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Placental Pathophysiology Underlying Fetal Growth Restriction

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ABSTRACT

Fetal growth restriction (FGR) is a major pregnancy issue that affects 5–10% of pregnancies worldwide. When the fetus fails not fulfill its genetic growth potential, it raises the risk of newborn morbidity, death, and long-term neurodevelopmental problems. Placental dysfunction, which hinders the flow of nutrients and oxygen from the mother to the fetus, is the main cause of FGR. Placental abnormalities such as maternal and fetal vascular malperfusion, villitis, abnormal trophoblast invasion, and inadequate spiral artery remodeling contribute to reduced blood flow and chronic fetal hypoxia. Oxidative stress further damages placental vessels, leading to symmetric or asymmetric growth restriction depending on the timing and severity of the insult. Early diagnosis is essential and relies on Doppler ultrasound, fetal and maternal biometry, and placental biomarkers such as PlGF and sFlt-1. Understanding placental pathology is crucial for timely intervention and improved pregnancy outcomes.

Keywords: Villitis, trophoblast invasion, maternal vascular malperfusion , fetal vascular malperfusion , placental malfunction, and fetal growth restriction.

1. Introduction

When a fetus does not reach its genetically programd growth potential, fetal growth restriction increases the risk of perinatal death and long-term neurodevelopmental problems worldwide. The placenta, which serves as a crucial interface for the flow of waste, gasses, and nutrition between the mother and fetus, has a significant impact on fetal growth. Any abnormalities in placental development or function may significantly limit fetal growth. This study focuses on the part placental malfunction plays in FGR, a condition that affects 5–10% of pregnancies and significantly raises the risk of adverse short- and long-term consequences. (1,2) Placental insufficiency, which can be caused by a variety of placental conditions such as villitis, fetal vascular malperfusion, and maternal vascular malperfusion, is the primary pathophysiological cause of fetal growth restriction. Adequate food availability is essential for fetal growth and is influenced by the formation of placental villi, uteroplacental blood flow, maternal nutrition, and the effectiveness of villous trophoblasts and fetoplacental circulation. The fetoplacental weight ratio at birth is a retrospective indicator of the placenta's efficiency in fostering fetal growth and can be used to forecast the likelihood of chronic disorders in later life through developmental programming. As the placenta matures near the end of the first trimester, problems associated to the placenta that cause growth restriction in the fetus may become evident.(3,4)

As the placenta develops a fully hemochorial structure, it undergoes substantial remodeling around the end of the first trimester or the start of the second trimester, which coincides with the start of maternal arterial blood flow. The placenta's eventual size and functioning ability can be affected by events that take place during this crucial

period.(5) Studies conducted in utero have shown that pregnancies affected by fetal growth restriction, whether or not they develop preeclampsia later, tend to have smaller placental volumes and This concept is supported by higher uterine blood flow resistance compared to typical pregnancies, starting in the early second trimester. (6) Fetal growth limitation is the term used to describe when a fetus does not reach its genetically allotted growth potential. The majority of non-infectious instances without genetic or congenital problems are believed to result from decreased uterine blood flow to the placenta, while they can have a variety of causes. (7,8)

Fetal growth restriction is a serious obstetric issue that affects 5–10% of pregnancies and raises the chances of perinatal morbidity and mortality. The primary reason is placental malfunction, which limits the fetus's access to essential oxygen and nutrients. This is mostly caused by structural and functional problems such as insufficient trophoblast invasion, insufficient spiral artery remodeling, and maternal vascular malperfusion. (9,10) Lesions include maternal vascular malperfusion, infarctions, villous hypoplasia, and oxidative stress-related vascular damage are frequently seen in histopathological examinations of FGR placentas.(11,12)

Inadequate uterine spiral artery remodeling during the early stages of pregnancy often results in this defect, which lowers placental perfusion and prolongs fetal hypoxia and nutrient deficiencies that affect development and health. Deep understanding of these placental systems is essential for improving fetal outcomes through early discovery, focused management techniques, and creative treatments. (13,14)

