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Placental Dysfunction in Fetal Growth Restriction: Emerging Biomarkers, Diagnostic Approaches, and Therapeutic Perspectives: a review article

Bayan Ali Alomari[1], **Abrar Talal Kerdawi**[1], **Marwah Ahmed Alatawi**[1], **Aeshah Ayoub Bakhsh**[1], **Ohoud Ali Alharbi**[1], **Rayan Mosaa Althagafi**[1], **Khulod Khaled Alsaadi**[1], **Jana Mansoor Aljohani**[1], **Alaa Mohammed Baraheem**[2], **Jehan Sameer Nagro**[3]

[1.] *Consultant Obstetrician and Gynecologist, King Abdulaziz Hospital, Jeddah, Saudi Arabia*
[2.] *Consultant Obstetrician and Gynecologist, East Jeddah Hospital, Jeddah, Saudi Arabia*
[3.] *Consultant Obstetrician and Gynecologist, Al Thaghr Hospital, Jeddah, Saudi Arabia*
Corresponding author: Bayan Ali Alomari
Consultant Obstetrician and Gynecologist, King Abdulaziz Hospital, Jeddah, Saudi Arabia
Email: A.alsmte@gmail.com

ABSTRACT

Background: Fetal growth restriction (FGR) is a major pregnancy complication, often accompanied by placental dysfunction, impaired vascular development and inadequate supply of oxygen and nutrient to the fetus. Prompt detection of placental abnormalities is critical in minimizing maternal and fetal complications.
Aim of Work: This review aimed to give an overview of pathophysiology of placental dysfunction in FGR, assess potential biomarkers and emerging diagnostic technologies, and review current treatments and future perspectives.
Methods: A comprehensive literature review was conducted using PubMed, Google Scholar, Scopus, and ScienceDirect. Literature search was conducted using keywords such as “Fetal Growth Restriction,” “Placental Dysfunction,” “Angiogenic Biomarkers,” “Placental Growth Factor,” “Doppler Ultrasound,” and “Therapeutic Approaches” and the relevant studies published mainly from 2016 until 2026 were identified.
Results: The results showed that abnormal trophoblast invasion, defective angiogenesis, oxidative stress and inflammation, and failure of nutrient transfer were identified as the key mechanisms underlying FGR. Angiogenic factors (notably PlGF and sFlt-1) could be useful biomarkers for early detection of FGR, while ultrasound biometry, placental Doppler velocimetry, and newer imaging techniques remain cornerstone diagnostic methods. Currently, management consists of fetal surveillance and delivery, with pharmacological interventions still in experimental phases.
Conclusion: Integrating emerging biomarkers with advanced diagnostic techniques may improve early identification and individualized management of FGR. Additional research in the clinic is necessary to identify therapies that can target the placenta and to find better ways to manage pregnancies.

Keywords: Fetal Growth Restriction; Placental Dysfunction; Placental Insufficiency; Angiogenic Biomarkers; Placental Growth Factor (PlGF); sFlt-1; Doppler Ultrasound; Placental Angiogenesis; Fetal Surveillance; Therapeutic Interventions.

INTRODUCTION

Fetal growth restriction (FGR) is one of the complications of pregnancy where the fetus fails to reach the growth potential set by its genetic makeup. It has been linked to poor outcomes for stillbirths, preterm delivery, child morbidity, and cardiovascular and metabolic complications later in life. Fetal growth restriction (FGR) is a pathological process often seen with small-for-gestational-age (SGA) fetuses, those with an estimated fetal weight (EFW) that is below the 10th percentile. Pathological

growth restriction is an important clinical dilemma due to the difference between constitutional small fetuses and those with pathological growth restriction. The Society for Maternal-Fetal Medicine (SMFM) defines FGR when EFW/ABC is less than the 10th percentile for gestational age but further fetal growth velocity and Doppler evaluation are needed for a proper risk stratification [1].

