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Impact of obesity, genetic predisposition, and comorbidities on pregnancy-related hypertension

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ABSTRACT

Purpose: This study aims to explore the impact of obesity, genetic predisposition, and comorbidities on pregnancy-related hypertension. Given the rising prevalence of maternal obesity and associated metabolic disorders, understanding how these factors contribute to hypertensive complications during pregnancy is crucial for developing effective prevention and management strategies. The study also examines the role of genetic susceptibility and pre-existing medical conditions in exacerbating hypertensive risks, emphasizing the need for a holistic approach in maternal healthcare.

Research Design and Methodology: This study employs a systematic literature review (SLR) to synthesize findings from existing research on the relationship between obesity, genetic factors, and comorbidities in relation to pregnancy-related hypertension. Relevant peer-reviewed articles from Elsevier, Emerald, Wiley, and Springer published after 2018 were analyzed to identify key trends, mechanisms, and clinical implications. The review integrates evidence from obstetrics, endocrinology, genetics, and public health to provide a comprehensive understanding of the topic.

Findings and Discussion: The study reveals that obesity significantly contributes to hypertensive disorders in pregnancy through mechanisms such as endothelial dysfunction, chronic inflammation, insulin resistance, and RAAS activation. Genetic predisposition, particularly polymorphisms in RAAS-related genes (AGT, ACE, AGTR1) and endothelial function genes (eNOS, VEGF), is strongly associated with an increased risk of hypertension. Additionally, pre-existing conditions such as diabetes mellitus, chronic hypertension, kidney disease, and autoimmune disorders further aggravate hypertensive complications.

Implications: The findings underscore the importance of early screening programs, personalized treatment approaches, and interdisciplinary prenatal care. Healthcare policymakers should develop standardized guidelines for managing hypertensive pregnancies complicated by obesity and comorbidities. The study highlights the importance of lifestyle interventions, genetic screening, and pharmacological advancements in reducing pregnancy-related hypertension risks and improving maternal-fetal health outcomes.

Introduction

Hypertensive disorders in pregnancy represent a substantial global health challenge, significantly contributing to maternal and fetal morbidity and mortality. These disorders, which encompass gestational hypertension, preeclampsia, and eclampsia, remain among the leading causes of adverse pregnancy outcomes, including preterm birth, intrauterine growth restriction, and maternal

mortality. The increasing prevalence of pregnancy-related hypertension is particularly alarming as it closely correlates with rising obesity rates worldwide. Obesity has emerged as a critical public health concern, exacerbating pregnancy-related complications by imposing excessive physiological stress on maternal cardiovascular and metabolic systems. This condition is associated with insulin resistance, increased systemic inflammation, and endothelial dysfunction, all of which collectively heighten the risk of hypertension during pregnancy. The mechanisms linking obesity to hypertensive disorders are complex and multifaceted, involving alterations in adipokine signaling, dysregulation of renin-angiotensin-aldosterone pathways, and heightened sympathetic nervous system activity. Furthermore, obesity predisposes pregnant individuals to oxidative stress and vascular dysfunction, further compounding their susceptibility to hypertensive complications. Given the substantial health risks associated with obesity-related hypertensive disorders, understanding the intricate pathophysiological mechanisms underlying this relationship is essential for improving maternal and neonatal health outcomes. However, despite the well-established link between obesity and pregnancy-related hypertension, clinical management remains challenging. The variability in maternal responses to obesity-induced hypertension underscores the need for a more comprehensive examination of additional risk factors that may exacerbate the condition. Consequently, further investigation is required to elucidate how maternal obesity interacts with other physiological and genetic determinants of hypertensive disorders during pregnancy.

While obesity alone constitutes a significant risk factor for hypertensive disorders during pregnancy, emerging evidence suggests that genetic predisposition and pre-existing comorbidities further amplify this risk. Genetic susceptibility plays a crucial role in modulating key physiological processes, including blood pressure regulation, metabolic homeostasis, and inflammatory responses, making individuals inherently more vulnerable to developing hypertension during pregnancy. Variants in genes associated with endothelial function, lipid metabolism, and inflammatory pathways have been implicated in pregnancy-related hypertension, suggesting that genetic factors may influence an individual's predisposition to developing hypertensive disorders under metabolic stress conditions such as obesity. Additionally, maternal comorbidities, including diabetes mellitus, metabolic syndrome, and chronic kidney disease, significantly elevate the likelihood of developing gestational hypertension and preeclampsia. These conditions contribute to endothelial dysfunction, vascular resistance, and impaired placental development, which are central mechanisms in the pathogenesis of hypertensive disorders during pregnancy. Beyond the immediate maternal and fetal risks, these complications have long-term consequences, increasing the offspring's susceptibility to future cardiovascular and metabolic diseases. Despite the growing recognition of the multifactorial nature of pregnancy-related hypertension, current research primarily examines obesity, genetic predisposition, and comorbidities as independent risk factors rather than as interrelated contributors to disease pathology. Consequently, gaps remain in understanding how these factors interact and collectively influence hypertensive disorders in pregnancy. Moreover, inconsistencies in clinical guidelines regarding the management of hypertensive disorders in obese pregnant women with underlying comorbidities further complicate treatment strategies. As the prevalence of maternal obesity and related hypertensive disorders continues to rise, addressing these gaps is critical for advancing evidence-based interventions that can effectively mitigate adverse maternal and fetal health outcomes.

