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Screening for fetal growth restriction and placental insufficiency

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A B S T R A C T

Fetal growth restriction (FGR) continues to be a leading cause of preventable stillbirth and poor neurodevelopmental outcomes in offspring, and furthermore is strongly associated with the obstetrical complications of iatrogenic preterm birth and pre-eclampsia. The terms small for gestational age (SGA) and FGR have, for too long, been considered equivalent and therefore used interchangeably. However, the delivery of improved clinical outcomes requires that clinicians effectively distinguish fetuses that are pathologically growth-restricted from those that are constitutively small. A greater understanding of the multifactorial pathogenesis of both early- and late-onset FGR, especially the role of underlying placental pathologies, may offer insight into targeted treatment strategies that preserve placental function. The new maternal blood biomarker placenta growth factor offers much potential in this context. This review highlights new approaches to effective screening for FGR based on a comprehensive review of: etiology, diagnosis, antenatal surveillance and management. Recent advances in novel imaging methods provide the basis for stepwise multi-parametric testing that may deliver cost-effective screening within existing antenatal care systems.

1. Introduction

Fetal growth restriction (FGR) is one of the most common pregnancy complications faced by obstetricians, affecting around 3–9% of all pregnancies. FGR may be the largest population-based attributable risk factor for preventable stillbirth, present in up to 30% of such cases [1–5]. Identifying reduced fetal growth is therefore of critical importance, since low-birthweight infants have a four-fold higher risk of perinatal death and experience worse neurodevelopmental outcomes, which include alterations in brain volume, myelination, cortical structure and connectivity [6]. They also have higher rates of conditions associated with prematurity, such as respiratory distress syndrome and necrotizing enterocolitis [7]. Not only does poor growth in utero impose a health risk in the perinatal period, but it can also 'program' the fetus for long-term disease, also known as the 'Barker hypothesis'. For example, school-aged children born growth-restricted have higher rates of impaired cognition, memory, attention and gross motor proficiencies [6]. By adulthood, low birthweight is associated with increased prevalence of hypertension, coronary artery disease, diabetes, metabolic syndrome, and dyslipidemia [8,9]. The consequences of low birthweight therefore extend well beyond the postnatal period, and the extent to which more effective perinatal care could address these concerns remains unknown.

2. Etiology

Whereas the pathophysiology of small fetuses may comprise maternal, fetal, or placental factors, elements of more than one category may also be present in individual circumstances. Maternal clinical risk factors for FGR include nulliparity [10], late maternal age [11], ethnicity (African-American and South Asian) and extremes of body mass index [12]. Maternal consumption of alcohol or drug use of cocaine, heroine, and cigarette smoke also increases the risk of FGR [13–15]. Prescription medications may also act as a teratogen for growth, most usually anti-seizure, anticoagulant and antineoplastic drugs (further information: http://motherrisk.org). On a global scale, maternal malnutrition can also contribute up to 40% of cases of FGR. This contribution is especially prevalent in developing countries, and is illustrated by the INTERGROWTH-21st project which demonstrated that, under optimal maternal conditions, fetuses grow similarly in different parts of the world [16].

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Lastly, IVF and twin pregnancies (especially monochorionic twins who experience twin-to-twin transfusion syndrome) are both at a higher risk of this condition [17]. Fetal factors contributing to reduced growth include: genetic syndromes or chromosomal aneuploidies (especially triploidy and trisomies 18 and 9, which may account for >10% of cases of early FGR [18]), some forms of congenital heart disease, genetic effects of consanguinity, inborn errors of metabolism, and a range of vertically transmitted maternal infections (including the ToRCH infections: toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes) [3,19]. Where the cause of FGR is suspected to be of fetal origin, invasive testing of the placenta, amniotic fluid or maternal serum may be used to establish single gene disorders or infections as a fetal diagnosis of FGR.

In the absence of suspected intrinsic fetal disease – which, as described above, is rare – the focus for recent screening strategies in otherwise normal pregnancies is on suspected abnormal placental function, often described as "placental insufficiency," as the placenta may be one of the largest contributors to underlying disease. Reduced or unstable utero-placental blood flow can cause hypoxia-reperfusion injury to placental villi, which often also triggers pre-eclampsia [20]. The placental villi are then disrupted in their normal development, developing syncytial knots, which have impaired secretion of the pro-angiogenic placenta growth factor (PlGF) and enhanced secretion of the anti-angiogenic protein soluble fms-like tyrosine kinase-1 (sFlt-1) [21]. Placentas of women with FGR fetuses demonstrate more severe placental pathologies, such as decidual vasculopathy, placental infarction, distal villous hypoplasia and fetal thrombotic vasculopathy [22,23]. Not only can these pathologic changes within the placenta be recognized by abnormal umbilical artery (UA) Doppler [24], they can also be recognized by an altered sFlt-1:PlGF ratio in maternal blood [25], which is currently speculated to be a powerful new adjunct to estimated fetal weight (EFW) measurement in the recognition of placental insufficiency as a cause of FGR [26].