Placental dysfunction is one of the key mechanisms in the pathogenesis of FGR, especially in pregnancies which are affected by poor uteroplacental circulation. The abnormal trophoblast invasion, poor remodeling of the spiral arteries, insufficient development of placental vascular bed and increased vascular resistance all result in a decreased supply of oxygen and nutrients to the developing fetus. These abnormalities can then lead to hypoxia, oxidative stress, endothelial dysfunction, and inflammation in the placenta that will ultimately affect fetal growth and development. Importantly, early onset FGR (before 32 weeks) and late onset FGR (at or after 32 weeks) have different clinical and placental profiles, which should be investigated and monitored differently [2].

Correct diagnosis depends on a combination of serial ultrasound biometry, fetal growth velocity and Doppler velocimetry. Umbilical artery Doppler is especially useful for detecting increased placental vascular resistance, and middle cerebral artery Doppler and the cerebroplacental ratio (CPR) can be used to determine fetal circulatory redistribution in response to hypoxemia. Furthermore, Doppler of uterine artery may assist in the diagnosis of reduced uteroplacental flow. The International Society of Ultrasound in Obstetrics & Gynecology (ISUOG) underlines that fetal size is not enough to distinguish pathological FGR from constitutional SGA and hence, the need for longitudinal assessment and multimodal approach [2].

Over the past few years, there has been a greater focus on the detection of circulating markers of placental dysfunction that occur prior to the onset of obvious fetal growth impairment. The most studied biomarkers include the balance of proangiogenic and antiangiogenic activity represented by placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1). A decrease in maternal PlGF or an increase in sFlt-1/PlGF has been linked to poor placental vascular function. In a prospective study of 367 pregnancies with SGA/FGR, Hong et al [3] showed significant relationships between abnormal PlGF levels, increased sFlt-1/PlGF ratios, Doppler abnormalities, and placental maternal vascular malperfusion. Moreover, new molecular methods based on microRNAs, messenger RNAs and other circulating molecules from the placenta provide exciting potential for improved detection of pathological pregnancies at an early stage .

Recent studies have also underscored the promising clinical importance of the role of angiogenic biomarkers in established diagnosis. A clinical use of angiogenesis biomarkers in fetal growth restriction (FGR) narrative review identified PlGF and sFlt-1 as potential biomarkers for the prediction, diagnosis, and monitoring of FGR, but these markers have yet to be sufficiently standardized for routine use. These results highlight the importance of better validating the use of multiple markers instead of a single one [4].

Even with advances in the diagnosis and technology, there is still a limited number of therapies available for established FGR, especially if there is irreversible placental dysfunction. The current management is more about monitoring of mother and fetus, optimal management of pregnancy and delivery at the right time as per the gestational age and fetus condition .

Aim of the Work

This review aims to investigate the pathogenetic processes involved in placental failure in fetal growth restriction, examine current and potential novel biomarker tools and imaging methods, and review the existing and future therapeutic options and outlook.

METHODS

The scientific articles used for this review were collected from scientific databases, by using the followings key terms; "Fetal Growth Restriction", "Placental Dysfunction", "Placental Insufficiency", "Angiogenic Biomarkers", "Placental Growth Factor", "sFlt-1", "Doppler Ultrasound", "Oxidative Stress", "Therapeutic Approaches". PubMed, Google Scholar, Scopus, and ScienceDirect served as the sources for these scientific databases. Selection of articles was made on the basis of predefined inclusion and exclusion criteria. Only abstracts and titles of studies were initially screened to identify studies relevant to the review objectives. Duplicate papers, case reports, non-full text publications and papers

not addressing placental dysfunction and FGR were excluded. Selected original articles and reviews, all as full text, open access, from 2016 to 2026, peer-reviewed articles, clinical trials, and observational studies were included. Prior publications were taken if they were relevant to current diagnostic guidelines and key principle.

