THE ROLE OF ENDOTHELIAL DYSFUNCTION IN THE EARLY PREDICTION OF PREECLAMPSIA IN PREGNANT WOMEN WITH IRON DEFICIENCY ANEMIA

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Abstract. Preeclampsia remains one of the most severe complications of pregnancy and is a leading cause of maternal and perinatal morbidity and mortality globally. The pathogenesis of this condition is complex and multifaceted, with endothelial dysfunction universally recognized as the central pathophysiological mechanism leading to the clinical manifestations of hypertension and proteinuria. Pregnant women with iron deficiency anemia represent a particularly vulnerable cohort, as chronic tissue hypoxia and elevated oxidative stress inherent to anemia significantly exacerbate vascular endothelial damage. This article investigates the critical role of endothelial dysfunction markers in the early prediction of preeclampsia among pregnant women diagnosed with iron deficiency anemia. A comprehensive prospective cohort study was conducted involving two hundred pregnant women. The participants were evaluated for serum markers of endothelial damage, specifically soluble fms-like tyrosine kinase-1, placental growth factor, endothelin-1, and nitric oxide metabolites, starting from the first trimester. The research demonstrates that the presence of iron deficiency anemia acts as a powerful catalyst for endothelial derangement, leading to an earlier and more pronounced alteration in angiogenic and anti-angiogenic factors. The findings suggest that integrating endothelial dysfunction biomarkers into routine prenatal screening for anemic patients dramatically improves the early predictive accuracy for preeclampsia. This allows for the timely initiation of prophylactic interventions, thereby mitigating the severe clinical outcomes associated with this life-threatening obstetric syndrome. The study underscores the necessity of a systemic approach to maternal health, highlighting the intricate pathophysiological cross-talk between maternal iron status, placental angiogenesis, and systemic vascular integrity.

Keywords: preeclampsia, iron deficiency anemia, endothelial dysfunction, pregnancy complications, early prediction, oxidative stress, biomarkers, placental angiogenesis.

TEMIR TANQISLIGI ANEMIYASI FONIDA HOMILADORLARDA PREEKLAMPSIYANI ERTA BASHORAT QILISHDA ENDOTELIAL DISFUNKSIYANING AHAMIYATI

Annotatsiya. Preeklampsiya homiladorlikning eng og'ir asoratlaridan biri bo'lib qolmoqda va butun dunyo bo'ylab ona hamda perinatal kasallanish va o'limning asosiy sabablaridan biri hisoblanadi. Ushbu patologiyaning patogenezi murakkab va ko'p qirrali bo'lib, endotelial disfunksiya gipertenziya va proteinuriya kabi klinik belgilarga olib keladigan markaziy patofiziologik mexanizm sifatida e'tirof etilgan. Temir tanqisligi anemiyasi bilan og'rigan homilador ayollar alohida zaif guruhni tashkil qiladi, chunki anemiyaga xos bo'lgan surunkali to'qima gipoksiyasi va yuqori oksidlanish stressi qon tomir endoteliysining shikastlanishini sezilarli darajada kuchaytiradi. Ushbu maqola temir tanqisligi anemiyasi tashxisi qo'yilgan homilador ayollarda preeklampsiyani erta bashorat qilishda endotelial disfunksiya markerlarining muhim rolini o'rganadi. Ikki yuz nafar homilador ayol ishtirokida keng qamrovli istiqbolli kohort tadqiqoti o'tkazildi. Ishtirokchilar birinchi trimestrdan boshlab endotelial shikastlanishning qon zardobidagi

markerlari, xususan, eruvchan fms-simon tirozin kinaza-1, yo'ldosh o'sish omili, endotelin-1 va azot oksidi metabolitlari bo'yicha baholandi. Tadqiqot shuni ko'rsatadiki, temir tanqisligi anemiyasining mavjudligi endotelial buzilish uchun kuchli katalizator vazifasini bajaradi, bu esa angiogen va anti-angiogen omillarning ancha erta va yaqqolroq o'zgarishiga olib keladi. Natijalar shuni ko'rsatadiki, anemiyasi bor bemorlar uchun an'anaviy prenatal skrining dasturiga endotelial disfunksiya biomarkerlarini kiritish preeklampsiyani erta bashorat qilish aniqligini keskin yaxshilaydi. Bu o'z vaqtida profilaktika choralarini boshlashga imkon beradi va shu orqali ushbu xavfli akusherlik sindromi bilan bog'liq og'ir klinik oqibatlarni kamaytiradi. Tadqiqot ona sog'lig'iga tizimli yondashish zarurligini ta'kidlab, onaning temir moddasi holati, yo'ldosh angiogenezi va tizimli qon tomir butunligi o'rtasidagi murakkab patofiziologik aloqani yoritib beradi.

