Seminars in Fetal & Neonatal Medicine 23 (2018) 119–125

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Screening for fetal growth restriction and placental insufficiency

Melanie C. Audette [a, b, *], John C. Kingdom [a, b, c]

[a] Lunenfeld–Tanenbaum Research Institute, Toronto, Canada
[b] Faculty of Medicine, University of Toronto, Toronto, Canada
[c] Maternal–Fetal Medicine Division, Department of Obstetrics and Gynaecology, Sinai Health System, Toronto, Canada

Keywords:
Fetal growth restriction
Small for gestational age
Placental insufficiency
Doppler ultrasound
Biomarkers

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].

* Corresponding author. Lunenfeld–Tanenbaum Research Institute, 60 Murray Street, 6th floor, Room 6-1020, M5T 3H7, Toronto, Ontario, Canada.
E-mail address: m.audette@mail.utoronto.ca (M.C. Audette).

https://doi.org/10.1016/j.siny.2017.11.004
1744-165X/

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

increases the detection of the SGA fetus compared with selective ultrasound (57% vs 20% detection of SGA infant respectively) [30], but the cost of such a program and the risk to women from false-positive testing caution against widespread adoption.

Reduced fetal growth velocity also may be used to identify true FGR fetuses with greater sensitivity than a mere EFW <10th centile, but implies the need for at least two ultrasound examinations. In a prospective observational study of 1116 women diagnosed with FGR, pregnancies that progressed along a pathological fetal growth trajectory had an increased risk of pre-eclampsia, abnormal UA Dopplers, earlier gestational age of delivery, and neonatal intensive care unit admission compared to fetuses with sustained growth trajectories [49]. Thus, serial AC measurements have refined the diagnostic accuracy to predict neonatal morbidity due to FGR.

4.3. Doppler ultrasonography

4.3.1. Umbilical artery

If abnormal development of the feto-placental vascular anatomy leads to a reduction in the placental surface area for maternal–fetal gas exchange which exceeds 30%, clinical manifestations occur via increased pulsatility in UA Doppler waveforms [50–52]. When the UA PI is > 95th percentile, the observed reduced or absent end-diastolic flow patterns are highly predictive of downstream placental vascular insufficiency [53]. These Doppler changes may precede acute fetal deterioration by up to seven days [54]. UA Doppler is therefore a useful diagnostic test in the setting of early-onset FGR detected by fetal biometry, but due to its rarity in the general population, UA Doppler is not recommended as a screening test in low-risk pregnancies [55]. In addition, late-onset FGR pregnancies typically have normal UA Doppler [56], therefore it provides minimal screening utility after 34 weeks gestation.

4.3.2. Uterine artery

Uterine artery (UtA) Doppler can identify placental insufficiency due to the most frequent pathology, namely maternal vascular malperfusion (MVM) of the placenta [24]. For example, in a study of 65,819 singleton pregnancies, UtA-PI in the highest decile at 20–24 weeks was found in 80% of stillbirths occurring <32 weeks gestation with concurrent conditions associated with placental insufficiency (pre-eclampsia, abruption and/or SGA) [57]. In another large cohort study, UtA Doppler resistance in the top decile was strongly associated with subsequent “preventable” stillbirth often associated with undiagnosed FGR [58]. Since no screening studies to date have tested any intervention, this ultrasound test is not recommended for routine use in low-risk pregnancies [55]. When performed later in the third trimester, when the most severe FGR pregnancies have delivered, UtA Doppler was found to have no adjunct role in addition to AC-derived detection of FGR [30]. UtA Doppler is therefore most useful as a diagnostic test in the setting of a pre-identified early-onset FGR. Likewise, fetal Doppler studies of the middle cerebral arteries and ductus venosus have prognostic utility in the setting of early-onset FGR [56,59], but are also not recommended for generalized screening of fetal health.

