Fetal Growth Restriction (FGR)—Fetal Evaluation and Antepartum Intervention

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Published online: 2 April 2013
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Abstract Fetal growth restriction (FGR) is a pathological condition that refers to a fetus that fails to reach his/her genetically predetermined growth potential. By epigenetic effects, substrate and energy deprivation in utero modify fetal metabolism with possible life-long impacts. Management of FGR still represents one of the main challenges for the obstetricians, both for the complexities of management of severe early FGR and for the diagnostic difficulties in late and term FGR. Late onset and term FGR define an intrauterine trajectory of growth that falls below its potential late in gestation, after 34 and 37 weeks of gestation, respectively. Ultrasound biometry examination is crucial for an accurate diagnosis of FGR. Pregnancies at risk of FGR should be considered for longitudinal ultrasound monitoring beyond the routine ultrasound screening at 20 weeks of gestation. Functional assessment of placental and fetal circulation by Doppler velocimetry and blood flow volume, together with computerized assessment of fetal heart rate variability, are key examinations in early and late FGR to assess severity of the disease and monitor fetal wellbeing. Appropriate timing of delivery in early FGR might change the outcome, and appropriate monitoring in late and term FGR might avoid unnecessary interventions.

Keywords Fetal growth restriction · FGR · Placental insufficiency · Fetal abdominal circumference · Doppler velocimetry · Computerized CTG · Timing of delivery · Intrauterine fetal demise · Fetal evaluation

Introduction

A small for gestational age (SGA) is defined by the World Health Organization as a newborn whose birth weight is less than 2,500 grams at term [1]. This definition is useful for under-developed areas of the world, where the exact gestational age is often unknown, and small and premature newborns are not assisted due to restricted availability of the resources.

Starting from the 1970s, in wealthy western countries, the term SGA has been introduced to define the newborn's birth weight as below the tenth percentile, based on the local birth weight charts and in relation to the gestational age at birth [2]. According to this definition, an SGA fetus could be a growth restricted fetus, or small because of chromosomal abnormality or congenital infection, or simply constitutionally small. Birth weight below the fifth or third percentile is occasionally adopted in order to increase the probability of recognizing a true growth restriction [3]. Thus, the usefulness of SGA definition can be recognized in the identification of classes of subjects, but not clinically to classify a single case.

Fetal growth restriction (FGR) is a pathological condition that refers to a fetus that fails to reach his/her genetically predetermined growth potential. It is associated with increased perinatal mortality and morbidity due to higher risk of intrauterine fetal demise (IUID), intrapartum morbidity, and increased rate of iatrogenic prematurity (before 34 weeks of gestation) [4]. Besides the short-term complications such as polycythemia, hypoglycemia, hypothermia, and respiratory difficulties due to induced prematurity [5•], FGR newborns have a higher risk of long-term complications such as

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developmental delay, and behavioral dysfunctions [6]. Moreover, an increasing number of reports suggests the causative link between FGR and metabolic syndrome in adulthood [7].

Management of FGR still represents one of the biggest challenges for obstetricians. For many decades, interest was mainly focused on early-onset FGR, due to the high risk of perinatal mortality and morbidity associated with this condition [8]. On the contrary, late-onset and term FGR were considered not to be at risk for significant perinatal morbidity. Recently, this concept has been challenged and revised [9, 10]. Indeed, more sophisticated biophysical assessment of placental function allows redefinition of the criteria under which placental insufficiency can be diagnosed [11•]. Similarly, advanced methods of ultrasound evaluation of the fetal growth and circulation made intrauterine identification of less severe forms of late-onset and term FGR feasible [12••].

Intrauterine “Fetal Programming”

It is a fact that harmful insults during intrauterine life can cause permanent changes in physiological metabolism of a newborn, increasing the risk of metabolic diseases in adult life. Fetal origin of adult disease, hypothesized by Barker and Colleagues, highlights the relationship between uterine growth impairment and risk of coronary heart disease and death in adult life [7]. Subsequently, Barker hypothesis was confirmed by a cohort study that involved newborns delivered during the Dutch famine of 1944–1945, when the adult daily energy consumption dropped from 1,800 to 400–800 calories per day [13]. This study demonstrated that the newborns exposed to energy shortage throughout all trimesters of pregnancy will have a greater risk as adults of developing various diseases such as metabolic syndrome, pulmonary or renal disease, and psychiatric disorders [14].