3. Fetal growth restriction classification and diagnosis

The current Canadian clinical guideline defines FGR as an EFW <10th percentile due to a pathological process, implying that the smaller fetus is failing to meet its natural growth potential [27]. The American guideline is similar, but defines FGR merely as an EFW <10th percentile [28]. In Europe, the TRUFFLE consortium (trial of randomized umbilical and fetal flow in Europe) used the definition of abdominal circumference (AC) < 10th percentile and UA Doppler pulsatility index (UA-PI) >95th percentile [2]. The Barcelona group defines FGR postnatally as the combination of an SGA newborn with birthweight <10th centile accompanied either by abnormal Doppler waveforms or merely by birthweight <3rd centile [29]. The Royal College of Obstetricians and Gynaecologists in the UK defines FGR as an AC or EFW <10th percentile; this remains the simplest clinically useful surrogate for FGR to date, with the exception of reduced growth velocity made by serial AC measurements [30].

Fetuses found to be < 3rd centile should always be considered high risk, as the highest rate of preventable stillbirth occurs below a birthweight in the 3rd centile (25.4 per 1000 births), whereas the lowest rate is found between the 70th and 84th centiles (2.4 per 1000 births) [31,32]. However, those fetuses whose growth falls between the 10th and 25th centile still incur twice the risk of perinatal mortality compared to those in the 75th–90th centile [7], demonstrating that perinatal risk occurs across a continuum of fetal growth ranges. The most recent large-scale population-based study indicates that fetuses outside the EFW centile range 25–85% have higher risk of perinatal complications, and therefore merit ongoing surveillance throughout gestation [33].

In addition to EFW centile, FGR can be delineated as early or late onset, depending on the gestational age of disease recognition [34]. Early-onset FGR, typically recognized <32 weeks of gestation, occurs in ~20–30% of all cases and is often discovered due to co-existing chronic hypertension or pre-eclampsia [2,35] and is largely associated with underlying placental pathology [22,24,36]. Late-onset FGR (≥32 weeks) occurs in ~70% of cases, but is less strongly associated with hypertensive disorders (~10% of cases) [35]. Stratification of FGR based on gestational age has great clinical utility since both the short-term maternal–fetal risks and the rate of disease progression differs, which in turn demands largely distinct management strategies.

4. Current methods of detection

4.1. Symphysis fundal height

Predating the use of ultrasound, Leopold's maneuvers and the measurement of symphysis fundal height (SFH) were historically used to assess gestational age and fetal growth. It remains an important component of the physical exam in antenatal care, especially in low-resource settings where ultrasound imaging is less available. Whereas extremes of SFH measurements are diagnostically important, SFH as a universal screening test for FGR is ineffective due to low sensitivity (17%) [37] and is not recommended in the Cochrane review [38]. The utility of SFH, may, however, be improved by customization which provides an individual predicted SFH growth curve based on physiologic variables of maternal height and weight, parity, previous birth weights, and ethnicity [39].

4.2. Ultrasound biometry

Estimated fetal weight is easily assessed using two-dimensional ultrasound measurements of the fetal AC, biparietal diameter and femur lengths. The Hadlock C formula is widely used [40,41], though multiple formulas exist which differ in their accuracy depending on the presence or absence of fetal asymmetry, especially short femurs [42]. EFW is then compared to a reference curve, ideally a fetal growth curve [43], as opposed to an unadjusted population-based birthweight curve (which disproportionately includes FGR fetuses at lower gestational ages) or to one that is customized for physiologic determinants of birthweight [44]. A meta-analysis approach, comparing the use of customized with population-based growth curves for the prediction of adverse outcomes associated with SGA birth in 20 observational studies, found similar rates for the prediction of serious adverse outcomes attributable to FGR [45]. Interestingly, a recent Scottish population-based analysis, involving 979,912 pregnancies, demonstrated no improvement in prediction of FGR-related morbidity by adopting partial customization tools [33]. Scotland is a relatively homogeneous population when compared with large North American urban centers, and customization may be most relevant in large multi-cultural cities with high rates of immigration [46], especially if fetal growth curves are not used to define growth in utero. Currently, we recommend adoption of an AC-derived fetal growth chart, such as that developed by Chitty et al. [43]. An alternative is to use the recently published World Health Organization INTERGROWTH-21 charts [47]. However, when compared to birthweight customization, it was concluded that local validation of this international population standard is needed prior to implementation to ensure accurate classification of infants at increased risk of perinatal morbidity and mortality [48].

Against the background of this debate, we know that universal third-trimester ultrasound evaluation of fetal growth substantially

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