5. Novel approaches to screening

5.1. Maternal serum biomarkers and multi-parametric models

The existence of serum biomarkers, obtained for the purposes of screening for Down Syndrome [60], has generated much interest in their potential use to identify pregnancies with severe placental dysfunction prior to the development of clinical complications [57,61–63]. Several large cohort studies have combined these markers with currently available surveillance approaches across each trimester in attempts to develop potential screening methods to predict cases of FGR. In 2014, a prospectively recruited cohort of 4970 women evaluated a multi-parameter screening model comprised of maternal risk factors, maternal serum pregnancy-associated plasma protein-A, β-human chorionic gonadotropin, maternal blood pressure and UtA Doppler preformed in the first trimester and reported a 73% sensitivity for early-onset FGR, which was reduced to 32% for late-onset FGR (false-positive rate of 15%) [63]. Subsequently, this group published a larger cohort of 9150 women in whom maternal characteristics, blood pressure, UtA-PI, PlGF, and sFlt-1 in the first trimester increased the sensitivity of detection for early-onset FGR to 86% and 66% for late-onset FGR (defined as birth weight <3rd percentile or ultrasound EFW <10th percentile plus abnormal Doppler measurements (false-positive rate 10%)) [64]. The overall prediction of FGR (67%) was significantly higher than for SGA (42%), illustrating the importance of making this diagnostic distinction [65].

In the second trimester, the SCOPE consortium examined 5606 pregnancies and found that the combination of 15-week biomarkers, clinical risk factors and 20-week ultrasonography had only a moderate detection for all SGA pregnancies (area under the curve (AUC): 0.69; 95% confidence interval (CI): 0.66–0.73; positive predictive value (PPV): 32%; negative predictive value (NPV): 91%), and this was mildly improved with the subset of women who had hypertensive SGA pregnancies (AUC: 0.84; 95% CI: 0.78–0.89; PPV: 20%; NPV: 98%) [66].

An alternative strategy is to universally screen using ultrasonography in the third trimester, when FGR is more likely to present [30]. Using a multi-parametric approach in the third trimester, Miranda et al. conducted a prospective nested case–control cohort study in 1590 women. Their integrated model comprised maternal risk factors, EFW, UtA Doppler, PlGF, and unconjugated estriol, achieving sensitivity of 61% for SGA increasing to 77% for FGR [29]. Interestingly, in women who presented with suspected pre-eclampsia between 20 and 34 weeks gestation, PlGF was found to have the highest sensitivity of 93% (95% CI: 84–98) and NPV of 90% (95% CI: 76–97) for FGR <3rd centile out of 47 biomarkers examined [26]. More recently, low PlGF (<5th centile) was demonstrated to predict FGR with underlying placental pathology with a sensitivity of 98% and specificity of 75% [67]. These studies emphasize the potential of just one robust biomarker, namely PlGF, to overcome the inherent limitation of one EFW ultrasound to recognize true FGR with high sensitivity. In this setting, PlGF may obviate the need for serial ultrasounds to define fetal growth velocity, at least in a majority of screening pregnancies where both EFW and PlGF are normal. This combination has the potential to achieve a much higher level of screening precision, such that any intervention in screen-positive women greatly outweighs potential harm in women who have false-positive tests.

5.2. Nucleic acids, proteins, vesicles, and metabolites

Non-invasive prenatal testing (NIPT) takes advantage of circulating fetal DNA (cfDNA) in maternal plasma to screen for aneuploidies. Similarly, circulating placental RNA (cpRNA) may also be detected in blood, serum, plasma, urine, and amniotic fluid as early as first trimester [68–70]. Accumulating evidence indicates that serum cpRNA, urinary metabolites, cord blood metabolites, and amino acid levels are altered in women who develop FGR compared to those who deliver infants in the normal birthweight range [68,71–73]. Placental exosomes, which are signaling extracellular vesicles currently being investigated for other conditions of placental dysfunction such as pre-eclampsia [74,75], may also provide novel insight into mechanisms of placental-mediated FGR. Future techniques for detection of specific analytes may also

include microarrays, next-generation sequencing, and digital polymerase chain reaction, which can identify RNA analogs (micro, circular and long noncoding RNA). These types of more sophisticated biomarkers may have the potential to distinguish certain types of FGR (i.e. fetal vs placental disease), but since placental contributions are much more common, it is likely that such biomarkers would have to outperform PlGF, which is rapidly emerging as an effective screening and diagnostic tool in the context of FGR.