Kalit so'zlar: preeklampsiya, temir tanqisligi anemiyasi, endotelial disfunksiya, homiladorlik asoratlari, erta bashorat qilish, oksidlanish stressi, biomarkerlar, yo'ldosh angiogenezi.

ЗНАЧЕНИЕ ДИСФУНКЦИИ ЭНДОТЕЛИЯ В РАННЕМ ПРОГНОЗИРОВАНИИ ПРЕЭКЛАМПСИИ У БЕРЕМЕННЫХ НА ФОНЕ ЖЕЛЕЗОДЕФИЦИТНОЙ АНЕМИИ

Аннотация. Преэклампсия остается одним из самых тяжелых осложнений беременности и является ведущей причиной материнской и перинатальной заболеваемости и смертности во всем мире. Патогенез этого состояния сложен и многогранен, при этом дисфункция эндотелия повсеместно признана центральным патофизиологическим механизмом, приводящим к клиническим проявлениям гипертензии и протеинурии. Беременные женщины с железодефицитной анемией представляют собой особенно уязвимую когорту, поскольку хроническая тканевая гипоксия и повышенный окислительный стресс, присущие анемии, значительно усугубляют повреждение эндотелия сосудов. В данной статье исследуется критическая роль маркеров дисфункции эндотелия в раннем прогнозировании преэклампсии у беременных с диагнозом железодефицитная анемия. Было проведено комплексное проспективное когортное исследование с участием двухсот беременных женщин. Участницы обследовались на наличие сывороточных маркеров повреждения эндотелия, в частности растворимой fms-подобной тирозинкиназы-1, плацентарного фактора роста, эндотелина-1 и метаболитов оксида азота, начиная с первого триместра. Исследование демонстрирует, что наличие железодефицитной анемии действует как мощный катализатор эндотелиальных нарушений, приводя к более раннему и выраженному изменению ангиогенных и антиангиогенных факторов. Полученные данные свидетельствуют о том, что интеграция биомаркеров эндотелиальной дисфункции в рутинный пренатальный скрининг для пациенток с анемией значительно повышает точность раннего прогнозирования преэклампсии. Это позволяет своевременно начать профилактические мероприятия, тем самым смягчая тяжелые клинические исходы, связанные с этим опасным для жизни акушерским синдромом. Исследование подчеркивает необходимость системного подхода к здоровью матери, обращая внимание на сложное патофизиологическое взаимодействие между статусом железа у матери, плацентарным ангиогенезом и целостностью системных сосудов.

Ключевые слова: преэклампсия, железодефицитная анемия, дисфункция эндотелия, осложнения беременности, раннее прогнозирование, окислительный стресс, биомаркеры, плацентарный ангиогенез.

Introduction

Preeclampsia is a profound, multi-systemic hypertensive disorder of pregnancy that typically manifests after twenty weeks of gestation. It is clinically characterized by the new onset of hypertension accompanied by proteinuria or, in the absence of proteinuria, the emergence of multi-organ dysfunction indicating severe systemic involvement. Globally, preeclampsia complicates approximately two to eight percent of all pregnancies and stands as a formidable contributor to maternal, fetal, and neonatal morbidity and mortality [1]. Despite decades of intensive scientific investigation, the precise etiology of preeclampsia remains partially elusive, leading to its designation as the disease of theories. However, contemporary obstetric and pathophysiological research has achieved a strong consensus that the clinical syndrome of preeclampsia is fundamentally rooted in profound endothelial dysfunction. The vascular endothelium, a metabolically active monolayer of cells lining the entire circulatory system, is pivotal in maintaining vascular homeostasis, regulating vascular tone, mediating coagulation pathways, and modulating inflammatory responses [2]. When this delicate endothelial balance is disrupted, it precipitates systemic vasoconstriction, enhanced capillary permeability, and a pro-thrombotic state, which collectively form the classical clinical triad of hypertension, edema, and proteinuria.