RESULTS

In the current review, studies focusing on the intricate interplay between placental dysfunction and fetal growth restriction (FGR), and especially the pathophysiological background, recent discoveries regarding biomarkers, strategies for diagnosis and therapeutic opportunities will be included. It also looks at the significance of placental angiogenic imbalance, oxidative stress, inflammation and impaired nutrient transport in fetal growth abnormalities. The articles selected were mainly published from 2016 to 2026. The findings are presented in the discussion section and are grouped under the following themes: placental dysfunction; molecular mechanisms of FGR; emerging biomarkers for identification and prediction; ultrasound, Doppler, and advanced methods to assess placental function; and current therapeutic strategies and future prospects of FGR management.

DISCCUSSION

1. Pathophysiological Mechanisms of Placental Dysfunction in Fetal Growth Restriction

Fetal growth restriction (FGR) is a complex condition of the pregnancy involving a major role for placental dysfunction in preventing the fetus from reaching its genetically determined growth potential. The placenta transfers enough oxygen, nutrients, hormones and eliminates waste products to support fetal growth. These functions are disrupted as a result of a complex interplay of pathological processes that includes abnormal trophoblast invasion, dysfunctional remodeling of the spiral arteries, impaired placental angiogenesis, oxidative stress, inflammation, and nutrient transport. Recent studies indicate the mechanisms are interrelated to generate a progressive placental insufficiency rather than pathological events occurring in isolation [5].

1.1 .Abnormal Trophoblast Invasion and Spiral Artery Remodeling

Growth restriction in the fetus is one of the earliest mechanisms leading to the placental dysfunction in FGR, and this is due to inadequate invasion of the extra-villous trophoblasts (EVTs) in the maternal decidua and myometrium. Normally, EVTs enter into the maternal spiral arteries and replace both the endothelial and muscular cells of the arteries, making them come to be low-resistance and high-capacity. This physiological remodeling will assure that there is continuous maternal blood flow into the intervillous space to provide the developing fetus with adequate oxygen and nutrients. In FGR pregnancies, inadequate invasion leads to failure of the spirals to remodel, ongoing vascular resistance, and diminished uteroplacental perfusion. This in turn leads to intermittent blood flow and poor oxygen to the placenta. Among pathological features of FGR, impaired placental vascular development and the decreased proliferation of trophoblasts are discussed by Umapathy et al [5]. In addition, Bujorescu et al. [6] reported that in pregnancies complicated by early onset FGR, histopathological examination revealed intrauterine mal-perfection of the maternal vessels, placental infarctions and abnormal villous maturation, which implicated defect in placentation as a cause of impaired fetal growth .

1.2 .Disordered Placental Angiogenesis and Vascular Development.

During normal placental development, vasculogenesis and angiogenesis must coordinate to form a network of blood vessels that gradually becomes more extensive to accommodate the growing demands of fetal metabolism. Several angiogenic factors control these processes, including vascular endothelial growth factor (VEGF), placental growth factor (PlGF) and angiopoietins. In FGR, abnormal vascular development is correlated with fewer branching of placental vessels, fewer placental terminal villous volumes and changes in vascular density and structure. These changes cause an increase in vascular resistance and a decrease in the available surface area for maternal–fetal exchange. Li et al. [7] recently identified molecular evidence of altered pathways involved in both angiogenesis and vasculogenesis in FGR placentas. They analyzed their transcriptomes to find hypoxia-inducible factor-1 alpha (HIF-1α) and VEGFA as key molecular regulators with a higher expression level in selective FGR patients correlating with clinical severity. These results indicate that a key aspect of placental vascular anomaly is the dysregulation of angiogenic signaling, leading to a loss of fetal growth .

