Review

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The Update of Fetal Growth Restriction Associated with Biomarkers

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Abstract

Fetal growth restriction (FGR) has a prevalence of about 10% worldwide and is associated with an increased risk of perinatal mortality and morbidity. FGR is commonly caused by placental insufficiency and can begin early (<32 weeks) or in late (≥32 weeks) gestational age. A false positive antenatal diagnosis may lead to unnecessary monitoring and interventions, as well as cause maternal anxiety. Whereas a false negative diagnosis exposes the fetus to an increased risk of stillbirth and renders the pregnancy ineligible from the appropriate care and potential treatments. The clinical management of FGR pregnancies faces a complex challenge of deciding on the optimal timing of delivery as currently the main solution is to deliver the baby early, but iatrogenic preterm delivery of infants is associated with adverse short- and long-term outcomes. Early and accurate diagnosis of FGR could aid in better stratification of clinical management, and the development and implementation of treatment options, ultimately benefiting clinical care and potentially improving both short- and long-term health outcomes. The aim of this review is to present the new insights on biomarkers of placenta insufficiency, including their current and potential value of biomarkers in the prediction and prevention for FGR, and highlight the association between biomarkers and adverse outcomes *in utero* to explore the specific mechanism of impaired fetal growth that establish the basis for disease later in life.

Keywords: Biomarkers; Fetal growth restriction; Placental insufficiency; Adverse outcome

Introduction

Birthweight has been historically used as a surrogate to assess fetal growth and newborns below the 10th percentile relative to "expected weight" at a given gestational age have been generally associated with poor outcomes.[1–3] However, adhering to this definition may result in inclusion of about 18%–22% small but healthy babies.[4] Given the population heterogeneity on birthweight, there is a distinct difference for newborns who reach their intended growth trajectory yet are inherently small for gestational age (SGA, <10th percentile), and newborns who do not reach their growth trajectory and are small (<10th percentile), which is commonly a result of placental insufficiency and is cumulatively known as fetal growth restriction (FGR). Thus, it is important to note that an SGA does not directly imply FGR. Despite advancements in clinical imaging and cellular and molecular analyses, there is no gold standard method to diagnose FGR and differentiate it from a small but healthy fetus.[5] The prevalence of FGR is ~11% in high-income countries, 19% in low-income countries, and 10% in middle-income countries, and the total neonatal deaths in low- and middle-income countries as a result of FGR are 21.9%.[6] FGR is associated with complications including pre-eclampsia (PE), preterm birth, stillbirth, perinatal asphyxia, and neonatal morbidity. Sufficient dilatation of the uteroplacental circulation via spiral artery remodeling early in pregnancy combined with rapid villous angiogenesis throughout pregnancy is essential for adequate placental development and function to support normal fetal growth and development.[7]

Since 2020, the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), Society for Maternal-Fetal Medicine (SMFM), and International Federation of Gynecology and Obstetrics (FIGO) published the guidelines for the diagnosis and management of FGR,[3,8,9] where FIGO emphasized the long-term adverse outcomes in the offspring, including neurodevelopmental disorders and metabolic conditions (cardiovascular disease, hypertension, diabetes, obesity).[3] FGR babies born at term have a high risk of stunting of growth and adult metabolic disease, while those born <32 gestational weeks are also at a high risk of neonatal death or neurodevelopment delay.[2,10–12] Noncommunicable conditions in adults born with FGR include highest risk of insulin resistance diabetes and hypertension in those born preterm and increased risk of insulin resistance, obesity, diabetes, and hypertension in those born SGA.[1] In terms of neurodevelopment, FGR neonates have a high risk of motor, cognitive, and learning impairments, as well as cerebral palsy.[5,13]

The placenta is a multifunctional organ responsible for a successful pregnancy, thus laying the foundation for

