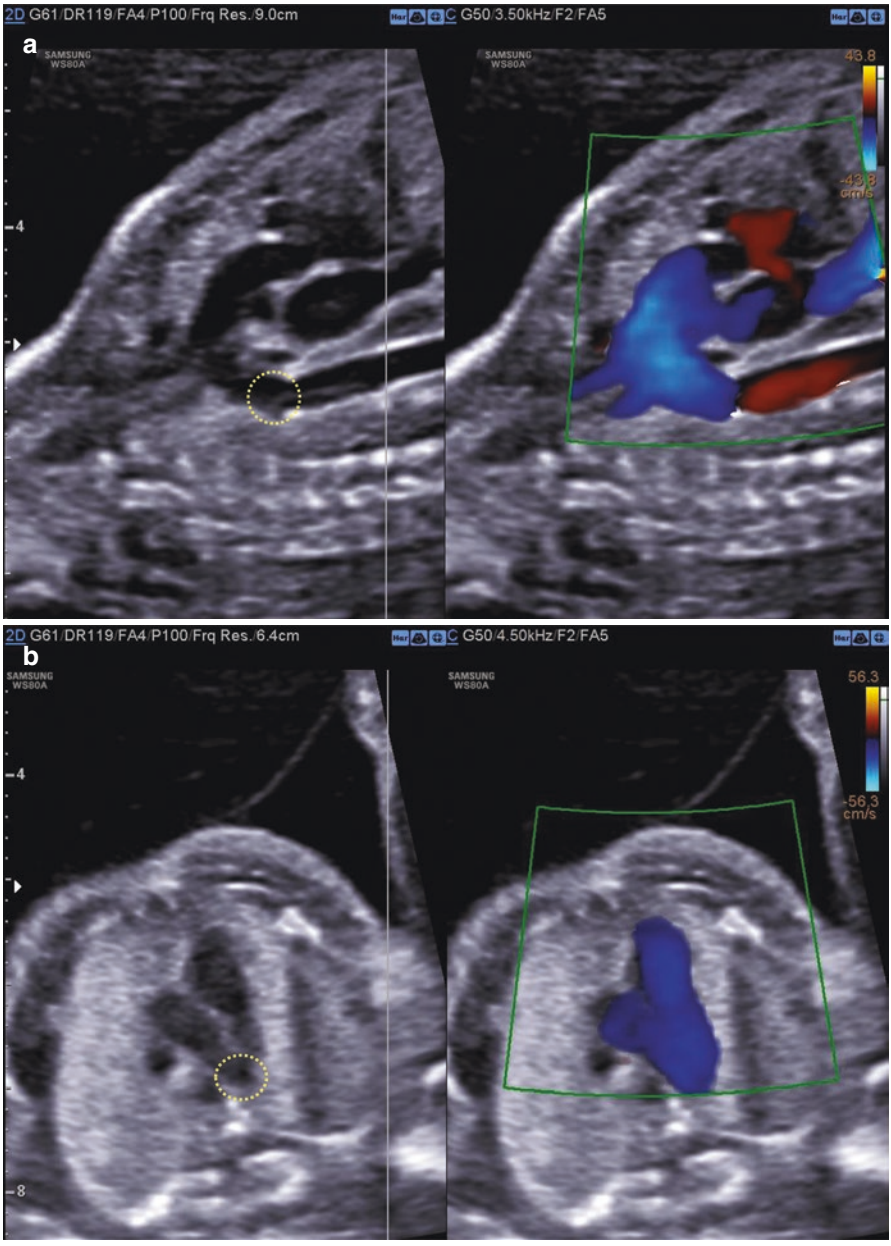

Fig. 10.4 Gray-scale (B-mode) and color Doppler imaging of the aortic isthmus (circled) on the longitudinal view of the aortic arch (**a**) and on the cross-sectional view of the upper thorax at the level of the three-vessel/trachea view (**b**)

reversal is always abnormal and can be observed in the case of chronic placental insufficiency associated with increased peripheral resistance and vasodilatation of the cerebral circulation.

As before mentioned, in the absence of randomized or prospective data, there is no role for the Doppler of the AoI for the diagnosis and the monitoring of early or late FGR. Even though from a pathophysiology point of view it is reasonable to hypothesize a relationship between the Doppler indices through the AoI and UA and DV Doppler features as a consequence of the changes in peripheral and cerebral resistances, controversial results have emerged from the studies evaluating such correlations [82, 89, 91, 92]. Regarding postnatal assessment, available data suggest an association between adverse perinatal outcome and neurodevelopmental deficits and abnormal Doppler recordings in the AoI in terms of predominant reversed diastolic blood flow and IFI <0.70 with net reversed diastolic flow through the AoI [82], even though this relationship has shown a low sensitivity [93].

E/A Ratio

Doppler ultrasound allows the evaluation of the diastolic component of the fetal cardiac cycle and has been suggested in the assessment of FGR fetuses based on the assumption that increased afterload and chronic hypoxia ultimately lead to increased preload and impairment of the diastolic function in the case of advanced fetal compromise.

The E/A ratio is one of the parameters suggested for the evaluation of the cardiac diastolic function in the fetus. It is defined by the ratio between the E (early or passive) velocity, which is measured during the early passive ventricular filling and is related to the process of myocardial relaxation and negative pressure applied by the ventricles, and the A (atrial, active, or late) velocity, which represents the active ventricular filling during atrial contraction.

The E/A ratio can be measured by evaluating the transmitral or the transtricuspidal waveforms obtained with pulsed-wave Doppler and continuous wave Doppler. Recordings are obtained at the level of the four-chamber view of the fetal heart, in which the Doppler sample gate is located just below either atrioventricular valve, where a biphasic waveform is usually displayed in the normal fetus (Fig. 10.5). It is recommended to keep the Doppler sample gate between 2 and 3 mm in order to avoid contamination with artifacts from wall motion and from the outflow tracts. The biphasic nature of the E/A waveform is lost if the Doppler gate is located too deep within the ventricle. There are some mild differences between both sides of the heart which are constantly observed in all normal pregnancies as the right E and A waveforms have higher velocities and their ratio is slightly lower than that of the left side [94]. Recordings must be performed in the absence of fetal breathing and without maternal and fetal movements.

Uncomplicated pregnancies show a progressive increase of the E/A ratio across gestation [95]. Conversely, in SGA fetuses the E/A ratio does not increase, and its values are significantly lower than in normal fetuses. A reduced E/A ratio indicates

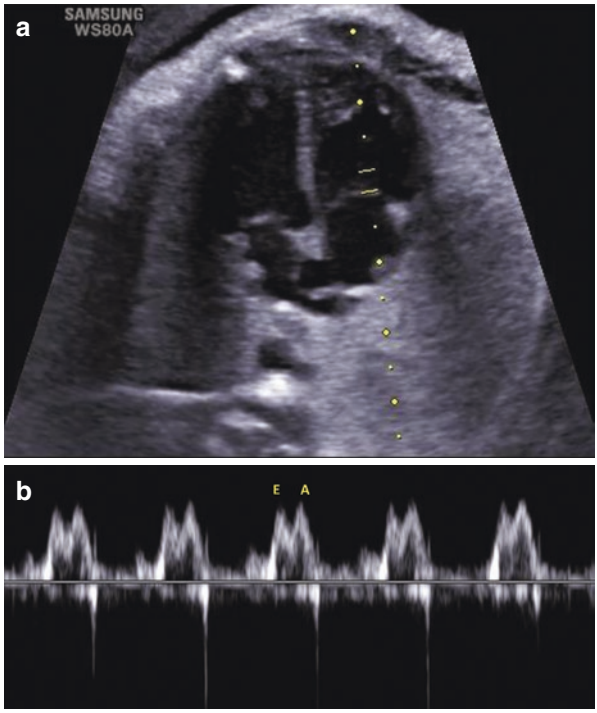

Fig. 10.5 Pulsed-wave Doppler assessment of the E/A ratio at the level of the tricuspid valve. (**a**) Four-chamber view of the fetal heart, in which the Doppler sample gate is located just below the tricuspid valve. (**b**) Biphasic waveform which is displayed in the normal fetus, representing the passive ventricular filling in early diastole (E component) and the active ventricular filling ("A," atrial, active, or late component) which occurs during atrial contraction

that the process of ventricular filling depends more on the atrial contraction than on the negative pressure during relaxation. The two main conditions affecting the ratios - i.e. chronic hypoxia and cardiac overload - might affect the relaxation process, thus reducing the E/A ratios. On a small cohort of FGR fetuses, Figueras et al. reported lower E/A ratios in both atrioventricular valves compared to normally grown fetuses with early deterioration of the right E/A ratio [96]. More recent data suggested that there is a "continuum" in the deterioration of the E/A ratio, with monophasic diastolic waves associated with abnormalities in all prenatal cardiac parameters in fetuses with severe FGR who eventually died or developed neurological damage [97]. However, this observation was not confirmed in prospective studies; therefore, to date there is no clinical role for the E/A ratio in the diagnosis and management of FGR fetuses.