1.3 .Placental Hypoxia and Oxidative Stress

Hypoxic exposure to placental tissue and repeated IRI due to reduced uteroplacental perfusion. This process generates reactive oxygen species (ROS) that can overwhelm the antioxidant defense of the placental cells leading to oxidative stress. ROS production in excess can harm the trophoblast and the structure of the placenta by damaging the cell membranes, proteins and lipids, and the mitochondrial structure. Hypoxia also stimulates the HIF-1α pathway, which is a regulation mechanism for cellular adaptation to low oxygen and affects angiogenic and metabolic pathways. The effects of oxidative and nitrative stress are vital to the development of FGR due to impaired nutrient transfer, premature cellular senescence and increased trophoblast cell death [8]. In addition, mitochondrial dysfunction lowers metabolic activity and an energy deficit is a further limitation in placental normal development. Together, these abnormalities form a vicious cycle of hypoperfusion leading to oxidative injury, which in turn exacerbates placental dysfunction .

1.4 .Inflammation and Immune Dysregulation

A favorable immune environment at the maternal–fetal interface is required to allow the invasion of trophoblasts, placental development and fetal tolerance. FGR is associated with changes in immune regulation that could result in placental inflammatory response and vascular impairment. Abnormal placentation has been linked to changes in the function of decidual natural killer cells, regulatory T lymphocytes, and macrophages. The production of pro-inflammatory cytokines such as tumor necrosis factor-a (TNF-a), interleukins (IL-6, IL-1 beta), may induce trophoblast apoptosis and endothelial damage. Moreover, inflammatory signaling can also modulate oxidative stress and angiogenic imbalance, contributing to further placental damage. In recent years, molecular studies have focused more and more on the interaction between inflammatory pathways and trophoblast dysfunction as part of the pathophysiological network underlying FGR [9].

1.5 .Placental nutrient transport and metabolic dysfunction.

Another key mechanism of FGR is the blockage or reduction of the transport of essential nutrients needed for development in the fetus. The syncytio-trophoblast controls the passage of glucose, amino acids, fatty acids and other metabolic substrates from the mother to the fetus. Placental insufficiency may also lead to a downregulation and/or dysfunction of certain nutrient transporters, such as amino acid transporters of the System A, which decreases the fetal availability of nutrients. Umapathy et al [5] found that the expression and activity of the System A transporters is found to be reduced by about 63% in FGR placentas compared to uncomplicated ones. In addition, alterations in placental glucose transfer and metabolic signaling pathways, for example the mechanistic target of rapamycin (mTOR) pathway, can contribute to inadequate fetal substrate supply. Such metabolic derangements ultimately restrict cell proliferation, organogenesis and fetal growth .

1.6 .Epigenetic Modifications and Molecular Control

Emerging evidence suggests that epigenetic modifications contribute to the development and progression of placental dysfunction in FGR. The alterations of the DNA methylation, histone modifications, and microRNAs expression could affect genes related to trophoblast differentiation, angiogenesis, inflammation, and nutrient transport. Specifically, hypoxia-associated molecular signaling and dysregulated microRNAs could lead to placental gene expression and cellular response to environmental stress changes. Li et al. [7] found eight differentially expressed miRNAs and several dysregulated mRNAs linked to placental hypoxia and vascular development, which further demonstrates molecular regulatory imbalances in FGR. The present results demonstrate the need to explore epigenetic mechanisms as potential contributors to placental dysfunction and future diagnostic or therapeutic targets .

In general, vascular, cellular, inflammatory, oxidative and metabolic dysfunctions are all involved in the onset of FGR. These interconnected mechanisms are essential for the determination of reliable biomarkers, better diagnosis at earlier stages and targeted therapeutic interventions.

2. Emerging Biomarkers for Early Detection and Prediction of Fetal Growth Restriction

Identification of reliable biomarkers of fetal growth restriction (FGR) is an imminent research priority, especially as conventional ultrasound assessment can detect growth abnormalities only when there is placental dysfunction. The goal of emerging biomarkers is to detect abnormalities in the placenta at an earlier stage; to better stratify the risk; to differentiate pathological FGR from the normally small fetus; and to predict the adverse perinatal outcome. Recent studies have targeted angiogenic factors, placental

proteins, inflammatory mediators, circulating nucleic acids, metabolomic and proteomic profiles as markers of abnormal placental function [10].

