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Elevated Risk of Preeclampsia in Obese Pregnancies: The Interaction Between Metabolic Dysregulation and Placental Dysfunction

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Abstract: Preeclampsia, a hypertension condition during pregnancy, presents considerable dangers to both maternal and fetal well-being. Maternal obesity is becoming acknowledged as a significant modifiable risk factor for preeclampsia; however, the underlying mechanisms are intricate and varied. This paper explores how metabolic dysregulation in obese pregnancies can lead to issues with the placenta. Key problems include insulin resistance, chronic inflammation, oxidative stress, and the role of anti-angiogenic factors like soluble fms-like tyrosine kinase-1 (sFlt-1) based on existing literature and data. Elevated leptin and reduced adiponectin levels, common in obesity, further exacerbate endothelial dysfunction and contribute to systemic inflammation. Additionally, obesity-related dyslipidemia worsens the oxidative and inflammatory processes that drive placental ischemia and vascular complications in preeclampsia. Through a synthesis of current research, this study highlights the intricate relationship between maternal obesity and the heightened risk of preeclampsia, emphasizing the need for targeted interventions in weight management to improve pregnancy outcomes.

Keywords: Preeclampsia, Metabolic Dysregulation, Anti-angiogenic Factors, Placental Dysfunction, Insulin Resistance.

1. Introduction

Pre-eclampsia is an enigmatic and often fatal hypertensive disorder, one of the most common complications of human pregnancy, impacting 5–7% of pregnancies worldwide. It is specified by sudden hypertension and proteinuria occurring out and about of 20 weeks of pregnancy. This condition may result in severe complications for mother and fetus (eclampsia, stroke as well as preterm delivery and intrauterine growth restriction) [1]. That is a major factor that contributes to maternal and perinatal morbidity and mortality, particularly in less-resourced settings. Hypertensive disorders, including preeclampsia, are significant contributors to maternal mortality worldwide, as indicated in a systematic analysis by the World Health Organization (WHO). According to the review, these disorders are accountable for 16.1% of maternal deaths in developed nations, rising to 25.7% in Latin America and the Caribbean, data which the authors say may be underestimated. While these figures are not as excessive in Africa and Asia (9.1% of all maternal deaths are associated with hypertensive disorders), the impact is still significant [2]. Whilst most symptoms can be relieved after

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delivery, the chronic risk calls for perpetual monitoring and alertness. The placenta is a crucial organ for fetal development and plays a significant role in the pathophysiology of pre-eclampsia.

Currently published data suggests chronic hypertension and diabetes and obesity may play a role, but the pathogenesis behind this condition [3]. Still, it is unclear how exactly these factors interact with maternal physiology, contributing to preeclampsia. Updates on common knowledge, considerations in general but with significant advances on risk factors identification, are not exhaustive on how modifiable factors, and especially maternal obesity with all widely discussable consequences, may determine the onset and course of preeclampsia. Moreover, there is a lack of information regarding the effectiveness of interventions centered on weight management on lowering the disease's incidence.

This study aims to synthesise the association of maternal obesity with pre-eclampsia risk through a combined observational and analytical approach. The research would be concentrated on obesity and predictors, having effects on raising risk of preeclampsia. This study may facilitate future research aimed at preventing preeclampsia by identifying significant modifiable risk variables, so enhancing maternal and newborn health outcomes and mitigating unfavorable effects.

2. Obesity as a Risk Factor for Preeclampsia

When it comes to pre-eclampsia risk factors, maternal obesity is one of the most significant and modifiable. Pre-pregnancy obesity (defined as BMI ≥30 kg m−2) has several metabolic derangements that are detrimental to pregnancy outcomes [1]. Insulin resistant, chronic low-grade inflammation, and dyslipidemia are all disease processes that many people believe may lead to the development of pre-eclampsia. Higher body mass index (BMI) is confirmed in epidemiological studies to be associated with an increased risk of pre-eclampsia in women than normal BMI. A study validated the risk factors for preeclampsia in 2,637 pregnant women from three regions. Overweight (BMI 25–30, OR 1.65) or obese (BMI 30–35, OR 2.34; BMI 35–40, OR 3.59; BMI >40, OR 6.04) were highly associated with increased preeclampsia risk. The most critical risk factors were obesity and overweight, with attributable risks of 64.9% and 64.4%, respectively.