Myocardial Performance Index

The myocardial performance index (MPI) – also named as Tei index – is a parameter that reflects both systolic and diastolic functions as the sum of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by the ejection time (EJT): (ICT + IRT)/EJT [98].

The MPI can be measured either with pulsed-wave (PW) or tissue Doppler technique. From a cross-sectional view of the fetal thorax, recordings must be performed from the four-chamber view of the heart with an apical projection and an angle of insonation below 20°. Using PW Doppler, a sample gate of about 3–4 mm needs to be placed to include both the lateral wall of the ascending aorta and the mitral valve where the clicks corresponding to the opening and closing of the two valves can be clearly visualized [99]. This allows the sampling of the E/A and of the aortic ejection waveforms. The isovolumetric contraction time (ICT), ejection time (ET), and isovolumetric relaxation time (IRT) can be calculated using the clicks of the mitral and aortic valves as landmarks as shown in Fig. 10.6. Briefly, the isovolumetric contraction time (ICT, ms) represents the time from closure of the mitral valve to the opening of the aortic valve; the isovolumetric relaxation time (IRT, ms) represents the time from closure of the aortic valve to the opening of mitral valve; the ejection time (ET, ms) or systolic time interval represents the time from opening of the aortic valve to its closure. Using Tissue Doppler technique, the MPI can be measured by placing a 2–3 mm pulsed-wave gate in the basal part of the left and right ventricular free walls (at the level of the mitral and tricuspid valve annulus, respectively). Peak annular velocities need to be measured during early diastole (E), atrial contraction (A), and systole (S) and provide the same waveform landmarks used with PW

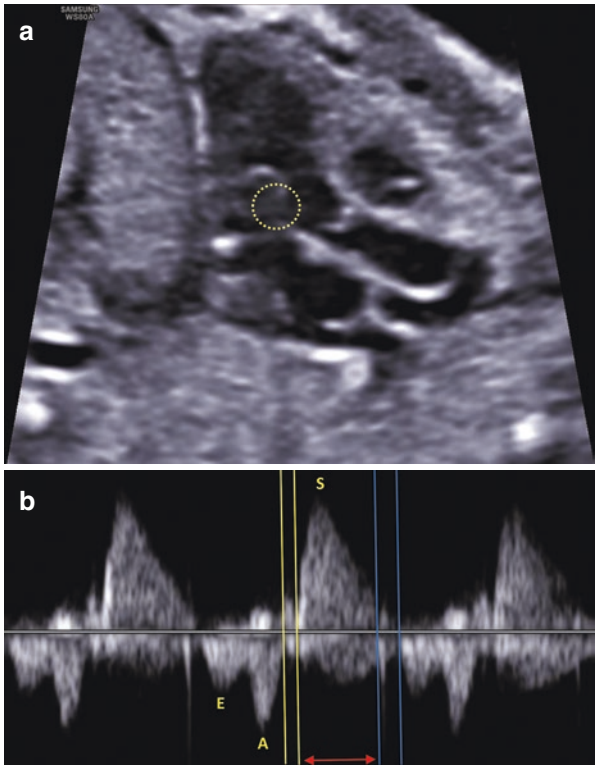

Fig. 10.6 Pulsed-wave Doppler assessment of the myocardial performance index (MPI). (**a**) Recordings must be performed from the four-chamber view of the heart with an apical projection of the heart; the sample gate needs to be placed to include both the lateral wall of the ascending aorta in order to sample the E/A and the aortic ejection (S) waveforms (circled in yellow). (**b**) The isovolumetric contraction time (ICT) (comprised between the yellow lines), ejection time (ET) (red arrow), and isovolumetric relaxation time (IRT) (comprised between the blue lines) are calculated using the clicks of the mitral and aortic valves as landmarks

Doppler. Using either technique, measurements of all the components need to be obtained from the same cardiac cycle.

A significantly higher MPI in FGR compared to appropriately grown fetuses was demonstrated by Hassan et al. [100]. Raised MPI is seen in the early stages of cardiac adaptation to FGR, presumably secondary to hypoxia, and remains elevated throughout the different stages of deterioration in FGR deterioration, similarly to the AoI and DV PI. Available evidence from longitudinal studies has demonstrated that an abnormal increase of the MPI can be detected prior to the UA Doppler becoming abnormal [93] and showing absent or reversed end-diastolic blood flow [101].

The finding of increased MPI has been suggested as a potential discriminator between FGR and SGA in fetuses showing reduced biometry but normal Doppler [102, 103]. Hernandez-Andrade et al. suggested that the combination of these parameters might be useful for defining the monitoring strategy and the optimal time of delivery [104]; however, there is no evidence-based strategy including the MPI among the parameters for the monitoring of FGR fetuses.

Maternal Doppler and Fetal Growth Restriction

Doppler Examination of the Uterine Arteries

Uterine arteries are paired vessels responsible for the blood supply of the uterus in the nonpregnant state and of the uterus and the feto-placental unit during pregnancy. These vessels, whose impedance is physiologically elevated with low diastolic flow in the nonpregnant state, undergo major anatomic and functional adaptation during pregnancy as a result of the trophoblastic invasion of the maternal spiral arterioles – named as "remodeling" – in the first half of gestation. Under normal conditions, a sharp decrease in uterine artery (UtA) impedance to flow occurs as placental implantation progresses, which is reflected by the increased flow in diastole and disappearance of the notch present in the nonpregnant UtA [105, 106]. The "remodeling" of the spiral arteries is usually completed by 24 weeks, and indeed less prominent changes in UtA Doppler occur in the third trimester.

While absolute velocities have been of little or no clinical importance, semiquantitative (PI) and qualitative assessment of the velocity waveforms is commonly evaluated. Qualitatively, the persistence of the protodiastolic "notch" of the a uterine artery Doppler waveform in the late second and third trimesters has been used to identify abnormal uterine circulation in pregnancy (Fig. 10.7) [71, 107]. Caution, however, should be used against relying solely on the presence of a notch in the uterine artery Doppler waveform to define an abnormal uterine circulation as clinicians should consider also the semiquantitative measurement of the PI, with a value >95th percentile for gestational age considered abnormal [108].

Different techniques for the assessment of the UtA Doppler have been described for the first vs the second and third trimesters [34]; however, FGR of placental origin manifests as early as the second trimester. From this gestation, UtA can be

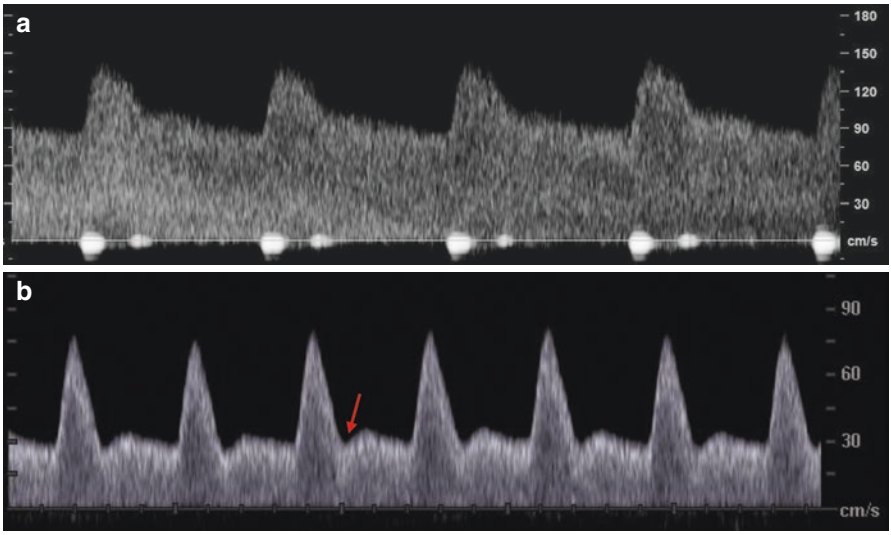

Fig. 10.7 Doppler assessment of the uterine artery Doppler. (**a**) Normal waveform showing high diastolic flow and absent notch. (**b**) Abnormal waveform showing low diastolic flow with notching (arrow)

visualized either transabdominally or transvaginally. Different reference ranges have been published for each approach [109, 110]; however, given its high accuracy and reproducibility, the transabdominal approach is performed unless a transvaginal scan is deemed as necessary for other reasons [111]. Transabdominally, the probe needs to be placed longitudinally in the lower lateral quadrant of the abdomen, angled medially. The UtA can be demonstrated by color Doppler velocimetry as it originates from the anterior division of the hypogastric artery and just before it enters the uterus at the uterine-cervical junction. Pulsed Doppler velocimetry of the uterine artery should be obtained 1 cm downstream from the crossover point between the UtA and the hypogastric artery and before the UtA divides into the uterine and cervical branches [3, 34]. In a small proportion of cases the uterine artery branches before the intersection of the external iliac artery and the sample volume should be placed on the artery just before the bifurcation of the uterine artery.

