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REVIEW ARTICLE

Fetal Growth Restriction (FGR): How the Differences Between Early and Late FGR Impact on Clinical Management?

Caitriona Monaghan[1] · **Baskaran Thilaganathan**[1]

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Abstract Fetal growth restriction (FGR) is associated with significantly increased perinatal mortality as well as immediate and long-term morbidity. One of the most challenging aspects of this condition is the ability to accurately define and adequately diagnose it in order to determine appropriate clinical management. Within a common pathogenesis of placental insufficiency, two phenotypes, early and late FGR, have emerged. Early FGR is easier to diagnose, however, as a consequence of extreme prematurity at presentation it can be extremely challenging to manage. Late fetal growth restriction is much more problematic to diagnose but relatively straightforward to manage as delivery is a reasonable option. Areas of research with regards to FGR, which require further evaluation, include the development of more accurate screening tools in order to identify those women at risk and validation of the role of aspirin in the prevention of this condition in a prospective adequately powered trial.

Keywords Fetal growth restriction · Early onset · Late onset · Definition · Management

Introduction

Fetal growth restriction (FGR) represents pathological inhibition of fetal growth and failure of the fetus to attain its growth potential [1]. Placental dysfunction is the leading cause of this condition, which affects approximately 3 % of pregnancies [2]. A major clinical challenge of FGR is the ability to accurately identify the truly growth restricted fetus. Detection rates in clinical practice vary, and it is reported that up to three-quarters of babies at risk of FGR are not identified prior to delivery [3]. Following a diagnosis of FGR, a subsequent clinical challenge involves determining optimum surveillance of the condition in order to adequately time delivery. FGR is associated with increased perinatal mortality, as well as immediate and long-term morbidity such as impaired cognitive development and cardiovascular and endocrine diseases in adulthood [4].

In this review, we will examine the current literature in order to highlight the implications of both early and late onset FGR and how fundamental differences between these diagnoses can impact on clinical management.

Etiology

Placental conditions resulting in placental insufficiency are the most frequent etiology of FGR and the subject of this review. Associated fetal etiologies include congenital abnormalities, chromosomal anomalies, and fetal infections. Affiliated maternal conditions include hypertension, diabetes, autoimmune disorders, cardiovascular disease, and substance abuse. These associations are, however, outside the scope of this paper. Within this common pathogenesis of placental insufficiency, two phenotypes of

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✉ Baskaran Thilaganathan
basky@pobox.com

[1] Fetal Maternal Medicine Unit, St. Georges University Hospital NHS Foundation Trust, St George's University of London, 4th Floor, Lanesborough Wing, London SW17 0QT, UK

FGR have emerged in clinical practice. They have been described relative to the gestation at which they occur i.e., early- and late-gestation FGR.

Definition

The definition of FGR remains to be one of the most controversial debates in present-day obstetrics. One of the major challenges of defining this condition relies on the the ability to differentiate a physiologically small baby i.e., one that is small for the expected gestational age (SGA) from a pathologically small fetus, which is growth restricted. There is international consensus that an SGA fetus is one in which the estimated fetal weight (EFW) is less than the 10th centile [5–7]. By definition, therefore, SGA will affect approximately 10 % of pregnancies. Whilst both the Royal College of Obstetricians and Gynaecologists (RCOG) and American Congress of Obstetricians and Gynecologists (ACOG) concur that SGA fetuses <10th centile have increased perinatal morbidity and mortality rates, FGR is not synonymous with SGA. Approximately, 50–70 % of SGA fetuses are constitutionally small, however, fetal growth is appropriate for maternal characteristics [5]. Conversely, not all fetuses with FGR are SGA as some will cross from the 90th to the 50th centile prior to delivery and therefore are failing to achieve their growth potential. Population based studies have demonstrated that antenatal detection of a small fetus regardless of SGA or FGR results in a reduction of adverse perinatal outcomes and stillbirth [8, 9]. Differentiation between these two entities, however, is important as FGR fetuses tend to have higher rates of in utero deterioration, stillbirth, and overall poorer perinatal outcomes [10].

