PATHOPHYSIOLOGICAL BASES OF OBESITY AND PREECLAMPSIA IN PREGNANCY AND THEIR IMPACT ON RENAL FUNCTION

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Abstract: Obesity during pregnancy is one of the most significant risk factors for maternal and fetal complications, with preeclampsia representing the most severe among them. The pathophysiological link between obesity and preeclampsia is complex, involving chronic low-grade inflammation, insulin resistance, endothelial dysfunction, and altered renal hemodynamics. The kidneys, being the primary regulators of fluid and electrolyte homeostasis and blood pressure, are particularly vulnerable to the metabolic disturbances associated with obesity. This review examines the pathophysiological mechanisms by which obesity promotes preeclampsia development, with particular emphasis on renal involvement. Key mechanisms discussed include glomerular hyperfiltration, renin-angiotensin-aldosterone system (RAAS) dysregulation, oxidative stress, and impaired placental vascularization as triggers of renal endothelial dysfunction. Understanding these interconnected pathways is essential for developing targeted diagnostic and preventive strategies in high-risk obese pregnant women.

Keywords: Obesity in pregnancy, Preeclampsia, Pathophysiology, Renal dysfunction, Glomerular hyperfiltration, Endothelial dysfunction, RAAS, Oxidative stress, Inflammation, Maternal outcomes.

Introduction

Pregnancy is associated with extensive physiological adaptations affecting virtually every organ system. Among these adaptations, the cardiovascular and renal systems undergo the most substantial changes to accommodate the growing fetal demands. These normal adaptations can be significantly disrupted by pre-existing or gestational conditions, of which obesity is one of the most prevalent and clinically challenging.

Obesity, defined as a body mass index (BMI) of 30 kg/m² or above, has reached epidemic proportions globally, including among women of reproductive age. Epidemiological data consistently demonstrate that obese pregnant women face a two- to four-fold higher risk of developing preeclampsia compared to their normal-weight counterparts. Preeclampsia, a multisystem hypertensive disorder of pregnancy occurring after 20 weeks of gestation, is characterized by new-onset hypertension, proteinuria, and end-organ dysfunction, with the kidneys being among the most affected organs.

The pathophysiological mechanisms linking obesity to preeclampsia and renal dysfunction are multifaceted and interdependent. They encompass metabolic dysregulation, chronic systemic inflammation, activation of the renin-angiotensin-aldosterone system (RAAS), endothelial injury, and oxidative stress. Collectively, these mechanisms impair normal renal adaptation to pregnancy, leading to glomerular injury, proteinuria, and reduced filtration capacity.

This review aims to systematically explore the pathophysiological bases of obesity-associated preeclampsia, with a focused analysis of its effects on renal function. A thorough understanding of these mechanisms provides the scientific foundation for early identification of high-risk patients and the development of targeted interventions.

Relevance

The global prevalence of obesity among pregnant women continues to rise, posing an increasing burden on maternal-fetal medicine. Preeclampsia remains one of the leading causes of maternal and perinatal mortality and morbidity worldwide. Understanding the pathophysiological mechanisms underlying this association is not only of academic interest but also of direct clinical relevance.

Renal dysfunction in preeclampsia is a critical determinant of disease severity and maternal outcome. Obese women exhibit subclinical alterations in renal function even prior to the development of frank preeclampsia, making early pathophysiological assessment a vital tool for risk stratification. Research into these mechanisms directly informs preventive strategies, monitoring protocols, and therapeutic approaches that can improve maternal and neonatal outcomes.

Aim

The aim of this review is to elucidate the pathophysiological mechanisms through which maternal obesity predisposes to preeclampsia, with a specific focus on the mechanisms of renal involvement. This study seeks to identify key biological pathways, discuss their interactions, and outline their clinical implications for the early diagnosis and management of renal dysfunction in obese pregnant women.

Main Part

1. Obesity and Metabolic Dysregulation in Pregnancy

Obesity is characterized by excess adipose tissue accumulation, which acts as an active endocrine organ secreting various adipokines, including leptin, adiponectin, resistin, and tumor necrosis factor-alpha (TNF-α). In obese pregnant women, the dysregulation of these adipokines contributes to insulin resistance, hyperinsulinemia, and dyslipidemia. Elevated insulin levels promote sodium retention and stimulate the sympathetic nervous system, resulting in increased blood pressure.