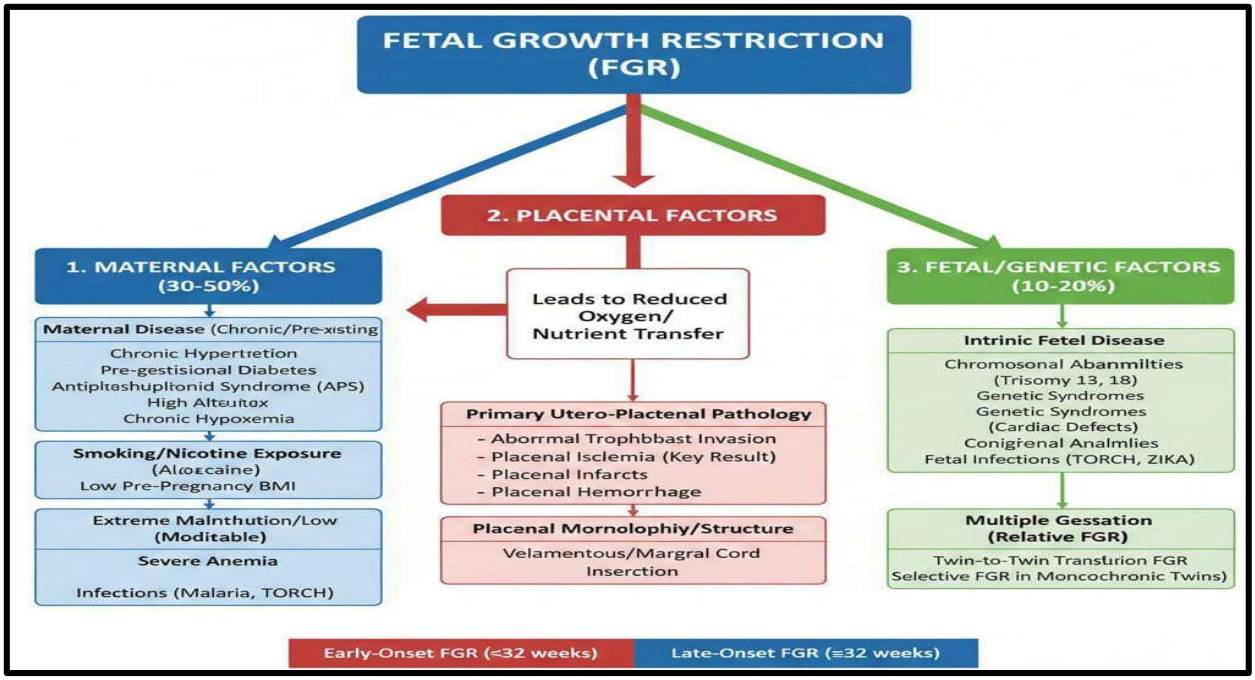

Fig.no.1 Stages of human fetal development

Eitology:

Placental dysfunction, which can be brought on by placental, maternal, fetal, or environmental factors, is the primary cause of fetal growth limitation. (15,16)

Defective trophoblast invasion, inadequate spiral artery remodeling, and maternal vascular malperfusion are important placental mechanisms that decrease uteroplacental blood flow and restrict the fetus's access to oxygen and nutrients.Placental insufficiency is made worse by maternal disorders such hypertension, preeclampsia, diabetes, autoimmune and renal illnesses, malnutrition, and anemia. (17,18)

Chromosome abnormalities, genetic disorders, congenital defects, and intrauterine infections are examples of fetal causes.

Environmental factors that can reduce placental oxygenation and hinder fetal growth include maternal smoking, alcohol use, exposure to pollutants, and high altitude. Placental dysfunction, which is brought on by a variety of factors affecting the placenta's structure or function, accounts for most cases of fetal growth restriction. (19,20)

