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The Potential Role of Folic Acid in Preventing and Managing Preeclampsia: A Systematic Review

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KEYWORDS

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ABSTRACT:

Preeclampsia, a life-threatening pregnancy complication, affects both maternal and fetal health. Folic acid, a crucial B-vitamin, plays a vital role in preventing birth defects and promoting healthy pregnancy outcomes. This review aims to explore the relationship between folic acid and preeclampsia, highlighting its mechanisms of action and potential therapeutic benefits. Folic acid's impact on endothelial function, homocysteine metabolism, antioxidant activity, and methylation processes, and placental development may prevent preeclampsia risk. Observational studies suggest that higher folic acid intake is associated with a reduced risk of preeclampsia, while randomized controlled trials demonstrate a trend towards a protective effect. However, results are not consistently replicated across different populations. Healthcare providers should consider individualized folic acid supplementation recommendations, taking into account medical history, dietary habits, and risk factors for preeclampsia. A balanced diet rich in folate-containing foods, combined with other essential vitamins and minerals, is essential for optimal outcomes. Future research directions include personalized approaches based on genetics and risk factors, exploring combined interventions, and investigating the impact of folic acid on DNA methylation and gene expression. Developing early biomarkers for preeclampsia risk could help identify women who could benefit from targeted interventions. In conclusion, folic acid plays a critical role in preventing preeclampsia by influencing various cellular processes. While its effects may vary based on individual health conditions and genetic factors, folic acid supplementation holds promise for improving maternal and fetal health outcomes.

1. Introduction to Preeclampsia and Folic Acid

Pregnancy is a transformative and crucial period in a woman's life, marked by various physical and physiological changes. However, it can also bring about certain complications that require careful attention and management. Preeclampsia is a pregnancy complication that affects pregnant women, and an important factor in ensuring a healthy pregnancy is the intake of essential nutrients like folic acid.(1) Preeclampsia is a complex disorder that typically occurs after the 20th week of pregnancy and is characterized by high blood pressure and damage to organs such as liver and kidneys. This condition can lead to serious complications for both the mother and fetus. While the exact cause of preeclampsia Is not fully understood, it's believed to be related to issues with the placenta, the organ that connects the developing fetus to the uterine wall. Preeclampsia often presents with symptoms such as high blood pressure, protein in the urine (a sign of kidney problems), swelling of the hands and face, severe headaches, and changes in vision. Left untreated, it can escalate into a more severe condition called Eclampsia, which involves seizures and can be life-threatening for both the mother and the baby. Early detection and proper prenatal care are essential in managing and minimizing the risks associated with preeclampsia. (2)

2. Methods

The databases available on the online web sources such as Google Scholar, Pubmed, Research gate and Biomed

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Central were considered using the keywords such as Preeclampsia, folic acid in pregnancy disorders, hypertensive disorders of pregnancy, nutritional role of folate in pregnancy and folate as therapeutic adjuct shown in figure 1.

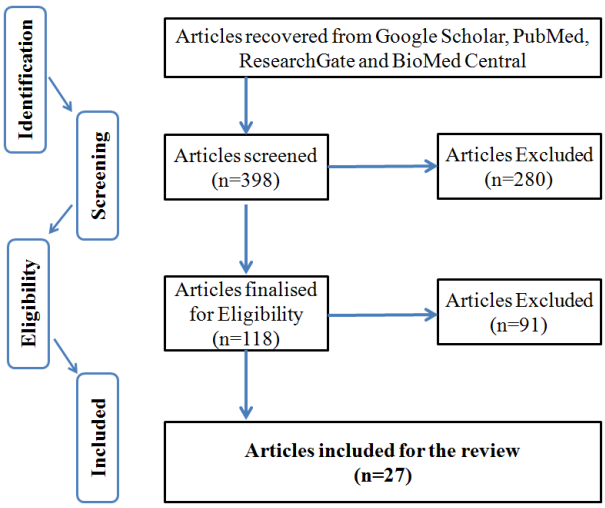

Figure 1. PRISMA flow diagram of the articles identified, screened and included from databases for the review.