Substrate and energy deprivation modify fetal metabolism with possible life-long impacts [15]. The fetus seems to use intrauterine habitat to predict and prepare himself for the postnatal environment. Thus, the organism alters its developmental path in order to produce a phenotype, a set of characteristics that can be observed, such as behavior, physiology, or metabolism, that will give a reproductive or survival advantage in postnatal life [15]. This process is called predictive adaptive response, and epigenetics is the key of understanding the relationship between intrauterine environment and gene expression. Briefly, it determines heritable changes in gene expression without altering DNA sequence due to modifications such as DNA methylation, histone modification, and changes in microRNA. These epigenetic modifications can involve just a specific organ or a single metabolic pathway, or can have an effect on overall health. The whole process is part of the so-called fetal programming. This is where the awareness of crucial importance of “healthy” intrauterine

environment, allowing the regular fetal growth and achievement of fetal maturity, comes from.

Placental Origin of Fetal Growth Restriction

Normal development and functional integrity of the placenta are essential prerequisites for appropriate fetal growth. Trophoblast is a metabolically active tissue that uptakes, modifies and transfers nutrients, produces hormones, exchanges gases, and eliminates waste substances. A complete transformation of maternal spiral arteries following the trophoblast invasion is crucial for the physiological development and functioning of the placenta. In pregnancies complicated by FGR of placental origin, this mechanism is inadequate [16], and leads to placental insufficiency with consequent functional deficit of variable degree and severity. The histopathological findings of the placenta include: altered cytotrophoblast proliferation, trophoblast apoptosis, villous necrosis with the subsequent fibrin deposition, syncytial knots, increased villous maturation, thickening of trophoblastic basement membrane, and multiple placental infarctions [17]. The proportion of these lesions is inversely correlated to the proportion of functional placenta, and can determine decreased delivery of oxygen and nutritional substances to the fetus, and increased resistance to placental blood flow in maternal [18] and fetal compartment [8].

Dysfunctional placental exchange can precede abnormal umbilical artery (UmA) Doppler velocimetry for a long period of time. Thus, nutrient deprivation of the fetus is a chronic process that is initiated far before fetoplacental abnormalities that can be identified by Doppler velocimetry [19]. Progressively, there will be a preferential shunting of the blood towards the vital organs (brain, heart and adrenals), with consequent hypoperfusion of the remaining districts and deprivation of abdominal adipose deposits [20••]. Indeed, fetus with a growth restriction is characterized by a preferential venous blood flow from umbilical vein towards the right atrium [21], and this process, together with nutritional deprivation, is at the basis of fetal biometrical asymmetry.

Clinical Diagnosis of Fetal Growth Restriction

Accurate determination of gestational age is a prerequisite for the diagnosis of FGR. Certain last menstrual period and first trimester ultrasound remain the gold standard for pregnancy dating. When these parameters are not available ultrasound at 19–20 gestational weeks can provide sufficient approximation [22]. Nevertheless, it is the ultrasound biometry assessment that is crucial for an accurate diagnosis of FGR. Pregnancies at risk of FGR should be considered for

longitudinal ultrasound monitoring beyond the routine screening at 20 weeks of gestation [23]. The following conditions increase the risk for FGR: 1) previous preeclampsia of placental origin or FGR [24]; 2) abnormal uterine artery (UtA) Doppler velocimetry at 20 weeks of gestation [25]; 3) congenital or acquired thrombophilia [26]; 4) hypertension of placental origin [27••]; and 5) decreased symphysis-fundal height measurement [28]. Likely, in the near future, positive first trimester serum markers for abnormal trophoblastic invasion will provide evidence of efficient prediction for FGR [29].

Measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) allow for the comparison of individual growth and local reference values or customized growth charts [30]. Beside the comparison with standard growth curves and an auxologic assessment of head to abdomen proportion, these measurements allow the calculation of estimated fetal weight (EFW). The most commonly used formulas are those suggested by Shepard et al. [31] and Hadlock et al. [32]. Based on these formulas, FGR is defined as an EFW below tenth, fifth or third percentile of local reference values and gestational age. EFW is of great importance when preterm delivery is expected, given the impact of birth weight on neonatal short-term and long-term outcomes. Nevertheless, taken alone, EFW below the tenth percentile has two major limitations: the biological and the statistical one. From the biological point of view, it has been suggested that a prematurely delivered newborn often does not reach its full growth potential; in fact, the prematurity is closely related to infective, inflammatory or hypoxic damage that can involve the placenta [33]. Consequently, the growth of a prematurely born fetus might be influenced by these factors. Therefore, birth weight references from 26 to 36 weeks of gestation, which include prematurely born neonates, might not reflect the true growth potential of individual fetuses. The second limitation is that, by using the definition of the tenth percentile, 10 % of normal fetuses will be defined as small for gestational age. This definition includes heterogeneous fetal conditions, among which a majority will be represented by constitutionally small, but healthy, newborns. Those fetuses do not require intensive surveillance and anticipated delivery.

Beside the absolute EFW measure, the evaluation of AC decline over time is helpful to differentiate FGR from SGA. Indeed, neonates with delayed growth of AC have worse neonatal outcome [34]. Ratios derived from biometric measurements, such as HC/AC ratio, are more informative while reflecting the proportion of somatic to visceral growth. This measurement provides integrated information regarding liver and adipose tissue growth early, as from second trimester of pregnancy [35]. By taking into account the HC/AC ratio, two distinct patterns of FGR have been described [36]. The first one, or symmetrical FGR, is characterized by

proportionally small development of the fetal body (normal HC/AC). This condition is more frequently associated with the factors that act at the early stages, such as congenital infections and aneuploidy. The second type, or asymmetrical FGR, is characterized by preserved growth of HC (adequate for gestational age) in contrast to AC that shows growth retardation (increased HC/AC ratio), and is typically associated with placental insufficiency [37••]. In fact, a newborn with a birth weight within normal ranges could still have suffered from intrauterine growth restriction, observed by a decline in AC of more than 40 percentiles [3] (Tables 1 and 2).

Assessing the Severity of Placental Insufficiency

Doppler velocimetry of the uterine arteries (UtA) provides important information on the origin of the FGR [11•, 25]. In case of FGR that originates from placental insufficiency, the UtA will be characterized by high blood flow resistance in the placenta, as assessed by high values of Pulsatility Index (PI) and Resistant Index (RI). The high impedance correlates with the UtA blood flow volume, which in FGR is reduced two to three-folds per unit fetal weight when compared to normally grown fetuses [18].

Mathematical model of the umbilical-placental circulation showed that PI of the umbilical artery (UmA) increases with the vascular disease of the placenta [38]. Fifty to sixty percent of the terminal arterial vessels must be obliterated before the increase in UmA PI can be observed. However, this process does not occur uniformly. Initially the raise of UmA PI values is slow, but beyond a certain cutoff (80–90 %), the blood flow in UmA deteriorates sharply [38]. At present, UmA PI evaluation constitutes the most valuable vessel for the assessment of FGR severity [8]. Abnormal Doppler velocimetry of the UmA is a consistent proxy of severe placental pathology [16]. The natural history of these fetuses, without adequate monitoring and medical intervention, is intrauterine death frequently associated with the occurrence of maternal hypertensive disorder. Growth restricted fetuses with normal UmA waveform usually fare better to term, and their minor adaptive changes challenge present monitoring techniques.

Once the diagnosis of FGR has been established, the main issue is the right timing of delivery. Several studies confirmed worse neonatal outcome of early FGR with absent or reversed end diastolic flow (ARED) in UmA than in appropriate for gestational age (AGA) newborns that were delivered prematurely, such as: lower Bayley motor development index, and lower Kaufman mental score at ≥ 2 years of age, mental retardation [39], and higher cognitive impairment at early school age, especially in boys [40••]. Similarly, later in