Recent studies emphasize the significant impact of maternal obesity on hypertensive disorders during pregnancy. According to Alves et al. (2024), obesity during pregnancy considerably elevates the risk of hypertensive disorders and other maternal-fetal complications. Maternal obesity has also been strongly associated with increased incidences of gestational diabetes, preeclampsia, and cardiovascular issues (Elgazzaz et al., 2024). These complications result from metabolic, inflammatory, and vascular dysfunctions that interfere with typical pregnancy adaptations. Additionally, genetic predisposition, pre-existing comorbidities, and early-life exposures further contribute to the development of hypertensive disorders in pregnancy (Stannard et al., 2024; Thomopoulos et al., 2024). Beyond pregnancy, maternal obesity and hypertension have long-term implications for offspring, increasing their risk of cardiometabolic diseases and neurodevelopmental disorders (Alves et al., 2024). The management of hypertensive disorders in pregnancy remains

complex due to their multifaceted nature and the absence of universally accepted clinical guidelines (Thomopoulos et al., 2024). Effective risk mitigation necessitates a multidisciplinary approach that incorporates lifestyle interventions, medical management, and early detection strategies (Alves et al., 2024). Obesity further exacerbates conditions such as insulin resistance and pregnancy-induced hypertension, leading to increased fetal anomalies and impaired fetal growth (Reed et al., 2023). The severity of these risks intensifies with higher obesity classes, significantly affecting both early (<34 weeks) and late-onset (≥34 weeks) hypertensive disorders (Grieger et al., 2021). Women with obesity are more likely to develop gestational hypertension and mild preeclampsia, which may progress to severe preeclampsia (Bohiltea et al., 2020). Excessive gestational weight gain further amplifies these risks, highlighting the necessity for targeted interventions (Grieger et al., 2021). Despite extensive research on the impact of maternal obesity, genetic predisposition, and comorbidities on pregnancy-related hypertension, significant gaps remain in fully understanding their combined effects. Existing studies have predominantly examined these factors in isolation, focusing either on obesity (Alves et al., 2024; Elgazzaz et al., 2024), genetic influences (Stannard et al., 2024; Thomopoulos et al., 2024), or comorbidities such as diabetes and metabolic syndrome (Reed et al., 2023). However, few studies have explored the interplay between these three variables and how their interactions exacerbate hypertensive disorders during pregnancy. This fragmented approach limits the development of a comprehensive model that can accurately predict the risk of pregnancy-related hypertension and guide personalized preventive strategies. Additionally, while obesity has been linked to increased gestational hypertension and preeclampsia severity (Bicocca et al., 2020; Bohîlţea et al., 2020), the extent to which genetic predisposition modulates these effects remains unclear. From a theoretical perspective, current models lack an integrative framework that explains how obesity, genetic susceptibility, and comorbidities collectively contribute to hypertensive disorders during pregnancy. While some studies suggest that early-life exposures and maternal metabolic adaptations play a role (Stannard et al., 2024), the precise mechanisms underlying this relationship remain poorly defined. Moreover, empirical research has yet to establish standardized clinical guidelines for managing hypertension in obese pregnant women with multiple risk factors (Thomopoulos et al., 2024). Given the increasing global burden of obesity-related pregnancy complications, a more holistic understanding is essential to bridge these gaps and inform evidence-based interventions that address the complexity of hypertensive disorders in pregnancy.

To address the identified research gaps, this study conducts a systematic literature review (SLR) to examine the combined effects of obesity, genetic predisposition, and comorbidities on pregnancy-related hypertension. Unlike previous studies that analyze these factors independently, this research provides an integrated perspective to understand better their interactions and cumulative impact on maternal and fetal health. The novelty of this study lies in its comprehensive synthesis of existing findings, aiming to establish a more transparent framework for identifying risk factors, improving clinical management, and guiding targeted interventions. Given the lack of standardized guidelines for managing hypertensive pregnancies complicated by obesity and comorbid conditions, this research seeks to contribute to the development of evidence-based recommendations that enhance prevention and treatment strategies. The primary research question in this study is: How do obesity, genetic predisposition, and comorbidities influence pregnancy-related hypertension? Additional questions include: What are the maternal and fetal consequences of these risk factors? Moreover, What strategies are effective in managing hypertension in obese pregnant women with comorbidities? This study aims to synthesize multidisciplinary evidence from obstetrics, genetics, endocrinology, and public health to bridge existing knowledge gaps. The findings will offer valuable insights for clinicians, researchers, and policymakers, providing a stronger foundation for improving maternal care and reducing the burden of hypertensive disorders in pregnancy.

Literature Review

Pregnancy-Related Hypertension

During pregnancy, the maternal cardiovascular system undergoes significant adaptations to accommodate the increasing metabolic demands of the fetus. Systemic vasodilation and increased plasma volume help regulate blood pressure and ensure adequate placental perfusion. However, in

cases of pregnancy-related hypertension, these physiological mechanisms fail, leading to endothelial dysfunction and vasoconstriction that contribute to elevated systemic blood pressure (Mol et al., 2016). The failure of trophoblast invasion into spiral arteries further disrupts placental blood flow, leading to placental insufficiency —a critical factor in the pathogenesis of preeclampsia and intrauterine growth restriction (IUGR) (Ortega et al., 2022). This disruption creates a hypoxic environment that increases oxidative stress, triggering an exaggerated maternal immune response that leads to systemic inflammation and vascular damage. The renin-angiotensin-aldosterone system (RAAS), which regulates fluid and electrolyte balance, becomes overactivated, leading to sodium retention, increased blood volume, and worsening hypertension (Maryam et al., 2024). This overactivation contributes to multi-organ complications in the mother, including renal dysfunction, hepatic impairment, stroke, and HELLP syndrome (Hemolysis, Elevated Liver Enzymes, and Low Platelet Count) (Brown et al., 2013). The fetus is also at significant risk, as reduced placental perfusion leads to fetal hypoxia, preterm birth, and restricted growth. Research suggests that exposure to hypertensive intrauterine environments may induce long-term cardiovascular and metabolic programming, increasing the offspring's susceptibility to hypertension and cardiovascular diseases later in life (Mol et al., 2016). Given these severe consequences, an early and multidisciplinary intervention approach is essential to mitigate risks and improve pregnancy outcomes.