6. Timing of delivery

In management of FGR, the entire clinical context, and especially gestational age, should be weighed in order to balance the risks of prematurity and potentially iatrogenic effects of delivery against those of stillbirth and long-term neurodevelopmental impairments. Despite ongoing research, delivery remains the only effective intervention to reduce perinatal mortality. The Growth Restriction Intervention Trial evaluated immediate versus delayed delivery in 548 women who presented with fetal compromise across a wide gestational range (24–36 weeks) [76]. This multicenter trial found no difference in perinatal mortality or major disability at two years between these two groups. The only difference occurred in extreme preterm deliveries <31 weeks, where 13% of babies in the immediate delivery group had neurological disability versus 5% for whom delivery was delayed [76]. This was a landmark publication, though its relevance has largely been superseded by the results of trials that focused separately on two broad categories of FGR. In early-onset FGR (between 26 and < 32 weeks of gestation), the TRUFFLE Consortium demonstrated that ductus venosus Doppler is the best monitoring tool to determine delivery [59]. In late-preterm FGR (between 34 and < 37 weeks gestation), induction of labour demonstrated a reduced stillbirth rate compared with expectant management (0.8% vs 3.1%), but interestingly no advantage for induction in term FGR pregnancies (37 to <39 weeks gestation) [77]. Similarly, the DIGITAT trial found that there was no difference in adverse outcomes between induction of labour and expectant monitoring in near-term FGR cases [78]. One caution with this trial is that a substantial population (>40%) of recruited subjects had no postnatal evidence of FGR. Currently, there is no international consensus for the optimal timing or mode of delivery across gestation in cases of FGR due to lack of power for important perinatal outcomes.

Figueras and Gratacós [56] recommend a stage-based approach to SGA and FGR pregnancies. (1) SGA fetuses: If no objective evidence of FGR is present, these fetuses should be delivered by induction of labour at 40 weeks. (2) FGR stage I: FGR fetuses presenting earlier in gestation with FGR and/or mild placental insufficiency (abnormal UA, UtA, middle cerebral artery or cerebral placental ratio Dopplers) should have weekly monitoring with induction of labour if undelivered by 37 weeks. (3) FGR stage II: FGR with severe placental insufficiency determined by UA absent end-diastolic velocity; these pregnancies can be monitored twice weekly with delivery by 34 weeks. (4) FGR stage III cases with advanced deterioration determined by UA reversed end-diastolic velocity or ductus venosus PI > 95th centile; pregnancy is generally monitored every 24–48 h, with delivery by cesarean section following maternal corticosteroids and magnesium sulfate administration by 30 weeks gestation. (5) FGR stage IV cases of severe FGR presenting with unprovoked FHR decelerations require immediate comprehensive sonographic evaluation to exclude intrinsic fetal causes. Structurally normal fetuses, in this context, typically show reversed ductus venosus a-wave flow, and have a degree of metabolic acidosis. They should therefore be delivered imminently by cesarean section at a tertiary level facility [56], without delay to administer steroids, if the fetal heart rate tracing is abnormal [79].

7. Potential therapies

Low-dose aspirin has been extensively studied for the prevention of placenta-related complications, principally pre-eclampsia and FGR. Systematic reviews of FGR pregnancies indicate a median increase in birth weight of around 150 g with this treatment [80]; however, this is insufficient to impact perinatal mortality or any composite of serious morbidity. To be effective, aspirin must be commenced by 16 weeks [81]; therefore, a screening strategy must be based either on clinical risk factors alone [28,82] or integrated as part of multi-parametric screening in early pregnancy during a window occurring before the onset of disease that allows for therapeutic intervention. Multi-parametric screening offers enhanced sensitivity for pre-eclampsia, but poses logistic challenges for implementation and significant additional costs [83]. Most recently, the UK Fetal Medicine Foundation deployed multiparametric screening in 26,941 women and randomized 1776 considered at high risk for preterm pre-eclampsia, demonstrating a substantial reduction in preterm pre-eclampsia (OR: 0.38; 95% CI: 0.2–0.74) using 150 mg aspirin daily, but this treatment had no effect upon the rate of preterm SGA birth (OR: 1.0; 95% CI: 0.42–2.46) [84].

Several research groups are currently investigating additional compounds that may augment fetal growth, in addition to aspirin. Two recent large randomized control trials focusing on low-molecular-weight heparin (LMWH) have clarified the role of this drug. The EPPI trial (Enoxaparin for the Prevention of Pre-eclampsia and Intrauterine growth restriction in women with a prior history), conducted in Australia and New Zealand, randomized 150 women, considered at risk for preterm pre-eclampsia and FGR, to enoxaparin LMWH or no LMWH (97% participants also took aspirin). In this trial no difference in clinical outcome was found [85]. These findings were consistent with the larger (249 participants) European Heparin–Preeclampsia (HEPEPE) trial of similar design [86]. However, a recent meta-analysis suggests that effects may be due to the distinct type of LMWH used, as dalteparin but not enoxaparin reduces the risk of FGR [87].