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long-term health outcomes for both the mother and her child. Placental cells are in contact with maternal blood and placental cellular products (DNA, RNA, proteins, etc.) can thus be found in the maternal circulation. Several studies have demonstrated changes in the concentration of placental biomarkers relating to changes in placental function and fetal health, reflecting the assessment of early placental development, which is driven by a combination of genetic and environmental factors.[14] Maternal blood biomarkers were originally developed for detecting aneuploidy and over the past decade have been proposed to help with risk stratification for PE,[15–18] but they could also be useful for early detection of FGR since both FGR and PE share commonalities including the underlying placental dysfunction.[19,20] As such we explore the use of placental biomarkers for the prediction and prevention of FGR and developing agents of treatment in this population and highlight the potential specific biomarkers for fetal origins of adult disease.

New insight of biomarkers for placental insufficiency

During pregnancy, the placenta releases trophoblast-specific nucleic acids, hormones, and growth factors directly into the maternal blood and the profile of this secretome provides information on the key indicators of placental growth and health.[14,21–24] In this section, we will focus on the key biomarkers for placental insufficiency and emphasize their important roles in promoting fetal growth and development.[25,26]

Aberrant blastocyst development

The early embryonic developmental stages are critical to healthy fetal development. Of particular importance is normal blastocyst development with trophoblast implantation and development. The untapped potential of certain placenta-enriched molecules, including placental growth factor (PlGF), human chorionic gonadotropin (hCG), pregnancy-associated plasma protein-A (PAPP-A), and soluble FMS-like tyrosine kinase 1 (sFlt-1) and epidermal growth factor receptor (EGFR) have been highlighted previously.[27] Upon further investigation of the molecular basis of the interaction between this molecule and placental morphology as well as fetal development, it was found that an overexpression of sFlt-1 was associated with a reduction in the differentiation of trophoblast cells. The aberrant development of cells in this phase has been implicated in several significant pathologies and abnormal fetal development, such as with FGR. The sFlt-1/PlGF ratio is a marker of the balance between anti- and pro-angiogenic factors, which are relevant to the health of placental vasculature endothelium.[24]

Critical to healthy blastocyst development is proper trophoblast development. The trophoblast layer of blastocyst development is highly regulated by several genes, namely cell-cycle genes. These products have been explored as a potential biomarker of this development, which is explored as a possible surrogate measure of FGR. Nguyen *et al.*[28] focused on TGFB3 to investigate the role in cell-cycling, which was implicated in its regulation of the cell cycle by stopping cells in G1 phase. This is relevant to FGR as mothers with FGR have shown differential expression of this gene, where it is down regulated, and also related to premature cell differentiation and uncontrolled cell proliferation. Chromosomal ploidy has severe phenotypic consequences as is evidenced by various pathologies where an abnormal number of chromosomes are present. There is evidence to suggest that this is true not only of nuclear DNA, but also of mitochondrial DNA (mtDNA) quantity. In a study of mtDNA, copy number has been associated with decreased trophoblast cell differentiation, and thus placental implantation.[29] In turn, this has had consequences on fetal development, where FGR phenotypes have been observed.

Chronic hypoxia

One hallmark of FGR is chronic hypoxia due to poor oxygen transfer from the mother to fetus.[30,31] The necessity of oxygen for the production of energy in aerobic systems has led to the development of a number of adaptive response pathways over time to cope with hypoxic conditions in humans.[32] Vangrieken *et al.*[33] indicated placental chronic hypoxia was associated with the mitochondrial generation of reactive-oxygen species (ROS), alterations in molecular pathways controlling mitochondrial content, and the targeting of proteins involved in oxidative stress response signalling pathways. These adaptations are proposed as having potential therapeutic benefits in the management of pathologies related to placental hypoxia. A key player in the general hypoxic stress response pathway is the binding of hypoxia-inducible factor 1 alpha (HIF-1α) to DNA targets within the nucleus at site of the hypoxia response element. This binding allows for the transcriptional regulation of downstream genes, relevant to the hypoxic response.[34] In addition to the upregulation of genes involved in the hypoxic stress response, there is an increase in the prevalence of measurable ROS under hypoxic conditions.[32,35,36] Taking a comparative genomics approach has led to the findings of differential expression of various genes in a hypoxic environment. In hypoxic conditions, insulin-like growth factor (IGF) has been associated with the upregulation of HIF-1α binding to the hypoxia-response element of genes upregulated as a result of the hypoxia adaptive stress response. One target of HIF-1α is the genes belonging to the group of vascular endothelial-like growth factor (VEGF).

