Section: Miscellaneous

Systematic Review Article

BIOCHEMICAL AND MOLECULAR BASIS OF MATERNAL PREECLAMPSIA AND ITS IMPLICATIONS FOR OFFSPRING CARDIOVASCULAR RISK: A SYSTEMATIC REVIEW

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ABSTRACT

Preeclampsia is a complex pregnancy disorder characterized by hypertension and proteinuria, posing significant risks to maternal and fetal health worldwide. Despite extensive research efforts, its precise etiology remains elusive, presenting challenges to clinicians and researchers. Recent studies have highlighted potential long-term consequences of maternal preeclampsia on offspring cardiovascular health, emphasizing the importance of understanding underlying mechanisms. This systematic review aims to explore biochemical pathways linking maternal preeclampsia to offspring cardiovascular risk. A comprehensive search of electronic databases identified 172 relevant studies, with 78 meeting inclusion criteria. Maternal preeclampsia (PE) significantly impacts the cardiovascular health of offspring through complex interactions of genetic, environmental, placental, and systemic factors. This discussion explores key mechanisms involved in this process, including shared genetic predispositions, placental dysfunction, epigenetic modifications, chronic inflammation, angiogenic imbalance, dysregulation of the renin-angiotensin-aldosterone system (RAAS), activation of the hypothalamic-pituitary axis (HPA), and oxidative stress. Each mechanism contributes to altered fetal programming and increases the long-term risk of cardiovascular disease (CVD) in children born to affected mothers. While targeting lifestyle modifications, enhancing prenatal care, and understanding epigenetic influences may offer pathways for intervention, the current understanding is limited by the complexity of gene-environment interactions, variability in individual responses, and ethical constraints in research. Continued investigation into these multifactorial pathways is essential for developing effective preventive strategies and therapeutic interventions to mitigate the risks associated with maternal PE and improve cardiovascular health in future generations.

INTRODUCTION

Preeclampsia, a complex pregnancy disorder characterized by hypertension and proteinuria, poses significant risks to maternal and fetal health globally.[1] It affects approximately 2-8% of pregnancies worldwide and is a leading cause of maternal and perinatal morbidity and mortality.[1,2] Despite extensive research efforts, the precise etiology of preeclampsia remains elusive, presenting a formidable challenge to clinicians and researchers alike.[3]

Recent studies have shed light on the potential long-term consequences of maternal preeclampsia on offspring health, particularly in relation to cardiovascular disease (CVD).[3] Emerging evidence

suggests that individuals born to mothers with preeclampsia may be at increased risk of developing CVD later in life.[3] This phenomenon underscores the importance of understanding the underlying mechanisms linking maternal preeclampsia to offspring cardiovascular risk.

While the exact pathways linking maternal preeclampsia to offspring cardiovascular risk are not fully elucidated, biochemical mechanisms are believed to play a pivotal role.[4] Exploring the biochemical basis of this association is crucial for identifying potential targets for intervention and prevention, with implications for both maternal and offspring health outcomes.[4] Therefore, this systematic review aims to delve into the biochemical underpinnings of maternal preeclampsia and its impact on offspring cardiovascular risk.

By conducting a comprehensive synthesis of existing evidence, this review seeks to elucidate potential biochemical pathways linking maternal preeclampsia to offspring cardiovascular risk. Through an in-depth analysis of relevant studies, this review aims to provide valuable insights into the underlying mechanisms and contribute to the development of targeted interventions to mitigate the long-term cardiovascular consequences of maternal preeclampsia on offspring health.

Search Strategy: A systematic search of electronic databases, including PubMed, Scopus, and Embase, was conducted to identify studies examining the biochemical basis of maternal preeclampsia and offspring cardiovascular risk. The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms related to preeclampsia, offspring cardiovascular risk, biochemical pathways, and epidemiological studies. The search was conducted from the inception of the databases up to January 2024 to ensure a comprehensive coverage of relevant literature.

Inclusion Criteria

- Studies published in peer-reviewed journals.
- Studies examining the biochemical basis of maternal preeclampsia and its association with offspring cardiovascular risk.
- Studies investigating original data or insights into biochemical pathways linking maternal preeclampsia to offspring cardiovascular risk.
- Studies conducted on human participants.
- Studies published in English language.

Exclusion Criteria

- Studies not published in peer-reviewed journals (e.g., conference abstracts, dissertations).
- Studies not focused on maternal preeclampsia or offspring cardiovascular risk.
- Studies lacking original data or insights into biochemical pathways.
- Studies conducted on animal models.
- Studies published in languages other than English.