During pregnancy, the maternal cardiovascular system undergoes significant adaptations to ensure optimal blood supply to the placenta and fetus. Typically, systemic vasodilation and increased plasma volume accommodate the growing metabolic demands of the fetus, leading to a physiological decrease in blood pressure. However, in pregnancy-related hypertension, these mechanisms fail, resulting in endothelial dysfunction and vasoconstriction that contribute to elevated systemic blood pressure (Possomato-Vieira & Khalil, 2016). The failure of trophoblast invasion into spiral arteries further disrupts placental blood flow, leading to placental insufficiency —a key factor in preeclampsia and intrauterine growth restriction (IUGR) (Burton et al., 2019). This impairment leads to an imbalance in angiogenic and anti-angiogenic factors, increasing oxidative stress and triggering an inflammatory response that exacerbates maternal vascular dysfunction. Dysregulation of the renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the pathophysiology of pregnancy-related hypertension. Overactivation of RAAS leads to excess sodium retention, increased blood volume, and hypertension, further worsening maternal cardiovascular strain (August & Sibai, 2022). This dysregulation not only affects maternal health but also increases the risk of multi-organ complications, including renal impairment, hepatic dysfunction, stroke, and HELLP syndrome (American College of Obstetricians and Gynecologists, 2020). Furthermore, Steegers et al. (2010) that exposure to hypertensive intrauterine environments may lead to fetal cardiovascular and metabolic programming, increasing the offspring's risk of developing hypertension and cardiovascular disease later in life. Given these severe maternal and fetal risks, early screening, timely intervention, and a multidisciplinary management approach are critical in mitigating adverse outcomes and ensuring better pregnancy health.

Obesity

Obesity during pregnancy is a well-established risk factor for hypertensive disorders, with multiple studies confirming its strong correlation with gestational hypertension and preeclampsia. Women classified as obese before pregnancy, particularly those with a BMI ≥30 kg/m², exhibit a significantly higher risk of developing pregnancy-related hypertension due to metabolic and vascular dysfunctions that accompany excess weight (Lynch et al., 2024). The accumulation of adipose tissue leads to a chronic pro-inflammatory state characterized by elevated levels of cytokines such as IL-6, TNF-α, and CRP, which contribute to endothelial dysfunction and vascular resistance, ultimately raising blood pressure levels during pregnancy (Spradley et al., 2015). Additionally, excess maternal weight increases placental oxidative stress, impairing normal fetal development and increasing the likelihood of placental insufficiency, a major contributor to hypertensive disorders (Poston et al., 2016). The renin-angiotensin-aldosterone system (RAAS) plays a crucial role in obesity-induced hypertension, as excessive adipose-derived angiotensinogen promotes sodium retention, fluid

imbalance, and increased vasoconstriction, exacerbating maternal hypertensive responses (Suwannasrisuk et al., 2020). Obese women with excessive gestational weight gain (GWG) face an even greater risk, as increased weight gain during pregnancy further disrupts metabolic homeostasis and worsens insulin resistance, heightening the likelihood of preeclampsia. These interconnected pathways underscore the multifactorial nature of obesity-related pregnancy hypertension, necessitating comprehensive prenatal care, and targeted interventions to mitigate maternal and fetal complications. Addressing maternal obesity through preconception counseling, dietary modifications, and regulated physical activity may offer a preventive approach to reducing the burden of hypertensive disorders in pregnancy (Lynch et al., 2024).

Obesity during pregnancy is a critical determinant of hypertensive disorders, contributing to gestational hypertension, preeclampsia, and long-term cardiovascular risks. Women classified as overweight or obese before pregnancy have a significantly higher incidence of hypertensive complications, mainly due to metabolic and vascular dysfunctions (Lewandowska et al., 2020). Excess adipose tissue functions as an endocrine organ, releasing inflammatory cytokines such as IL-6, TNF-α, and CRP, which induce systemic inflammation and endothelial dysfunction, ultimately compromising vascular homeostasis and leading to elevated blood pressure (Divella et al., 2016). Additionally, obesity disrupts the renin-angiotensin-aldosterone system (RAAS), causing excess sodium retention and fluid accumulation, further exacerbating hypertensive responses in pregnant women (August & Sibai, 2022). Beyond maternal complications, obesity-induced hypertension also negatively impacts placental function, leading to restricted fetal growth, preterm birth, and an increased risk of stillbirth (American College of Obstetricians and Gynecologists, 2020). The placental insufficiency observed in obese pregnancies results from reduced trophoblast invasion and increased oxidative stress, both of which impair uteroplacental circulation and fetal nutrient exchange. Maternal insulin resistance, commonly seen in obese pregnant women, amplifies vascular dysregulation, worsening the risk of severe preeclampsia and multi-organ dysfunction. These interconnected mechanisms highlight the necessity for early risk stratification and tailored interventions, including preconception counseling, weight management programs, and lifestyle modifications, to mitigate pregnancy-related hypertension and its associated adverse outcomes. Without comprehensive maternal health strategies, the escalating prevalence of obesity will continue to drive increased rates of hypertensive disorders in pregnancy, posing long-term risks for both maternal and neonatal health.