Abnormal UtA Doppler best identifies the severe early-onset complications of impaired placentation. The systematic review and meta-analysis conducted by Cnossen et al. in 2008 further demonstrated the role of UtA Doppler ultrasonography as a predictor of FGR, particularly when performed in the second trimester and particularly for early FGR [107]. It is important to note that there is a continuum of Doppler abnormality of the UtA ranging from mild increase of the PI above the 95th percentile for the gestation to severe abnormality of the PI with bilateral protodiastolic notching, which seems to impact on the likelihood of complications during the index pregnancy.

There is also evidence that a high impedance to flow in the uterine arteries during the third trimester is associated with an increased risk of adverse perinatal events

regardless of fetal size in pregnancies with normal UA Doppler [113–115], thus supporting the concept that abnormally raised UtA PI in the third trimester may help in discriminating between SGA and late FGR, as discussed later in this chapter [57, 58, 116].

Maternal Hemodynamics and Fetal Growth Restriction

Placental perfusion and function are among the determinants of the intrauterine growth of the fetus, the remaining being represented by the intrinsic growth potential of the fetus. In the last decade, great interest has arisen toward maternal cardiovascular function in order to understand how placental perfusion is sustained under normal circumstances [117, 118] and which are the features of suboptimal hemodynamic adaptation to the pregnancy. This research field, which traditionally relies on dedicated cardiology evaluation by means of echocardiography, has been further implemented with the advent of novel semiautomated devices such as the ultrasound cardiac output monitor (USCOM) [119–121], which allows the measurements of the cardiac systolic parameters by means of pulsed-wave Doppler.

Normal pregnancy is characterized by a longitudinal increase of the cardiac output (CO) which is coupled with a reduction of the systemic vascular resistance (SVR). According to the historical pathophysiology theory, hypertensive disorders of the pregnancy (HDP) are secondary to impaired placental function as a result of suboptimal remodeling of the spiral arteries, which precludes the reduction of the resistance of the uterine circulation, which is characterized by high resistance in the nonpregnant state and in early pregnancy, into a low resistance circulation. Such abnormality of the implantation process can also explain FGR within the context of HDP [122, 123]. Nevertheless, available evidence has shown that placental pathology does not invariably demonstrate the obliteration of the placental villi in preeclampsia, particularly at late gestation [124], and fetal size is not invariably small in preeclampsia [125].

As early as 2008, Valensise et al., within a cohort of women identified at risk of HDP based on abnormal midtrimester uterine artery Doppler, demonstrated the existence of two different hemodynamic patterns in the context of preeclampsia, the former, which was eventually defined as “early” preeclampsia, being associated with reduced CO, increased systemic vascular resistance SVR, and small fetal size, and the latter, named as “late preeclampsia,” showing the opposite hemodynamic pattern and associated with normal size or large fetuses [126]. This hypothesis of the existence of two phenotypes of preeclampsia associated with specular incidence of FGR and large for gestational age has been further supported Verlohren et al. [127].

Other authors have suggested that placenta should not be considered in isolation without regard to the fact that its function is dependent on the perfusion by the maternal circulation [128]. Low CO and high SVR represent the hemodynamic surrogates of abnormal cardiovascular adaptation to the pregnancy with placental underperfusion, and it is not surprising that both of them have been related to FGR

[129]. Very recently Ferrazzi et al. suggested that the presence or the absence of FGR may represent a better discriminator than gestational age at onset of the two different phenotypes of preeclampsia, the "early preeclampsia" one being associated with FGR and the "late preeclampsia" one being related with normal or increased fetal size [130]. It is important to point out that all the above represent research findings with no acknowledged role in the diagnosis or in the management of FGR; however, these data suggest that the assessment of the maternal cardiovascular function during pregnancy may become a reliable tool for a pathophysiology approach for the diagnosis and the treatment of conditions of abnormal placental function such as HDP and FGR.

How to Diagnose Early and Late Fetal Growth Restriction

A prerequisite for the correct diagnosis of FGR is accurate dating of the pregnancy, ideally in the first trimester [131]. Furthermore, based on the assumption that fetal size is influenced by ethnicity, sex, parity, maternal size, and genetic factors, antenatal growth charts customized for maternal characteristics have been developed in order to improve the detection of abnormalities of the fetal growth [132–136]. Such approach has recently been challenged by the results from the Intergrowth study, which has shown that fetal growth patterns do not seem to be influenced by ethnic factors in healthy pregnancies under optimal environmental conditions [137]. Additionally, the quantitative comparison of the published fetal growth charts shows minimal differences which are unlikely to be of clinical impact. There is currently no evidence that routine use of customized growth charts can improve the detection and clinical outcomes in early FGR, in which the underlying severe placental dysfunction is almost invariably associated with fetal smallness and Doppler abnormalities. On the other hand, some authors suggest that a customized approach may improve the detection of third trimester SGA fetuses with normal UA Doppler but at risk of perinatal complications, although this is not widely agreed and does not represent the standard of care [132, 133, 135].

Multiple definitions of FGR have been suggested over the decades by national and international societies which have been summarized in Table 10.1 [20]. As it can be noted, most of them do not distinguish between early and late FGR; however, current thinking on the natural history of FGR differentiates these two types of FGR in terms of biochemical, histological, and clinical features and not only in terms of gestational age at diagnosis, which is conventionally set at or below 32 weeks for early FGR and beyond 32 weeks for late-onset FGR.

An EFW <10th percentile is acknowledged as the best clinical surrogate of FGR [138]. However, it is important to point out that EFW below the 10th centile for the gestation, albeit being diagnostic for fetal smallness, does not necessarily implies FGR, particularly when detected beyond 32 weeks [20, 21]. According to the criteria recently agreed through a Delphi procedure by a panel of International Fetal Medicine experts, early FGR is defined either by severe fetal smallness (EFW or AC <3rd centile) or "late" UA Doppler abnormalities (AEDF, REDF) taken in isolation or by a combination of fetal smallness and UA PI above the 95th percentile for

Table 10.1 Fetal growth restriction definition in recent literature

Institution/author	FGR definition
Baschat et al. 2007	Combination of small fetal abdominal circumference (AC) with elevated umbilical artery Doppler blood flow resistance
Cochrane 2013	Failure to reach the growth potential
DIGITAT 2012	Estimated fetal weight or an abdominal circumference below the 10th centile for gestational age
ACOG 2013	Fetuses with an estimated fetal weight that is less than the 10th percentile for gestational age
RCOG 2013	Small for gestational age (SGA) refers to an infant born with a birthweight less than the 10th centile Fetal growth restriction (FGR) is not synonymous with SGA
SOGC 2013	Intrauterine growth restriction refers to a fetus with an estimated fetal weight <10th percentile on ultrasound that, because of a pathologic process, has not attained its biologically determined growth potential
PORTO 2013	EFW <5th percentile and umbilical artery PI >95th percentile
TRUFFLE 2013	AC <10th percentile and umbilical artery PI >95th percentile

Reproduced from Dall'Asta et al. [20]
EFW estimated fetal weight, *PI* pulsatility index

gestation or UtA PI above the 95th percentile for the gestation detected before 32 weeks [16]. Such definition – which includes not only a biometric cut off but also Doppler indices of feto-placental function and is currently endorsed by most Fetal Medicine specialists [9, 16, 142] – summarizes the current understanding on the pathogenesis of FGR, which consists in pathological smallness caused by an underlying functional problem.