Plasma volume expansion given with nitric oxide donors and anti-hypertensives has also been shown to improve both maternal and fetal hemodynamics, to prolong pregnancy (~17 days), and to increase birthweight in cases of FGR occurring with hypertensive disorders [88]. However, this treatment approach needs to be tested in a larger randomized clinical trial before incorporation into practice. The Sildenafil Therapy In Dismal prognosis Early-onset intrauterine growth Restriction (STRIDER) trial international consortium has commenced several studies to investigate whether maternal treatment with sildenafil (a phosphodiesterase-5 inhibitor) can improve uteroplacental flow to deliver improved perinatal outcomes in established FGR pregnancies [89]. These results of the UK STRIDER trial were recently reported in abstract form by Alfirevic et al. at the 14th World Congress in Fetal Medicine and showed no effect of this drug on fetal growth [90]. Data in sheep models of FGR have shown that vascular endothelial growth factor (VEGF) adenovirus administration increases UtA vasodilation, blood flow, and fetal growth [91]. As such, the multi-center EVERREST trial is currently examining the progression of outcomes in fetuses with extreme FGR (<3rd centile and weighing <600 g) presenting between 20 and 27 weeks of gestation [92]. After characterization of their cohort, the aim of their study is to conduct a randomized pilot clinical trial, testing maternal VEGF gene therapy in severe early-onset FGR pregnancies [93]. Lastly, folic acid supplementation pre and post conception may also play a protective role against SGA pregnancies; however, in most resource-rich settings, women are rarely folate deficient [94].

8. Conclusions

The identification of SGA babies is an incomplete and imprecise surrogate marker of FGR. Research studies that include the rigor of distinguishing FGR from SGA are now being rewarded with more stringent data (higher sensitivity in screening studies) which, in turn, may lead to the delivery of improved overall clinical outcomes following specific interventions. The sensitivity for FGR will be enhanced if a cost-effective approach can be found to measure fetal growth velocity, as opposed to EFW, because a wide group of fetuses at <25th centile have increased risks of morbidity and mortality related to FGR. In this context maternal serum angiogenic growth factor testing at an initial EFW ultrasound, especially PlGF, holds great promise as a substitute for interval growth EFW ultrasounds. Therefore, future large-scale intervention studies are highly likely to combine ultrasound and PlGF to determine screening precision prior to implementing an intervention in screen-positive women.

Practice points and research directions

- The delivery of improved clinical outcomes will be enhanced by more accurate methods that distinguish fetuses that are pathologically growth-restricted from those that are constitutively small and healthy.
- Low-dose aspirin does not appear to promote fetal growth in pregnancies with suspected placental insufficiency in early pregnancy. A greater understanding of the placental basis of both early- and late-onset FGR may lead to improvements in screening and diagnosis (such as use of the PlGF blood test) and offer insight into new treatment strategies that preserve placental function in a disease-specific targeted manner.
- Fetuses growing in the 25th–85th centile range have the lowest rates of severe perinatal morbidity and mortality. Improved clinical outcomes for FGR pregnancies may require greater attention, for example by defining subsequent fetal growth velocity in all fetuses with an EFW <25th centile.
- The new maternal blood biomarker PlGF holds great potential as an adjunct to ultrasound for both the diagnosis and management of FGR pregnancies. A single measurement of PlGF in pregnancies with an EFW <25th centile may reduce the need for subsequent growth ultrasounds by indicating constitutionally normal growth at <25th centile.
- Though multi-parameter screening algorithms in early pregnancy have high test precision, they are presently not justified since no intervention strategy in screen-positive women has demonstrated any significant overall benefit.

Conflicts of interest

None declared.

Funding sources

Alva Foundation and Canadian Institutes of Health Research grant (643020) to J.C.K.