Genetic Predisposition

Genetic predisposition plays a crucial role in determining susceptibility to pregnancy-related hypertension, with a family history of hypertension, preeclampsia, or cardiovascular disease significantly increasing a woman's risk of developing hypertensive disorders during pregnancy. Studies on blood pressure heritability suggest that genetic and environmental factors interact to regulate vascular function, highlighting the importance of inherited traits in maternal cardiovascular adaptation (Pazoki et al., 2018). One of the key genetic mechanisms involved in pregnancy-induced hypertension is the renin-angiotensin-aldosterone system (RAAS), which governs sodium homeostasis, blood volume, and vascular response. Variations in angiotensinogen (AGT), angiotensin-converting enzyme (ACE), and angiotensin II type 1 receptor (AGTR1) genes have been linked to altered blood pressure regulation and placental perfusion, exacerbating the risk of hypertensive complications (Delforce et al., 2019). Genetic polymorphisms in endothelial nitric oxide synthase (eNOS) have been linked to impaired nitric oxide (NO) production, a crucial molecule that facilitates vascular relaxation and maintains endothelial function. Reduced NO bioavailability due to eNOS gene mutations contributes to vasoconstriction and an increased risk of preeclampsia (Yuan et al., 2020). Moreover, genes regulating vascular endothelial growth factor (VEGF) and inflammatory cytokines, such as TNF-α, have been identified as key players in placental dysfunction and maternal vascular inflammation, thereby worsening hypertensive disorders in pregnancy (Kurlander et al., 2020). Beyond genetic predisposition, recent findings suggest that epigenetic modifications, including DNA methylation and microRNA expression, influence blood pressure regulation across generations, underscoring the long-

term effects of pregnancy-induced hypertension on maternal and fetal health (Obeagu & Obeagu, 2024).

Epigenetic modifications play a crucial role in pregnancy-related hypertension, as environmental factors influence gene expression and vascular function, increasing the susceptibility to hypertensive disorders during pregnancy. Maternal hypertension has been shown to induce epigenetic alterations in fetal DNA, which may predispose offspring to hypertension and metabolic disorders later in life (Broséus et al., 2022). These modifications, particularly DNA methylation of genes regulating vascular function and inflammation, can lead to impaired endothelial responses and dysregulated placental circulation, further exacerbating hypertensive complications in pregnancy (Baetens et al., 2024). In addition to DNA methylation, histone modifications and chromatin remodeling have also been implicated in the dysregulation of blood pressure homeostasis, particularly in maternal hypertensive conditions. Beyond DNA modifications, microRNAs (miRNAs) have emerged as key regulators of vascular function, modulating the expression of genes related to angiogenesis, inflammation, and endothelial repair. Yaacoub et al. (2024) indicate that abnormal miRNA expression patterns in preeclamptic pregnancies contribute to vascular dysfunction and increased systemic inflammation, worsening pregnancy-related hypertension. Furthermore, research on umbilical cord blood DNA methylation suggests that offspring of mothers with pre-eclampsia exhibit distinct epigenetic changes in immune system regulation, supporting the intergenerational transmission of hypertension risk (Zhu et al., 2024). These findings emphasize the importance of epigenetic biomarkers for early detection and the need for personalized interventions to mitigate long-term cardiovascular risks associated with pregnancy-related hypertension.

The Influence of Comorbidities on Pregnancy-Related Hypertension

Diabetes mellitus is a well-established risk factor for pregnancy-related hypertension, with both gestational diabetes mellitus (GDM) and pre-existing type 2 diabetes significantly increasing the risk of hypertensive complications during pregnancy. Padilla et al. (2022) insulin resistance, a hallmark of diabetes, disrupts endothelial function and vascular homeostasis, contributing to increased systemic blood pressure and heightened vascular inflammation. This metabolic dysfunction not only accelerates the progression of gestational hypertension but also elevates the risk of preeclampsia, a severe hypertensive disorder characterized by widespread endothelial dysfunction and placental insufficiency (Plows et al., 2018). Furthermore, hyperglycemia exacerbates chronic inflammation, leading to increased production of pro-inflammatory cytokines and further impairing vascular relaxation and endothelial stability (Xue et al., 2023). Beyond metabolic disturbances, placental dysfunction is a key mediator between diabetes and pregnancy-related hypertension, as elevated glucose levels alter trophoblast function, reducing placental perfusion and increasing oxidative stress (Echeverria et al., 2020). Ottanelli et al. (2020) suggest that women with both obesity and gestational diabetes exhibit more significant placental hypoxia and endothelial stress, intensifying their predisposition to hypertensive disorders in pregnancy. Chronic hypertension before pregnancy is another critical factor, as pre-existing vascular damage leads to impaired placental adaptation, further elevating the likelihood of superimposed preeclampsia. Given these complex interactions, early screening, tailored interventions, and a multidisciplinary approach are essential to mitigating the risks associated with pregnancy-related hypertension in women with diabetes and other pre-existing conditions.