Late FGR is more common but less severe with absent or mild placental abnormalities. UA Doppler may be normal and cannot be relied for its diagnosis, however late growth restricted fetuses may react with decreased MCA impedance in response to hypoxemia. The recently agreed diagnostic criteria for late FGR include either severe fetal smallness detected beyond 32 weeks (EFW or AC <3rd percentile for gestational age) or two out of three among (1) EFW or AC <10th percentile for gestation, (2) longitudinal reduction of the fetal growth in terms of EFW or AC reduced by over two quartiles compared to those measured in the second trimester, and (3) CPR below the 5th percentile for the gestation or UA PI above the 95th percentile for gestational age [16]. As before mentioned, it is uncertain whether such growth assessment should be performed using population-based [136], customized [132–135], or universal fetal growth charts [137]. Additionally, there is great uncertainty as regards which is the optimal screening strategy – either universal or selective or contingent assessment of the fetal growth [140–142] – and which is the optimal gestational time frame for the evaluation of the fetal growth at late gestation. Recently published randomized data have shown that the universal screening of the fetal growth can identify up to three times higher number of late FGR fetuses [141] and that screening at 36 weeks performs better than the screening at 32 weeks [143]. Finally, it is important to note that beyond 32 weeks, an EFW or an AC >10th percentile for the gestational age does not necessarily exclude late FGR. Several groups have demonstrated that even apparently

normally grown third trimester fetuses with reduced CPR are at increased risk of perinatal complications, thus suggesting that a reduced CPR per se may represent a Doppler sign of misdiagnosed placental insufficiency and failure to reach the growth potential [17–19, 63, 144].

Doppler Ultrasound and Management of Early Fetal Growth Restriction

The Trial Randomizing Umbilical and Fetal Flow in Europe (TRUFFLE) is the only randomized controlled trial which has evaluated and demonstrated the effectiveness of a standardized monitoring and delivery protocol for early FGR fetuses.

Based on the assumption that cCTG and DV represent those parameters which safely allow to delay delivery before fetal compromise occurs, the TRUFFLE protocol has demonstrated that the 2-year neurodevelopmental outcome of surviving early FGR fetuses is significantly better among those delivered based on late DV changes [9, 65–67, 69], even though no differences were noted among the three randomization arms of the TRUFFLE as regards the primary outcome – i.e., survival without neurodevelopmental impairment. DV has been demonstrated to be the most important Doppler parameter in the prediction of the short-term risk of intrauterine death (IUD) in early FGR [44]. Absent or reversed DV A-wave has been associated with increased risk of IUD (40–70%), and late-stage acidemia independently forms gestational age at delivery and shortly precedes spontaneous decelerations at CTG monitoring. DV PI above the 95th centile has also been related to a high risk of adverse outcome, although at lesser extent than that of reversed or absent DV A-wave [65]. Similarly, STV becomes abnormal in the case of advanced fetal deterioration [76], providing information similar to those of late DV changes for the short-term prediction of IUD. Although the optimal cutoff value of the STV for delivery has yet to be clarified, it is important to point out that, between 26 and 32 weeks, expectant management is accepted as long as either the DV or the STV is abnormal but not if both are abnormal [9, 65]. The lower cCTG-STV cutoff was chosen assuming the STV lowest cutoff clinically appropriate given the high chance of hypoxemia/acidemia below that. The presence of spontaneous, repetitive fetal heart rate decelerations or maternal indications should trigger delivery independently of DV and cCTG-STV evaluation.

The concept that perinatal outcomes in FGR fetuses are not negatively affected by expectant management is not novel, as it was also reported in a former randomized trial on FGR [145]. Nevertheless, the inclusion criteria in the GRIT study were not as strict as those of the TRUFFLE study, and the decision on how to monitor and when to deliver FGR fetuses was not standardized.

Safety nets for delivery within the late DV group of the TRUFFLE cohort included, other than absent or reversed "A-" wave of the DV, also STV <2.6 msec below 29 weeks and <3.0 msec between 29 and 32 weeks, spontaneous decelerations at CTG, UA REDF between 30 and 32 weeks, UA AEDF between 32 and 34 weeks, or UA PI >95th centile beyond 34 weeks. Umbilical artery Doppler per

se is therefore not informative as to when delivery should be undertaken, unless the gestation is above 30 weeks [9, 65–67].

Within the TRUFFLE protocol, and particularly in the late DV group, safety nets accounted for a significant amount of indications for delivery, both in the primary [9, 65] and in a recently published secondary analysis of the datasets [69]. A subanalysis of babies delivered <32 weeks' gestation, in other words those whose management was strictly defined by the protocol, showed that more than one third delivered based on safety net criteria and another one third for other fetal or maternal reasons. Hence, in clinical practice, a significant proportion of fetuses will be delivered because of cCTG-STV abnormalities, even before DV changes occur. However, overall data from the TRUFFLE trial and its subanalyses have shown a better outcome by the integrated use of both DV and cCTG-STV [9, 65–67].

Beyond 32 weeks of gestation, the timing of delivery should no longer rely on DV and STV but should be based on UA Doppler. More specifically, delivery should be undertaken if AEDF between 32 and 34 weeks and if UA PI >95th centile when the gestation is above 34 weeks.

According to the TRUFFLE protocol, there is no role for the MCA Doppler or CPR in the management of early FGR fetuses. A secondary analysis of the datasets from the TRUFFLE cohort could not demonstrate any impact of the MCA PI measured close to delivery and its change over time on neonatal and 2-year neurodevelopmental outcome, thus concluding that gestational age at delivery remains the most important factor in determining neonatal survival without adverse outcome and, together with birthweight, infant outcome [56].

As regards the timing for fetal monitoring, a secondary analysis of the TRUFFLE cohort has shown that it is not possible to predict the occurrence of abnormal STV or A-wave indicating delivery, concluding that STV should be monitored at least on a daily basis [146]. On the other hand, fetal Doppler can be measured twice a week or on alternate days in the case of advanced fetal compromise.

Within the TRUFFLE protocol, there is no role for the biophysical profile and conventional CTG in the monitoring of early FGR fetuses. Similarly, the evaluation of uterine artery Doppler is not recommended given the lack of data supporting its usefulness in the management of early FGR [42, 147]. Furthermore, there is no data as regards the decision for inpatient versus outpatient management of FGR fetuses. Most cases of isolated FGR are monitored in an outpatient setting even though the decision for inpatient monitoring can be taken on a subjective basis. Of note, 60–70% of cases of early FGR are associated with hypertensive complications of the pregnancy [9]. In such cases, particularly in the case of PE, admission seems advisable despite the lack of clinical evidence.

Doppler Ultrasound and Management of Late Fetal Growth Restriction

Given its relatively high frequency, late FGR is estimated to be responsible for over 50% of cases of IUD and misdiagnosed in most of them. Differently from early FGR, for which an evidence-based protocol for diagnosis, monitoring, and timing

of delivery exists, there is no prospective nor randomized trial which has led to an evidence-based approach for the management of late FGR.

The Prospective Observational Trial to Optimize Pediatric Health in Intrauterine Growth Restriction (PORTO) study demonstrated that EFW <3rd centile for gestation is associated with adverse perinatal outcomes regardless of UA, MCA, and other Doppler parameters, thus showing that EFW <3rd centile represents an indicator of severity of the restriction of the fetal growth [139].

The CPR was first described for the monitoring of FGR fetuses [61] and is currently considered an early sign of placental chronic hypoxia, hence among the discriminators between constitutionally small fetuses and growth-restricted ones [16, 57–59]. However, its actual clinical significance is yet to be determined as it has not been clarified whether abnormally reduced CPR represents an adaptive mechanism or an indicator of ongoing functional compromise [148, 149]. Available data suggest that late FGR fetuses with low CPR are at increased risk of IUD and of obstetrics intervention due to intrapartum distress and neonatal morbidity regardless of birthweight [42, 150] and also of adverse neurodevelopmental outcomes [54]. Therefore, even though the CPR is currently widely used for the monitoring of FGR fetuses beyond 32 weeks, it is uncertain whether delivery based on reduced CPR is beneficial [148].

As regards maternal Doppler, abnormalities of the UtA PI in the third trimester have been associated with SGA and with an increased risk of adverse perinatal outcomes including stillbirth, obstetric intervention due to fetal distress, and neonatal acidemia [58]. Computerized CTG also represents a primary tool for the monitoring of late FGR fetuses; however, it has not been clarified which STV cutoff should be considered indicative of fetal acidemia and lead to the decision to expedite delivery before term.

In conclusion, albeit in the absence of grade A evidence and guidelines, available data suggest that an EFW <3rd centile and abnormalities of the CPR and of the UtA PI are to be considered risk factors for severity of adverse perinatal outcomes and perinatal death in late FGR [58]. Therefore, in the presence of such abnormal findings, we suggest close Doppler and cCTG monitoring – i.e., twice weekly between 32 and 37 weeks – and delivery at 37 weeks.