3. Common Mechanisms Linking Obesity and Pre-Eclampsia

Lopez-Jaramillo et al. elucidated the significant overlap between obesity and preeclampsia in various metabolic and inflammatory markers, thereby highlighting the pathogenic connections between the two conditions. Both obesity and preeclampsia are characterized by hyperinsulinemia and insulin resistance, which are pivotal contributors to endothelial dysfunction and impaired vasodilation — key mechanisms in the pathogenesis of preeclampsia [4].

In individuals with obesity, there is often an imbalance in the levels of key adipokines, particularly leptin and adiponectin. These adipokines act in metabolic regulation and inflammation. Leptin is a hormone produced primarily by adipose tissue and is responsible for regulating energy balance and appetite. However, in obese individuals, leptin levels are elevated due to increased fat mass. Conversely, adiponectin, another adipokine, typically exerts anti-inflammatory and vasoprotective effects, including enhancing insulin sensitivity and reducing oxidative stress. On the other hand, the adipokine adiponectin has been shown to have anti-inflammatory and vasoprotective effects such as the increase of insulin sensitivity and decrease of oxidative stress. In obesity, however, a global reduction in adiponectin is observed acting synergically to amplify the inflammatory condition with a great impact on vascular impairment. High leptin plus low adiponectin set a pro-inflammatory and pro-oxidative milieu which may enhance endothelial dysfunction and aggravate the onset of pre-eclampsia. On the other hand, systemic inflammation marker including pro-inflammatory cytokines TNF-α and IL-6, and increased level of high-sensitivity C-reactive protein (hs-CRP) are significantly

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correlated in both conditions, contributing to systemic inflammation and oxidative stress, and further damaging endothelial function. Dyslipidemia is also common in obesity and preeclampsia and participates in the development of cardiovascular disease in obesity [4]. The association between maternal obesity and preeclampsia is well-established but supported by a large body of evidence, such as the work by O'Brien et al. and He et al. [5][6]. These two studies provide convincing evidence that risk of preeclampsia increases along with increasing maternal BMI, supporting a dose-response relationship between BMI and preeclampsia [7][8].

He et al.'s analysis demonstrated that preeclampsia risk increases with elevated BMI. They derived adjusted odds ratios for the respective categories of BMI: Among overweight women (BMI 25-29.9), the adjusted odds ratio was 1.71, compared with women with a normal BMI. For these authors, the adjusted odds ratios for the development of preeclampsia in obese women (BMI ≥ 30) was 2.48, giving an odds ~2.5 times the risk of the development of preeclampsia compared to women of normal weight [6].

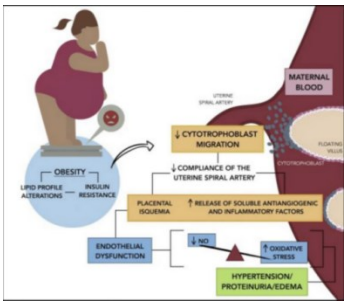

Figure 1: Mechanisms linking obesity to preeclampsia [4]

This complexity is demonstrated in the interactions between metabolic, inflammatory, and vascular mechanisms between maternal obesity and preeclampsia as shown in figure 1. Insulin resistance, a frequent sequela of obesity, is a key mediator in this association and can also contribute to the pathogenesis of preeclampsia. Hyperinsulinemia secondary to insulin resistance in obese pregnant women impairs normal cytotrophoblast activity (the cells that remodel the uterine spiral arteries). Such remodeling is essential to enlarge the spiral arteries into larger, low-resistance vessels that can supply sufficient blood to the placenta. Conversely, in obesity, hypoxia-associated insulin resistance alters cytotrophoblast migration/invasion contributing to incomplete remodeling of uterine spiral arteries. This poor remodeling results in placental ischemia [4].