References

[1] Damodaram M, Story L, Kulinskaya E, Rutherford M, Kumar S. Early adverse perinatal complications in preterm growth-restricted fetuses. Aust N. Z J Obstet Gynaecol 2011;51:204–9.
[2] Lees C, Marlow N, Arabin B, 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.
[3] Nardozza LMM, Caetano ACR, Zamarian ACP, et al. Fetal growth restriction: current knowledge. Arch Gynecol Obstet 2017;295:1061–77.
[4] Flenady V, Wojcieszek AM, Middleton P, et al. Stillbirths: recall to action in high-income countries. Lancet 2016;387:691–702.
[5] International Stillbirth Alliance Collaborative for Improving Classification of Perinatal Deaths, Flenady V, Wojcieszek AM, Ellwood D, et al. Classification of causes and associated conditions for stillbirths and neonatal deaths. Semin Fetal Neonatal Med 2017;22:176–85.
[6] Miller SL, Huppi PS, Mallard C. The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome. J Physiol (Lond) 2016;594:807–23.
[7] Francis JH, Permezel M, Davey MA. Perinatal mortality by birthweight centile. Aust N. Z J Obstet Gynaecol 2014;54:354–9.
[8] Barker DJ. Fetal origins of coronary heart disease. BMJ 1995;311:171–4.
[9] Barker DJ. In utero programming of chronic disease. Clin Sci 1998;95:115–28.
[10] Shah PS. Knowledge Synthesis Group on Determinants of LBW/PT births. Parity and low birth weight and preterm birth: a systematic review and meta-analyses. Acta Obstet Gynecol Scand 2010;89:862–75.
[11] Odibo AO, Nelson D, Stamilio DM, Sehdev HM, Macones GA. Advanced maternal age is an independent risk factor for intrauterine growth restriction. Am J Perinatol 2006;23:325–8.
[12] Han Z, Mulla S, Beyene J, Liao G, McDonald SD. Knowledge Synthesis Group. Maternal underweight and the risk of preterm birth and low birth weight: a systematic review and meta-analyses. Int J Epidemiol 2011;40:65–101.
[13] Jaddoe VWV, Bakker R, Hofman A, et al. Moderate alcohol consumption during pregnancy and the risk of low birth weight and preterm birth. The generation R study. Ann Epidemiol 2007;17:834–40.
[14] McCowan LME, Dekker GA, Chan E, et al. Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study. BMJ 2009;338. b1081–1.
[15] Gouin K, Murphy K, Shah PS. Knowledge Synthesis group on Determinants of Low Birth Weight and Preterm Births. Effects of cocaine use during pregnancy on low birthweight and preterm birth: systematic review and metaanalyses. Am J Obstet Gynecol 2011;204. 340.e1–12.
[16] Villar J, Papageorghiou AT, Pang R, et al. The likeness of fetal growth and newborn size across non-isolated populations in the INTERGROWTH-21st project: the fetal growth longitudinal study and newborn cross-sectional study. Lancet Diabetes Endocrinol 2014;2:781–92.
[17] Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol 2004;103:551–63.
[18] Snijders RJ, Sherrod C, Gosden CM, Nicolaides KH. Fetal growth retardation: associated malformations and chromosomal abnormalities. Am J Obstet Gynecol 1993;168:547–55.
[19] Dall'Asta A, Brunelli V, Prefumo F, Frusca T, Lees CC. Early onset fetal growth restriction. Matern Health Neonatol Perinatol 2017;3:2.
[20] Mizuuchi M, Cindrova-Davies T, Olovsson M, Charnock-Jones DS, Burton GJ, Yung H-W. Placental endoplasmic reticulum stress negatively regulates transcription of placental growth factor via ATF4 and ATF6β: implications for the pathophysiology of human pregnancy complications. J Pathol 2016;238:550–61.
[21] Drewlo S, Levytska K, Sobel M, Baczyk D, Lye SJ, Kingdom JCP. Heparin promotes soluble VEGF receptor expression in human placental villi to impair endothelial VEGF signaling. J Thromb Haemost 2011;9:2486–97.
[22] Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. Fetal Diagn Ther 2014;36:117–28.
[23] Spiel M, Salahuddin S, Pernicone E, et al. Placental soluble fms-like tyrosine kinase expression in small for gestational age infants and risk for adverse outcomes. Placenta 2017;52:10–6.
[24] Levytska K, Higgins M, Keating S, et al. Placental pathology in relation to uterine artery doppler findings in pregnancies with severe intrauterine growth restriction and abnormal umbilical artery Doppler changes. Am J Perinatol 2017;34:451–7.
[25] Korzeniewski SJ, Romero R, Chaiworapongsa T, et al. Maternal plasma angiogenic index-1 (placental growth factor/soluble vascular endothelial growth factor receptor-1) is a biomarker for the burden of placental lesions consistent with uteroplacental underperfusion: a longitudinal case–cohort study. Am J Obstet Gynecol 2016;214. 629.e1–629.e17.
[26] Griffin M, Seed PT, Duckworth S, et al. Prediction of delivering a small for gestational age infant and adverse perinatal outcome in women with suspected pre-eclampsia. Ultrasound Obstet Gynecol 2017 Apr 12. https://doi.org/10.1002/uog.17490 [Epub ahead of print].
[27] Lausman A, Kingdom J, Maternal Fetal Medicine Committee, Gagnon R, Basso M, Bos H, et al. Intrauterine growth restriction: screening, diagnosis, and management. J Obstet Gynaecol Can 2013;35:741–57.
[28] American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 134: fetal growth restriction. Obstet Gynecol 2013;121:1122–33.
[29] Miranda J, Rodriguez-Lopez M, Triunfo S, 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.
[30] 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.
[31] Vasak B, Koenen SV, Koster MPH, et al. Human fetal growth is constrained