Chronic kidney disease (CKD) is a significant contributor to pregnancy-related hypertension, as impaired renal function disrupts blood pressure regulation and sodium homeostasis, increasing the risk of gestational hypertension and preeclampsia. Women with pre-existing CKD often experience reduced renal perfusion, which leads to fluid retention, endothelial dysfunction, and heightened systemic vascular resistance, all of which exacerbate hypertensive complications (Hahka et al., 2024). Additionally, CKD is associated with chronic inflammation and oxidative stress, mechanisms that have been linked to placental dysfunction and fetal growth restrictions (Awazu, 2022). Impaired renal filtration further results in the accumulation of nephrotoxic metabolites, increasing the likelihood of placental insufficiency and intrauterine growth restriction (IUGR) (Yokota et al., 2021). Beyond CKD, autoimmune disorders such as systemic lupus erythematosus (SLE) and antiphospholipid

syndrome (APS) play a critical role in pregnancy-related hypertension, as these conditions trigger immune-mediated vascular inflammation, increasing the risk of endothelial dysfunction and thrombosis (Cavalli et al., 2022). Women diagnosed with APS exhibit hypercoagulability, which promotes microvascular thrombosis within the placenta, leading to preeclampsia and fetal growth abnormalities. Furthermore, elevated pro-inflammatory cytokines and autoantibody activity in SLE contribute to vascular remodeling defects, further predisposing pregnant women to severe hypertensive disorders (Tan et al., 2022). Given these challenges, effective management of pregnancy-related hypertension in women with CKD or autoimmune disorders requires personalized risk assessment and multidisciplinary care to prevent severe maternal and fetal complications.

Research Design and Methodology

Study Design

This study adopts a systematic literature review (SLR) methodology. It is a qualitative research approach designed to systematically identify, evaluate, and synthesize relevant academic literature on pregnancy-related hypertension and its relationship with obesity, genetic predisposition, and comorbidities. The SLR method ensures a structured and transparent review process, allowing for a comprehensive assessment of existing research while minimizing bias. This approach is particularly suitable for synthesizing knowledge from multiple sources, critically analyzing different perspectives, and identifying research gaps in hypertensive disorders in pregnancy.

Sample Population or Subject of Research

The research comprises peer-reviewed journal articles, books, and academic reports published in reputable scientific databases, including Elsevier, Emerald, Wiley, and Springer. The inclusion criteria focus on studies published after 2015 to ensure the review captures the latest advancements in understanding pregnancy-related hypertension and its associated risk factors. The selected literature must provide empirical data or comprehensive reviews on topics including obesity, genetic predisposition, and comorbidities such as diabetes mellitus, chronic kidney disease, and autoimmune disorders. Studies with limited relevance, outdated perspectives, or lacking methodological rigor are excluded from the analysis.

Data Collection Techniques and Instrument Development

Data collection follows a structured and systematic search strategy across electronic databases. The study uses specific keyword combinations such as "pregnancy-related hypertension," "obesity and gestational hypertension," "genetic risk factors for hypertension in pregnancy," and "comorbidities affecting hypertensive disorders in pregnancy" to retrieve relevant studies. Boolean operators (AND, OR) are applied to refine the search and ensure comprehensive coverage. The screening process involves a title and abstract review, followed by a full-text evaluation to assess each study's thematic relevance, methodological quality, and contribution to the research focus. Extracted data are systematically categorized using a coding framework, grouping studies based on risk factors, pathophysiology, and management strategies.

Data Analysis Techniques

The analysis follows a thematic synthesis approach, where data extracted from the selected studies are categorized, analyzed, and synthesized to generate core themes that align with the research objectives. Qualitative content analysis is applied to identify patterns, contradictions, and emerging insights within literature. A narrative synthesis is then conducted to integrate findings from different sources, ensuring a critical, structured, and coherent interpretation of the impact of obesity, genetic predisposition, and comorbidities on pregnancy-related hypertension. To assess the quality of the included studies, an evaluation framework is used to determine methodological rigor, reliability, and validity.

Findings and Discussion

Findings

Obesity significantly contributes to the development and progression of pregnancy-related hypertension (PRH), which includes conditions such as gestational hypertension and preeclampsia. Obese individuals typically experience physiological changes that disrupt normal blood pressure regulation during pregnancy. The excess adipose tissue in obese women serves as a source of chronic inflammation, leading to the increased production of pro-inflammatory cytokines, such as IL-6, TNF-α, and CRP (Divella et al., 2016). This inflammation contributes to endothelial dysfunction, impairs blood vessel dilation, increases vascular resistance, and raises blood pressure. Additionally, insulin resistance, a hallmark of obesity, further exacerbates the risk of pregnancy-related hypertension by increasing the vascular tone and decreasing the ability of blood vessels to relax appropriately (Plows et al., 2018). Activating the renin-angiotensin-aldosterone system (RAAS) in obesity leads to sodium retention, increased blood volume, and vasoconstriction, all of which contribute to elevated blood pressure during pregnancy (Poston et al., 2016). Furthermore, obesity during pregnancy negatively affects placental function, leading to insufficient placental perfusion and increasing the risk of intrauterine growth restriction (IUGR) and preterm birth (Reed et al., 2023). The combination of obesity and other metabolic conditions, such as gestational diabetes, significantly amplifies the risk of hypertensive complications, further increasing the likelihood of maternal cardiovascular issues and fetal health complications, including macrosomia and neonatal hypoxia (Alves et al., 2024).

Genetic predisposition is an essential, non-modifiable factor that plays a crucial role in the development of pregnancy-related hypertension (PRH). Family history is a significant indicator, with studies showing that women who have a family history of hypertension, preeclampsia, or cardiovascular diseases are at a heightened risk of developing hypertensive complications during pregnancy (Pazoki et al., 2018). Several genetic markers have been identified, particularly those associated with the renin-angiotensin-aldosterone system (RAAS), which regulates blood pressure and fluid balance. Polymorphisms in genes such as angiotensinogen (AGT), angiotensin-converting enzyme (ACE), and angiotensin II receptor type 1 (AGTR1) have been associated with the dysregulation of blood pressure during pregnancy, which can lead to gestational hypertension and preeclampsia (Yuan et al., 2020). Other key genes regulating vascular health include endothelial nitric oxide synthase (eNOS), which is crucial for vasodilation. Genetic variations in eNOS contribute to endothelial dysfunction, which can further exacerbate the risks of hypertension during pregnancy (Cavalli et al., 2022). Studies utilizing genome-wide association studies (GWAS) have identified specific genetic variants associated with the development of gestational hypertension and preeclampsia, highlighting the potential for genetic screening as part of early risk stratification in pregnant women (Pazoki et al., 2018). Additionally, epigenetic modifications caused by maternal hypertension may increase the risk of hypertension and cardiovascular diseases in the offspring later in life, demonstrating the intergenerational impacts of pregnancy-related hypertension (Zhu et al., 2024).