A randomized study is needed in order to overcome such uncertainty as regards the optimal monitoring strategy and timing of delivery of late FGR. In these fetuses, the risk of IUD or perinatal death is low. On the other hand, late preterm and early-term delivery are risk factors for mild but relevant neonatal complications which may impact on short-term and potentially also on long-term outcome and neurodevelopment [151, 152]. Therefore, we believe that the implementation of a protocol for the antenatal management of late FGR to be tested within a randomized trial will need a joint risk-benefit assessment by obstetricians and neonatologists. The ongoing trial by the TRUFFLE group and the planned TRUFFLE 2 randomized controlled study are likely to provide further insights into the actual role of the cerebral Doppler – on its own or paired with UA within the CPR – in the management of late-onset FGR and particularly to clarify whether anticipating delivery based on

abnormal CPR is beneficial for the short- and long-term health of the late FGR fetus (http://www.truffle-study.org/research/).

Conclusion

- UA Doppler is related to fetal acidemia and provides both diagnostic and prognostic information for the management of FGR. The use of UA Doppler in a high-risk population reduces perinatal morbidity and mortality and is considered the primary surveillance tool in small fetuses. UA AEDF or REDF is mostly found in early FGR and has been reported to be present on average 1 week before acute fetal deterioration.
- Cerebral Doppler is not useful for the diagnosis and the management in early FGR. A potential role of MCA Doppler for the differential diagnosis between SGA and late FGR has been demonstrated; nevertheless MCA Doppler testing of suspected late FGR fetuses has not been evaluated in randomized trials, and to date no specific intervention has been shown to improve outcomes based on abnormal findings.
- The CPR has shown a good correlation with adverse outcome in FGR but also in apparently normally grown fetuses close to term and has been suggested for the differential diagnosis between SGA and FGR fetuses with normal UA Doppler.
- DV flow waveforms become abnormal only in advanced stages of fetal compromise, and the DV PI is inversely related to cord pH at birth. Evidence from the TRUFFLE has shown the crucial role of DV Doppler for the management of preterm growth-restricted fetuses before 32 weeks of gestation. There is no available data on DV Doppler in late FGR fetuses.
- The "heart-sparing effect" is the result of intrinsic mechanisms responsible for the autoregulation of the coronary flow which are activated in cases of chronic hypoxia – such as FGR – and leads to an increased blood supply to the fetal heart. No role of the "heart-sparing effect" for the diagnosis or the management of early or late FGR has been demonstrated to date.
- Doppler of the aortic isthmus, myocardial performance index, and E/A ratio represent Doppler cardiac parameters which have been studied in the context of FGR. There is no evidence-based role for any of them for the management or the diagnosis of early or late FGR.
- Abnormal UtA Doppler best identifies the severe early-onset complications of impaired placentation, particularly when performed in the second trimester and particularly for early FGR. There is also evidence that a high impedance to flow in the uterine arteries during the third trimester is associated with an increased risk of adverse perinatal events regardless of fetal size in pregnancies with normal umbilical artery Doppler, thus supporting the concept that raised UtA PI in the third trimester may help in discriminating between SGA and late FGR.
- There is no evidence-based role for Doppler assessment of the maternal cardiac function for the diagnosis or the management of FGR.

- According to the randomized evidence from the TRUFFLE study, beyond 32 weeks, the timing of delivery should be decided either based on late DV changes or safety net criteria, which include STV <2.6 ms below 29 weeks and <3.0 ms between 29 and 32 weeks, spontaneous decelerations at CTG, UA REDF between 30 and 32 weeks, UA AEDF between 32 and 34 weeks, or UA PI >95th centile beyond 34 weeks. Umbilical artery Doppler per se is not informative as to when delivery should be undertaken unless the gestation is above 30 weeks.
- Albeit in the absence of grade A evidence and guidelines for late FGR, available data suggest that an EFW <3rd centile and abnormalities of the CPR and of the UtA PI are to be considered independent indicators of severity of adverse perinatal outcomes and perinatal death in late FGR. These parameters should be taken into account when considering the option of delivery in late FGR.

References

1. Mcintire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med. 1999;340:1234–8.
2. Garite TJ, Combs CA, Maurel K, Das A, Huls K, Porreco R, et al. A multicenter prospective study of neonatal outcomes at less than 32 weeks associated with indications for maternal admission and delivery. Am J Obstet Gynecol. 2017;217:72.e1–9.
3. Society for Maternal-Fetal Medicine Publications Committee, Berkley E, Chauhan SP, Abuhamad A. Doppler assessment of the fetus with intrauterine growth restriction. Am J Obstet Gynecol. 2012;206:300–8.
4. Yanney M, Marlow N. Paediatric consequences of fetal growth restriction. Semin Fetal Neonatal Med. 2004;9:411–8.
5. Marlow N, Wolke D, Bracewell MA, Samara M, The Epicure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med. 2005;352:9–19.
6. Low J, Handley M, Burke S, Peters RD, Pater EA, Killen HL, et al. Association of intrauterine growth retardation and learning deficits at age 9 to it years. Am J Obstet Gynecol. 1992;162:1499–505.
7. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. Am J Obstet Gynecol. 2011;204:288–300.
8. Kennelly MM, Farah N, Turner MJ, Stuart B. Aortic isthmus Doppler velocimetry: role in assessment of preterm fetal growth restriction. Prenat Diagn. 2010;30:395–401.
9. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol. 2013;42:400–8.
10. Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. Lancet. 1992;339:283–7.
11. Gardosi J, Giddings S, Buller S, Southam M, Williams M. Preventing stillbirths through improved antenatal recognition of pregnancies at risk due to fetal growth restriction. Public Health. 2014;128:698–702.
12. Van den Wijngaard JA, Groenenberg IA, Wladimiroff JW, Hop WC. Cerebral Doppler ultrasound of the human fetus. Br J Obstet Gynaecol. 1989;96:845–9.
13. Rizzo G, Arduini D, Romanini C. Doppler echocardiographic assessment of fetal cardiac function. Ultrasound Obstet Gynecol. 1992;2:434–45.

14. Stampalija T, Casati D, Monasta L, Sassi R, Rivolta MW, Muggiasca ML, et al. Brain sparing effect in growth-restricted fetuses is associated with decreased cardiac acceleration and deceleration capacities: a case-control study. BJOG. 2016;123:1947–54.
15. Hecher K, Campbell S, Doyle P, Harrington K, Nicolaides K. Assessment of fetal compromise by Doppler ultrasound investigation of the fetal circulation, arterial, intracardiac, and venous blood flow velocity studies. Circulation. 1995;91:129–38.
16. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48:333–9.
17. Khalil A, Morales-Rosello J, Khan N, Nath M, Agarwal P, Bhide A, et al. Is cerebroplacental ratio a marker of impaired fetal growth velocity and adverse pregnancy outcome? Am J Obstet Gynecol. 2017;216:606.e1–606.e10.
18. Khalil A, Thilaganathan B. Role of uteroplacental and fetal Doppler in identifying fetal growth restriction at term. Best Pract Res Clin Obstet Gynaecol. 2017;38:38–47.
19. Morales-Roselló J, Khalil A, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B. Changes in fetal Doppler indices as a marker of failure to reach growth potential at term. Ultrasound Obstet Gynecol. 2014;43:303–10.
20. Dall'Asta A, Brunelli V, Prefumo F, Frusca T, Lees CC. Early onset fetal growth restriction. Matern Health Neonatol Perinatol. 2017;3:2.
21. Dall'Asta A, Lees C. Early second-trimester fetal growth restriction and adverse perinatal outcomes. Obstet Gynecol. 2018;131:739–40.
22. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, et al. Predictable progressive Doppler deterioration in IUGR: does it really exist? Am J Obstet Gynecol. 2013;209:539.e1–7.
23. Turan OM, Turan S, Gungor S, Berg C, Moyano D, Gembruch U, et al. Progression of Doppler abnormalities in intrauterine growth restriction. Ultrasound Obstet Gynecol. 2008;32:160–7.
24. Baschat AA, Güclü S, Kush ML, Gembruch U, Weiner CP, Harman CR. Venous Doppler in the prediction of acid-base status of growth-restricted fetuses with elevated placental blood flow resistance. Am J Obstet Gynecol. 2004;191:277–84.
25. Ferrazzi E, Bellotti M, Galan H, Pennati G, Bozzo M, Rigano S, et al. Doppler investigation in intrauterine growth restriction – from qualitative indices to flow measurements: a review of the experience of a collaborative group. Ann N Y Acad Sci. 2001;943:316–25.
26. Kiserud T, Kessler J, Ebbing C, Rasmussen S. Ductus venosus shunting in growth-restricted foetuses and the effect of umbilical circulatory compromise. Ultrasound Obstet Gynecol. 2006;28:143–9.
27. Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackelöer BJ, Kok HJ, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol. 2001;18:564–70.
28. Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, intracardiac, and arterial blood flow measurements in intrauterine growth retardation; relationship with fetal blood gases. Am J Obstet Gynecol. 1995;173:10–5.
29. Rizzo G, Capponi A, Arduini D, Romanini C. The value of fetal arterial, cardiac and venous flows in predicting pH and blood gases measured in umbilical blood at cordocentesis in growth retarded fetuses. Br J Obstet Gyanecol. 1995;102:963–9.
30. Kingdom JC, Burrell SJ, Kaufmann P. Pathology and clinical implications of abnormal umbilical artery Doppler waveforms. Ultrasound Obstet Gynecol. 1997;9:271–86.
31. Khare M, Paul S, Konje J. Variation in Doppler indices along the length of the cord from the intraabdominal to the placental insertion. Acta Obstet Gynecol Scand. 2006;85:922–8.
32. Acharya G, Wilsgaard T, Berntsen G, Maltau J, Kiserud T. Reference ranges for serial measurements of blood velocity and pulsatility index at the intra-abdominal portion, and fetal and placental ends of the umbilical artery. Ultrasound Obstet Gynecol. 2005;26:162–9.
33. Acharya G, Wilsgaard T, Berntsen G, Maltau J, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. Am J Obstet Gynecol. 2005;192:937–44.

34. Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol. 2013;41:233–9.
35. Morrow RJ, Adamson SL, Bull SB, Ritchie JW. Effect of placental embolization on the umbilical arterial velocity waveform in fetal sheep. Am J Obstet Gynecol. 1989;161:1055–60.
36. Thompson RS, Trudinger BJ. Doppler waveform pulsatility index and resistance, pressure and flow in the umbilical placental circulation: an investigation using a mathematical model. Ultrasound Med Biol. 1990;16:449–58.
37. Soothill PW, Bobrow CS, Holmes R. Small for gestational age is not a diagnosis. Ultrasound Obstet Gynecol. 1999;13:225–8.
38. Bobrow CS, Soothill PW. Fetal growth velocity: a cautionary tale. Lancet. 1999;353:1460.
39. McCowan LM, Harding JE, Stewart AW. Umbilical artery Doppler studies in small for gestational age babies reflect disease severity. BJOG. 2000;107:916–25.
40. Figueras F, Eixarch E, Gratacos E, Gardosi J. Predictiveness of antenatal umbilical artery Doppler for adverse pregnancy outcome in small-for-gestational-age babies according to customised birthweight centiles: population based study. BJOG. 2008;115:590–4.
41. Doctor BA, O'Riordan MA, Kirchner HL, Shah D, Hack M. Perinatal correlates and neonatal outcomes of small for gestational age infants born at term gestation. Am J Obstet Gynecol. 2001;185:652–9.
42. Severi FM, Bocchi C, Visentin A, Falco P, Cobellis L, Florio P, et al. Uterine and fetal cerebral Doppler predict the outcome of third-trimester small-for-gestational age fetuses with normal umbilical artery Doppler. Ultrasound Obstet Gynecol. 2002;19:225–8.
43. Pardi G, Cetin I, Marconi AM, Lanfranchi A, Bozzetti P, Ferrazzi E, et al. Diagnostic value of blood sampling in fetuses with growth retardation. N Engl J Med. 1993;328:692–6.
44. Figueras F, Gratacos E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther. 2014;36:86–98.
45. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2013;11:CD007529.
46. RCOG Green Top Guidline No. 31. The investigation and management of the small-for-gestational age fetus. January 2014.
47. Arduini D, Rizzo G, Romanini C. The development of abnormal heart rate patterns after absent end-diastolic velocity in umbilical artery: analysis of risk factors. Am J Obstet Gynecol. 1993;168:43–50.
48. Brar H, Platt L. Reverse end diastolic flow velocity on umbilical artery velocimetry in high pregnancies: an ominous finding with adverse pregnancy outcome. Am J Obstet Gynecol. 1988;159:559–61.
49. Valcamonico A, Danti L, Frusca T, Soregaroli M, Zucca S, Abrami F, et al. Absent end diastolic velocity in umbilical artery: risk of neonatal morbidity and brain damage. Am J Obstet Gynecol. 1994;170:796–801.
50. Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, et al. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol. 2002;19:140–6.
51. Mari G, Abuhamad AZ, Cosmi E, Segata M, Altaye M, Akiyama M. Middle cerebral artery peak systolic velocity: technique and variability. J Ultrasound Med. 2005;24:425–30.
52. Mari G, Deter RL. Middle cerebral artery flow velocity waveforms in normal and small for gestational age fetuses. Am J Obstet Gynecol. 1992;166:1262–70.
53. Hernandez-Andrade E, Stampalija T, Figueras F. Cerebral blood flow studies in the diagnosis and management of intrauterine growth restriction. Curr Opin Obstet Gynecol. 2013;25:138–44.
54. Meher S, Hernandez-Andrade E, Basheer SN, Lees C. Impact of cerebral redistribution on neurodevelopmental outcome in small-for-gestational-age or growth-restricted babies: a systematic review. Ultrasound Obstet Gynecol. 2015;46:398–404.

55. Eixarch E, Meler E, Iraola A, Illa M, Crispi F, Hernandez-Andrade E, et al. Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution. Ultrasound Obstet Gynecol. 2008;32:894–9.
56. Stampalija T, Arabin B, Wolf H, Bilardo CM, Lees C, TRUFFLE investigators. Is middle cerebral artery Doppler related to neonatal and 2-year infant outcome in early fetal growth restriction. Am J Obstet Gynecol. 2017;216:521.e1–13.
57. Parra-Saavedra M, Simeone S, Triunfo S, Crovetto F, Botet F, Nadal A, et al. Correlation between histological signs of placental underperfusion and perinatal morbidity in late-onset small-for-gestational-age fetuses. Ultrasound Obstet Gynecol. 2015;45:149–55.
58. Figueras F, Savchev S, Triunfo S, Crovetto F, Gratacos E. An integrated model with classification criteria to predict small-for-gestational-age fetuses at risk of adverse perinatal outcome. Ultrasound Obstet Gynecol. 2015;45:279–85.
59. Triunfo S, Crispi F, Gratacos E, Figueras F. Prediction of delivery of small-for-gestational-age neonates and adverse perinatal outcome by fetoplacental Doppler at 37 weeks' gestation. Ultrasound Obstet Gynecol. 2017;49:364–71.
60. Cruz-Martínez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. Obstet Gynecol. 2011;117:618–26.
61. Gramellini D, Folli MC, Raboni S, Vadora E, Merialdi A. Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome. Obstet Gynecol. 1992;79:416–20.
62. Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol. 2003;21:124–7.
63. Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebro-umbilical ratio: a prospective observational study. Am J Obstet Gynecol. 2013;208:124.e1–6.
64. Kiserud T. Physiology of the fetal circulation. Semin Fetal Neonatal Med. 2005;10:493–503.
65. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lancet. 2015;385:2162–72.
66. Bilardo CM, Hecher K, Visser GH, Papageorghiou AT, Marlow N, Thilaganathan B, et al. Severe fetal growth restriction at 26–32 weeks: key messages from the TRUFFLE study. Ultrasound Obstet Gynecol. 2017;50:285–90.
67. Frusca T, Todros T, Lees C, Bilardo CM, TRUFFLE Investigators. Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe. Am J Obstet Gynecol. 2018;218:S783–9.
68. Ganzevoort W, Mensing Van Charante N, Thilaganathan B, Prefumo F, Arabin B, Bilardo CM, et al. How to monitor pregnancies complicated by fetal growth restriction and delivery before 32 weeks: post-hoc analysis of TRUFFLE study. Ultrasound Obstet Gynecol. 2017;49:769–77.
69. Visser GH, Bilardo CM, Derks JB, Ferrazzi E, Fratelli N, Frusca T, et al. Fetal monitoring indications for delivery and 2-year outcome in 310 infants with fetal growth restriction delivered before 32 weeks' gestation in the TRUFFLE study. Ultrasound Obstet Gynecol. 2017;50:347–52.
70. Baschat AA, Turan OM, Turan S. Ductus venosus blood-flow patterns: more than meets the eye? Ultrasound Obstet Gynecol. 2012;39:598–9.
71. Baschat AA, Hecher K. Fetal growth restriction due to placental disease. Semin Perinatol. 2004;28:67–80.
72. Baschat AA. Fetal responses to placental insufficiency: an update. BJOG. 2004;111:1031–41.
73. Turan OM, Turan S, Sanapo L, Rosenbloom JI, Baschat AA. Semiquantitative classification of ductus venosus blood flow patterns. Ultrasound Obstet Gynecol. 2014;43:508–14.
74. Cosmi E, Ambrosini G, D'Antona D, Saccardi C, Mari G. Doppler, cardiotocography, and biophysical profile changes in growth-restricted fetuses. Obstet Gynecol. 2005;106:1240–5.

