



PATHOGENESIS OF PLACENTAL DYSFUNCTION IN PREECLAMPSIA AND FETAL GROWTH RESTRICTION: THE ROLE OF ENDOTHELIAL DYSFUNCTION AND VASCULAR MECHANISMS

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Abstract. Placental dysfunction is a central pathogenetic mechanism underlying preeclampsia and fetal growth restriction (FGR), which remain leading causes of maternal and perinatal morbidity and mortality worldwide. These conditions are primarily associated with impaired trophoblast invasion and inadequate remodeling of spiral arteries, resulting in high-resistance uteroplacental blood flow. Endothelial dysfunction plays a pivotal role in this process and is characterized by angiogenic imbalance, activation of the coagulation cascade, and systemic inflammatory response.

The aim of this study is to analyze current concepts of vascular and molecular mechanisms of placental dysfunction, with a particular focus on endothelial function and angiogenic factors. Changes in levels of sFlt-1, PlGF, and VEGF and their impact on vascular tone and placental perfusion are discussed. Special attention is given to the role of hemostasis and immune factors, including regulatory T cells.

The findings demonstrate that integration of laboratory biomarkers, ultrasound data, and clinical parameters significantly improves early diagnosis and prediction of pregnancy complications. These results highlight the importance of developing personalized clinical algorithms.

Keywords: placental dysfunction, preeclampsia, fetal growth restriction, endothelial dysfunction, angiogenic factors, sFlt-1, PlGF, hemostasis, vascular biology.

ПАТОГЕНЕЗ ПЛАЦЕНТАРНОЙ ДИСФУНКЦИИ ПРИ ПРЕЭКЛАМПСИИ И ЗАДЕРЖКЕ РОСТА ПЛОДА: РОЛЬ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ И СОСУДИСТЫХ МЕХАНИЗМОВ

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Аннотация. Плацентарная дисфункция является ключевым патогенетическим звеном развития преэклампсии и задержки внутриутробного роста плода (ЗВУР), которые остаются ведущими причинами материнской и перинатальной заболеваемости и смертности. В основе данных осложнений лежат нарушения инвазии трофобласта и ремоделирования спиральных артерий, приводящие к формированию высокорезистентного маточно-плацентарного кровотока. Центральную роль в патогенезе играет эндотелиальная дисфункция, сопровождающаяся ангиогенным дисбалансом, активацией коагуляционного каскада и системным воспалительным ответом.

Цель исследования. Анализ современных представлений о сосудистых и молекулярных механизмах плацентарной дисфункции с акцентом на роль эндотелия и ангиогенных факторов. Рассматриваются изменения уровней sFlt-1, PlGF и VEGF, а также их влияние на сосудистый тонус и перфузию плаценты. Особое внимание уделено роли гемостаза и иммунологических факторов, включая регуляторные Т-клетки.

Показано, что интеграция лабораторных маркеров, ультразвуковых данных и клинических параметров позволяет улучшить раннюю диагностику и прогнозирование осложнений беременности. Полученные данные подчеркивают необходимость разработки персонализированных клинических алгоритмов.

Ключевые слова: плацентарная дисфункция, преэклампсия, задержка роста плода, эндотелиальная дисфункция, ангиогенные факторы, sFlt-1, PlGF, гемостаз, сосудистая биология.

PREEKLAMPSIYA VA HOMILA RIVOJLANISHINING KECHIKISHIDA PLATSENTAR DISFUNKTSIYA PATOGENEZI: ENDOTELIAL DISFUNKTSIYA VA TOMIR MEKANIZMLARINING ROLI

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Annotatsiya. Platsentar disfunktsiya preeklampsiya va homila rivojlanishining kechikishi (HRK) patogenezida asosiy o'rin tutadi va ona hamda perinatal kasallanish va o'limning yetakchi sabablaridan biri hisoblanadi. Ushbu holatlar trofoblast invaziyasining buzilishi va spiral arteriyalarning yetarli darajada qayta shakllanmasligi bilan bog'liq bo'lib, yuqori qarshilikka ega uteroplatsentar qon oqimini yuzaga keltiradi. Endotelial disfunktsiya ushbu jarayonning markaziy bo'g'ini bo'lib, angiogen muvozanatning buzilishi, koagulyatsiya tizimi faollashuvi va yallig'lanish reaksiyasi bilan namoyon bo'ladi.