Comorbid conditions, such as diabetes mellitus, chronic hypertension, chronic kidney disease (CKD), and autoimmune disorders, significantly amplify the risk of developing pregnancy-related hypertension (PRH). Gestational diabetes mellitus (GDM) and type 2 diabetes increase the risk of gestational hypertension and preeclampsia, mainly due to insulin resistance and vascular inflammation (Xue et al., 2023). Insulin resistance in diabetic patients impairs blood vessel function and promotes sodium retention, further elevating blood pressure (Padilla et al., 2022). In women with chronic hypertension before pregnancy, the likelihood of developing superimposed preeclampsia increases significantly, leading to severe forms of hypertension and complications such as placental insufficiency, preterm birth, and fetal growth restriction (IUGR) (Steegers et al., 2010). Chronic kidney disease (CKD) also poses a significant risk factor, as kidney dysfunction impairs sodium regulation and blood pressure control, leading to further exacerbation of hypertensive disorders during pregnancy (Awazu, 2022). The dysregulation of renal function in CKD patients also impairs placental perfusion, contributing to adverse outcomes such as IUGR and preterm birth (Awazu, 2022). Additionally, autoimmune disorders, primarily systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) contribute to PRH by promoting systemic inflammation and vascular

dysfunction, thereby increasing the risk of preeclampsia and placental thrombosis (Cavalli et al., 2022).

Pregnancy-related hypertension (PRH) has serious consequences for both mother and fetus, affecting maternal and fetal health both during pregnancy and in the long term. Maternal complications related to PRH include stroke, renal failure, HELLP syndrome, eclampsia, and the need for emergency cesarean sections (Broséus et al., 2022). Women who develop hypertension during pregnancy are at increased risk for developing chronic hypertension, diabetes type 2, and cardiovascular diseases later in life, with studies indicating that women who had hypertensive pregnancies are at higher risk for these chronic conditions after childbirth (Brown et al., 2013). For the fetus, the risks are substantial. Placental insufficiency often leads to intrauterine growth restriction (IUGR), and babies born to mothers with PRH are at higher risk of preterm birth and fetal hypoxia (Grieger et al., 2021). Furthermore, exposure to a hypertensive intrauterine environment has been linked to long-term health risks in offspring, including increased susceptibility to metabolic disorders and hypertension in adulthood, demonstrating the intergenerational consequences of PRH (Broséus et al., 2022).

Managing pregnancy-related hypertension (PRH) requires a multifaceted approach, particularly in cases complicated by obesity and comorbid conditions. Regular blood pressure monitoring and the appropriate use of antihypertensive medications are essential in managing PRH (Thomopoulos et al., 2024). However, there are still no standardized guidelines for managing hypertensive pregnancies with obesity and comorbidities, indicating a gap in current clinical practice. A holistic approach involving lifestyle modifications is crucial for preventing PRH and managing existing hypertension. A balanced diet, regular exercise, and effective weight management, both before and during pregnancy, are vital in controlling blood pressure and reducing the risk of complications (Lynch et al., 2024). A multidisciplinary approach involving obstetricians, cardiologists, endocrinologists, nutritionists, and nurses is necessary for comprehensive care and improved maternal and fetal health outcomes (Thomopoulos et al., 2024). Genetic screening for women with known risk factors could help identify those most likely to develop PRH, enabling early intervention and improved management (Pazoki et al., 2018). Furthermore, early screening programs targeted at women with obesity or pre-existing chronic conditions are crucial for reducing the burden of PRH and improving maternal health outcomes. Policy recommendations should include the development of clinical guidelines tailored to managing hypertensive pregnancies complicated by obesity and comorbid conditions, ultimately improving clinical care and reducing the risks associated with pregnancy-related hypertension.

Discussion

Obesity, genetic predisposition, and comorbidities play a significant role in increasing the risk of pregnancy-related hypertension, as highlighted in this study. Numerous studies have established that obesity serves as an independent risk factor for gestational hypertension and preeclampsia while also exacerbating associated complications. The physiological mechanisms through which obesity contributes to pregnancy-related hypertension include endothelial dysfunction, chronic inflammation, insulin resistance, and the activation of the renin-angiotensin-aldosterone system (RAAS). A higher pre-pregnancy body mass index (BMI) and excessive gestational weight gain (GWG) are strongly correlated with an increased risk of gestational hypertension and preeclampsia, which can lead to severe complications for both the mother and the fetus. The findings of this study reinforce the understanding that maternal obesity not only influences blood pressure but also contributes to impaired placental function, leading to placental insufficiency and intrauterine growth restriction (IUGR). Furthermore, studies suggest that the severity of obesity directly impacts the degree of hypertension during pregnancy, with morbidly obese women being at significantly greater risk for severe hypertensive complications, preterm birth, and fetal distress. This association underscores the need for targeted interventions aimed at managing maternal weight before and during pregnancy to mitigate the risk of pregnancy-related hypertension and its adverse consequences for maternal and neonatal health. Moreover, obesity-induced metabolic dysregulation

can contribute to oxidative stress, which further disrupts vascular function and blood pressure regulation, aggravating hypertensive complications in pregnancy.