75. Baschat AA, Gembruch U, Harmann CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol. 2001;18:571–7.
76. Schwarze A, Gembruch U, Krapp M, Katalinic A, Germer U, Axt-Fliedner R. Qualitative venous Doppler flow waveform analysis in preterm intrauterine growth-restricted fetuses with ARED flow in the umbilical artery – correlation with short-term outcome. Ultrasound Obstet Gynecol. 2005;25:573–9.
77. Chaoui R. The fetal 'heart-sparing effect' detected by the assessment of coronary blood flow: a further ominous sign of fetal compromise. Ultrasound Obstet Gynecol. 1996;7:5–9.
78. Baschat AA, Gembruch U, Reiss I, Gortner L, Diedrich K. Demonstration of fetal coronary blood flow by Doppler ultrasound in relation to arterial and venous flow velocity waveforms and perinatal outcome – the 'heart-sparing effect'. Ultrasound Obstet Gynecol. 1997;9:162–72.
79. Crispi F, Figueras F, Cruz-Lemini M, Bartrons J, Bijnens B, Gratacos E. Cardiovascular programming in children born small for gestational age and relationship with prenatal signs of severity. Am J Obstet Gynecol. 2012;207:121.e1–9.
80. Hernandez-Andrade E, Benavides-Serralde JA, Cruz-Martinez R, Welsh A, Mancilla-Ramirez J. Evaluation of conventional Doppler fetal cardiac function parameters: E/A ratios, outflow tracts, and myocardial performance index. Fetal Diagn Ther. 2012;32:22–9.
81. Cruz-Martinez R, Figueras F, Benavides-Serralde A, Crispi F, Hernandez-Andrade E, Gratacos E. Sequence of changes in myocardial performance index in relation to aortic isthmus and ductus venosus Doppler in fetuses with early-onset intrauterine growth restriction. Ultrasound Obstet Gynecol. 2011;38:179–84.
82. Del Río M, Martínez JM, Figueras F, Bennasar M, Olivella A, Palacio M, et al. Doppler assessment of the aortic isthmus and perinatal outcome in preterm fetuses with severe intrauterine growth restriction. Ultrasound Obstet Gynecol. 2008;31:41–7.
83. Del Río M, Martinez JM, Figueras F, Bennasar M, Palacio M, Gomez O, et al. Doppler assessment of fetal aortic isthmus blood flow in two different sonographic planes during the second half of gestation. Ultrasound Obstet Gynecol. 2005;26:170–4.
84. Rizzo G, Capponi A, Vendola M, Pietrolucci ME, Arduini D. Relationship between aortic isthmus and ductus venosus velocity waveforms in severe growth restricted fetuses. Prenat Diagn. 2008;28:1042–7.
85. Acharya G. Technical aspects of aortic isthmus Doppler velocimetry in human fetuses. Ultrasound Obstet Gynecol. 2009;33:628–33.
86. Ruskamp J, Fouron JC, Gosselin J, Raboisson MJ, Infante-Rivard C, Proulx F. Reference values for an index of fetal aortic isthmus blood flow during the second half of pregnancy. Ultrasound Obstet Gynecol. 2003;21:441–4.
87. Bonnin P, Fouron JC, Teyssier G, Sonesson SE, Skoll A. Quantitative assessment of circulatory changes in the fetal aortic isthmus during progressive increase of resistance to umbilical blood flow. Circulation. 1993;88:216–22.
88. Fouron JC. The unrecognized physiological and clinical significance of the fetal aortic isthmus. Ultrasound Obstet Gynecol. 2003;22:441–7.
89. Makikallio K, Jouppila P, Rasanen J. Retrograde net blood flow in the aortic isthmus in relation to human fetal arterial and venous circulations. Ultrasound Obstet Gynecol. 2002;19:147–52.
90. Makikallio K, Jouppila P, Rasanen J. Retrograde aortic isthmus net blood flow and human fetal cardiac function in placental insufficiency. Ultrasound Obstet Gynecol. 2003;22:351–7.
91. Jouppila P, Kirkinen P. Increased vascular resistance in the descending aorta of the human fetus in hypoxia. Br J Obstet Gynaecol. 1984;91:853–6.
92. Arabin B, Siebert M, Jimenez E, Saling E. Obstetrical characteristics of a loss of end-diastolic velocities in the fetal aorta and/or umbilical artery using Doppler ultrasound. Gynecol Obstet Investig. 1988;25:173–80.
93. Fouron JC, Gosseli J, Raboisson MJ, Lamoureux J, Tison CA, Fouron C, et al. The relationship between an aortic isthmus blood flow velocity and the postnatal neurodevelopmental status of fetuses with placental circulatory insufficiency. Am J Obstet Gynecol. 2005;192:497–503.

94. Van der Mooren K, Barendregt LG, Wladimiroff JW. Fetal atrioventricular and outflow tract flow velocity waveforms during normal second half of pregnancy. Am J Obstet Gyencol. 1991;165:668–74.
95. Tulzer G, Khowsathit P, Gudmundsson S, Wood DC, Tian ZY, Schmitt K, et al. Diastolic function of the fetal heart during second and third trimester: a prospective longitudinal Doppler-echocardiographic study. Eur J Pediatr. 1994;153:151–4.
96. Figueras F, Puerto B, Martinez JM, Cararach V, Vanrell JA. Cardiac function monitoring of fetuses with growth restriction. Eur J Obstet Gynecol Reprod Biol. 2003;110:159–63.
97. Mäkikallio K, Räsänen J, Mäkikallio T, Vuolteenaho O, Huhta JC. Human fetal cardiovascular profile score and neonatal outcome in intrauterine growth restriction. Ultrasound Obstet Gynecol. 2008;31:48–54.
98. Tei C, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function – a study in normal and dilated cardiomyopathy. J Cardiol. 1995;26:357–66.
99. Van Mieghem T, Klaritsch P, Doné E, Gucciardo L, Lewi P, Verhaeghe J, et al. Assessment of fetal cardiac function before and after therapy for twin-to-twin transfusion syndrome. Am J Obstet Gynecol. 2009;200:400.e1–7.
100. Hassan WA, Brockelsby J, Alberry M, Fanelli T, Wladimiroff J, Lees CC. Cardiac function in early onset small for gestational age and growth restricted fetuses. Eur J Obstet Gynecol Reprod Biol. 2013;171:262–5.
101. Benavides-Serralde A, Scheier M, Cruz-Martinez R, Crispi F, Figueras F, Gratacos E, et al. Changes in central and peripheral circulation in intrauterine growth-restricted fetuses at different stages of umbilical artery flow deterioration: new fetal cardiac and brain parameters. Gynecol Obstet Investig. 2011;71:274–80.
102. Pérez-Cruz M, Cruz-Lemini M, Fernández MT, Parra JA, Bartrons J, Gómez-Roig MD, et al. Fetal cardiac function in late-onset intrauterine growth restriction vs small-for-gestational age, as defined by estimated fetal weight, cerebroplacental ratio and uterine artery Doppler. Ultrasound Obstet Gynecol. 2015;46:465–71.
103. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Changes in myocardial performance index and aortic isthmus and ductus venosus Doppler in term, small-for-gestational age fetuses with normal umbilical artery pulsatility index. Ultrasound Obstet Gynecol. 2011;38:400–5.
104. Hernandez-Andrade E, Crispi F, Benavides-Serralde JA, Plasencia W, Diesel HF, Eixarch E, et al. Contribution of the myocardial performance index and aortic isthmus blood flow index to predicting mortality in preterm growth-restricted fetuses. Ultrasound Obstet Gynecol. 2009;34:430–6.
105. Jurkovic D, Jauniaux E, Kurjak A, Hustin J, Campbell S, Nicolaides KH. Transvaginal color Doppler assessment of the uteroplacental circulation in early pregnancy. Obstet Gynecol. 1991;77:365–9.
106. Jauniaux E, Jurkovic D, Campbell S, Hustin J. Doppler ultrasonographic features of the developing placental circulation; correlation with anatomic findings. Am J Obstet Gynecol. 1992;166:585–7.
107. Cnossen JS, Morris RK, ter Riet G, Mol BW, van der Post JA, Coomarasamy A, et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. CMAJ. 2008;178:701–11.
108. Sciscione AC, Hayes EJ; Society for Maternal-Fetal Medicine. Uterine artery Doppler flow studies in obstetric practice. Am J Obstet Gynecol. 2009;201:121–6.
109. Gòmez O, Figueras F, Fernàndez S, Bennasar M, Martìnez JM, Puerto B, et al. Reference ranges for uterine artery mean pulsatility index at 11–41 weeks of gestation. Ultrasound Obstet Gynecol. 2008;32:128–32.
110. Papageorghiou AT, Yu CK, Bindra R, Pandis G, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. Ultrasound Obstet Gynecol. 2001;18:441–9.