Traditionally, the umbilical artery Doppler (UAD) has been used as a way of identifying FGR secondary to placental insufficiency. The progressive hemodynamic changes in the fetoplacental circulation secondary to placental insufficiency have been described by various research groups. In 1990, Thompson et al. reported that Doppler indices from the UAD started to increase once 60–70 % of the placental vascular tree was not functioning [11]. A subsequent decrease in impedance to flow in the middle cerebral artery (MCA) Doppler because of 'brain sparing effect' was noted by Hecher et al. [12]. Late Doppler changes described include absent or reversed end-diastolic flow (EDF) in the UAD (Fig. 1) and increased resistance in venous blood flow e.g., ductus venosus (DV). One of the drawbacks of using the UAD as a diagnostic marker of FGR is that whilst these changes are observed in the most severe subset of FGR fetuses, it fails to identify cases of mild placental disease or in FGR fetuses near term (late FGR). It has also been criticized in the setting of SGA as fetuses <10th centile with a normal UA pulsatility index (PI) have significantly poorer outcomes than appropriately grown fetuses [10]. The UA Doppler alone, therefore, is not a reliable tool to differentiate FGR from SGA fetuses.

Following this work, attempts were made to refine the definition of FGR in an effort to improve perinatal outcomes. This was the main objective of the multicenter prospective PORTO study, which examined over 1100 singleton pregnancies with EFW < 10th centile. They assessed a wide range of FGR definitions and concluded