Beyond obesity, genetic predisposition has been identified as a crucial factor contributing to pregnancy-related hypertension. This study reveals that genetic polymorphisms within the RAAS system, including variants in the angiotensinogen (AGT), angiotensin-converting enzyme (ACE), and angiotensin II type 1 receptor (AGTR1) genes, are closely linked to increased blood pressure during pregnancy. Additionally, polymorphisms in endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), and tumor necrosis factor-alpha (TNF-α) genes contribute to vascular dysfunction and inflammatory responses that further exacerbate gestational hypertension and preeclampsia. The role of epigenetics in pregnancy-related hypertension has also been emphasized, with evidence suggesting that maternal hypertension leads to DNA methylation modifications in genes responsible for vascular regulation, thereby increasing the risk of hypertension and cardiovascular diseases in offspring. The concept of fetal programming suggests that exposure to hypertensive intrauterine environments results in long-term metabolic and cardiovascular alterations in the child, increasing their predisposition to hypertension and related disorders in adulthood. Additionally, genome-wide association studies (GWAS) have identified multiple genetic loci associated with hypertensive disorders in pregnancy, strengthening the understanding of the heritable component of pregnancy-related hypertension. These findings indicate the necessity for genetic and epigenetic screening to identify high-risk individuals early and implement preventive strategies, thereby reducing the burden of hypertension-related complications during pregnancy.

This study highlights that pre-existing comorbidities such as diabetes mellitus, chronic hypertension, chronic kidney disease (CKD), and autoimmune disorders significantly heighten the risk of pregnancy-related hypertension. Diabetes mellitus, whether pre-existing type 2 diabetes or gestational diabetes mellitus (GDM), has been shown to exacerbate hypertensive disorders through mechanisms such as insulin resistance, endothelial dysfunction, and systemic inflammation. Women with diabetes during pregnancy are at substantially higher risk of developing gestational hypertension and preeclampsia due to impaired glucose metabolism and increased oxidative stress. Similarly, chronic hypertension before pregnancy is a significant risk factor for superimposed preeclampsia, which is a more severe form of hypertension that develops in women with pre-existing high blood pressure. This condition often leads to worsened placental perfusion, increasing the likelihood of fetal complications such as IUGR and preterm birth. Chronic hypertension is also linked to persistent endothelial dysfunction and excessive RAAS activation, leading to increased sodium retention, expanded blood volume, and systemic vasoconstriction, all of which contribute to worsening hypertension during pregnancy. Given the compounding effects of diabetes and chronic hypertension, a proactive approach involving early screening and comprehensive management is necessary to minimize the risks associated with these conditions.

Chronic kidney disease (CKD) is another major contributor to pregnancy-related hypertension due to its role in blood pressure regulation and sodium balance. Women with CKD experience impaired sodium excretion and disruptions in fluid balance, both of which significantly increase their risk of developing gestational hypertension and severe preeclampsia. The link between CKD and preeclampsia is well-documented, with studies indicating that kidney dysfunction exacerbates hypertension by contributing to endothelial dysfunction, systemic inflammation, and oxidative stress. Additionally, CKD affects placental function, as impaired renal filtration can lead to the accumulation of toxins in the maternal bloodstream, negatively impacting placental health and fetal development. This can result in adverse pregnancy outcomes such as placental insufficiency, intrauterine growth restriction (IUGR), and an increased risk of neonatal morbidity. Women with CKD often require more complex blood pressure management during pregnancy, as conventional antihypertensive treatments may pose risks to fetal development, necessitating careful selection of medications. Beyond CKD, autoimmune disorders such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are also associated with an increased risk of pregnancy-related hypertension. These conditions contribute to hypertensive complications through systemic inflammatory responses and vascular abnormalities that impair normal placental function. In particular, APS is strongly linked to preeclampsia due to its role in abnormal blood clot formation (thrombosis) in the placenta, leading

to restricted fetal blood supply and an elevated risk of placental insufficiency. The presence of autoimmune conditions in pregnancy further complicates hypertensive management, underscoring the need for specialized care and monitoring for affected individuals.

The maternal and fetal consequences of pregnancy-related hypertension are far-reaching, affecting both short-term and long-term health outcomes. For mothers, the immediate complications include an increased risk of stroke, acute kidney injury, HELLP syndrome (Hemolysis, Elevated Liver Enzymes, and Low Platelet Count), and eclampsia, all of which require urgent medical intervention. Hypertensive disorders in pregnancy are also linked to an increased likelihood of cesarean delivery due to the heightened risk of labor complications and fetal distress. Beyond the immediate postpartum period, women who develop gestational hypertension or preeclampsia have a significantly elevated risk of future cardiovascular diseases, including chronic hypertension, coronary artery disease, and type 2 diabetes. These long-term consequences highlight the importance of early diagnosis and long-term monitoring for women with a history of hypertensive pregnancy disorders. For the fetus, pregnancy-related hypertension poses significant risks, including intrauterine growth restriction (IUGR), preterm birth, and neonatal hypoxia due to impaired placental blood flow. Babies born to mothers with hypertensive disorders are more likely to require neonatal intensive care and have an increased risk of perinatal complications. Furthermore, fetal exposure to maternal hypertension has been linked to epigenetic changes that predispose offspring to metabolic and cardiovascular diseases in adulthood. These findings underscore the importance of managing pregnancy-related hypertension effectively to mitigate both maternal and fetal risks and improve long-term health outcomes.