Tadqiqot maqsadi. Platsentar disfunktsiyaning tomir va molekulyar mexanizmlarini tahlil qilishdan iborat bo'lib, bunda endotelial funktsiyaning roli va angiogen omillar alohida ko'rib chiqiladi. sFlt-1, PlGF va VEGF darajalaridagi o'zgarishlar hamda ularning qon tomir tonusi va platsenta perfuziyasiga ta'siri o'rganiladi. Shuningdek, gemostaz va immunologik omillar, jumladan regulyator T-hujayralar ahamiyati ko'rib chiqiladi.

Natijalar laborator markerlar, ultratovush tekshiruv va klinik ma'lumotlarni integratsiya qilish homiladorlik asoratlarini erta aniqlash va prognozlashni yaxshilashini ko'rsatadi. Bu esa individual klinik yondashuvlarni ishlab chiqish zarurligini tasdiqlaydi.

Kalit so'zlar: platsentar disfunktsiya, preeklampsiya, homila rivojlanishining kechikishi, endotelial disfunktsiya, angiogen omillar, sFlt-1, PlGF, gemostaz, tomir biologiyasi

Introduction. Placental dysfunction represents a fundamental pathological process underlying a wide spectrum of obstetric complications, including preeclampsia, fetal growth restriction (FGR), and antenatal fetal demise [2,5]. These conditions remain among the leading causes of maternal and perinatal morbidity and mortality worldwide, despite significant advances in obstetric care. The complexity of placental pathology reflects the interplay of vascular, immunological, and metabolic factors that converge to impair normal placental development and function [1,3,6,8]. Preeclampsia is a multisystem disorder characterized by new-onset hypertension and end-organ dysfunction after 20 weeks of gestation. FGR, on the other hand, is defined as the failure of the fetus to achieve its genetically predetermined growth potential [8,9,10]. Although clinically distinct, both conditions share a common pathophysiological basis rooted in abnormal placentation and placental insufficiency [2,4,5,7]. The process of placentation involves the invasion of extravillous trophoblasts into the maternal decidua and the remodeling of spiral arteries into low-resistance, high-capacitance vessels. This transformation is essential for adequate uteroplacental perfusion [1,6,9]. In pathological pregnancies, trophoblast invasion is shallow and incomplete, leading to persistent high-resistance vessels and reduced blood flow to the placenta. Endothelial dysfunction has emerged as a central mechanism linking abnormal placentation to systemic maternal manifestations. The maternal endothelium plays a critical role in vascular homeostasis, regulating vasodilation, coagulation, and inflammatory responses [3,8]. Disruption of endothelial function leads to vasoconstriction, increased vascular permeability, and a prothrombotic state. One of the key features of placental dysfunction is the imbalance between proangiogenic and antiangiogenic factors [5,7,10]. Elevated levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and reduced levels of

placental growth factor (PlGF) have been consistently associated with preeclampsia and FGR. These factors contribute to endothelial injury by inhibiting vascular endothelial growth factor (VEGF) signaling and impairing angiogenesis. In addition to angiogenic imbalance, immune dysregulation plays a crucial role in the pathogenesis of placental dysfunction [2, 3, 5, 9]. The maternal–fetal interface requires a finely tuned immune tolerance, mediated in part by regulatory T cells (Treg). Disruption of this balance can lead to inflammatory responses that further impair trophoblast invasion and vascular remodeling [1, 2, 3, 4].

The aim of this study is to provide a comprehensive analysis of the vascular and endothelial mechanisms underlying placental dysfunction in preeclampsia and FGR, with a focus on integrating molecular, cellular, and clinical perspectives.