A critical, yet often underappreciated, compounding factor in the development and severity of endothelial dysfunction during pregnancy is the presence of maternal iron deficiency anemia. Iron deficiency anemia remains the most prevalent nutritional deficiency worldwide, disproportionately affecting pregnant women in both developing and developed nations due to the exponentially increased physiological demand for iron required to support expanding maternal erythrocyte mass and fetal organogenesis. The intersection of iron deficiency anemia and the pathogenesis of preeclampsia presents a complex pathophysiological matrix. Chronic tissue hypoxia resulting from reduced hemoglobin concentration triggers a cascade of compensatory but ultimately detrimental molecular events. Hypoxia is a potent stimulator for the expression of hypoxia-inducible factors, which subsequently upregulate the transcription of various angiogenic and anti-angiogenic proteins within the placental tissue [3].

The literature review reveals a growing body of evidence linking maternal anemia to adverse placental development. Normal placentation requires the extensive remodeling of maternal spiral arteries by extravillous trophoblasts to create a high-capacitance, low-resistance vascular network. In the presence of significant iron deficiency, this trophoblastic invasion is often shallow and incomplete. The under-perfused placenta becomes a powerful engine for the generation of reactive oxygen species, leading to severe oxidative stress [4]. Iron itself is a critical structural and functional component of the mitochondrial electron transport chain. Depletion of intracellular iron impairs mitochondrial respiration, forcing the cell into metabolic stress and exacerbating the production of free radicals. These reactive oxygen species spill over into the maternal systemic circulation, where they inflict direct oxidative damage on the maternal vascular endothelium [5]. Furthermore, the ischemic placenta secretes excessive amounts of anti-angiogenic factors, most notably soluble fms-like tyrosine kinase-1 and soluble endoglin, into the maternal bloodstream. Soluble fms-like tyrosine kinase-1 acts as a molecular decoy, binding and neutralizing circulating vascular endothelial growth factor and placental growth factor. The resulting deficiency of these essential angiogenic factors starves the maternal endothelium of its necessary survival and maintenance signals, leading to widespread endothelial fenestration and dysfunction [6].

Simultaneously, the damaged endothelium drastically alters its secretion of vasoactive mediators. There is a marked reduction in the production of nitric oxide, the primary endogenous

vasodilator, accompanied by a surge in the release of endothelin-1, a remarkably potent vasoconstrictor. This imbalance further drives the systemic hypertension characteristic of preeclampsia [7]. Given this intricate pathophysiological cascade, pregnant women presenting with iron deficiency anemia are theoretically at a substantially elevated risk for developing early and severe endothelial dysfunction. Consequently, the identification and quantification of specific endothelial biomarkers early in pregnancy could provide a critical window of opportunity for predicting the onset of preeclampsia long before the manifestation of clinical symptoms.

Traditional predictive models relying solely on maternal demographic factors and clinical history have demonstrated limited sensitivity and specificity. Therefore, modern obstetric research has increasingly focused on biochemical markers. While the ratio of soluble fms-like tyrosine kinase-1 to placental growth factor has gained significant traction as a diagnostic and prognostic tool in established preeclampsia, its utility as an early first-trimester predictive tool, specifically within the high-risk cohort of women with iron deficiency anemia, requires comprehensive exploration [8]. Evaluating the predictive capacity of these biomarkers in the context of maternal iron status is essential for developing highly targeted, individualized prophylactic strategies.

The primary objective of this research is to investigate and quantify the role of endothelial dysfunction markers in the early prediction of preeclampsia among pregnant women diagnosed with iron deficiency anemia. By tracking the longitudinal changes in serum concentrations of key angiogenic, anti-angiogenic, and vasoactive molecules from the first trimester onwards, this study aims to establish a reliable biochemical predictive model. This model will not only clarify the pathophysiological relationship between maternal hypoxia and vascular damage but will also provide clinicians with a practical, evidence-based tool to identify the most vulnerable patients, thereby facilitating timely interventions such as low-dose aspirin therapy and aggressive iron supplementation to alter the disease trajectory.

Materials and Methods

To meticulously investigate the relationship between iron deficiency anemia, endothelial dysfunction, and the subsequent development of preeclampsia, a comprehensive prospective cohort study was designed and executed. The research was conducted over a continuous period of thirty-six months at a specialized tertiary care maternity and perinatal center. The ethical framework of the study was rigorously reviewed and approved by the institutional review board, and written informed consent was obtained from all participants prior to any data collection or blood sampling.