below optimal for perinatal survival. Ultrasound Obstet Gynecol 2015;45:162–7.
[32] Moraitis AA, Wood AM, Fleming M, Smith GCS. Birth weight percentile and the risk of term perinatal death. Obstet Gynecol 2014;124:274–83.
[33] Iliodromiti S, Mackay DF, Smith GCS, et al. Customised and noncustomised birth weight centiles and prediction of stillbirth and infant mortality and morbidity: a cohort study of 979,912 term singleton pregnancies in Scotland. PLoS Med 2017;14, e1002228.
[34] Figueras F, Gratacós E. Stage-based approach to the management of fetal growth restriction. Prenat Diagn 2014;34:655–9.
[35] Unterscheider J, Daly S, Geary MP, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol 2013;208, e1–6. 290.
[36] Walker MG, Fitzgerald B, Keating S, Ray JG, Windrim R, Kingdom JCP. Sex-specific basis of severe placental dysfunction leading to extreme preterm delivery. Placenta 2012;33:568–71.
[37] Sparks TN, Cheng YW, McLaughlin B, Esakoff TF, Caughey AB. Fundal height: a useful screening tool for fetal growth? J Matern Fetal Neonatal Med 2011;24:708–12.
[38] Robert Peter J, Ho JJ, Valliapan J, Sivasangari S. Symphysial fundal height (SFH) measurement in pregnancy for detecting abnormal fetal growth. Cochrane Database Syst Rev 2012, CD008136.
[39] Gardosi J, Francis A. Controlled trial of fundal height measurement plotted on customised antenatal growth charts. Br J Obstet Gynaecol 1999;106:309–17.
[40] Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements – a prospective study. Am J Obstet Gynecol 1985;151:333–7.
[41] Burd I, Srinivas S, Paré E, Dharan V, Wang E. Is sonographic assessment of fetal weight influenced by formula selection? J Ultrasound Med 2009;28:1019–24.
[42] Proctor LK, Rushworth V, Shah PS, et al. Incorporation of femur length leads to underestimation of fetal weight in asymmetric preterm growth restriction. Ultrasound Obstet Gynecol 2010;35:442–8.
[43] Chitty LS, Altman DG, Henderson A, Campbell S. Charts of fetal size: 3. Abdominal measurements. Br J Obstet Gynaecol 1994;101:125–31.
[44] Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. Lancet 1992;339:283–7.
[45] Chiossi G, Pedroza C, Costantine MM, Truong VTT, Gargano G, Saade GR. Customized vs population-based growth charts to identify neonates at risk of adverse outcome: systematic review and Bayesian meta-analysis of observational studies. Ultrasound Obstet Gynecol 2017;50:156–66.
[46] Melamed N, Ray JG, Shah PS, Berger H, Kingdom JC. Should we use customized fetal growth percentiles in urban Canada? J Obstet Gynaecol Can 2014;36:164–70.
[47] Kiserud T, Piaggio G, Carroli G, 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.
[48] Anderson NH, Sadler LC, McKinlay CJD, McCowan LME. INTERGROWTH-21st vs customized birthweight standards for identification of perinatal mortality and morbidity. Am J Obstet Gynecol 2016;214. 509.e1–7.
[49] Barker DJP, Thornburg KL. Placental programming of chronic diseases, cancer and lifespan: a review. Placenta 2013;34:841–5.
[50] Burton GJ, Woods AW, Jauniaux E, Kingdom JCP. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta 2009;30:473–82.
[51] Chaddha V, Viero S, Huppertz B, Kingdom J. Developmental biology of the placenta and the origins of placental insufficiency. Semin Fetal Neonatal Med 2004;9:357–69.
[52] Baschat AA. Fetal growth restriction – from observation to intervention. J Perinat Med 2010;38:239–46.
[53] Rahman A, Zhou Y-Q, Yee Y, et al. Ultrasound detection of altered placental vascular morphology based on hemodynamic pulse wave reflection. Am J Physiol Heart Circ Physiol 2017;312:H1021–9.
[54] Ferrazzi E, Bozzo M, Rigano S, 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.
[55] Alfirevic Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. Cochrane Database Syst Rev 2015;4, CD001450.
[56] Figueras F, Gratacós E. An integrated approach to fetal growth restriction. Best Pract Res Clin Obstet Gynaecol 2017;38:48–58.
[57] Poon LCY, Volpe N, Muto B, Yu CKH, Syngelaki A, Nicolaides KH. Second-trimester uterine artery Doppler in the prediction of stillbirths. Fetal Diagn Ther 2013;33:28–35.
[58] Singh T, Leslie K, Bhide A, D'Antonio F, Thilaganathan B. Role of second-trimester uterine artery Doppler in assessing stillbirth risk. Obstet Gynecol 2012;119:256–61.
[59] Ganzevoort W, Mensing van Charante N, Thilaganathan B, et al. How to monitor pregnancies complicated by fetal growth restriction and delivery below 32 weeks: a post-hoc sensitivity analysis of the TRUFFLE-study. Ultrasound Obstet Gynecol 2017;49:769–77.
[60] Cuckle H, Maymon R. Development of prenatal screening – a historical overview. Semin Perinatol 2016;40:12–22.
[61] Alkazaleh F, Chaddha V, Viero S, et al. Second-trimester prediction of severe placental complications in women with combined elevations in alpha-fetoprotein and human chorionic gonadotrophin. Am J Obstet Gynecol 2006;194:821–7.