2.1 .Angiogenic Biomarkers: PlGF and sFlt-1

The two most common markers of placental dysfunction that have been investigated are placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1). PlGF promotes the proliferation of endothelial cells as well as tissue vascularization while sFlt-1 is an anti-angiogenic protein that traps PlGF and VEGF, reducing their activity. Low levels of PlGF and high levels of sFlt-1/PlGF in mothers with placental insufficiency may reflect impaired placental angiogenesis. A narrative review of Clinical Use of Angiogenesis Biomarkers in Fetal Growth Restriction stressed the importance of their potential use in predicting FGR, in monitoring the disease process, and in improving clinical risk assessment [4]. In addition, Kim et al [11] conducted a meta-analysis of 22 observational studies showing significantly lower levels of PlGF in pregnancies that subsequently developed FGR and small-for-gestational-age (SGA) birth. The overall sensitivity of PlGF was however modest (29%), meaning that it cannot be used as a standalone screening test. The findings are in agreement with the idea of using angiogenic biomarkers in combination with maternal traits and ultrasound assessment.

2.2 .Placenta-Derived Proteins and Novel Circulating Biomarkers.

Proteins derived from the placenta are another potential class of biomarkers that could be related to trophoblast activity, placental development and maternal–fetal interaction. Pregnancy-associated plasma protein-A (PAPP-A), placental protein 13 (PP13), soluble programmed death-ligand 1 (sPD-L1) are some proteins that have gained more attention in recent years. Wang et al [12] conducted a prospective nested case-control study, which included 50 women whose pregnancies became FGR and 100 women whose pregnancies did not become FGR. The investigators also noticed significantly lower sPD-L1 levels in affected pregnancies, with the area under the receiver operating characteristic curve (AUC) of 0.75 for overall FGR and 0.84 for early-onset FGR. However, there were no significant differences between groups for other proteins such as placenta-specific protein 1 (PLAC1) or netrin-1. These results indicate that sPD-L1 can serve as an early biomarker, but further multicenter studies are needed to validate its predictive value and clinical utility .

2.3 .Proteomic Biomarkers and Molecular Signatures

The use of new proteomic technologies has led to the identification of proteins involved in abnormal placental growth and fetal development. Targeted proteomic analysis provides the possibility to measure alterations of many proteins in the blood at one time instead of using individual biomarkers. Investigators compared plasma samples from 44 women with placental-mediated FGR to 44 healthy pregnant women in a Zhou et al [13]`s study, with the use of Olink targeted proteomics. A protein panel was identified in the investigation to contain proteins and biological pathways associated with placental dysfunction, which could give more information for early detection of affected pregnancies. However, the candidates need independent validation before clinical use .

2.4 .Metabolomic Biomarkers and Emerging Multi-Omics Approaches

A further approach worth investigating, in the metabolomics technique, which identifies alterations in small molecules active in energy production, amino acid metabolism, lipid metabolism and oxidative stress. In a systematic review published in Nature Communications, Conde-Agudelo et al. [10] studied metabolomic signatures of FGR and SGA, demonstrating the promise of metabolic signatures to describe abnormal fetal and placental development. Recently, Cao et al [14] have explored amniotic fluid using integrated proteomic and metabolomic profiling. They found a protein-based diagnostic signature consisting of platelet derived growth factor A (PDGFA) and phosphorylated STAT5A with an AUC of 0.780 in an independent validation set. In addition, a molecular signature consisting of IREB2, HLA-C, and PLXNB2 showed promise in differentiating persistent FGR from transient growth restriction. While these results are encouraging, the procedure of amniotic fluid sampling is invasive and the molecular signatures identified need to be clinically validated.