Regulation of gene expression

DNA and the coding regions of the gene are only the beginning of the story. Characterizing the genomic and proteomic networks associated with genes involved in the FGR phenotype is critical to understanding the signaling pathways involved in FGR, and thus inform treatment of FGR. One challenge that, once overcome, will become key to identifying FGR is determining biomarkers that are readily detectable and representative of FGR in early development. Thus far much of research and studies identifying biomarkers associated with FGR are from the late second trimester to term. Not surprisingly, genes associated with FGR often fall within the functional categories of angiogenesis and energy homeostasis.[37] (Table 1).

Table 1

Key gene protein product biomarkers associated with placental insufficiency.

Gene	Function	FGR expression	Category
VEGF	Member of VEGF growth factor family – promotes angiogenesis	Lower circulating levels associated with FGR	Angiogenesis
ENG	Glycoprotein in vascular endothelium	Overexpression associated with FGR	Angiogenesis
FLT1	VEGFR–angiogenesis	Overexpression associated with FGR	Angiogenesis
LEP	Hormone secreted by white adipocytes for regulation of energy homeostasis	Overexpression associated with FGR	Energy homeostasis
IGFBP-1	One of six binding proteins regulates activity of IGF-1 in metabolic regulation	Increased levels associated with FGR	Energy homeostasis

ENG: Endoglin; FGR: Fetal growth restriction; FLT1: FMS-related receptor tyrosine kinase 1; IGF: Insulin-like growth factor; IGFBP-1: Insulin-like growth factor binding protein 1; LEP: Leptin; VEGF: Vascular endothelial-like growth factor; VEGFR: Member of vascular endothelial growth factor receptor.

The regulation of these genes is central to the identification of biomarkers in FGR. One such regulatory mechanism is that of epigenetics. DNA methylation is a crucial investigation for the identification of epigenetic changes. By comparing blood circulating messenger RNA (mRNA) in preterm FGR with normal controls, Hannan *et al.*[38] found mRNA EMP1 could be a promising biomarker of severe placental insufficiency, thus circulating mRNAs can be used to monitor fetal wellbeing and identify the high risk of severe placental insufficiency. Another critical regulatory mechanism is that of microRNAs (miRNAs). Kim *et al.*[39] present maternal plasma miRNAs as potential biomarkers for detecting risk of SGA births. Some altered miRNAs (miR-28-5p and miR-301a-3p) showed sexually dimorphic expression in FGR pregnancies. Lee *et al.*[40] demonstrated three genes (*INS*, *MEG3*, and *ZFP36L2*) implicated in epigenetic imprinting, suggesting that abnormal DNA methylation patterns are likely to alter gene expression, INS is a gene coding insulin associated with glucose metabolism in fetal development.[41] Homeobox genes such as HLX play a critical role in trophoblast function and involve molecular and cellular mechanisms.[42]

Clinical approach of biomarkers in FGR

For early severe FGR, the clinical decision-making involving delivery is challenging, as it may raise the risk of extreme prematurity. Therapeutic angiogenesis can improve oxygen and nutrient transport to support normal fetal growth *in utero*, maternal gene therapy has shown potential benefit in this population. To improve the morbidity and mortality, maternal gene therapy has shown potential benefit in this population. For late-onset FGR, the main difficulty is timely diagnosis. Accurate diagnosis of FGR could aid in better stratification of clinical management and the development and application of treatment options, ultimately benefitting clinical care and potentially improving both short- and long-term health outcomes.