Table 1 Summary of principal findings in early fetal growth restriction

Early-onset fetal growth restriction		
Author	Design	Results
Burton et al. (2009) [16]	Review with excellent updated insight into abnormal trophoblastic invasion in early gestation.	Abnormal invasion of trophoblastic cells into decidua and maternal spiral arteries, and failure of loss of smooth muscle and the elastic lamina accompanies fetal growth restriction and early-onset preeclampsia.
Ferrazzi et al. (1999) [18]	90 FGR and 37 AGA were assessed for uterine artery Doppler 7 days before delivery. Placental pathology was examined blindly after delivery.	The presence of abnormal UtA Doppler velocimetry in FGR is an indicator of ischemic placental lesions. Patients with hypertension, without abnormal UtA Doppler had normal weight newborn, and normal placental histology.
Karsdorp et al. (1994) [8]	FGR with positive end diastolic velocities ($n=214$), AEDF ($n=178$), and REDF ($n=67$).	Compared to the presence of the end diastolic flow, AEDF and REDF were associated to the increased risk of perinatal mortality (OR 4 and 10.6, respectively). AREDF increased the risk of cerebral hemorrhage, anemia, or hypoglycemia.
Wienerroither et al. (2001) [42] Schreuder et al. (2002) [43] Valcamonico et al. (2004) [41]	Analysis of the long-term effects of AREDF in FGR on intellectual, neurologic and social development.	FGR with abnormal umbilical artery PI have a higher risk of long-term impairment of intellectual development.
Ferrazzi et al. (2002) [58]	26 women with the diagnosis of severe and early (<32 weeks) FGR were followed longitudinally to delivery.	There is a temporal sequence in Doppler changes in early FGR: early changes are increased Uma-PI and decreased MCA-PI; late changes are AREDF and DV alterations. DV PI is a better predictor of non intact neonatal outcome than is gestational age before 31 weeks of gestation.
Bilardo et al. (2004) [59] Baschat et al. (2007) [44]	Investigation of Doppler velocimetry changes (and STV) in relation to perinatal outcome in severe early FGR.	Besides the gestational age at delivery and birth weight, abnormalities in DV represents the best predictor of perinatal outcome and could be useful in timing of delivery.

FGR fetal growth restriction; *AGA* appropriate for gestational age; *UtA* uterine arteries; *Uma-PI* Umbilical artery pulsatility index; *MCA-PI* middle cerebral artery pulsatility index; *AEDF* absent end diastolic flow; *REDF* reverse end diastolic flow; *AREDF* absent or reverse end diastolic flow; *DV* ductus venosus; *STV* short term variation

childhood, survivors with ARED in Uma had higher incidence of neurodevelopmental sequelae [41–43]. Yet, one of the most important decision-making factors is the gestational age at delivery, which constitutes in large series the main predictor of post-partum outcome also in the presence of FGR [44, 45]. As a matter of fact, the largest neonatal database, The Vermont Oxford Neonatal Database, does not differentiate between FGR and premature neonates. A proper comparison of FGR outcomes, matched not only for gestational age and weight at birth, but most importantly, analyzed according to the criteria adopted for the timing of delivery, is still missing. The impact of decision-making criteria adopted for delivery might be derived from two studies. In the GRIT study, a randomized controlled trial, the effect of delivering early vs. delaying the birth was compared in cases in which there was a clinical uncertainty (thus, subjective), and when Uma PI showed absent or reverse end diastolic flow. The percentages of neonatal deaths were 8 % and 4 % at 32 weeks of gestation for

an average weight varying from 1,200 gr to 1,400 gr, respectively [46]. In the TRUFFLE study, conversely the timing of delivery was based on longitudinal monitoring of ductus venosus (DV) and computerized fetal heart rate monitoring [47]. In the cohort of 509 FGR newborns, the composite results showed that the percentage of neonatal deaths was 4 %, for an average weight of 980 gr at 31 weeks of gestation. The lower percentage of neonatal deaths than the one of the GRIT study was achieved in fetuses delivered almost one week earlier and 300 grams less. Thus, the decision-making policy is extremely complex, particularly before 32 weeks of gestation, while challenged by the fact that besides growth restriction, there is an issue of prematurity. In those cases a clinician has to balance between: 1) the decision to prolong the pregnancy, thus gaining in fetal maturity, but exposing the fetus to intrauterine hypoxia/acidemia up to, in extreme cases, to intrauterine demise; and 2) the decision to deliver in order to distance the fetus from the hostile intrauterine environment, but risking the consequences of severe fetal prematurity.