4. Anti-angiogenic Factors in Preeclampsia

Anti-angiogenic factors which contribute to the vascular dysfunction characteristic of the disease have been implicated among mechanisms of the pathophysiology of preeclampsia. Soluble anti-angiogenic factors (e.g., soluble fms-like tyrosine kinase-1 [sFlt-1]) alter the physiological equilibrium between angiogenic and anti-angiogenic factors, contributing to inadequate placentation and systemic endothelial dysfunction [9]. Placental ischemia initiates an avalanche of deleterious processes, first with the subsequent release of soluble anti-angiogenic factors and pro-inflammatory cytokines into the maternal circulation. This results in the disturbance in the balance of pro-angiogenic and anti-angiogenic factors resulting in global endothelial dysfunction [4]. While it is recognized that obesity may exacerbate the renal hemodynamic and blood pressure responses to placental ischemia in pregnant rats by stimulating increased sFlt-1 production in the placenta, the sFlt-1 protein is an antagonist of vascular endothelial growth factor (VEGF), a molecule essential for endothelial integrity that binds to and inhibits VEGF activity. Moreover, T cells release sFlt-1 in reaction to placental ischemia, which activates and dysfunctions maternal endothelial cells in

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opposition to VEGF and placental growth factor (PlGF). Women with gestational hypertension have elevated sFlt-1 and decreased free PlGF and VEGF levels. In addition, the RUPP model has revealed that during pregnancy this disturbance is associated with elevated plasma and placental sFlt-1 and decreased free VEGF and PlGF. These data support the notion that the placenta is a major contributor to levels of sFlt-1, as well as that placental hypoxia is a major stimulus for its secretion [10].

5. Oxidative Stress and Inflammatory Pathways

Additionally, further characteristics of endothelial dysfunction include lower production of nitric oxide (NO), which is an essential contributor to vascular tone and promotes vasodilation. The reduced bioavailability of NO contributes to increased vascular resistance and hypertension, major clinical hallmarks of preeclampsia. Moreover, the damaged endothelium worsens the typical signs of preeclampsia (e.g., proteinuria and edema) by permitting protein to leak into the urine and fluid to accumulate into the tissues due to the deficient endothelial barrier function. In addition, oxidative stress is responsible for amplifying the pathological impact of obesity on pregnancy (Figure 1). In obesity, reactive oxygen species (ROS) levels are increased as a consequence of more production, due to the upregulation of NADPH oxidase and other ROS producing enzymes and a diminished capacity of neutralization in the form of antioxidants. Within the placenta, accumulation of ROS is significant and compounds the endothelial damage done by ROS through augmenting the inhibition of the production of NO, further contributing to vascular dysfunction. This oxidative stress not only worsens placental ischemia but also maintains the pathologic loops of inflammation, oxidative stress, and endothelial dysfunction, and thus is responsible for the vicious cycle that promotes preeclampsia. Also, oxidative stress emphasises the impact of dyslipidaemia in the pathophysiology of preeclampsia. During pregnancy, dyslipidemia defined by increased triglyceride and low-density lipoprotein (LDL) cholesterol are further aggravated [4]. These lipid-related abnormalities lead to cellular accumulation of oxidized-LDL (oxLDL) in the vascular endothelium, sustaining low-grade inflammation and further dysfunction of the endothelium. OxLDL triggers an inflammatory cascade and, thus, increases the expression of anti-angiogenic factors, leading to a vicious circle of vascular damage that maintains and intensifies the hypertensive status [11].

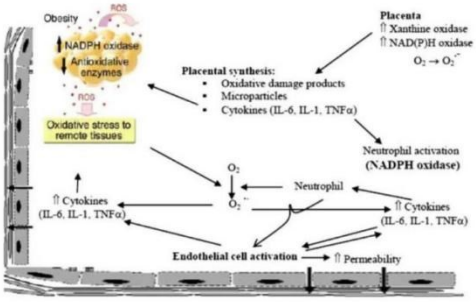

Figure 2: Mechanisms Linking Placental Oxidative Stress to Maternal Vascular Dysfunction

Figure 2 provides an overview of the detailed mechanisms through which the placental oxidative stress arising from obesity leads to the maternal vascular dysfunction. In obese pregnancies, there is a major increase in ROS generation, mostly mediated by increased activity of enzymes including NADPH oxidase and xanthine oxidase. The process of long-term oxidative stress resulting in increased ROS generation later causes a significant amount of damage at the cellular level within the placenta. The oxidative stress that occurs causes damage to placental tissues and leads to the release of a number of damage associated molecules and proinflammatory cytokines, including IL-6, IL-1

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and TNF-α [2]. Placenta synthesizes and releases these cytokines, which are produced during oxidative damage contributing to local as well as systemic inflammation.