Application in screening and diagnosis

Screening for FGR is a challenge as the randomized controlled trails from the conventional ultrasonic screening have not shown any benefit in the third trimester[43] and the other study shows poor effectiveness of antenatal detection of FGR.[44] Alternatively, multiple biomarkers have been investigated for screening and diagnosis of FGR, including PAPP-A, hCG, PlGF and sFlt-1,[45–47] Gaccioli *et al.*[47] summarized the predictive accuracy of maternal circulating biomarker for FGR, including early onset biomarkers and angiogenic factors, hormonal factors, endothelial stress markers, and cytokine, combined Dopplers with angiogenic factors could help to better predict FGR.[47,48] However, further investigation and potential guide are needed before its wide adoption. Early-onset FGR had lower fetal fraction in the cDNA test than uncomplicated pregnancies, which can serve as a biomarker for screening asymptomatic women for possible placental-related diseases. Although NIPT is not the first line of a screening method for assessing FGR in the first trimester, it has the potential clinical value for further investigation to identify more biomarkers related to FGR.[49] ISUOG, SMFM, and FIGO published the guidelines for the diagnosis and management of FGR.[3,8,9] Three out of six guidelines recommend that PAPP-A could be the major first-trimester biomarker for SGA. Standard antenatal care in the United Kingdom and biochemical markers to access the women for pre-existing risk factors are shown in reference.[43] Overall, several groups are focusing on developing tests to screen the risk for FGR.[14,20,23,24,43,45–48,50,51]

Biomarker measurement is very challenging because the best marker to identify FGR has not yet been found, and there are multiple placental phenotypes.[14] Based on obstetric measures, low PlGF could be able to predict the FGR cases with significant abnormal placental pathology, which had the worst prognosis.[5] Screening using this sFlt-1/PlGF ratio in conjunction with ultrasonic imaging at around 36 gestational weeks could prevent adverse events.[24] Another trial provided novel evidence supporting the adoption of PlGF testing as a diagnostic adjunct in women presenting with suspected PE.[52] By screening of 22 proteins to find a combination of markers providing the best diagnostic performance to detect FGR, researchers found low serine peptidase inhibitor Kunitz type-1 (SPINT1) was significantly associated with low birth weight. Future studies could confirm to which extent whether SPINT1 drives placental disease or is a byproduct of another mechanism.[48,53]

Treatment and prevention

Maternal gene therapy aims to facilitate the expression of proteins in the mother that has translated benefits to the fetus, which may be useful for the treatment of FGR. Placental IGF gene therapy may improve placental transfer of glucose and amino acid and rescue fetal growth.[54] The EVERREST clinical trial investigated to improve placental function by administering VEGF into uterine arteries.[55] The ethical and social acceptability of using placenta-directed gene therapy will be influenced by the risks to the mother and the fetus, including the potential risk for fetal gene transfer.[56] Nawathe and David[57] translated these results to human clinical trial, which still needs to assess the risk of the intraplacental transport and the response from the fetus. Zhang *et al.*[58] found promising results in targeting the placenta via placental chondroitin sulfate, and they suggested placental surface-functionalized nanoparticles might be potential tools in targeted therapy of pregnancy complications.

Several clinical trials are developing to improve the placental insufficiency. For example, the EVERREST trial that is developing a therapy for FGR (NCT02097667); GRAFD trial aims to get the relationship between angiogenic factor with feto-placental Doppler to manage FGR (NCT02245477); a clinical trial aiming to explore the role of maternal serum VEGF in FGR complications (NCT02245477); EG-VEGF trial is to assess the potential prognostic value of seric concentrations of EG-VEGF for PE and/or FGR (NCT01490489); an ongoing trial is to investigate cord blood irisin and nesfatin-1 levels in FGR and to determine the association with abnormal fetal doppler findings (NCT03808571).