Materials and Methods. This study represents a comprehensive analytical synthesis of current evidence combined with a conceptual modeling approach to understand placental dysfunction. Data were derived from experimental studies, clinical trials, and translational research focusing on vascular biology, angiogenesis, and endothelial function in pregnancy. The methodological framework integrates clinical data, laboratory biomarkers, and molecular mechanisms. Key parameters analyzed include uterine artery Doppler indices, circulating angiogenic factors, markers of endothelial activation, and coagulation profiles. The study incorporates a conceptual model based on four main domains: placental vascular development, endothelial function, angiogenic signaling, and immune regulation.

Table 1. Key Parameters in Placental Dysfunction Analysis

Domain	Parameters	Clinical Relevance
Vascular	Uterine artery PI	Placental perfusion
Angiogenic	sFlt-1, PlGF	Endothelial health
Hemostasis	D-dimer, fibrinogen	Thrombosis risk
Immune	Treg, cytokines	Tolerance mechanisms

Statistical and computational approaches include correlation analysis, predictive modeling, and integration of multimodal datasets.

Results. The analysis demonstrates that placental dysfunction is characterized by a cascade of vascular and endothelial abnormalities. One of the earliest detectable changes is increased resistance in uterine arteries, reflecting impaired spiral artery remodeling. Elevated levels of sFlt-1 were associated with decreased bioavailability of VEGF and PlGF, leading to endothelial dysfunction. This was accompanied by increased levels of endothelin-1 and reduced nitric oxide production, resulting in vasoconstriction.

Table 2. Angiogenic Imbalance in Preeclampsia and FGR

Marker	Normal Pregnancy	Preeclampsia/FGR
PlGF	High	Low
sFlt-1	Low	High
VEGF	Balanced	Suppressed

These changes contribute to systemic endothelial activation, which manifests clinically as hypertension, proteinuria, and organ dysfunction. Coagulation abnormalities were also observed, including increased fibrin deposition in placental vessels and activation of the coagulation cascade. This creates a prothrombotic environment that further compromises placental blood flow. Immune analysis revealed decreased Treg activity and increased pro-inflammatory cytokines, suggesting a shift toward a pro-inflammatory state. This contributes to endothelial injury and impaired vascular adaptation [2, 5, 8, 9].

Discussion. The findings of this study underscore the central role of endothelial dysfunction in the pathogenesis of placental disorders [1,4,7]. Endothelial cells act as a critical interface between the placenta and maternal circulation, and their dysfunction has widespread systemic effects [6,8]. The angiogenic imbalance observed in preeclampsia and FGR is a key driver of endothelial injury. sFlt-1 acts as a decoy receptor, binding VEGF and PlGF and preventing their interaction with endothelial receptors. This results in impaired angiogenesis and vascular instability [1,7,8]. The role of immune mechanisms is increasingly recognized. Treg cells are essential for maintaining immune

tolerance during pregnancy. Their reduction leads to increased inflammation and contributes to vascular damage [2,4]. This highlights the importance of integrating immunological parameters into the study of placental dysfunction. From a clinical perspective, the identification of biomarkers such as the sFlt-1/PlGF ratio has significantly improved the ability to predict and diagnose preeclampsia. However, challenges remain in translating these findings into effective therapeutic strategies [3, 5, 6, 7, 10]. Emerging approaches include the use of targeted therapies to restore angiogenic balance, such as apheresis to remove sFlt-1, and the use of nitric oxide donors to improve endothelial function [1,2,9]. The integration of laboratory markers into clinical algorithms represents a promising direction for personalized medicine. Combining Doppler ultrasound, biochemical markers, and clinical risk factors can improve early detection and management [4,6,8,10].

Conclusion. Placental dysfunction in preeclampsia and fetal growth restriction is a complex process driven by vascular, endothelial, and immune mechanisms. Endothelial dysfunction serves as a central link connecting abnormal placentation to systemic maternal disease. The imbalance between angiogenic factors, combined with coagulation abnormalities and immune dysregulation, creates a pathological environment that compromises placental function. Future research should focus on developing integrated diagnostic models and targeted therapies aimed at restoring vascular and endothelial homeostasis. The advancement of personalized medicine in obstetrics will depend on the ability to combine clinical, laboratory, and molecular data to improve outcomes for both mother and fetus.

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