The role of neutrophil activation in increasing oxidative stress is also illustrated in the figure. Activated neutrophils, a type of white blood cell, begin to produce more superoxide anions through NADPH oxidase when the placental is stressed. This both maintains the local oxidative stress and connects the local placental failure with a more wide-spread systemic inflammatory response. The ongoing recruiting of neutrophils and elevated synthesis of ROS can worsen endothelial injury and lead to increased permeability and dysfunction of the vascular system. This neutrophil-driven amplification of oxidative stress due to neutrophils is a necessary step in the progression of placental oxidative stress into systemic vascular complications.

6. Endothelin-1 and Vascular Reactivity

Endothelin-1 (ET-1), a potent vasoconstrictor. Studies indicate the elevation of ET-1 in preeclamptic women and this elevation has been suggested to correlate with the severity of the disease [7]. Under normal conditions, Nitric oxide (NO) acts to diminish levels of endothelium derived contracting factor (ET-1), however, NO production is down regulated and ET-1 production is up regulated leading to vasoconstriction, and hence, hypertension [9]. This is further potentiated in obesity, where both patients with excess weight and endothelial dysfunction present increased levels of ET-1 [8].

In the context of the environmental burden, increases in obesity worldwide, especially in low- and middle-income countries that are urbanising, are mainly due to changes in the composition of diets. Some of these are: Increased intake of energy-dense, nutrient-deficient meals coupled with diminished physical activity. A positive energy balance leads to obesity and contributes to the development of metabolic syndrome components, including insulin resistance and persistent low-grade inflammation. Graded inflammation is among the central mechanisms by which endothelial dysfunction occurs [12]. Genetic factors could modulate how different populations metabolise fat and glucose, resulting in differences in insulin sensitivity, as shown by variation in insulin resistance and metabolic syndrome between ethnic groups [13]. In addition, socio-economic factors such as limited access to healthcare, fewer education and healthy food options perpetuate these disparities. And indeed, prevalence is also affected by environmental factors, as nutrition, exercise, and stress exposure play a significant role in this regard.

Genetically, certain polymorphisms and mutations involved in metabolic regulation, vascular function, and inflammatory pathways predispose the individual to obesity and preeclampsia. Polymorphisms in pro-inflammatory cytokine genes or those related to oxidative stress can lead to a heightened inflammatory response in an obese woman and therefore increase preeclampsia susceptibility. On the other hand, as much as hereditary factors are important in preeclampsia development, environmental and socioeconomic factors seem to have a stronger effect. For instance, several studies in Europe have shown that pregnant women with preeclampsia exhibit elevated plasma levels of asymmetric dimethylarginine (ADMA), which is closely linked to endothelial dysfunction [14].

7. Conclusion

The connection between obesity and pre-eclampsia is complex, involving interaction of genetic and environmental factors and widespread change at the cellular and molecular level, not only increasing the likelihood of the birth complicating hypertensive disorder occurring, but also increasing its severity. The chronic low-grade inflammation and metabolic derangements, which is essential to the pathogenesis of pre-eclampsia, will result in a pro-inflammatory milieu during obesity. The pathogenesis of preeclampsia is characterized by an increased production of anti-angiogenic factors

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(e.g., sFlt-1) in obese pregnancies, which disrupts the delicate balance between pro-angiogenic factors such as VEGF and PlGF. This leads to endothelial dysfunction, which is a central feature of preeclampsia and manifests as increased vascular resistance and hypertension. Furthermore, obesity-related oxidative stress exacerbates vascular injury by increasing the production of ROS, which impairs endothelial function and promotes a cycle of inflammation and vascular dysfunction. This heightened oxidative stress and inflammation elevate the likelihood of severe preeclampsia, rendering obese women more susceptible to problems such as eclampsia, stroke, and organ damage. Genetic predisposition is a significant risk factor for both obesity and preeclampsia. Polymorphisms and mutations in genes associated with metabolic regulation, vascular function, and inflammatory pathways can increase an individual's vulnerability to these conditions. For instance, alterations in genes that regulate endothelin-1 production and oxidative stress responses may result in more pronounced vascular reactivity and endothelial dysfunction in obese individuals, increasing the likelihood of developing preeclampsia.

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