Potential specific biomarkers for fetal origins of adult disease

SGA, FGR, and prematurity have been associated with long-term chronic diseases, promoting the developmental origins of adult health and disease concept by David Barker, who stated that the fetal environment determines pathologies later in life.[59,60] There have been robust, well-documented relationships between low birth weight and adverse outcomes in adulthood.[61] Research suggests adverse fetal adverse environment temporarily or permanently affects fetal or neonatal anatomy and physiology including epigenetics and metabolism to which abnormal alterations could cause chronic disease.[62,63] However, associations between specific maternal serum biomarkers during pregnancy and later offspring outcomes may bring light to specific mechanisms of impaired fetal growth toward specific diseases encountered in adulthood, rather than lower birth weight alone, a popular surrogate for an adverse fetal environment, which could further support the Barker Hypothesis.[64–66]

These biomarkers may also be universal and suggest an adverse fetal environment. More research is needed to elucidate these markers in pregnancy in general; however, we hypothesize these biomarkers would be enriched in cases of FGR, PE, and preterm, which are conditions associated with an adverse intrauterine environment. For example, one recent study showed placental IGF1 receptor protein positively associated with serum triglycerides in children,[67] which emphasized that adverse intrauterine environment is associated with the potential risk of obesity and type 2 diabetes. Abnormal biomarkers may suggest abnormal organ growth (ie, liver) in the fetus, which may ultimately decrease the important reserves (eg, cell number and growth) that are important to face and resist environmental insults later in life.[60]

Cardiovascular disease

Sustained restriction of nutrients and oxygen to the fetus is associated with cardiovascular remodeling and epigenetic changes, fetal cardiac and arterial remodeling and a subclinical state of cardiovascular dysfunction.[68] Cardiac deterioration is associated with cord blood biomarkers and not maternal blood biomarkers.[69] B-type natriuretic peptide and troponin are known biomarkers of cardiac dysfunction, which are increased in cord blood in early and late-onset FGR.[69,70] Reduced uteroplacental blood flow and oxygen and nutrient delivery could cause aberrant fetal growth where the main physiological mechanisms are fetal hemodynamic redistribution and epigenetic alterations. First discussion of the concept of epigenetic programing of cardio-renal disease in FGR included nurim involved in cardiac remodeling,[71] long intergenic non-coding RNAs involved in cardiovascular disease.[71,72] Yzydorczyk *et al.*[73] indicate early endothelial dysfunction may relate with long-term cardiovascular-related diseases, decreased NO bioavailability, impaired eNOS functionality, oxidative stress, endothelial progenitor cells dysfunction, epigenetic factors, and vascular senescence.

Neurological disease

In the past decade, the neurodevelopmental outcome in children born with FGR has gained more attention. FGR babies have more risk of abnormal neurodevelopmental outcomes,[2,74–76] because of less adaption with small brain size, the cerebral blood flow redistributions with placental insufficiency. Although fetal circulatory redistribution to preferentially direct more flow to the brain, also called "brain sparing," serves to protect the brain, it consequently results in asymmetric fetal growth.[77] The mechanism of the brain injury occurs in part because of aberrant activation of the complement cascade and reprograming, dysregulated neural cell proliferation, slower maturation of oligodendrocyte, as well as hypomyelination, and programmed cell death.[78] The placenta produces hormones and neurotransmitters production and transfers nutrients to the fetus, thus having a direct influence on brain development. This intimate connection between the placenta and the brain is termed the "placenta-brain axis."[79,80] Decreased indoleamine 2,3-dioxygenase expression as a result of hypoxia may therefore lead to decreased clearance of superoxide and an inflammatory response, potential increasing placental 5-hydroxytryptamine synthesis, with consequences for brain growth.[81] The synthesis of serotonin occurs between the placenta and fetal brain, it should occur "placenta-brain axis" by the investigation of placental degradation of tryptophan.[12] The full effects

of FGR and placental hypoxia on placental tryptophan catabolism are largely unknown but likely to be determining vulnerability to damage arising from hypoxia, oxidative stress, or inflammation.