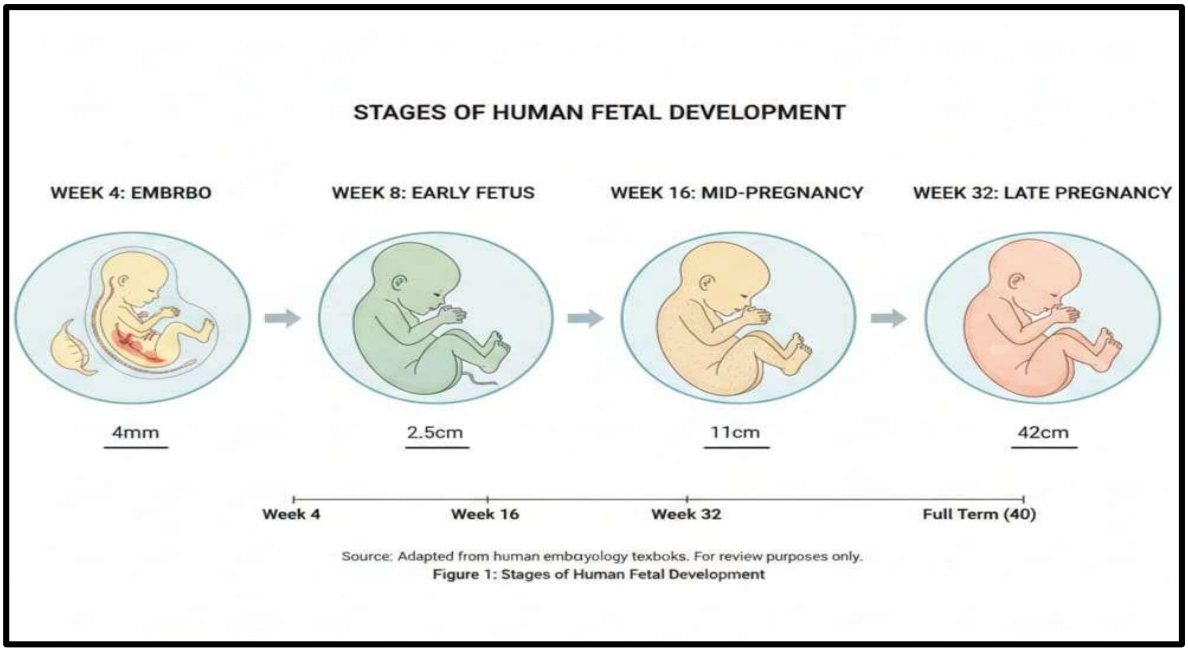

Fig no. 2 Etiology of fetal growth restrictio

Define intrauterine growth restriction:

Fetal growth restriction is the inability of a fetus to reach its genetic growth potential. Measurements of fetal and infant growth are used as indirect signals because it is challenging to accurately assess this potential. The phrase "small for gestational age" is used when the actual birth weight or the fetal weight ascertained by ultrasound before delivery is less than the 10th percentile for that gestational age. (21)

Higher chances of unfavorable outcomes and an increased chance of FGR are correlated with smaller fetal or neonatal sizes. A threshold below the 10th percentile, with severe cases dropping below the 3rd percentile, is typically used to determine if the fetus or baby is classified as SGA. Size alone cannot accurately discriminate between newborns who are little but otherwise healthy and those whose size is reduced due to placental, maternal, or fetal disorders limiting growth. The prognosis and proper clinical care depend on this distinction (22).

Normal placental structure and function:

Placental Structure and Function: vascularization to promote communication between the mother and the fetus. Maternal spiral artery trophoblastic invasion guarantees sufficient perfusion. While cytotrophoblasts preserve structural integrity, the syncytiotrophoblast layer controls the movement of gases and nutrients(23). Growth factors such as VEGF, PlGF, and IGF are crucial for placental angiogenesis. The placenta rapidly develops from the trophoblast. The placenta grows as a temporary organ to aid in the fetus's development throughout pregnancyIts structural components, the decidua (maternal part) and chorionic villi (fetal part), work together to make it easier for the mother and fetus to exchange waste materials, nutrients, and oxygen. (28).

In order to sustain pregnancy and control fetal growth, the placenta also produces hormones such progesterone, placental lactogen, and human chorionic gonadotropin. Gonadotropin, or hCG For optimal placental perfusion and effective maternal-fetal exchange, adequate vascularization and trophoblast invasion are required. (29).