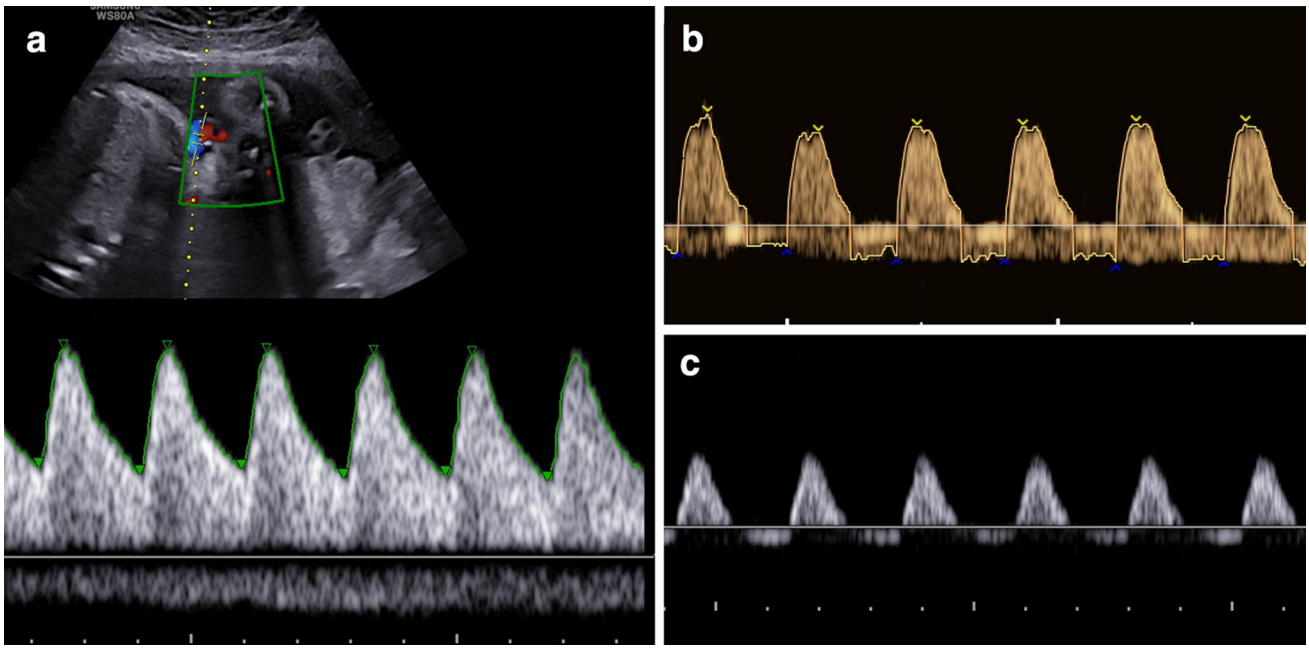

Fig. 1 **a** Positive end-diastolic flow (EDF) in the umbilical artery. **b** Absent. **c** Reversed EDF in the same vessel

that abnormal UA Doppler and EFW < 3rd centile was strongly and most consistently associated with adverse perinatal outcome [13]. In 2015, a global Delphi consensus was undertaken by 45 experts in order to address the inconsistencies in the definitions associated with FGR. A Delphi procedure aims for refinement of opinions by participating experts, while minimizing confounding factors present in other group response methods [14]. The Delphi consensus explored the concept of defining FGR by a non sized-based approach in order to enable clinicians to identify all fetuses at risk.

Early- Versus Late-Gestation FGR

Following the introduction of the terms early and late gestation FGR, there has been widespread variation in the cut-off values used to define these diagnoses. In 2014, Savchev et al. examined 656 consecutive singleton pregnancies diagnosed with FGR, in order to evaluate the optimal gestational age cut-off to maximize the differences between the two phenotypes. They determined that a gestational age cut-off of 32 weeks at diagnosis maximized the differences between early and late-onset FGR [15].

Besides reaching expert opinion on a definition of placental FGR, the Delphi procedure also aimed to develop a consensus-based definition for both early and late-onset disease [4]. Table 1 displays the mandatory and optional criteria of both early and late FGR defined by the Delphi consensus.

Commonalities and Differences in Early- and Late-Gestation FGR

The underlying commonality between early and late gestation FGR is that they occur as a consequence of placental insufficiency. Studies have shown that placental insufficiency in early FGR is associated with histological signs of early abnormal implantation [16]. To date, this association has not been demonstrated in late-gestation FGR. There is ongoing debate as to whether the placental insufficiency in late-gestation FGR is a consequence of milder disease compared to early-onset FGR or as a result of placental dysfunction occurring later in pregnancy. The key principles of management of both early and late onset FGR are the same, i.e., optimizing surveillance in order to time delivery and avoid excessive obstetric intervention and neonatal sequelae of iatrogenic preterm birth. Both conditions are also associated with increased incidence of poor neurodevelopmental, cardiovascular, and metabolic long-term outcomes for the affected fetus [10, 17–19]. Table 2

Table 1 Consensus-based definitions for early and late FGR in the absence of congenital anomalies

Early FGR (*<32 weeks' gestation*)
AC/EFW < 3rd centile or absent EDF in umbilical artery
Or
AC/EFW < 10th centile combined with PI uterine artery >95th centile and/or PI umbilical >95th centile
Late FGR (*>32 weeks' gestation*)
AC/EFW < 3rd centile
Or (at least 2 out of 3 of the following)
AC/EFW < 10th centile
Crossing centiles of more than two quartiles[a]
CPR < 5th centile

AC abdominal circumference, *CPR* cerebroplacental ratio, *EDF* end-diastolic flow, *EFW* estimated fetal weight, *PI* pulsatility index

[a] Growth centiles are noncustomized

Table 2 Early- versus late-gestation FGR

Early-gestation FGR (<32 weeks)	Late-gestation FGR (>32 weeks)
Less common: 1–2 %	More common: 3–5 %
Easy to diagnose	Difficult to diagnose and distinguish from SGA
Severe placental disease, highly associated with pre-eclampsia (PET)	Mild placental disease, low association with PET
Difficult to manage due to prematurity	Easier to manage as delivery is an option

displays the key characteristics, which can aid differentiation between early and late FGR phenotypes.