In conclusion, emerging biomarkers offer great promise for enhancing the early diagnosis and understanding of FGR. But no one biomarker is at present sensitive and specific enough for universal screening. Future studies should focus on integrating angiogenic, inflammatory, proteomic and metabolomic markers with maternal risk factors and ultrasound results to create more accurate, non-invasive, and clinically useful predictive models.

3. Diagnostic Approaches and Assessment of Placental Function in Fetal Growth Restriction

Diagnosis of fetal growth restriction (FGR) requires a complete evaluation of fetal growth, placental function, and fetal cardiovascular adaptation. Modern diagnostic methods use not only to detect fetuses with reduced growth but also to differentiate pathological FGR from constitutionally small-for-gestational-age (SGA) fetuses. The development of ultrasound biometry, Doppler velocimetry and maternal biomarkers, combined with advanced imaging techniques, has been highlighted to enhance the diagnostic accuracy and predict adverse perinatal outcomes in recent studies [15].

3.1 .Ultrasound Assessment and Fetal Biometry

Ultrasound is a crucial test to evaluate suspected FGR. The estimated fetal weight (EFW) is obtained by fetal biometrics (e.g. Abdominal circumference (AC), head circumference (HC) and femur length (FL)) and compared to the growth reference for every gestational age. EFW or AC < 10 percentile suggest FGR, and < 3 percentile suggests severe growth restriction. A single measurement is not sufficient to reliably distinguish pathological growth restriction from constitutional smallness, however. Hence, serial ultrasound and evaluation of fetal growth velocity are important in the detection of growth decline. To reduce variability related to measurement, fetal biometry is recommended to be repeated at least every two weeks, as outlined in the German-Austrian-Swiss clinical guideline. The 2024 Royal College of Obstetricians and Gynecologists (RCOG) Green-top Guideline also highlights the importance of assessing the growth velocity of the abdominal circumference over time rather than the estimated fetal weight [16].

3.2 .Doppler Velocimetry for Placental and Fetal Circulation

Doppler ultrasound is an important non-invasive tool for evaluating fetoplacental circulation and detecting higher vascular resistance of placental insufficiency. Umbilical artery (UA) Doppler measures the resistance in the placental blood flow. The PI, the lack of end-diastolic velocity, and the presence of reversed end-diastolic velocity all reflect a decreased degree of placental perfusion and are correlated with an increased perinatal risk. When oxygen is limited to the fetus, the middle cerebral artery (MCA) Doppler can give information on fetal circulatory redistribution (brain-sparing response). The cerebroplacental ratio (CPR) is the ratio of MCA PI/UA PI, which is a combination of these parameters and may improve the identification of fetuses with hypoxic adaptation. In a prospective observational study with 184 pregnancies, arterial Doppler parameters in early- and late-onset FGR showed the value of studying several vascular territories in assessing severity of disease and neonatal outcome [17].

3.3 .Uterine Artery and Ductus Venosus Doppler Assessment

The Doppler signal of the uterine artery (UtA) helps to quantify maternal uteroplacental blood flow and can help identify impaired remodeling of the spiral artery (UtA) and increased vascular resistance (VA). High uterine artery PI, especially during early pregnancy, may represent impaired placentation and be associated with an increased risk of placental-mediated complications. Ductus venosus (DV) Doppler, on the other hand, assesses fetal venous circulation and cardiac function, and gives key information regarding advanced fetal cardiovascular compromise. Abnormal DV waveforms, especially if there is no or reversed flow during atrial contraction, may be a sign of greater fetal deterioration and a risk for adverse outcomes. The Society of Obstetricians and Gynecologists of Canada (SOGC) guideline suggests that all Doppler probes, including uterine artery, umbilical artery, MCA, CPR and DV, be used together to monitor early onset FGR. These results clearly show that the assessment of the maternal and fetal circulatory system gives a more complete assessment than a single Doppler parameter [18].