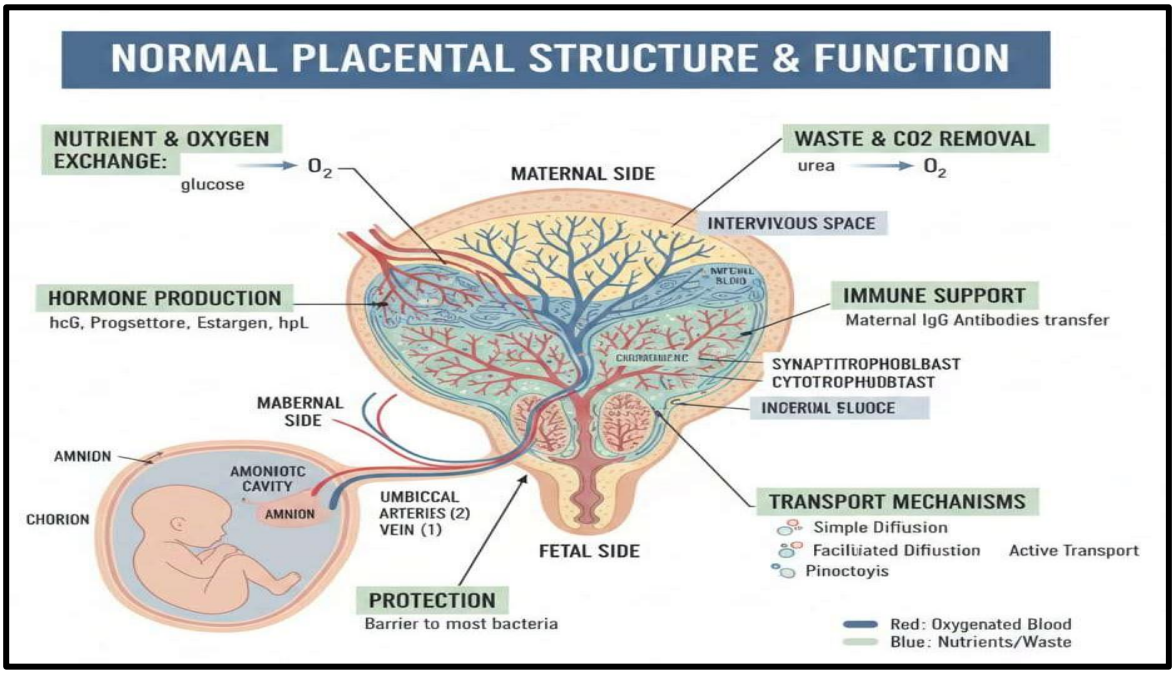

Fig no. 2 Normal placental structure and fuction

The pathophysiology of FGR :

The primary causes of placental dysfunction are aberrant trophoblast invasion and poor spiral artery remodeling, which limit uteroplacental blood flow and cause chronic fetal hypoxia and nutrient deficiencies. Additional factors include oxidative stress, inflammation, disruptions in hypoxia-inducible factor (HIF-1α) signaling, and imbalances between pro-angiogenic agents like PlGF and VEGF and anti-angiogenic ones like sFlt-1 (30, 31). A broad differential diagnosis for Congenital and chromosomal abnormalities, congenital infections, maternal smoking, placental problems, and maternal health disorders are all included in the category of small fetuses. When there are signs of placental insufficiency, such as abnormal Doppler readings or structural ultrasonography, these options should be assessed.

Placental insufficiency, which encompasses the fetus's adaptive responses, inflammation, and placental activities, is still the most prevalent pathophysiological mechanism in fetal growth limitation. Normal fetal growth requires cellular development. Up to 20 weeks of pregnancy, there is hyperplasia; between 20 and 28 weeks, there is hyperplasia with hypertrophy; beyond 28 weeks, there is a rapid accumulation of muscle, fat, and connective tissue. (32,33,34).

About 90% of the fetal weight gain occurs during the second half of pregnancy, with daily growth rates rising from roughly 5 g at 14–19 weeks to 10 g at 20–29 weeks, peaking at 25–35 g during 30–36 weeks, and then declining to 15 g. After 30 weeks, the abdominal circumference grows by 1 inch per week, and between 14 and 32 weeks, the symphysio-fundal height grows by around 1 cm every week. These alterations are the outcome of a complex process that is impacted by interactions between thyroid, adrenal, pituitary, and pancreatic hormones, including insulin. (35,36).

Table I Classification of intrauterine growth restriction

Category	Biometry Criteria	Etiological Factors	Key Doppler/Feature	Risk Profile
Early FGR (<32w)	EFW/AC <10th percentile, often <3rd	Placental dysfunction, maternal hypertension	Abnormal UA PI, uterine artery notching	High perinatal mortality, preterm delivery.[23]
Late FGR (≥32w)	EFW/AC <10th percentile	Placental insufficiency, constitutional smallness	Abnormal CPR, DV flow, normal UA early	Moderaterisk, neurodevelopmental concerns[24]
SGA (non-FGR)	Birthweight <10th percentile	Genetic/ethnic factors	Normal Doppler flows	Low adverse outcomes, healthy small fetuses[25]

Isolated Biometry	AC <10th, EFW >10th	Nutritional/placental	Normal flows initially	Monitor for progression to FGR [26]

Recent Case Reports and Studies (2022–2025):

A 28-year-old first-time mother had reduced fetal movements for two days at 32 weeks gestation. A clinical examination revealed a fundal height of 28 weeks, while an ultrasound assessed fetal weight below the fifth percentile and Doppler showed no end-diastolic flow in the umbilical artery, indicating placental insufficiency (46,47).