Early FGR is less common and represents approximately 20–30 % of all cases of growth restriction. It is associated with severe placental insufficiency and pre-eclampsia (PET) in up to 50 % of cases [10]. As a result of frequently abnormal UA Dopplers it is often easy to diagnose. However, because of extreme prematurity, it can be particularly challenging to manage. Late-gestation FGR is more common and constitutes approximately 70–80 % of all cases of growth restriction. It is associated with mild placental insufficiency and PET in approximately 10 % of cases [10]. UA Doppler studies are typically within normal limits, which make this condition more difficult to diagnose and monitor. As a consequence of a later gestation at presentation, cases of late FGR are typically easier to manage as elective delivery outside the realms of extreme prematurity is a possibility.

Clinical Management of Early-Gestation Fetal Growth Restriction

Severe early onset FGR affects approximately 0.4 % of pregnancies and is associated with significantly increased perinatal morbidity and mortality rates [20]. A considerable contributor to increased perinatal complications is iatrogenic preterm delivery, which may be indicated secondary to suspected fetal hypoxia, maternal pre-eclampsia or both. Despite reports of improvements in survival rates for extremely low birth weight and low gestation age infants, since the 1990s until recently, these rates were thought to vary between 7 and 33 % for severely growth restricted fetuses less than 28 weeks' gestation [21–23]. In addition to survival, there are significant long-term health implications for these neonates, which are strongly associated with both the preterm gestations at which they are delivered and as a consequence of growth restriction pathology itself [24–26].

Prenatal identification of FGR results in the reduction of adverse perinatal outcomes and stillbirth [27, 28]. In 2010, a meta-analysis reported that low-dose aspirin therapy commenced at or before 16 weeks' gestation was associated with a significant reduction in the prevalence of intrauterine growth restriction (IUGR) [29]. In order to identify those pregnancies at risk of FGR and to initiate therapy, the development of first trimester prediction models remains a key component of fetal medicine research [30]. Predictors examined to date include maternal characteristics, for example, maternal age, ethnicity, past history of hypertension etc., and biophysical parameters such as maternal mean arterial blood pressure (MAP), PI of first trimester uterine artery Dopplers. Biochemical markers that have been associated with a predictive capacity for placental disorders include placental growth factor (PIGF) and soluble Fms-like tyrosine kinase 1 (sFlt-1). A recent study examining first trimester algorithms specific for early and late FGR reported that significant contributors to early disease include black ethnicity, chronic hypertension, previous FGR, MAP, uterine artery Dopplers, PIGF, and s-Flt 1. This model achieved an overall detection rate of 86.4 % for early-onset FGR with a false positive rate of 10 % [30].

The diagnosis of early FGR is typically facilitated by the presence of maternal pre-eclampsia, abnormal fetal Dopplers, or both. The progression of Doppler abnormalities and clinical deterioration of growth-restricted fetuses is variable and dependent on the degree of placental dysfunction, gestational age, and the coexistence of maternal disease [31].

Once early FGR is diagnosed, the challenge of when to deliver a growth-restricted fetus, especially the one displaying signs of deterioration, is a contentious issue. Previously, it was believed that the intrauterine 'stress' of FGR conferred a survival benefit over appropriately grown counterparts. This belief, however, has not been substantiated by large population studies [32]. In 2011, the Growth Restriction Intervention Trial (GRIT), a multi-centered randomized controlled trial involving 548 pregnant women was conducted. GRIT-recruited women with FGR between 24 to 36 weeks' gestation, where a UA Doppler waveform was recorded, and the responsible clinician was unsure whether to deliver the fetus immediately or delay delivery. Recruited patients were randomized into "deliver now" and "defer delivery" groups until it could safely be delayed no longer. The strategies to monitor the women in the "defer delivery'' group and the final mode of delivery were decided by the attending obstetrician. GRIT reported no significant difference in overall mortality or two-year outcomes associated with immediate or deferred delivery in fetuses with growth restriction showing signs of deterioration [33]. A two-year follow-up study of these infants was published in the Lancet in 2004. The lack of difference in mortality rates was interpreted on the basis that clinicians were delivering sick preterm fetuses at the correct time to minimize mortality [34]. There was, however, an observed increase in disability in the immediate delivery (13 %) versus the delayed delivery (5 %) cohort in fetuses less than 31 weeks' gestation. The authors suggested that obstetricians might be delivering too early in an effort to reduce the effects of terminal hypoxemia on the fetal brain [34]. Despite failing to determine a significant difference in outcome whether delivery was immediate or delayed, this work highlighted the need to standardize care for the fetus with early gestation FGR and determine what parameters should be used to monitor and trigger delivery. Between