S100B is an acidic calcium-binding protein, which is mainly concentrated in the central nervous system and is associated with brain injury as a circulating biochemical marker caused by fetal chronic hypoxia in FGR and its levels are increased in FGR babies with intraventricular hemorrhage as revealed by testing in cord blood.[82–85] Yue *et al*.[86] presented inflammatory markers, such as interleukin (IL) -6, IL-8, and IL-10, which are also related with FGR neonates with intraventricular hemorrhage and hypoxic ischemic encephalopathy. The other biochemical markers include adrenomedullin, activin A, neuronal-specific enolase (NSE), and glial fibrillary acid protein, related with ischemia reperfusion injury. Cai[87] focused on the link between obesity, abnormal placental function and neuroinflammation. Tumor necrosis factor-alpha, IL-6, and macrophage chemotactic protein 1 played an important role in the brain injury in FGR.[88] 2,3-dioxygenase mRNA and protein expression (Tumor necrosis factor-alpha, IL-1β, and interferon-gamma), and other kynurenine pathway enzymes and kynurenine output are reduced in FGR compared with the normal controls.[89]

Metabolic and other disease

Altered placental morphology has also been linked to metabolic disorders such as hypertension in children [90] and adults.[1,60] Epigenetics is a driver of fetal programing of hypertension,[91–93] induced vascular dysfunction,[94–96] reduced deregulated expression of vascular growth and proliferation factors, such as VEGF, PGF, sFlt may also cause adult hypertension,[93] neuroendocrine impairment, several neuroendocrine pathways altered in FGR, show the evidence of the adult hypertension origin in fetal life.[65,97–99] Low birth weight has a possible impact on the prevalence of hypertension and chronic kidney disease.[66,100] Cord and maternal sera in pregnancies that produced small neonates share dysfunctional lipoproteins with proatherogenic properties, providing evidence for Barker's hypothesis[101]: oxidized low-density lipoproteins in cord blood from neonates with FGR [19] and maternal serum and umbilical cord blood leptin concentrations with FGR.[102–104] One recent study shows placental IGF1 receptor protein positively associated with serum triglycerides in children,[67] which emphasize the adverse intrauterine environment is associated with the potential risk of obesity and type 2 diabetes.

Future direction

The advancements in genomic, proteomic and metabonomic and genomic technologies are making possible in the clinical application and investigation of biomarkers in FGR. The prognostic value of biomarker between placenta, hypoxia, and inflammation could further disentangle the interplay. These can be used to study their potential role in pregnancy disease prediction. CRISPR technology is an efficient genome-scale editing tool with the new advances in inducing mutations (eg, knockout, gene insertions, etc.) by CRISPR-Cas9 technology which has provided new insights into the placental development and help to understand the pathological changes in FGR.[105] Monitoring of specific organ function may be able to predict adverse outcomes in FGR. Furthermore, organ dysfunction might have important consequences in fetal programming of postnatal specific organ disease later in adulthood. Early life events, including both fetal and neonatal environments including health status and care received may be important to predicting disease onset in adulthood. As we are moving toward precision medicine, the aim is to have robust clinical biomarkers for specific organ dysfunction in addition to classical markers for FGR like fetal biometric assessment, and in culmination may yield a strong predictive power to guide clinical management and treatment for FGR to avoid or mitigate adverse outcomes.

Conclusion

As an update on current important and potential biomarkers related with FGR, we summarize how the biomarkers help with the screening, diagnosis, and treatment in FGR fetuses, and the prediction and prevention of the adverse outcomes in FGR babies. Overall, we demonstrate the role of hypoxia, biomarkers of aberrant blastocyst development and gene expression, and provide update on the investigations of these relationships with placental insufficiency. As we progress toward precision medicine, this review focuses on using biomarkers as an approach for improving the identification of FGR, which could positively impact its clinical management including its relationship with treatment, and how to prevent the adverse outcomes of FGR during the fetal period.

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Conflicts of Interest

None.

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