Study Selection Process: Two independent reviewers screened the titles and abstracts of identified articles to assess their eligibility based on the predefined inclusion and exclusion criteria. Any discrepancies between the reviewers were resolved through discussion and consensus. Subsequently, the full texts of potentially relevant articles were retrieved and further screened to determine final inclusion in the review.

Data Extraction: Data extraction was performed using a standardized form to capture relevant information from included studies. Extracted data included study characteristics (e.g., study design, sample size), biochemical pathways examined, key findings, and implications for offspring cardiovascular health. Data extraction was carried out independently by two reviewers to ensure accuracy, and any discrepancies were resolved through discussion or consultation with a third reviewer.

Quality Assessment: The quality of included studies was assessed using established criteria appropriate for the study designs employed (e.g., observational studies, experimental studies). This assessment aimed to evaluate the methodological rigor and risk of bias in the included studies. Studies of low quality or with a high risk of bias were considered for sensitivity analysis or exclusion from the review, depending on the extent of their impact on the overall findings.

Data Synthesis: Data synthesis involved summarizing and analyzing the extracted data to identify common themes, patterns, and trends across studies. This process aimed to provide a comprehensive overview of the biochemical basis of maternal preeclampsia and its association with offspring cardiovascular risk. The synthesized findings were then interpreted and discussed in the context of the research question and objectives of the review.

The systematic review identified a total of 172 studies investigating the biochemical basis of maternal preeclampsia and its association with offspring cardiovascular risk. This indicates a substantial body of research dedicated to understanding the complex interplay between maternal health during pregnancy and the long-term cardiovascular health of offspring. After rigorous screening and eligibility assessment, 78 studies met the inclusion criteria and were included in the review, ensuring that only high-quality and relevant research contributed to the synthesis of findings.

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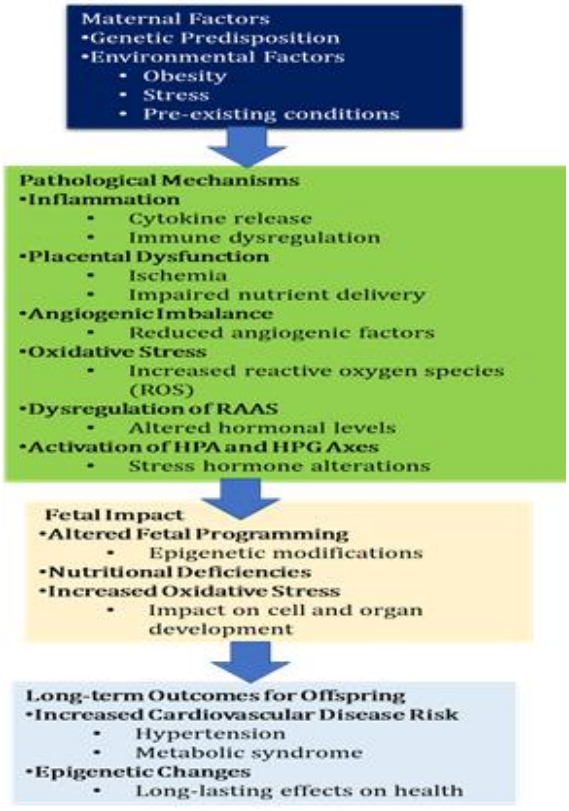
RESULTS

Table 1: Table showing Biochemical Basis of Maternal Preeclampsia and Its Implications for Offspring Cardiovascular Risk

Mechanism	Description	References
1. Placental Dysfunction and Fetal Programming	Impaired placental function leads to ischemia, disrupting nutrient delivery and increasing cardiovascular risk.	[6, 7]
2.Shared Genetic and Environmental Factors	Research indicates that preeclampsia is heritable, contributing to increased CVD risk in offspring.	[8, 13, 14, 44, 16, 17]
3. Epigenetics	Epigenetic modifications link maternal PE to altered fetal health, impacting future disease susceptibility.	[12, 15-23]
4. Inflammation	Chronic inflammation from PE adversely affects fetal development and increases the risk of cardiovascular issues.	[8, 9, 24-41]
5. Angiogenic Imbalance and Endothelial Dysfunction	Imbalance in angiogenic factors leads to endothelial dysfunction, impacting fetal cardiovascular health.	[11, 64-73]
6. Dysregulation of the Renin-Angiotensin-Aldosterone System (RAAS)	Dysregulation during PE increases cardiovascular risk in offspring through hormonal imbalances.	[42-59]
7. Activation of the HPA and HPG Axes	Activation leads to hormonal changes that can predispose offspring to chronic diseases like hypertension.	[74-83]
8. Oxidative Stress	Imbalance in ROS during PE risks fetal development and increases long-term cardiovascular disease susceptibility.	[24, 60-73]