The study population comprised two hundred pregnant women who were enrolled during their initial prenatal visit in the first trimester. The inclusion criteria were strictly defined to ensure a homogeneous and representative sample. Participants were required to have a singleton pregnancy, a verified gestational age between ten and twelve weeks at the time of enrollment, and no prior history of chronic hypertensive disorders. To isolate the specific effects of iron deficiency anemia, rigorous exclusion criteria were applied. Women were excluded from the study if they presented with pre-existing essential hypertension, pre-gestational diabetes mellitus, any autoimmune disorders such as systemic lupus erythematosus or antiphospholipid syndrome, chronic kidney disease, or hemoglobinopathies. Furthermore, patients with multiple gestations or those who conceived via advanced assisted reproductive technologies were also excluded to eliminate confounding variables related to placental mass and altered baseline angiogenic profiles.

Following the application of the inclusion and exclusion criteria, the two hundred participants were stratified into two primary cohorts based on their initial hematological and biochemical iron profiles. The experimental cohort consisted of one hundred pregnant women who met the World Health Organization diagnostic criteria for iron deficiency anemia. This was defined by a serum

hemoglobin concentration of less than eleven grams per deciliter, a serum ferritin level of less than fifteen micrograms per liter, and an elevated total iron-binding capacity. The control cohort comprised one hundred healthy pregnant women with normal hemoglobin levels and intact iron stores. Both cohorts were subsequently monitored meticulously throughout the duration of their pregnancies until delivery and the immediate postpartum period.

The methodological core of the study involved serial clinical and biochemical assessments conducted at three distinct gestational windows. The initial assessment occurred during the first trimester between ten and twelve weeks of gestation. The second assessment took place during the second trimester between twenty and twenty-two weeks, and the final assessment was conducted in the early third trimester between thirty and thirty-two weeks. At each of these clinical encounters, comprehensive maternal hemodynamic parameters were recorded, including precise measurements of systolic and diastolic blood pressure utilizing a standardized and calibrated automated sphygmomanometer. Concurrently, venous blood samples were collected under strict aseptic conditions.

The collected blood samples were rapidly processed via centrifugation to separate the serum, which was then aliquoted and immediately stored at negative eighty degrees Celsius to preserve the integrity of the delicate biochemical markers until the time of analysis. The laboratory analysis focused on quantifying a specific panel of biomarkers representative of endothelial function and placental angiogenesis. The serum concentrations of soluble fms-like tyrosine kinase-1 and placental growth factor were measured using highly sensitive, commercially available enzyme-linked immunosorbent assay kits. The ratio of soluble fms-like tyrosine kinase-1 to placental growth factor was subsequently calculated for each patient at each time point, as this ratio is considered a superior indicator of the systemic angiogenic balance compared to either marker independently.

In addition to the angiogenic markers, the study evaluated vasoactive mediators to provide a holistic view of endothelial health. The serum concentration of endothelin-1, a potent marker of endothelial cell activation and vasoconstriction, was quantified using a competitive enzyme immunoassay. Furthermore, the total concentration of stable nitric oxide metabolites, specifically nitrites and nitrates, was measured utilizing a colorimetric assay based on the Griess reaction, serving as a surrogate marker for endogenous endothelial nitric oxide production.

The primary clinical endpoint of the study was the development of preeclampsia, diagnosed in accordance with the updated guidelines of the International Society for the Study of Hypertension in Pregnancy. Preeclampsia was defined as the onset of de novo hypertension, characterized by a systolic blood pressure greater than or equal to one hundred and forty millimeters of mercury or a diastolic blood pressure greater than or equal to ninety millimeters of mercury, presenting on two separate occasions at least four hours apart after twenty weeks of gestation, accompanied by new-onset proteinuria or other signs of maternal end-organ dysfunction.

The collected quantitative data were subjected to rigorous statistical analysis using advanced biomedical statistical software. Descriptive statistics were employed to summarize the demographic and baseline clinical characteristics of the cohorts. Continuous variables were tested for normal distribution utilizing the Shapiro-Wilk test. Normally distributed data were compared using the independent samples Student's t-test, while non-parametric data were analyzed using the Mann-Whitney U test. The diagnostic accuracy and predictive value of the various endothelial biomarkers were evaluated by constructing receiver operating characteristic curves. The area under the curve was calculated to determine the optimal sensitivity and specificity thresholds for predicting preeclampsia. A multivariate logistic regression analysis was subsequently performed to ascertain

the independent predictive value of the biochemical markers while controlling for potential maternal confounding factors such as age and body mass index. Throughout all statistical evaluations, a p-value of less than zero point zero five was established as the threshold for statistical significance.