Table 2 Summary of principal findings on late and term fetal growth restriction

Late-onset and term fetal growth restriction		
Author	Design of the study	Results
Oros et al. (2011) [10]	180 fetuses suspected to be FGR at third-trimester ultrasonography with confirmed birth weight < 10th percentile were followed longitudinally.	The proportion of fetuses with normal Doppler velocimetry in UtA, UmA, MCA, and CPR was 98.6 %, 94.5 %, 85 %, and 49.6 %, respectively.
Sanz-Cortes et al. (2010) [9]	FGR fetuses with normal umbilical PI matched with AGA controls were studied by functional MRI at 37 weeks to measure markers of brain microstructure and metabolism.	FGR fetuses with normal umbilical artery Doppler present microstructural and metabolic brain changes, suggesting the existence of an abnormal in utero brain development in fetuses with this condition.
Cruz-Martinez et al. (2009) [59]	Frontal brain perfusion and MCA-PI were assessed in 60 FGR with normal UmA-PI and compared to AGA.	FGR with normal UmA-PI had a higher proportion of increased frontal brain perfusion and decreased MCA-PI than AGA.
Figueras et al. (2009) [67]	Evaluation of neurobehavioral outcomes of term FGR with normal UmA-PI.	Term FGR newborns without placental insufficiency had poorer neurobehavioral competencies.
Parra-Saavedra M. et al. (2013) [12]	The impact of umbilical vein flow volume and middle cerebral artery PI on perinatal outcome of late FGR were analyzed by a post hoc test.	Umbilical Vein flow volume <67 ml/min/kg) and MCA PI were the best predictors of labor and delivery and neonatal outcome.

FGR fetal growth restriction; AGA appropriate for gestational age; UtA uterine arteries; UmA-PI umbilical artery pulsatility index; MCA-PI middle cerebral artery pulsatility index; CRP cerebral-placental ratio

Biophysical Monitoring of Fetal Wellbeing

Biophysical monitoring of fetal wellbeing is based on: 1) evaluation of the fetal growth (although it cannot detect short-term changes in wellbeing); 2) amniotic fluid evaluation; 3) Doppler interrogation of fetal districts; 4) fetal heart rate variability; and 5) fetal biophysical profile.

Amniotic Fluid Amniotic fluid estimation is based on a semi-quantitative assessment obtained by summing the four major vertical pouches of amniotic fluid (amniotic fluid index, AFI) [48]. The reduction of amniotic fluid is a biophysical evidence of reduced fluid turnover in the fetus, and mostly a decrease in fetal kidney function. AFI per se does not constitute the decision making tool for the timing of delivery. In severe early FGR, it is a marker for more frequent Doppler velocimetry evaluation and fetal heart rate monitoring [49].

Umbilical Artery Doppler velocimetry interrogation of FGR is based on indices of severity. UmA PI above the 95th percentile requires examination twice per week; in the presence of AEDF the examination should be performed every other day [50]. Monitoring of FGR with UmA Doppler velocimetry showed a reduction in mortality (OR 0.71; 95 % CI 0.52–0.98), hospital admission, induction of labor, and delivery by cesarean section [51, 52]. In late or term IUGR, in which UmA Doppler velocimetry might be normal, AFI determines the frequency of fetal wellbeing assessment. When hypertensive disorders emerge as a consequence of severe placental damage the vicious circle

of high blood pressure and coagulation disorders often require a strict daily fetal monitoring.

Middle Cerebral Artery The fetal response to chronic hypoxia is a redistribution of blood circulation, shifting the blood from visceral compartments to vital organs such as brain, heart and adrenal glands. This adaptation is called brain-sparing effect. Middle cerebral artery (MCA) is the most easily accessible cerebral vessel, and thus the redistribution of the blood flow at the level of the brain can be documented by increased diastolic flow and decreased PI in MCA [53]. These changes usually occur in the presence of increased UmA PI, and precede the comparison of AEDF [54]. Cerebral-placental ratio (the ratio between the MCA and UmA) can identify placental-umbilical deterioration prior to the appearance of Doppler velocimetry alterations in UmA and MCA taken singularly [55]. While brain-sparing effect is generally thought to be protective, in reality, there is an association between reduced Doppler velocimetry indices in MCA and low levels of pO₂ and high levels of pCO₂ [5], and the brain vasodilatation was found to be associated to an increased incidence of neurological complications of the neonate. A study by Cruz-Martinez et al. documented suboptimal scores for social performance, attention, state organization and motor skills among late FGR neonates that had abnormal prenatal MCA Doppler [56]. Nevertheless, in case of extreme prematurity, where gestational age is a crucial predictor of neonatal outcome [45], and the knowledge that most likely it is the acidemia rather than hypoxemia

that causes irreversible developmental consequences [57], brain vasodilatation does not constitute per se the indication for delivery [58, 59]. In cases of severe FGR, in-utero monitoring should continue favoring fetal maturity, until extreme changes in UmA, such as reverse end diastolic flow, or alteration in DV, occur [50]. At this point, the late cardio-vascular manifestations become more likely [58]. In case of advanced stages of fetal hypoxia due to the loss of the compensatory mechanism, brain vascular resistance might increase as a consequence of cerebral tissue edema, and MCA PI values apparently return to normal values.