111. Ferreira AE, Mauad Filho F, Abreu PS, Mauad FM, Araujo Júnior E, Martins WP. Reproducibility of first- and second-trimester uterine artery pulsatility index measured by transvaginal and transabdominal ultrasound. Ultrasound Obstet Gynecol. 2015;46:546–52.
112. Li N, Ghosh G, Gudmundsson S. Uterine artery Doppler in high-risk pregnancies at 23–24 gestational weeks is of value in predicting adverse outcome of pregnancy and selecting cases for more intense surveillance. Acta Obstet Gynecol Scand. 2014;93:1276–81.
113. Khalil AA, Morales-Rosello J, Elsaddig M, Khan N, Papageorghiou A, Bhide A, et al. The association between fetal Doppler and admission to neonatal unit at term. Am J Obstet Gynecol. 2015;213:57.e1–7.
114. Papageorghiou AT, Yu CK, Cicero S, Bower S, Nicolaides KH. Second-trimester uterine artery Doppler screening in unselected populations: a review. J Matern Fetal Neonatal Med. 2002;12:78–88.
115. Valiño N, Giunta G, Gallo DM, Akolekar R, Nicolaides KH. Uterine artery pulsatility index at 30–34 weeks' gestation in the prediction of adverse perinatal outcome. Ultrasound Obstet Gynecol. 2016;47:308–15.
116. Cruz-Martinez R, Savchev S, Cruz-Lemini M, Mendez A, Gratacos E, Figueras F. Clinical utility of third-trimester uterine artery Doppler in the prediction of brain hemodynamic deterioration and adverse perinatal outcome in small-for-gestational-age fetuses. Ultrasound Obstet Gynecol. 2015;45:273–8.
117. Flo K, Wilsgaard T, Vårtun A, Acharya G. A longitudinal study of the relationship between maternal cardiac output measured by impedance cardiography and uterine artery blood flow in the second half of pregnancy. BJOG Int J Obstet Gynaecol. 2010;117:837–44.
118. Ghi T, degli Esposti D, Montaguti E, Rosticci M, Tancredi S, Youssef A, et al. Maternal cardiac evaluation during uncomplicated twin pregnancy with emphasis on the diastolic function. Am J Obstet Gynecol. 2015;213:376.e1–8.
119. Valensise H, Tiralongo GM, Pisani I, Farsetti D, Lo Presti D, Gagliardi G, et al. Maternal hemodynamics early in labor: a possible link with obstetric risk? Ultrasound Obstet Gynecol. 2018;51:509–13.
120. Tiralongo GM, Pisani I, Vasapollo B, Khalil A, Thilaganathan B, Valensise H. Effect of a nitric oxide donor on maternal hemodynamics in fetal growth restriction. Ultrasound Obstet Gynecol. 2018;51:514–8.
121. Gagliardi G, Tiralongo GM, LoPresti D, Pisani I, Farsetti D, Vasapollo B, et al. Screening for pre-eclampsia in the first trimester: role of maternal hemodynamics and bioimpedance in non-obese patients. Ultrasound Obstet Gynecol. 2017;50:584–8.
122. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta. 2006;27:939–58.
123. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376:631–44.
124. Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. Fetal Diagn Ther. 2014;36:117–28.
125. Xiong X, Demianczuk NN, Saunders LD, Wang FL, Fraser WD. Impact of preeclampsia and gestational hypertension on birth weight by gestational age. Am J Epidemiol. 2002;155:203–9.
126. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008;52:873–80.
127. Verlohren S, Melchiorre K, Khalil A, Thilaganathan B. Uterine artery Doppler, birth weight and timing of onset of pre-eclampsia: providing insights into the dual etiology of late-onset pre-eclampsia. Ultrasound Obstet Gynecol. 2014;44:293–8.
128. Thilaganathan B. Pre-eclampsia is primarily a placental disorder: AGAINST: pre-eclampsia: the heart matters. BJOG. 2017;124:1763.
129. Stott D, Papastefanou I, Paraschiv D, Clark K, Kametas NA. Longitudinal maternal hemodynamics in pregnancies affected by fetal growth restriction. Ultrasound Obstet Gynecol. 2017;49:761–8.

130. Ferrazzi E, Stampalija T, Monasta L, Di Martino D, Vonck S, Gyselaers W. Maternal hemodynamics: a method to classify hypertensive disorders of pregnancy. Am J Obstet Gynecol. 2018;218:124.e1–124.e11.
131. Salomon LJ, Alfirevic Z, Bilardo CM, Chalouhi GE, Ghi T, Kagan KO, et al. ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol. 2013;41:102–13.
132. Gardosi J, Clausson B, Francis A. The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size. BJOG. 2009;116:1356–63.
133. Odibo AO, Cahill AG, Odibo L, Roehl K, Macones GA. Prediction of intrauterine fetal death in small-for-gestational-age fetuses: impact of including ultrasound biometry in customized models. Ultrasound Obstet Gynecol. 2012;39:288–92.
134. Smith NA, Bukowski R, Thomas AM, Cantonwine D, Zera C, Robinson JN. Identification of pathologically small fetuses using customized, ultrasound and population-based growth norms. Ultrasound Obstet Gynecol. 2014;44:595–9.
135. Ghi T, Cariello L, Rizzo L, Ferrazzi E, Periti E, Prefumo F, et al. Customized fetal growth charts for parents' characteristics, race and parity by Quantile regression analysis: a cross-sectional multicenter Italian study. J Ultrasound Med. 2016;35:83–92.
136. Kiserud T, Piaggio G, Carroli G, Widmer M, Carvalho J, Neerup Jensen L, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. PLoS Med. 2017;14:e1002220.
137. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Cheikh Ismail L, Lambert A, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014;384:869–79.
138. Miranda J, Rodriguez-Lopez M, Triunfo S, Sairanen M, Kouru H, Parra-Saavedra M, et al. Prediction of fetal growth restriction using estimated fetal weight vs a combined screening model in the third trimester. Ultrasound Obstet Gynecol. 2017;50:603–11.
139. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol. 2013;208:290.e1–6.
140. Triunfo S, Crovetto F, Scazzocchio E, Parra-Saavedra M, Gratacos E, Figueras F. Contingent versus routine third-trimester screening for late fetal growth restriction. Ultrasound Obstet Gynecol. 2016;47:81–8.
141. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet. 2015;386:2089–97.
142. Bakalis S, Silva M, Akolekar R, Poon LC, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by fetal biometry at 30–34 weeks. Ultrasound Obstet Gynecol. 2015;45:551–8.
143. Roma E, Arnau A, Berdala R, Bergos C, Montesinos J, Figueras F. Ultrasound screening for fetal growth restriction at 36 vs 32 weeks' gestation: a randomized trial (ROUTE). Ultrasound Obstet Gynecol. 2015;46:391–7.
144. Dall'Asta A, Ghi T, Rizzo G, Cancemi A, Aloisio F, Arduini D, et al. Early labor cerebroplacental ratio assessment in uncomplicated term pregnancies and prediction of adverse perinatal outcomes: a prospective, multicentre study. Ultrasound Obstet Gynecol. 2018; https://doi.org/10.1002/uog.19113.
145. GRIT Study Group. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. BJOG. 2003;110:27–32.
146. Wolf H, Arabin B, Lees CC, Oepkes D, Prefumo F, Thilaganathan B, et al. Longitudinal study of computerized cardiotocography in early fetal growth restriction. Ultrasound Obstet Gynecol. 2017;50:71–8.
147. Ghosh GS, Gudmundsson S. Uterine and umbilical artery Doppler are comparable in predicting perinatal outcome of growth-restricted fetuses. BJOG. 2009;116:424–30.
148. DeVore GR. The importance of the cerebroplacental ratio in the evaluation of fetal Well-being in SGA and AGA fetuses. Am J Obstet Gynecol. 2015;213:5–15.

149. Ghi T, Frusca T, Lees CC. Cerebroplacental ratio in fetal surveillance: an alert bell or a crash sound? Am J Obstet Gynecol. 2016;214:297–8.
150. Vergani P, Roncaglia N, Andreotti C, Arreghini A, Teruzzi M, Pezzullo JC, et al. Prognostic value of uterine artery Doppler velocimetry in growth-restricted fetuses delivered near term. Am J Obstet Gynecol. 2002;187:932–6.
151. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ. 1989;298:564–7.
152. Barker DJ. Fetal origins of coronary heart disease. BMJ. 1995;311:171–4.