[62] Proctor LK, Toal M, Keating S, et al. Placental size and the prediction of severe early-onset intrauterine growth restriction in women with low pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 2009;34:274–82.
[63] Crovetto F, Crispi F, Scazzocchio E, et al. First-trimester screening for early and late small-for-gestational-age neonates using maternal serum biochemistry, blood pressure and uterine artery Doppler. Ultrasound Obstet Gynecol 2014;43:34–40.
[64] Crovetto F, Triunfo S, Crispi F, et al. First-trimester screening with specific algorithms for early- and late-onset fetal growth restriction. Ultrasound Obstet Gynecol 2016;48:340–8.
[65] Crovetto F, Triunfo S, Crispi F, et al. Differential performance of first-trimester screening in predicting small-for-gestational-age neonate or fetal growth restriction. Ultrasound Obstet Gynecol 2017;49:349–56.
[66] McCowan LME, Thompson JMD, Taylor RS, et al. Prediction of small for gestational age infants in healthy nulliparous women using clinical and ultrasound risk factors combined with early pregnancy biomarkers. PLoS One 2017;12, e0169311.
[67] Benton SJ, McCowan LM, Heazell AEP, et al. Placental growth factor as a marker of fetal growth restriction caused by placental dysfunction. Placenta 2016;42:1–8.
[68] Cox B, Leavey K, Nosi U, Wong F, Kingdom J. Placental transcriptome in development and pathology: expression, function, and methods of analysis. Am J Obstet Gynecol 2015;213:S138–51.
[69] Tsui NBY, Jiang P, Wong YF, et al. Maternal plasma RNA sequencing for genome-wide transcriptomic profiling and identification of pregnancy-associated transcripts. Clin Chem 2014;60:954–62.
[70] Whitehead CL, Walker SP, Tong S. Measuring circulating placental RNAs to non-invasively assess the placental transcriptome and to predict pregnancy complications. Prenat Diagn 2016;36:997–1008.
[71] Favretto D, Cosmi E, Ragazzi E, et al. Cord blood metabolomic profiling in intrauterine growth restriction. Anal Bioanal Chem 2012;402:1109–21.
[72] Maitre L, Fthenou E, Athersuch T, et al. Urinary metabolic profiles in early pregnancy are associated with preterm birth and fetal growth restriction in the Rhea mother–child cohort study. BMC Med 2014;12:110.
[73] Whitehead CL, McNamara H, Walker SP, et al. Identifying late-onset fetal growth restriction by measuring circulating placental RNA in the maternal blood at 28 weeks' gestation. Am J Obstet Gynecol 2016;214. 521.e1–8.
[74] O'Brien M, Baczyk D, Kingdom JC. Endothelial dysfunction in severe pre-eclampsia is mediated by soluble factors, rather than extracellular vesicles. Sci Rep 2017;7:5887.
[75] Mitchell MD, Peiris HN, Kobayashi M, et al. Placental exosomes in normal and complicated pregnancy. Am J Obstet Gynecol 2015;213:S173–81.
[76] Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M. GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. Lancet 2004;364:513–20.
[77] Rabinovich A, Tsemach T, Novack L, et al. Late preterm and early term: when to induce a growth restricted fetus? A population-based study. J Matern Fetal Neonatal Med 2017 Mar 22:1–7.
[78] Boers KE, Vijgen SMC, Bijlenga D, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). BMJ 2010;341. c7087–7.
[79] Simchen MJ, Alkazaleh F, Adamson SL, et al. The fetal cardiovascular response to antenatal steroids in severe early-onset intrauterine growth restriction. Am J Obstet Gynecol 2004;190:296–304.
[80] Henderson JT, Whitlock EP, O'Conner E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force 2014. Rockville, MD: Agency for Healthcare Research and Quality (US); April 2014. Report No.: 14-05207-EF-1.
[81] Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstet Gynecol 2010;116:402–14.
[82] Bartsch E, Medcalf KE, Park AL, Ray JG. High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ 2016;353. i1753.
[83] O'Gorman N, Wright D, Rolnik DL, Nicolaides KH, Poon LC. Study protocol for the randomised controlled trial: combined multimarker screening and randomised patient treatment with ASpirin for evidence-based PREeclampsia prevention (ASPRE). BMJ Open 2016;6, e011801.
[84] Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017;377:613–22.
[85] Groom KM, McCowan LM, Mackay LK, et al. Enoxaparin for the prevention of preeclampsia and intrauterine growth restriction in women with a history: a randomized trial. Am J Obstet Gynecol 2017;216. 296.e1–296.e14.
[86] Haddad B, Winer N, Chitrit Y, et al. Enoxaparin and aspirin compared with aspirin alone to prevent placenta-mediated pregnancy complications: a randomized controlled trial. Obstet Gynecol 2016;128:1053–63.
[87] Mastrolia SA, Novack L, Thachil J, et al. LMWH in the prevention of pre-eclampsia and fetal growth restriction in women without thrombophilia. A systematic review and meta-analysis. Thromb Haemost 2016;116:868–78.
[88] Valensise H, Vasapollo B, Novelli GP, et al. Maternal and fetal hemodynamic effects induced by nitric oxide donors and plasma volume expansion in