3.4 .Advanced Placental Imaging with Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has become a potentially useful complimentary technique to study the structure and function of the placenta, especially in cases where there is a suspected placental insufficiency. In contrast to traditional ultrasound, MRI allows for detailed tissue characterization and can be used to investigate placental oxygenation, perfusion and microstructural abnormalities. Placental dysfunction has been investigated with quantitative imaging biomarkers such as T2-mapping, blood oxygenation level dependent (BOLD) imaging, arterial spin labeling (ASL) and intravoxel incoherent motion (IVIM). A review published in Magnetic Resonance in Medical Sciences highlighted the potential of quantitative MRI parameters to provide objective measurements of placental oxygenation and perfusion. However, there are currently some shortcomings in the routine use of imaging markers: imaging protocols are not standardized, and there is still insufficient large scale clinical validation [19].

3.5 .Biochemical Assessment and Integration of Diagnostic Methods

Biochemical assessment can be used alongside the imaging technique to provide molecular evidence of placental dysfunction. The maternal circulation of PlGF and the sFlt-1/PlGF ratio is especially helpful for exploring angiogenic imbalance due to placental disease. This may help differentiate between FGR mediated by the placenta and constitutionally small for gestational age fetuses, with their integration into fetal biometry and Doppler parameters. Furthermore, fetal heart-rate patterns can be assessed also using cardiotocography (CTG) and computerized CTG can detect fetal compromise. Villalaín et al [15] highlighted the importance of a systematic approach to diagnosis including precise pregnancy dating, accurate assessment of maternal risk, careful fetal anatomical evaluation, measurement of angiogenic markers and Doppler fetal surveillance. Another systematic review of artificial intelligence and machine-learning applications highlighted their potential for promising diagnostic performance, with multimodal AI models showing potential benefits over single-modality diagnostic methods, and combining clinical, ultrasound, imaging and molecular information. But external validation is required before these technologies can be integrated into regular obstetric care [20].

In summary, a comprehensive and longitudinal diagnostic solution is needed for placental function in FGR. Combining the use of fetal growth, Doppler, biochemistry, and diagnostic imaging in the making can improve the detection, classification, and early prediction of adverse perinatal outcomes.

4. Therapeutic Perspectives and Future Directions in the Management of Fetal Growth Restriction

Fetal growth restriction (FGR) is a significant problem in obstetric management, as there is no single accepted intervention that will reverse established placental insufficiency. The primary goals of current therapeutic strategies are to identify pregnancies at high risk, optimize maternal health, monitor fetal health and determine the optimal timing of delivery to minimize perinatal morbidity and mortality. In recent years, there has been a growing interest in preventive interventions, pharmacological approaches aimed at placental vascular dysfunction, and new strategies to improve placental function. The effectiveness of most experimental treatments, however, is not known and close fetal monitoring is still the basis of clinical management [1].

4.1 .Preventive Strategies and Maternal Interventions

Prevention of placental dysfunction is an important component of FGR management particularly if there are known risk factors with the mother. Women with a risk of preeclampsia should consider taking low-dose aspirin, particularly before 16 weeks of pregnancy. Potential benefits include antiplatelet aggregation, antiutero-placental vascular dysfunction, and vaso-modulation of the placenta. However, aspirin is best thought of as a preventative rather than a treatment for established FGR, in selected high-risk pregnancies. Optimization of maternal nutrition, quitting smoking, managing chronic hypertension, and regulating preexisting medical conditions are also crucial steps to take to improve pregnancy outcomes. The International Society of Ultrasound in Obstetrics and Gynecology has stressed the need for early detection of maternal risk factors and proper surveillance to reduce the risk of complication associated with placental insufficiency [21].