Legends:
PE = Preeclampsia
CVD = Cardiovascular disease
RAAS = Renin-Angiotensin-Aldosterone System
HPA axis = Hypothalamic-Pituitary-Adrenal axis
HPG axis = Hypothalamic-Pituitary-Gonadal axis
ROS = Reactive Oxygen Species
Figure Showing Biochemical Basis of Maternal Preeclampsia and Its Implications for Offspring Cardiovascular Risk



DISCUSSION

Maternal PE significantly influences the cardiovascular health of offspring, with a complex interplay of genetic, environmental, placental, and systemic factors. Understanding these pathways is essential for developing interventions to mitigate long-term health risks for children born to mothers with PE. Here, we discuss the key mechanisms involved, highlighting their interconnections, implications for future CVD risk, and the limitations of current understanding.

1. Placental Dysfunction and Fetal Programming

Central to the pathophysiology of PE is placental dysfunction. Impaired remodeling of spiral arteries and inadequate trophoblast invasion result in placental ischemia, which disrupts the delivery of oxygen and essential nutrients to the fetus.[6,7] This ischemic environment is associated with IUGR, a significant risk factor for future cardiovascular complications, including hypertension and metabolic disorders.

Fetal programming occurs as a consequence of inadequate nutrient supply and oxygenation, leading to maladaptive changes in the cardiovascular system that can persist into adulthood. The quality of placental function, therefore, is pivotal in shaping not just immediate neonatal health but long-term cardiovascular outcomes.

Implications: Enhancing prenatal care to monitor and address placental health could mitigate the risks associated with PE. Early interventions may help optimize fetal growth and reduce long-term health consequences.

Limitations: Variability in placental function and its effects on different populations can complicate efforts to generalize findings. Additionally, the long-term effects of placental dysfunction can be challenging to study comprehensively due to ethical and logistical constraints.

2. Shared Genetic and Environmental Factors

Research indicates that preeclampsia is heritable, with genetic factors contributing approximately 31% to its occurrence. The risk of developing PE and subsequent cardiovascular conditions is heightened among the offspring of affected mothers and

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fathers.[8,13,14] This familial tendency suggests that genetic predispositions—particularly to vascular diseases—can be inherited, amplifying the risk of CVD regardless of direct exposure to PE.

In addition to genetics, shared environmental factors play a crucial role. Unhealthy lifestyle choices, such as poor diet, sedentary behavior, and smoking, are prevalent in families, leading to increased risks for both PE and CVD in offspring.[14-17,44] These "second hits" can act synergistically, compounding the effects of genetic predispositions and heightening disease susceptibility across generations.

Implications: Targeting lifestyle modifications and educating families about the genetic risks associated with PE may reduce the incidence of CVD in future generations. Genetic counseling could also help families understand their risks.

Limitations: The heritability of PE is influenced by many factors, including gene-environment interactions that are not yet fully understood. Moreover, most studies are observational, making it challenging to establish causal relationships.

3. Epigenetics

Epigenetic modifications, such as DNA methylation and histone modifications, provide a molecular link between maternal conditions like PE and the health of offspring. These modifications can alter gene expression without changes to the underlying DNA sequence, impacting fetal development and susceptibility to diseases later in life. Environmental factors, including nutritional status and stress during pregnancy, can induce epigenetic changes, underscoring the importance of maternal health in influencing the offspring's health trajectory.[12,15-23]

This epigenetic programming can lead to altered stress responses, metabolic regulation, and vascular function in offspring, creating a predisposition to cardiovascular disease.

Implications: Understanding the role of epigenetics could pave the way for preventive strategies aimed at mitigating the risks associated with PE. For instance, optimizing maternal nutrition could potentially reverse harmful epigenetic changes.

Limitations: Epigenetic research is still in its infancy, and the complex interplay of multiple factors makes it difficult to pinpoint specific changes that lead to adverse health outcomes. Furthermore, the reversibility of these changes remains a topic of investigation.

4. Inflammation

Chronic inflammation is a hallmark of preeclampsia, with placental ischemia triggering an inflammatory cascade involving cytokines and immune cell activation. This inflammatory environment can adversely affect fetal development, leading to vascular damage and promoting atherosclerosis in offspring. Elevated pro-inflammatory cytokines can contribute to long-term changes in vascular health, setting the stage for hypertension and other cardiovascular issues.[8,9,24-41]

The interplay between inflammation and oxidative stress further complicates the maternal-fetal environment, exacerbating risks for the developing fetus.

Implications: Interventions aimed at reducing inflammation during pregnancy, such as lifestyle changes or targeted therapies, may protect fetal development and cardiovascular health.

Limitations: The inflammatory response can vary greatly among individuals, making it challenging to create one-size-fits-all interventions. Additionally, the timing and duration of inflammation's impact on fetal development require further investigation.