Despite the absence of an infection or maternal hypertension, the patient was closely monitored. Due to abnormal fetal cardiac rhythms, a 1.4 kg male baby was delivered by emergency cesarean section at 33 weeks. The infant required oxygen and nutrition in the NICU for ten days. (48,49).

A placental examination showed a weight of 320 g (below the 10th percentile), pale infarcted areas, and marginal cord insertion. Histopathology, which revealed increased syncytial knots, villous hypoplasia, and maternal vascular malperfusion, demonstrated severe placental dysfunction (50).

This case highlights the significance of early Doppler monitoring and placental evaluation in identifying and managing fetal growth restriction in high-risk pregnancies. This example highlights the importance of early Doppler monitoring in managing high-risk pregnancies and highlights the importance of placental exploration in identifying the causes of fetal growth restriction. (51,52).

A 2023 study by Sharma et al. showed a connection between reduced Placental Growth Factor (PlGF) levels in severe FGR cases and placental infarction. In 2024, FGR placentas showed increased hypoxia markers, particularly Hypoxia-Inducible Factor 1-alpha (HIF-1α), suggesting a hypoxic environment. Additionally, almost 70% of FGR cases had placental vascular malperfusion, according to a 2025 study by Patel et al., highlighting the critical significance of decreased placental blood flow. When taken as a whole, these results demonstrate how crucial placental disease is to the pathophysiology (53,54,55) .

Table II Three main types of causative factors associated with FGR

Group	Key Examples and Details
Group I: Maternal Utero-Placental Insufficiency	Preeclampsia, chronic hypertension, diabetes, autoimmune diseases (e.g., lupus), malnutrition, smoking, thrombophilias; leads to reduced nutrient/oxygen transfe[37,38]
Group II: Feto-Placental Circulation Alteration	Umbilical cord abnormalities (e.g., velamentous insertion), placental infarction, thrombosis, fetal anemia, twin-twin transfusion; impairs blood flow dynamics[39,40]
Group III: Genomics and Fetal Growth Limitation	Chromosomal aneuploidies (e.g., trisomy 18, 13, 21), copy number variants (e.g., Xp28 microdeletion, Xp22.33 duplication), single gene disorders, uniparental disomy, Silver-Russell syndrome (epigenetic/methylation defects), confined placental mosaicism (CPM in 9-16% isolated FGR cases)[41,42] .
Cross-Category Factors	Infections (TORCH: toxoplasmosis, rubella, CMV, herpes), environmental toxins/drugs, maternal stress/hypoxia, multiple gestation; these interact across groups, e.g., infection exacerbating placental insufficiency or genetic risk[43,44,45]

High-risk factors for mothers –

- Substance and Drug Exposure: Both active and passive substance and drug exposure smoking, alcohol consumption, teratogenic drugs (such as folic acid antagonists, anticonvulsants, antimetabolites, and anticancer medicines), and past or present use of illegal drugs (56).
- Obstetric History : Previous pregnancies with growth-restricted babies or stillbirths in the obstetric history raise the risk of severe growth restriction in subsequent pregnancies by 50%, particularly if the previous stillbirth happened before 32 weeks. (57).
- Parity and Inter-Pregnancy Interval : Parity and inter-pregnancy interval, encompassing nulliparity or parity greater than 5, as well as intervals shorter than 6 months or longer than 10 years(58).
- Medical Conditions : Sickle cell disease, type II diabetes, renovascular issues, systemic lupus erythematosus, antiphospholipid antibody syndrome, bronchial asthma, maternal hypertensive diseases, and cardiovascular abnormalities(59).
- Immunologic and Hematologic Problems : Hematologic and immunologic disorders, such as acquired thrombophilia(60).

Diagnosis, Management, and Prevention of intrauterine growth restriction :

The foundation of FGR management is early detection and continuous monitoring. Doppler examinations

combined with serial ultrasound evaluations aid in monitoring fetal health. Low-dose aspirin and antioxidants may enhance uteroplacental circulation in high-risk women (61,62,63,64).