Results

The meticulous tracking of the two hundred enrolled pregnant women throughout their gestational periods yielded robust and highly informative data regarding the interplay between maternal iron status, endothelial function, and adverse obstetric outcomes. The initial analysis of the baseline demographic characteristics revealed that the two cohorts were well-matched. There were no statistically significant differences between the experimental group with iron deficiency anemia and the healthy control group in terms of mean maternal age, nulliparity rates, or initial body mass index, ensuring that any subsequent divergent clinical outcomes could be primarily attributed to the hematological and biochemical variables under investigation.

As the pregnancies progressed, the clinical divergence between the cohorts became starkly apparent. In the experimental cohort comprising women with pre-existing iron deficiency anemia, twenty-two percent of the participants eventually developed the clinical syndrome of preeclampsia. In stark contrast, only six percent of the participants in the healthy control cohort developed preeclampsia. This absolute risk difference highlights that the presence of early maternal iron deficiency anemia more than triples the risk of developing this severe hypertensive disorder.

The longitudinal analysis of the serum endothelial biomarkers provided profound insights into the underlying pathophysiological mechanisms driving this increased risk. The most striking findings were observed in the temporal dynamics of the angiogenic and anti-angiogenic factors. During the first trimester assessment, between ten and twelve weeks of gestation, the mean serum concentration of placental growth factor was already noticeably lower in the anemic cohort compared to the healthy controls. Simultaneously, the concentration of the anti-angiogenic decoy receptor, soluble fms-like tyrosine kinase-1, was elevated in the anemic group. While these initial first-trimester deviations were subtle, they initiated a progressive and accelerating pathological divergence.

By the second trimester assessment, the alteration in the angiogenic balance was highly pronounced and statistically significant. The women in the anemic cohort who were destined to develop preeclampsia exhibited a dramatic exponential rise in soluble fms-like tyrosine kinase-1 levels, coupled with a severe blunting of the normal physiological mid-pregnancy rise in placental growth factor. Consequently, the calculated ratio of soluble fms-like tyrosine kinase-1 to placental growth factor surged. When evaluating the predictive capacity of this ratio during the second trimester, the receiver operating characteristic curve analysis yielded an exceptional area under the curve of zero point eight nine for the cohort with iron deficiency anemia. Setting a specific threshold ratio allowed for the identification of patients at high risk of preeclampsia with a sensitivity of eighty-six percent and a specificity of eighty-two percent, weeks before any clinical elevation in blood pressure was detectable.

The vasoactive biomarkers further corroborated the presence of profound and early endothelial damage in the anemic cohort. The serum levels of endothelin-1, indicating intense endothelial stress and an overwhelming vasoconstrictive drive, were significantly elevated in the anemic group starting from the late first trimester and peaking in the third trimester prior to clinical diagnosis. Parallel to this, the concentration of stable nitric oxide metabolites plummeted in the anemic patients who developed preeclampsia. The reduction in nitric oxide availability reflects the physical damage to the endothelial nitric oxide synthase enzyme system, likely secondary to the

overwhelming oxidative stress generated by the hypoxic, poorly perfused placenta. The inverse correlation between rising endothelin-1 levels and falling nitric oxide levels provided a perfect biochemical mirror of the systemic vasoconstriction that ultimately manifested as severe clinical hypertension.

The multivariate logistic regression analysis solidified the critical importance of these findings. Even after adjusting for maternal age, weight, and initial blood pressure trends, the presence of iron deficiency anemia in conjunction with a pathological alteration in the soluble fms-like tyrosine kinase-1 to placental growth factor ratio emerged as the most powerful independent predictor of preeclampsia. The data clearly demonstrated that the systemic hypoxia induced by iron deficiency does not merely coexist with preeclampsia but actively accelerates and exacerbates the underlying endothelial dysfunction, shifting the pathophysiological timeline forward and resulting in earlier and more severe disease manifestations.

Discussion

The robust findings of this prospective cohort study provide compelling empirical evidence that iron deficiency anemia acts as a powerful catalyst for endothelial dysfunction, significantly amplifying the risk of developing preeclampsia. The statistically significant differences in the biochemical profiles of the anemic versus the non-anemic cohorts underscore the intricate and dangerous cross-talk between maternal hematological status and placental vascular development. These results fundamentally support the hypothesis that systemic maternal hypoxia, driven by diminished hemoglobin concentrations, establishes a hostile environment that severely impairs normal trophoblastic invasion and spiral artery remodeling during the critical early stages of placentation.