pregnancies with gestational hypertension complicated by intrauterine growth restriction with absent end-diastolic flow in the umbilical artery. Ultrasound Obstet Gynecol 2008;31:55–64.
[89] Ganzevoort W, Alfirevic Z, Dadelszen von P, et al. STRIDER: sildenafil Therapy in Dismal prognosis Early-onset intrauterine growth Restriction – a protocol for a systematic review with individual participant data and aggregate data meta-analysis and trial sequential analysis. Syst Rev 2014;3:23.
[90] Alfirevic Z. Early fetal growth restriction: randomized control trial of Sildenafil therapy. In: Abstract presentation, 14th world congress in fetal medicine; June 2017. Slovenia.
[91] Carr DJ, Wallace JM, Aitken RP, et al. Uteroplacental adenovirus vascular endothelial growth factor gene therapy increases fetal growth velocity in growth-restricted sheep pregnancies. Hum Gene Ther 2014;25:375–84.
[92] Spencer R, Ambler G, Brodszki J, et al. EVERREST prospective study: a 6-year prospective study to define the clinical and biological characteristics of pregnancies affected by severe early onset fetal growth restriction. BMC Pregn Childbirth 2017;17:43.
[93] David AL, Torondel B, Zachary I, et al. Local delivery of VEGF adenovirus to the uterine artery increases vasorelaxation and uterine blood flow in the pregnant sheep. Gene Ther 2008;15:1344–50.
[94] Zhang Q, Wang Y, Xin X, et al. Effect of folic acid supplementation on preterm delivery and small for gestational age births: a systematic review and meta-analysis. Reprod Toxicol 2017;67:35–41.