Delivery Timing necessitates balancing the risks of intrauterine fetal death against concerns about prematurity. This process is guided by maternal and family risk profiles, nutritional status, precise fetal weight estimates, accurate gestational dating, gravidogram tracking, fundal height measurements, cardiotocography (CTG), and biometric ultrasound parameters (AC, HC, BPD, FL) (65,66,67,68).

Placental histopathology after delivery validates the diagnosis. Fetal growth restriction management involves balancing the risks of medically induced preterm birth with the prevention of fetal injury or death due to prolonged gestation. (69,70,71,72).

Doppler ultrasonography examination of the uterine artery, umbilical artery, middle cerebral artery, ductus venosus flow velocities, and cerebroplacental ratio is crucial for predicting fetal outcomes and guiding decisions about pregnancy termination. FGR is the term used to describe a fetus that does not attain its genetically determined growth potential. Ultrasound measurements that show the anticipated fetal weight or belly circumference below the 10th percentile for gestational age are typically used to determine this. (73,74,75,76).

To differentiate between aberrant growth, Doppler velocimetry measures fetal and placental blood flow (77,78,79,80). constraints and little but healthy fetuses.Effective monitoring and management must consider maternal, fetal, and placental risk factors in addition to functional indicators such fetal heart rate variability in order to optimize outcomes for both mother and fetus. (81,82,83).

Future Direction:

Future research on fetal growth restriction focuses on improving early diagnosis and distinguishing pathological FGR from constitutionally small fetuses through advanced biomarkers and precision diagnostics. Metabolomics has identified lipids, amino acids, vitamin D, and folic acid as promising predictors of fetal development, although clinical utility requires validation across populations and core outcome standardization.

Biomarkers like sFlt-1/PlGF ratios and umbilical vein blood flow are under investigation for enhanced risk stratification, while trials such as TRUFFLE-2 assess the utility of cerebroplacental ratios and computerized cardiotocography in managing late-onset FGR.Research also explores fetal and placental adaptations, with emphasis on preterm cardiovascular and lung development, and neuroprotection strategies including physiological cord clamping and beta-blockers. Emerging technologies like advanced placental histology, MRI for brain injury assessment, genomic analysis for risk prediction, and nanoparticle-based drug delivery are promising tools for targeted therapies.

Multicenter studies on uterine vein blood flow combined with integrated Doppler and biochemical models aim to enable personalized treatment approaches to reduce FGR-related morbidity and improve perinatal outcomes. and nanoparticle-based drug delivery are promising tools for targeted therapies. Multicenter studies on uterine vein blood flow combined with integrated Doppler and biochemical models aim to enable personalized treatment approaches to reduce FGR-related morbidity and improve perinatal outcomes.

Results

According to this review, the primary cause of fetal growth restriction (FGR) is placental malfunction. Defective trophoblast invasion, insufficient spiral artery remodeling, placental infarction, maternal and fetal vascular malperfusion, and villous hypoplasia are among the important findings. These anomalies cause the fetus to receive less oxygen and nutrients, which hinders its growth. Doppler ultrasound and biomarkers including PlGF, sFlt-1, and HIF-1α have been reported to be helpful in the early detection and tracking of FGR.

Discussion

According to the reviewed research, placental malfunction is a major factor in the development of FGR. Poor fetal growth and unfavorable pregnancy outcomes are caused by prolonged fetal hypoxia and nutrient shortage brought on by reduced placental blood flow. Fetal outcomes and care can be enhanced by early diagnosis by placental biomarkers and Doppler investigations. Additional investigation into molecular processes, biomarkers, and targeted therapeutics may lessen difficulties associated with FGR and enhance the health of mothers and newborns.

Conclusion:

Complex placental dysfunction, which interferes with the proper passage of nutrients and oxygen from mother to baby, is the primary cause of fetal growth restriction. Fetal growth is hampered by the structural and cellular abnormalities brought on by this placental impairment, including decreased placental volume, aberrant villi, trophoblast dysfunction, and poor vascular development. These placental abnormalities raise the risk of long-term metabolic and cardiovascular illnesses in adulthood in addition to impairing fetal development and raising perinatal morbidity and death. Understanding the placenta's crucial involvement in FGR emphasizes the necessity of early discovery, continuous monitoring, and focused therapies to enhance the affected infant's immediate and long-term health outcomes.

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