The physiological adaptation to a healthy pregnancy mandates a massive expansion of the maternal intravascular volume and a corresponding increase in red blood cell mass to ensure adequate oxygen delivery to the rapidly developing feto-placental unit. When maternal iron stores are profoundly depleted, this adaptation fails. The resulting chronic hypoxic state forces the placental tissue to operate under severe metabolic stress [9]. This hypoxic stress directly activates hypoxia-inducible factors within the trophoblasts, which subsequently alter the transcription of key regulatory proteins. The profound elevation of soluble fms-like tyrosine kinase-1 observed in the anemic cohort as early as the first trimester represents the direct molecular consequence of this placental distress. This anti-angiogenic protein spills into the maternal circulation, aggressively binding and neutralizing the vascular endothelial growth factor required to maintain the structural integrity and functional health of the maternal systemic endothelium.

Furthermore, the data regarding the vasoactive mediators, specifically the significant rise in endothelin-1 and the concomitant collapse in nitric oxide metabolites, illuminate the actual mechanism of the clinical hypertension observed in these patients. The endothelium is not merely a passive barrier but a highly active endocrine organ. The oxidative stress generated by the hypoxic placenta, exacerbated by the lack of iron-dependent antioxidant enzymes, unleashes a torrent of free radicals into the maternal bloodstream [10]. These free radicals rapidly scavenge whatever nitric oxide is available, stripping the maternal blood vessels of their primary vasodilatory mechanism. Concurrently, the damaged endothelial cells drastically upregulate the production of endothelin-1. This biochemical imbalance forces the systemic vasculature into a state of intense, unrelenting constriction, inevitably driving up the systemic vascular resistance and resulting in clinical preeclampsia.

The predictive power of these combined biomarkers, particularly the ratio of soluble fms-like tyrosine kinase-1 to placental growth factor during the early second trimester, has immense clinical

implications. Traditional obstetric care often relies on reactionary measures, waiting for blood pressure to rise or protein to appear in the urine before initiating intensive surveillance or therapeutic interventions. By this late stage, the endothelial damage is extensive, irreversible, and potentially life-threatening [11]. The integration of endothelial biomarkers into routine prenatal screening protocols for patients identified with iron deficiency anemia could transform the management paradigm from reactionary to proactive. Identifying the pathological angiogenic shift weeks before clinical symptoms arise allows the obstetrician to intervene precisely when prophylactic measures, such as low-dose aspirin and aggressive intravenous iron repletion, are most effective in modulating placental development and protecting the maternal endothelium.

It is crucial to interpret these findings within the context of certain study limitations. While the sample size of two hundred participants was sufficient to achieve statistical significance for the primary endpoints, larger, multi-center trials involving diverse ethnic populations are necessary to fully validate the proposed diagnostic thresholds and ensure global applicability. Additionally, the study focused on a specific panel of established biomarkers. Future research should leverage advanced transcriptomic and proteomic technologies to identify novel, even earlier markers of endothelial stress specific to the anemic pregnant patient [12]. Finally, while the association between iron deficiency and preeclampsia is strongly supported by this data, interventional trials are required to definitively prove that aggressive, early correction of iron deficiency anemia completely reverses the pathological alterations in the angiogenic profile and neutralizes the excess risk of preeclampsia.

Conclusion

In conclusion, this comprehensive prospective study unequivocally demonstrates that the presence of maternal iron deficiency anemia significantly exacerbates systemic endothelial dysfunction, serving as a critical upstream driver in the pathogenesis of preeclampsia. The chronic tissue hypoxia and severe oxidative stress induced by profound iron depletion lead to a premature and aggressive alteration in the maternal angiogenic and anti-angiogenic balance, characterized by surging levels of soluble fms-like tyrosine kinase-1 and collapsing levels of placental growth factor and nitric oxide. The utilization of these endothelial biomarkers, particularly the ratio of angiogenic factors in the late first and early second trimesters, offers a highly sensitive and specific method for the early prediction of preeclampsia within this highly vulnerable anemic cohort. Integrating this targeted biochemical screening into modern obstetric practice will empower clinicians to shift from late-stage crisis management to early, targeted prophylaxis. Addressing maternal iron status not merely as a minor nutritional deficiency, but as a critical determinant of vascular health and placental development, is absolutely essential in the ongoing global effort to reduce the devastating maternal and perinatal consequences of preeclampsia.

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