2005 and 2010, the trial of randomized umbilical and fetal flow in Europe (TRUFFLE) was conducted. This was a prospective multi-center randomized management study of FGR performed in 20 European perinatal centers [35]. Women were recruited if they had a singleton fetus between 26 and 32 weeks' gestation with an AC < 10th centile and UA Doppler PI > 95th centile. Participants were randomized into one of three groups and intervention i.e., delivery of the fetus was determined according to the criteria of the randomised group which included reduced short term variation (STV) on computerized cardiotocography (cCTG), PI of the DV > 95th centile or late DV changes such as absent or reversed a wave. In all groups, delivery could be undertaken in the presence of maternal indications or clear abnormalities on the CTG. The aim was to deliver within 24 h of the decision and after 32 weeks' gestation, the timing of delivery was determined according to local protocol. The overall perinatal death rate was 8 and 70 % of neonates survived without significant morbidity. Death, severe morbidity, and interval to delivery were all closely related to the presence of maternal hypertensive disorders [35]. A two-year neurodevelopmental update on these infants was published in the Lancet in 2015. Normal outcome was observed in 81 % of infants and there was a 1 % overall cerebral palsy rate [36]. Despite failing to detect a significant difference between the groups the combination of cCTG and DV Doppler to monitor early-onset FGR has resulted in the best published outcomes of any study to date. TRUFFLE has set the precedence for determining the best parameters, i.e., cCTG and DV Doppler used to monitor pregnancies affected by early-onset FGR.

To date, there are no evidence-based therapies to treat early-onset FGR associated with placental insufficiency. Lifestyle modifications such as stopping work, refraining from aerobic exercise, and admission for bed rest have all been suggested in an attempt to enhance the utero-placental circulation [20]. These interventions however, are not supported by evidence from randomized controlled trials. Sildenafil Citrate is a potent vasodilator, which selectively inhibits phosphodiesterase-5 inhibitors and, as a consequence, enhances the action of cyclic guanosine monophosphate. Promising results from the use of sildenafil citrate in animal models of growth restriction prompted its application to human pregnancies affected by pre-eclampsia [37]. Small trials have reported some effect on birth weight and an increased tendency to survival to discharge following the use of sildenafil in human pregnancies complicated by pre-eclampsia and growth restriction respectively [38, 39]. There have been no reports to date that sildenafil is associated with significant fetotoxicity. In order to determine whether sildenafil improves perinatal outcomes for early gestation FGR, the sildenafil therapy in dismal prognosis early-onset intrauterine growth restriction (STRIDER) trial is currently underway and results are anticipated in 2020.

Clinical Management of Late-Gestation FGR

Despite representing a significant contributing factor to adverse perinatal outcome and stillbirth, the detection of FGR developing late in pregnancy remains poor [40]. The challenge of late gestation FGR remains to be the diagnosis of the condition rather than the clinical management. The Delphi consensus defined late FGR as greater than 32 weeks' gestation with two solitary parameters of abdominal circumference (AC) and estimated fetal weight (EFW) less than the 3rd centile. There are four contributory parameters, which include EFW/AC < 10th centile, crossing centiles on growth charts of more than two quartiles, and cerebroplacental (CPR) ratio less than the 5th centile [4]. Despite a more specific, standardized definition of late gestation FGR, the question of how to screen and identify these fetuses remains an unresolved issue.