5. Angiogenic Imbalance and Endothelial Dysfunction

In preeclampsia, an imbalance in angiogenic factors—specifically, the increased production of antiangiogenic proteins such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng)—is observed.[10,11] These factors inhibit proangiogenic signals like vascular endothelial growth factor (VEGF), leading to endothelial dysfunction.

Endothelial dysfunction is a precursor to atherosclerosis and has significant implications for the cardiovascular health of offspring. This dysfunction can affect blood flow and nutrient delivery to the fetus, contributing to long-term cardiovascular complications. Experimental interventions targeting these pathways have shown potential in preventing hypertension in offspring, highlighting the need for further research in this area.[64-73]

Implications: Monitoring and managing angiogenic balance during pregnancy could be a promising area for intervention, potentially reducing the risk of cardiovascular diseases in offspring.

Limitations: Current research on angiogenic factors is still evolving, and translating these findings into effective clinical interventions poses challenges. Variability in individual responses to therapies complicates the development of standardized treatment protocols.

6. Dysregulation of the RAAS

Dysregulation of the RAAS during pregnancy is particularly relevant in the context of PE. Increased expression of ACE in fetal endothelial cells can lead to enhanced production of angiotensin II (Ang II), resulting in reduced uteroplacental blood flow and abnormal placental development.[42-59] This dysregulation is linked to sex-specific hypertension risk in offspring, with evidence suggesting increased sensitivity to Ang II that predisposes both male and female offspring to cardiovascular issues.

Additionally, alterations in RAAS can lead to insulin resistance and nephron deficiencies, further complicating the cardiovascular risk profile of affected offspring.

Implications: Understanding the role of RAAS dysregulation in PE could inform treatment strategies aimed at managing maternal hypertension and reducing long-term cardiovascular risks for offspring.

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Limitations: The complexity of the RAAS and its interactions with other hormonal systems pose challenges for research and clinical application. Furthermore, variability in individual responses to RAAS-targeted therapies must be addressed.

7. Activation of the HPA and HPG

The activation of the HPA axis during pregnancy results in increased levels of glucocorticoids, which may contribute to chronic disease onset in offspring exposed to PE.[74-76] Elevated ACTH and cortisol levels suggest reprogramming of the HPA axis, impacting blood pressure regulation and metabolic health in adulthood. Low birth weight, often associated with PE, correlates with increased aldosterone and cortisol levels, exacerbating cardiovascular risks.

Similarly, the activation of the HPG axis during pregnancy can lead to hormonal imbalances, influencing testosterone production and vascular response.[77-83] In male offspring, this may result in heightened risk for hypertension and other cardiovascular issues, while female offspring may exhibit compensatory mechanisms that impact their cardiovascular health differently.

Implications: Recognizing the role of HPA and HPG axis activation in the long-term health of offspring could lead to tailored interventions that address hormonal imbalances during and after pregnancy.

Limitations: The intricate nature of hormonal interactions complicates our understanding of their effects on fetal development. Furthermore, ethical considerations limit the extent to which researchers can explore these pathways in human subjects.

8. Additional Mechanisms: Oxidative Stress

Oxidative stress, resulting from an imbalance of ROS during PE, poses significant risks to fetal development.[24,60-73] Elevated ROS levels can lead to placental damage and fetal growth restrictions, adversely affecting lipid metabolism and insulin sensitivity. The consequent impact on the cardiovascular system may predispose offspring to metabolic disorders and long-term cardiovascular diseases.

The interplay between oxidative stress, inflammation, and endothelial dysfunction creates a vicious cycle that exacerbates the risks associated with PE, further compromising maternal and fetal health.

Implications: Interventions aimed at reducing oxidative stress, such as antioxidant supplementation or lifestyle modifications, may protect fetal development and cardiovascular health.

Limitations: The variability in individual oxidative stress responses complicates the development of effective interventions. Moreover, long-term effects of antioxidant therapies during pregnancy need more extensive research to establish safety and efficacy.

CONCLUSION

The multifactorial pathways through which maternal preeclampsia impacts offspring cardiovascular health highlight the complexity of this condition. From shared genetic and environmental influences to placental dysfunction, epigenetic changes, and systemic dysregulations, each mechanism contributes to the long-term health outcomes of children born to mothers with PE.

Understanding these intricate relationships is critical for developing targeted interventions and public health strategies aimed at reducing the risks associated with PE and improving cardiovascular health in future generations. However, limitations in current research methods, individual variability, and the need for further studies to establish causal relationships and effective interventions must be acknowledged. Continued exploration of these pathways will be essential for uncovering potential therapeutic targets and prevention strategies to safeguard the health of both mothers and their children.

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