Venous District Doppler interrogation of the venous districts is of great importance. The analysis of the flow wave in DV allows indirect measurement of the quantity of the blood that DV deviates directly to the right atrium, thus depriving the liver of blood enriched by oxygen and nutrients [21]. Decreased or reversed a wave is the reflection of the dilatation of the DV [60, 61]. Ultimately, the pulsatile pattern in umbilical vein (UV) is determined by the presence of increased central venous pressure [62]. According to three prospective non-randomized trials, the dilatation of DV, as assessed by the PI of the waveform sampled at the inlet of the vessel, proved to be the best predictor of poor neonatal outcome in severe FGR [44, 58, 59]. The clinical advantage of assessing DV dilatation and abnormal PI is its occurrence a few days before the appearance of abnormal computerized cardiotocography (CTG).

Fetal Heart Rate Standard CTG or non-stress test (NST) is a monitoring tool widely used for the surveillance of high-risk pregnancies. This method provides information regarding the fetal wellbeing throughout the evaluation of the FHR frequency base line, its variability, and periodical changes. A reactive CTG reflects an adequate oxygenation of the central nervous system (CNS). Nevertheless, due to visual interpretation, the important limitation of this method is a significant intra-operator and inter-operator variability. In most European countries, the limitation of the visual analysis of FHR has been widely overcome by adopting a computerized FHR analysis, which is capable of measuring the short-term variation (STV) of FHR variability. Moreover, in premature fetuses the autonomous nervous system is immature making the interpretation of CTG complex. In these cases, and especially in FGR, the computerized CTG (cCTG) can be helpful. Thus, the advantages of cCTG are the reduction of the inconsistencies in visual interpretation of the CTG, and, more importantly, the ability to provide measurements of the homeostasis of sympathetic and parasympathetic nervous autonomous system throughout the assessment of the short-term and long-term variability.

These measurements revealed to be more indicative of the fetal acid-base status [63].

Fetal Biophysical Profile The fetal motility, which is part of the biophysical profile, has been adopted in the USA as a monitoring tool. This direct fetal assessment derives from earlier studies on fetal behavioral states. Fetal heart-rate (FHR) response to movements shows coherent patterns after 32 weeks of gestation, thus making possible to correlate heart-rate patterns to behavioral states. As a matter of fact, fetal movements should be reflected in a healthy fetus by accelerations in the FHR recordings. This is the reason why visual analysis of FHR after 32 weeks of gestation might exploit the presence or absence of small and large acceleration to assess fetal wellbeing. The fetal biophysical profile sums up the same positive parameters as observed by real time ultrasound and fetal heart rate recording. Fetal motility is usually not affected by increased placental resistance, the reason why the fetal biophysical profile might be useful tool for monitoring early FGR in the presence of severe UmA abnormalities. Indeed, the global fetal activity will start to decline in the presence of severe hypoxemia/acidemia [64], and thus fetal biophysical profile, will result affected late in the cascade of the fetal deterioration [49].

Late Onset and Term Fetal Growth Restriction

Late-onset and term FGR define an intrauterine trajectory of growth that falls below its potential late in gestation, after 34 and 37 weeks of gestation, respectively. Recognition of late and term FGR should be based on ultrasound fetal biometry of HC and AC [23] and their ratio [37]. UtA Doppler velocimetry might help to identify possible placental involvement as well as minor abnormalities of UmA Doppler velocimetry [11•], as emphasized by cerebral-placental ratio.