Current screening strategies for detecting FGR include measuring symphysial fundal height (SFH). In a low-risk population, however, this method will detect less than 25 % of SGA fetuses [41]. Serial or one-off routine third trimester ultrasound scans in unselected populations is not associated with an improved perinatal outcome [42]. A recent study by Triunfo et al. evaluated the use of third-trimester ultrasound screening for late FGR on a contingent basis, determined by the risk in the second trimester in an unselected population. They concluded that when predicting late FGR, a strategy of third-trimester ultrasound in 50 % of the population, based on the combined first- and second-trimester risks, was equivalent to routinely scanning the whole population of pregnant women [41]. The same research group recently performed a study aimed at developing the best performing first trimester algorithms, specifically for the prediction of early and late gestation FGR. Significant contributions for predicting late FGR were chronic hypertension, autoimmune disease, previous FGR, smoking status and nulliparous women, MAP, uterine artery Doppler, PlGF, and sFlt-1. The model achieved a detection rate of 65.8 % with a 10 % of false positive rate [30].

In addition to the challenges of identifying the late gestation growth restricted fetus, research over the last decade has focused on identifying predictors of poor outcome associated with this condition. Alterations of fetal Doppler do not follow the typical pattern of deterioration in late-gestation FGR as they do in early onset disease. Numerous vascular territories including the uterine artery and fetal middle cerebral arterial (MCA) Doppler have

been examined with regards to their sensitivity for predicting hypoxia in late-onset FGR. An abnormal uterine artery Doppler has been shown to be comparable to UA Doppler when predicting adverse outcome in late gestation FGR [43]. The oxygen requirements of the fetal brain increase with advancing gestation. As a consequence of this, one of the first hemodynamic alterations, which occurs in the presence of hypoxia is cerebral vasodilation. A reduced PI in the fetal MCA Doppler has been associated with increased risk of adverse perinatal outcome and subsequent abnormal neurodevelopment [44, 45]. The CPR, which is calculated as a ratio between the MCA-PI and the UA-PI, has been shown to be more sensitive to hypoxia than the individual components and a better predictor of adverse perinatal outcome [43]. CPR should be considered as an important assessment tool for late-onset FGR fetuses in the third trimester as early diagnosis of fetal hypoxia can optimize obstetric management and improve neonatal outcome.

In order to optimize monitoring of these fetuses and accurately assess for signs of deterioration necessitating delivery, Figueras et al. have suggested a stage-based protocol for the management of FGR. One of the principal steps involves differentiating a SGA fetus from the one, which is truly growth restricted. They suggest examining all Doppler parameters including uterine (UA, MCA, and CPR) to assist in this diagnosis. The four stage management protocol suggests monitoring frequency and delivery cut-offs based on the expected pathophysiological process, which ranges from mild insufficiency (stage I) to high suspicion of fetal acidosis (stage IV) [10]. A recurring theme in the literature with regards to the management of FGR is the need for standardization of care to improve overall perinatal outcome.

Conclusion

An accurate definition of FGR remains to be a contentious issue in the field of obstetrics. Important changes in the concept of defining this condition include a non size-based approach as well as differentiating between early and late-onset disease. As a consequence of significant prematurity, the challenge of early FGR remains to be appropriate timing of delivery. The TRUFFLE study has set the standard for monitoring and determining timing of delivery for these fetuses in order to optimize perinatal outcome. Late-onset FGR continues to test the clinician's skills of diagnosis. Once diagnosed, delivery is an option. However, further research needs to establish an optimal monitoring strategy and threshold for scheduled birth. The proverb "prevention is better than cure" is applicable to many aspects of modern medicine and as such, future research should be aimed at developing an accurate screening test for FGR. This screening test should then be implemented in a research setting in order to validate the role of aspirin in the prevention of FGR in an adequately powered prospective trial.

Compliance with ethical standards

Conflict of interest None.

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