4.2 .Pharmacological Therapies and Experimental Interventions

Several drugs have been studied with regard to their ability to improve placental perfusion and fetal growth. Phosphodiesterase-5 inhibitors, such as sildenafil, were suggested to help improve nitric oxide-mediated vasodilatation and to increase uteroplacental blood flow. However, clinical trials have not been consistent in their results. Sharp et al [22] have conducted a randomized controlled trial (STRIDER) in severe early onset FGR's and established that there was no evidence to suggest that sildenafil prolonged pregnancies and improved the perinatal outcome. Moreover, the Dutch STRIDER trial showed more cases of neonatal pulmonary hypertension in the sildenafil-treated than placebo-treated infants (18.8% versus 5.1%). Further results also indicated that there was no improvement in neurodevelopment in children. For this reason, sildenafil is not recommended for the treatment of FGR outside research environments .

Other experimental therapies are pravastatin, nitric oxide donors, melatonin, insulin-like growth factor (IGF) therapy, and VEGF-targeted agents. The goal of these treatments is to restore endothelial function, decrease oxidative stress, control angiogenesis and re-establish placental vascular activity. These new therapeutic approaches were reviewed by Stone [23] who found that several of these approaches exhibit promising biological activity, but adequate clinical data demonstrating efficacy and safety are lacking. In particular, an investigation into the use of pravastatin in clinical trials is currently underway, but this should not be regarded as a proven treatment for placental-mediated FGR at this time .

4.3 .Fetal Monitoring and Delivery Timing.

Optimal fetal monitoring and early delivery are the most useful management choices at this time, because placenta insufficiency can't be reversed. Typically, surveillance includes frequent ultrasound exams, umbilical artery doppler, cardiotocography (CTG) and amniotic fluid examination. The Society for Maternal-Fetal Medicine (SMFM, 2020, 2024) suggested that serial umbilical artery Doppler assessment should be performed at 1–2-week intervals after the diagnosis of FGR and more frequently if there is absent end diastolic flow or reversed end diastolic flow with the Doppler. The decision for delivery depends on Doppler status, degree of growth restriction and gestation. Timing of delivery is determined by gestational age, severity of fetal growth, and Doppler abnormalities. Severe FGR or reduced umbilical artery diastolic flow is recommended for delivery at 37 weeks, absent end-diastolic flow is recommended for delivery at 33–34 weeks, and reversed end-diastolic flow is recommended for delivery at 30–32 weeks. Antenatal corticosteroids are given if preterm delivery is thought to be imminent, and magnesium sulfate is used for fetal neuroprotection when delivery is likely to occur before 32 weeks [1].

4.4 .Future Therapeutic Perspectives

Emerging data suggest that future treatments will be individually tailored to the mechanism causing placental dysfunction. There is scope for treatments that aim to specifically modulate angiogenic pathway, protect mitochondria, act as an antioxidant or enhance trophoblast function and placental vasculature. In addition, recent developments in stem-cell therapy, extracellular vesicles and gene therapy could offer novel avenues for the recovery of placental function. These interventions, however, are still essentially experimental and have not yet been sufficiently preclinically investigated and clinically tested before being considered for routine obstetric use. Stone [23] highlighted the need for developing effective interventions that can be used as prevention and treatment, which aim at the underlying placental pathology and not only on fetal growth measurements.

Overall, future management of FGR will rely on the integration of early risk identification, placental biomarkers with high reliability, personalized fetal surveillance, and evidence-based delivery planning. There is a particular need for larger multi-center, randomized controlled trials to test new drug therapies; identify pregnancies at high risk for these drugs; and assess the safety of these drugs for the mother and baby.

CONCLUSION

Placental dysfunction is a basic mechanism involved in the development of fetal growth restriction via abnormal vascular development, angiogenic imbalance, oxidative stress, inflammation, and impaired nutrient transport. There are emerging biomarkers such as PlGF and sFlt-1 which are of great potential for earlier detection and better risk appraisal. The use of biochemical markers along with ultrasound and Doppler evaluation can improve diagnosis, and fetal monitoring. While there is limited treatment available there is some hope that targeted pharmacological interventions and molecular research will offer new opportunities for treatment. Additional clinical investigations are needed to enhance pregnancy outcomes and develop appropriate management options on a case-by-case basis.

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