There are at least two uncertainties for the obstetrician managing this condition. Firstly, late-FGR is difficult to identify, and, secondly, the distinction between truly growth restricted fetus accompanied by a suboptimal placental function, and constitutionally small and healthy fetus is difficult. Such distinction is challenging, since most of diagnostic and prognostic indices of early FGR appear normal in term period. Indeed, only 15 % of late FGR is associated with an abnormal UmA Doppler velocimetry [65]. Nevertheless, the placental damage might be present although to a lesser extent to that at which abnormalities in UmA Doppler velocimetry appear [38]. In addition, in a subset of other late FGR environmental factors might play a major role in determining growth restriction, such as heavy maternal smoking [66], poor maternal nutrition [13], and others. Thorough consideration of these diagnostic criteria could be helpful in proper definition of FGR versus SGA,

important differentiation as supported by the analysis of perinatal outcomes [67, 68]. In the longitudinal post-natal studies by Figueras et al., SGA was defined based on the inclusion criteria. As a matter of fact, cases were characterized by: a strict definition of gestational age by ultrasound in the first trimester, birth weight below the local reference standards, and significantly smaller HC, even if within the cross sectional reference values. Although in the presence of normal UmA Doppler velocimetry, these are three proofs of principles of true growth restriction. At 2 years of age, these newborns showed significantly lower neurodevelopmental score in the problem solving and personal-social areas than controls. We agree with the conclusion of the study's authors: "Perinatal and neurodevelopmental outcome in small-for-gestational-age fetuses with normal umbilical artery Doppler is suboptimal, which may challenge the role of umbilical artery Doppler to discriminate between normal-SGA and growth-restricted fetuses" [68].

The identification of late and term FGR raises the question of optimal intervention, which at present is represented by the decision of appropriate timing of delivery. This decision should be supported by adequate diagnostic tools that are able to identify fetuses at risk. In such scenario, it would be possible to target interventions based on true indication, without the risk to harm in case the intervention is used too liberally. This issue has been addressed by DIGITAT trial, in which an unselected population of term fetuses with an EFW below the tenth percentile was randomized between immediate induction of labor or expectant management [69]. The incidence of adverse outcomes did not differ between the two groups, both at delivery and at 2 years of age [70]. Therefore, it appears that loose diagnostic and monitoring criteria might cause unnecessary intervention without benefit in case of constitutionally small fetuses, obscuring the possible advantage of early intervention in fetuses at real risk.

Future Directions

In the last few years, in a small case series, the assessment of new diagnostic tools parameters in the evaluation of late and term FGR has been proposed. Subtle, opposite changes in flow patterns of UmA and MCA, as expressed by cerebral-placental ratio, have been shown to correlate with MRI abnormalities and abnormal neonatal neurobehavioral development [10]. Additional criteria, such as UV flow measurements [19], proved to be of value in the subset of late FGR [12•]. In a cohort of 186 late FGR, UV blood flow volume below 68 mL/min/kg was associated with neonatal acidosis in 19 % of cases versus 6.3 % of controls ($p < 0.003$) [12•]. The defined critical value is almost identical to the cut-off value reported previously by our group in FGR 24 hours prior to delivery: 66.3 mL/min/kg [19].

Advanced analysis of FHR patterns, specifically assessing changes in the regulation of the heart rate, might be beneficial in the assessment of late FGR. Early signs of hypoxemia can be identified in the changes of the autonomous nervous system modulation of the FHR. This can be assessed by new promising methods adopted from the adult cardiology, such as spectral analysis and phase rectified signal averaging (PRSA) of FHR [71]. Both methods might be more specific than conventional cardiotocography analysis in identifying in-utero early hypoxemic changes. Indeed, this new heart rate variability assessment has shown abnormalities in about 30 % of FGR, compared to only 5–8 % analysed with conventional computer analysis [72]. Moreover, heart rate variability analysis can be even improved by trans-abdominal fetal ECG recording [73].

Conclusions

New scientific and technologic advancements have greatly improved the identification of early and late placental dysfunction, and the differentiation between fetal growth restriction of placental origin and constitutionally small fetuses. This distinction is of crucial importance for the surveillance and intervention management planning. Although further research is needed, lately special emphasis has been placed on the recognition and monitoring of late and term FGR, bringing this neglected area of fetal medicine out of subjective clinical protocols.

Conflict of Interest Enrico Ferrazzi received travel expenses reimbursed or covered by Cure Onlus in 2012.

Tamara Stampalija declares that she has no conflict of interest.

Karina Makarenko declares that she has no conflict of interest.

Daniela Casati declares that she has no conflict of interest.

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- Of importance
- Of major importance

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