Furthermore, adipose tissue-derived free fatty acids promote lipotoxicity in renal tubular and glomerular cells, impairing their normal function. Hyperglycemia associated with insulin resistance leads to advanced glycation end-products (AGEs) that further damage the glomerular basement membrane and podocytes, reducing the glomerular filtration rate (GFR). These metabolic disturbances, while often subclinical in the first trimester, progressively worsen as pregnancy advances, setting the stage for overt renal dysfunction.

2. Chronic Inflammation and Endothelial Dysfunction

Obesity is associated with a state of chronic, low-grade systemic inflammation. Adipose tissue macrophages in obese individuals produce elevated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), TNF-α, and C-reactive protein (CRP). This inflammatory milieu disrupts normal endothelial function, reducing nitric oxide (NO) bioavailability and promoting vasoconstriction.

In the context of pregnancy, endothelial dysfunction represents a central mechanism in the pathogenesis of preeclampsia. Healthy pregnancy requires adequate vasodilation and increased renal perfusion to accommodate the rising GFR. Endothelial dysfunction in obese women blunts this physiological vasodilation, leading to increased renal vascular resistance and impaired glomerular perfusion. The glomerular endotheliosis — swelling and vacuolation of glomerular endothelial cells — observed in preeclampsia is closely linked to this inflammatory endothelial injury.

Soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) imbalance further contribute to endothelial dysfunction. Elevated sFlt-1 levels, reported in obese pregnant women even before clinical preeclampsia onset, antagonize vascular endothelial growth factor (VEGF) signaling, disrupting glomerular endothelial integrity and causing proteinuria.

3. RAAS Activation and Renal Hemodynamic Alterations

The renin-angiotensin-aldosterone system plays a pivotal role in regulating blood pressure and renal function. In normal pregnancy, the RAAS is upregulated to support plasma volume

expansion, yet vascular sensitivity to angiotensin II (Ang II) is reduced due to elevated levels of angiotensin-(1-7) and prostacyclin. In obese pregnant women, this balance is disrupted.

Adipose tissue itself contributes to RAAS activation by producing angiotensinogen, the precursor of angiotensin I. Elevated Ang II levels in obese individuals promote renal vasoconstriction, reduce renal blood flow, and stimulate aldosterone secretion, leading to sodium and water retention and exacerbated hypertension. These changes increase the glomerular capillary pressure, initially causing hyperfiltration, but over time resulting in glomerular injury and reduced nephron function.

Additionally, autoantibodies against the angiotensin II type 1 receptor (AT1-AA), detected at higher levels in obese preeclamptic women, further amplify Ang II signaling, contributing to renal vasoconstriction and trophoblast dysfunction. RAAS dysregulation thus represents a central node connecting obesity, impaired placentation, and renal injury in preeclampsia.

4. Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, is markedly elevated in obese individuals. Excess fatty acid oxidation in mitochondria and activation of NADPH oxidase in adipose and vascular tissues generate high levels of superoxide anion and hydrogen peroxide. These reactive species oxidize low-density lipoproteins, damage cellular membranes, and inactivate nitric oxide, further exacerbating endothelial dysfunction.

In the kidney, oxidative stress targets podocytes, mesangial cells, and tubular epithelial cells, leading to structural injury and functional impairment. Mitochondrial dysfunction in renal cells reduces their energy production capacity, impairing active transport mechanisms and contributing to tubular proteinuria. In obese pregnant women, these oxidative mechanisms are amplified by the additional metabolic demands of pregnancy and the ischemia-reperfusion injury associated with abnormal placentation.

5. Impaired Placentation and Renal Consequences

Abnormal placentation, characterized by defective trophoblast invasion and inadequate spiral artery remodeling, is a hallmark of preeclampsia. The resulting uteroplacental ischemia triggers the release of anti-angiogenic factors, inflammatory mediators, and oxidative stress products into the maternal circulation. These circulating factors act on the maternal vasculature, including renal vessels, inducing widespread endothelial injury.

In obese women, pre-existing endothelial dysfunction and inflammatory states may impair early trophoblast invasion, increasing the likelihood of abnormal placentation. The subsequent release of sFlt-1 and soluble endoglin from the ischemic placenta exacerbates glomerular endothelial

damage. The net result is glomerular endotheliosis, reduced GFR, and proteinuria — the hallmark renal manifestations of preeclampsia.