Compared to previous research, the findings of this study demonstrate consistency with numerous studies that have highlighted the role of obesity, genetic predisposition, and comorbidities in pregnancy-related hypertension. Alves et al. (2024) emphasized that maternal obesity significantly contributes to an increased risk of preeclampsia and neonatal complications through mechanisms involving chronic inflammation, endothelial dysfunction, and metabolic disturbances. This aligns with the findings of Bohiltea et al. (2020), who reported that obesity not only raises the likelihood of developing gestational hypertension but also increases the severity of preeclampsia, particularly when compounded by insulin resistance and systemic inflammation. Furthermore, the current study corroborates the work of August and Sibai (2022), who identified genetic predisposition as a key determinant of hypertensive disorders during pregnancy. Specifically, polymorphisms in the angiotensin-converting enzyme (ACE) and angiotensin II type 1 receptor (AGTR1) genes have been associated with elevated blood pressure in pregnant women, highlighting the role of inherited genetic factors in gestational hypertension. As highlighted in this study, the role of epigenetics in pregnancy-related hypertension is strongly supported by Baetens et al. (2024), who demonstrated that intrauterine exposure to maternal hypertension can induce epigenetic modifications that predispose offspring to hypertension and cardiovascular disease later in life. This growing body of evidence reinforces the notion that pregnancy-related hypertension is a multifactorial condition influenced by a complex interplay of genetic, metabolic, and environmental factors. By integrating these perspectives, the present study not only supports previous research but also offers new insights into how obesity, genetic susceptibility, and comorbid conditions interact to exacerbate hypertensive complications in pregnancy.

The findings of this study have significant practical implications for the prevention and management of pregnancy-related hypertension. Given that obesity and diabetes are among the primary risk factors targeted interventions focusing on weight management and metabolic regulation before and during pregnancy are crucial. Early screening programs for women with obesity, a history of hypertension, or diabetes can facilitate the early detection of pregnancy-related hypertension risks, allowing for more timely and effective interventions. Additionally, closer blood pressure monitoring in pregnant women with a genetic predisposition to hypertension can help identify individuals at high risk for complications, ensuring early medical intervention. From a clinical perspective, more specific management guidelines are needed to address pregnancy-related hypertension influenced by obesity and comorbidities, including more personalized therapeutic approaches based on patients' genetic and epigenetic profiles. Moreover, a multidisciplinary approach

involving obstetricians, internists, nutritionists, and other healthcare professionals is essential to optimize the care of pregnant women with high-risk factors. Public health policies should also focus on improving maternal education regarding maintaining a healthy lifestyle and providing adequate support to manage modifiable risk factors. Enhancing prenatal counseling and lifestyle interventions tailored to high-risk individuals could significantly reduce the incidence and severity of pregnancy-related hypertension. By implementing these strategies, healthcare providers and policymakers can work towards more effective prevention and management approaches, ultimately improving maternal and neonatal health outcomes. These findings emphasize the need for an integrated and proactive approach to mitigating the burden of hypertensive disorders in pregnancy.

Conclusion

This study provides a comprehensive examination of the impact of obesity, genetic predisposition, and comorbidities on pregnancy-related hypertension. By synthesizing existing literature, the study highlights the multifactorial nature of hypertensive disorders in pregnancy, demonstrating how metabolic dysfunction, genetic susceptibility, and underlying medical conditions collectively exacerbate hypertension risk. The findings reveal that obesity, through mechanisms such as endothelial dysfunction, chronic inflammation, insulin resistance, and RAAS activation, significantly contributes to the development and severity of hypertensive disorders in pregnancy. Moreover, genetic predisposition plays a crucial role in maternal blood pressure regulation, with specific polymorphisms in the RAAS and endothelial function-related genes linked to an increased risk of gestational hypertension and preeclampsia. Additionally, pre-existing comorbidities, including diabetes mellitus, chronic hypertension, kidney disease, and autoimmune disorders, further complicate hypertension management in pregnant women, increasing the likelihood of adverse maternal and neonatal outcomes. These findings reinforce the need for an integrative approach in assessing and managing pregnancy-related hypertension by considering both modifiable and non-modifiable risk factors.

This study contributes to the scientific and clinical understanding of pregnancy-related hypertension by emphasizing the interplay between metabolic, genetic, and pathophysiological factors. The originality of this research lies in its holistic perspective, bridging gaps in current knowledge by integrating findings from obstetrics, endocrinology, genetics, and public health. The practical implications extend to healthcare management, emphasizing the necessity for early screening programs, personalized monitoring strategies, and interdisciplinary collaboration in prenatal care. Policymakers should consider developing more specific guidelines for managing hypertensive pregnancies influenced by obesity and comorbidities. At a managerial level, hospitals and healthcare systems must implement targeted lifestyle interventions and structured monitoring frameworks to mitigate the risks of hypertension. Public health strategies should focus on increasing awareness among pregnant women regarding weight management, nutritional intake, and early screening to prevent severe hypertensive complications.

Despite its contributions, this study has certain limitations. The reliance on existing literature means that findings are constrained by the methodologies and scope of prior studies, which may vary in sample size, geographic representation, and clinical approaches. Additionally, while genetic predisposition has been highlighted as a crucial factor in pregnancy-related hypertension, further research is required to establish clear genetic markers for clinical risk stratification. Future research should focus on longitudinal studies that track maternal and fetal health outcomes over time to assess the long-term impact of hypertension in pregnancy. Moreover, studies investigating the efficacy of personalized interventions based on genetic and metabolic profiling could provide valuable insights into improving the management of hypertension. Expanding research into diverse populations will also be essential to ensure that findings are applicable across different demographic and ethnic groups. Future researchers should explore novel prevention and treatment strategies, including pharmacogenomic approaches and targeted nutritional interventions, to further refine the management of hypertensive disorders in pregnancy.

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