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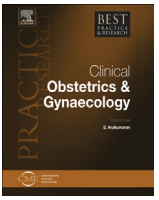

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Early onset fetal growth restriction

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Fetal growth restriction remains a challenging entity with significant variations in clinical practice around the world. The different etiopathogenesis of early and late fetal growth restriction with their distinct progression of fetal severity and outcomes, compounded by doctors and patient anxiety adds to the quandary involving its management. This review summarises the literature around diagnosing and monitoring early onset fetal growth restriction (early onset FGR) with special emphasis on optimal timing of delivery as guided by recent research advances.

Introduction

The diagnosis and management of fetal growth restriction (FGR) still remain an unresolved dilemma in modern day obstetrics. This is due to several reasons such as unclear diagnostic criteria, variable monitoring methods, complex confounding factors affecting different gestational ages and obstetrician and patient anxiety. These factors are further compounded by lack of robust evidence although recently progress has been made in this regard [1,2]. FGR is known to be associated with significant neonatal morbidity and mortality [3,4] which has large economic implications for the health service. It has been shown that improved detection of FGR could potentially save £360,000 a year in a unit with 3000 births (www.perinatal.org.uk). As our understanding continues to evolve, and given that there is no treatment for this condition, it is crucial to make an accurate diagnosis at a correct gestational age as this will determine the timing of delivery and the perinatal outcomes associated with it. Over the last couple of decades, it has become clear that FGR can start early in the gestation when it is termed early onset fetal growth restriction (early onset FGR); and this follows a more severe

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trajectory in terms of neonatal outcome as compared to late onset fetal growth restriction (late onset FGR) [5]. Studies have shown that early onset FGR can rapidly deteriorate from umbilical artery and venous abnormalities to abnormal biophysical profile leading to interventions and significant neonatal morbidity and mortality [6–8]. Furthermore, early onset FGR has shown to be associated with other pathologies such as preeclampsia (PET) and increased perinatal mortality as compared to late onset FGR which is associated with a milder form of PET [9,10]. Therefore, there is a clear need to identify the gestational age cut off to be able to label FGR as early or late, given the wider implications for antenatal management and delivery. Unfortunately, studies done until now have used arbitrary cut off gestational ages [7,8,11–13] to diagnose early onset FGR. However, this wide difference in the gestational age cut off might be considered acceptable in the broader medical community, given the variable guidance followed and the logistics of available diagnostic tools. Also, given the lack of robust research in early onset FGR, it is likely that the different gestational age ranges could be a result of consensus rather than scientific reasoning. However, a recent large prospective study evaluated the gestational age cut off according to perinatal mortality and adverse perinatal outcome in a cohort of 656 pregnancies with FGR [14]. They identified 32 weeks as the diagnostic cut off for maximising differences between early onset FGR and late onset FGR, particularly in the absence of umbilical artery Doppler information.

Definition

The agreed definition of the American College of Obstetricians and Gyneoclogists (ACOG) and the Royal College of Obstetricians and Gynaecologists (RCOG) to identify a growth restricted fetus is based on either the estimated fetal weight (EFW) or abdominal circumference (AC) < 10^{th} centile. However it became imperative to ascertain exactly which sonographic findings are truly associated with adverse perinatal outcomes. In this regard, the PORTO study [15]analysed 1100 pregnancies with EFW < 10^{th} centile and looked at various sonographic biometric and Doppler flow markers. The authors concluded that EFW < 3^{rd} centile along with abnormal umbilical artery Doppler velocimetry was consistently associated with adverse perinatal outcome and therefore could be taken as a definition of FGR. This definition gains further credence from the multicentre TRUFFLE study [5]where 503 women with FGR fetuses were recruited and followed until delivery to describe the perinatal morbidity and mortality depending on the sonographic features and gestational age of diagnosis. More recently in an attempt to accurately define FGR by international consensus, a Delphi consensus methodology was used. Experts provided there opinion on various parameters to diagnose both early and late onset FGR. For early FGR, three solitary parameters of AC or EFW < 3^{rd} centile and absent umbilical end diastolic flow and four contributory markers of AC or EFW < 10^{th} centile with a PI > 95^{th} centile in either umbilical or uterine flow were agreed upon [16].

Q2 Etiopathogenesis

It is imperative to understand the pathogenesis resulting in early onset FGR and late onset FGR to be able to guide management and delivery; particularly they are governed by different placental disorders. Early onset FGR stems from the reduction of the villous vascular area, typically more than 30%, occurring in the second trimester and resulting in increased resistance to the umbilical arterial flow [17]. This usually causes fetal biometry which, in conjunction with raised umbilical artery resistance constitutes the diagnosis of early onset FGR [18]. Early onset FGR constitutes up to 30% of all FGR and is less common than late onset FGR which constitutes up to 70% [19]. Late onset FGR occurs in the third trimester and is more associated with impaired maturation of the villi rather than reduction in the surface area. As a result, the umbilical arterial blood flow may not necessarily be impeded as the villous immaturity does not impact on the resistance; rather, it hampers the gaseous and nutrient exchange [20]. The fetus senses the hypoxic conditions and responds by reducing impedance in the middle cerebral artery (MCA) [21]. Therefore, whilst umbilical artery Doppler is crucial in the diagnosis and monitoring of early onset FGR, the middle cerebral artery (MCA) Doppler is probably more useful to diagnose late onset FGR. The progression of the condition in early onset FGR can take many weeks unless pre-eclampsia supervenes, and is more variable in late onset FGR [Figure 1]. In early onset FGR the sequence usually starts from abnormal Doppler velocimetry in the umbilical artery, MCA, ductus

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