6. Glomerular Hyperfiltration and Progressive Renal Injury

In early obesity, the kidneys compensate for increased metabolic demands through glomerular hyperfiltration — an increase in the single-nephron GFR driven by afferent arteriolar dilation and elevated intraglomerular pressure. While this initially maintains overall renal function, chronic hyperfiltration damages the glomerular basement membrane and podocytes, leading to proteinuria and eventual nephron loss.

In pregnancy, superimposed on this background of hyperfiltration, the additional hemodynamic demands further stress glomerular structures. Obese pregnant women with preeclampsia demonstrate significantly reduced eGFR compared to both lean pregnant controls and obese women without preeclampsia, indicating that the combination of obesity-driven hyperfiltration and preeclamptic glomerular endotheliosis accelerates renal functional decline.

Microalbuminuria, detectable before overt proteinuria, serves as an early biomarker of glomerular injury in this population. Its detection in the first and second trimesters of pregnancy in obese women may allow identification of those at highest risk for subsequent preeclampsia and severe renal complications.

Discussion

The pathophysiology of obesity-associated preeclampsia and its renal consequences represents an intricate network of metabolic, inflammatory, hemodynamic, and oxidative mechanisms. Obesity creates a pro-inflammatory, pro-oxidant milieu that impairs endothelial function, dysregulates the RAAS, and promotes glomerular injury even before pregnancy. When superimposed on the normal physiological demands of pregnancy and abnormal placental development, these mechanisms converge to cause preeclampsia with significant renal involvement.

The kidney occupies a central position in this pathophysiology. Renal responses to the metabolic and hemodynamic stresses of obesity — including hyperfiltration, sodium retention, and reduced NO-mediated vasodilation — contribute directly to the hypertension and proteinuria that define preeclampsia. Conversely, the anti-angiogenic and inflammatory signals originating from an ischemic placenta in preeclampsia compound preexisting renal injury in obese women, creating a vicious cycle that worsens both conditions.

Understanding these interconnected pathways has important clinical implications. It suggests that preventive strategies targeting obesity-related inflammation, RAAS activation, and oxidative stress — ideally initiated before or in early pregnancy — may attenuate preeclampsia

risk. Biomarkers of early renal injury, including microalbuminuria and urinary neutrophil gelatinase-associated lipocalin (NGAL), hold promise as tools for early risk stratification in this high-risk population.

Results

A review of current literature confirms that obese pregnant women exhibit a distinct pattern of renal and systemic pathophysiological alterations that predispose them to preeclampsia. Key findings include: elevated circulating levels of pro-inflammatory cytokines (IL-6, TNF-α, CRP) correlating with BMI and preeclampsia incidence; RAAS activation with increased angiotensinogen and AT1-AA levels; elevated sFlt-1 and reduced PlGF, reflecting angiogenic imbalance; reduced NO bioavailability and impaired endothelium-dependent vasodilation in renal and systemic vessels; increased oxidative stress markers, including urinary 8-isoprostane and plasma malondialdehyde; and glomerular hyperfiltration in early pregnancy transitioning to reduced eGFR, elevated creatinine, and proteinuria in established preeclampsia.

These findings are consistent across population-based studies, clinical trials, and experimental models, providing strong evidence for the pathophysiological framework outlined in this review. Importantly, many of these alterations precede clinical preeclampsia onset by weeks, underscoring the potential for early detection and intervention.

Conclusion

Obesity in pregnancy creates a complex pathophysiological environment that markedly elevates the risk of preeclampsia and associated renal dysfunction. The mechanisms involved — chronic inflammation, RAAS dysregulation, endothelial dysfunction, oxidative stress, and impaired placentation — are interrelated and mutually reinforcing. The kidneys, as key regulators of blood pressure and fluid homeostasis, bear a disproportionate burden of these pathological processes.

Early recognition of renal dysfunction through biochemical and hemodynamic markers in obese pregnant women can facilitate timely risk stratification and intervention, potentially preventing progression to severe preeclampsia. Future research should focus on identifying novel biomarkers and therapeutic targets within these pathophysiological pathways to improve maternal and fetal outcomes in this high-risk population. Integrating comprehensive renal functional assessment into routine prenatal care for obese women is strongly recommended based on current pathophysiological evidence.

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