3. The Role of Folic Acid in Pregnancy

Folic acid, a type of B-vitamin, plays a critical role in preventing birth defects and promoting the healthy development of the baby's neural tube, which eventually becomes the baby's brain and spinal cord. Adequate intake of folic acid before and during pregnancy can significantly reduce the risk of neural tube defects such as spina bifida. Neural tube defects occur very early in pregnancy, often before a woman even knows she's pregnant.(1,3,4) Therefore, it's recommended that women of child bearing age, whether they are planning to conceive or not, ensure they have an adequate intake of folic acid. This is usually achieved through a combination of dietary sources such as leafy greens, citrus fruits, beans, and fortified cereals, as well as through prenatal supplements.

4. The Role of Folic Acid in DNA Synthesis and Methylation

Folic acid, also known as folate or vitamin B9, is a water-soluble vitamin B that plays a crucial role in various biochemical processes in the body. One of its most important functions is its involvement in DNA synthesis and methylation, both of which are essential for proper cell function, growth, and development. DNA, or deoxyribonucleic acid, is the genetic material that carries the instructions for the development, function, and reproduction of all living organisms. Folic acid is necessary for DNA synthesis because it is a key donor of one-carbon units, which are essential building blocks for the synthesis of nucleotides. Without sufficient folic acid, the synthesis of nucleotides and, consequently, DNA replication would be compromised, potentially leading to errors in the genetic code. DNA methylation is an epigenetic modification that involves the addition of a methyl group (CH_3) to specific cytosine bases in the DNA molecule. This modification plays a critical role in regulating gene expression by affecting how tightly the DNA is wound around histone proteins, thus influencing whether a gene is turned on or off. Folic acid is essential for DNA methylation because it contributes to the synthesis of S-adenosyl methionine (SAM), which is a universal methyl donor in various cellular reactions, including DNA methylation. SAM transfers its methyl group to cytosine residues in DNA, leading to the addition of a methyl group and affecting gene expression patterns. Proper DNA methylation is vital for controlling cell differentiation and growth(5).

5. Folic Acid's Impact on Endothelial Function and Vascular Health in preeclampsia:

The exact biochemical mechanisms linking folic acid to the development of preeclampsia are still being investigated, and our understanding is continually evolving. However, some research has provided insights into potential connections between folic acid and the risk of preeclampsia Inadequate folic acid intake during pregnancy has been associated with an increased risk of neural tube defects in developing fetus due to impaired DNA synthesis and methylation. Additionally, disruptions in DNA methylation patterns have been linked to various health conditions, including cancer, cardiovascular diseases, and neurological disorders.(5) To ensure optimal DNA synthesis and methylation, it's important to maintain a balanced diet that includes foods rich in folic acid, such as leafy greens, legumes, citrus fruits, and fortified grains(6). In some cases, healthcare providers may recommend folic acid supplements, particularly for pregnant women or individuals at risk of deficiency. However, it's essential to consult with a healthcare professional before making any significant changes to your diet or supplement regimen. Endothelial function refers to the health and proper functioning of the endothelium. This layer of cells plays a vital role in regulating blood vessel tone, blood flow, and overall cardiovascular health. Folic

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acid, a vitamin B, has been linked to improved endothelial function and vascular health through various mechanisms.

6. Nitric Oxide Production and endothelial function: One of the key ways folic acid influences endothelial function is by promoting the production of nitric oxide (NO). Nitric oxide is a molecule that acts as a vasodilator, causing blood vessels to relax and expand. This helps to regulate blood pressure, improve blood flow, and prevent the development of hypertension (high blood pressure). Folic acid enhances the availability of a molecule called tetrahydrobiopterin (BH4), which is essential for the proper function of the enzyme responsible for synthesizing nitric oxide. Increased nitric oxide production contributes to better endothelial function and improved vascular health(7). Preeclampsia involves dysfunction of the endothelium, the inner lining of blood vessels. The author has found a derangement in the vascular endothelial function in hypertensive disorders of pregnancy (8). Folic acid is thought to play a role in maintaining endothelial function by influencing the production of nitric oxide (9), a molecule that helps dilate blood vessels and regulate blood pressure. Our earlier findings on the assessment of plasma markers of endothelial function in hypertensive disorders of pregnancy showed a possible correlation with activation platelet activation that linked with pathophysiology of disease progression. (10) Proper endothelial function is crucial for healthy blood flow and preventing high blood pressure, which is a hallmark of preeclampsia.

7. Antioxidant Protection: Folic acid also has antioxidant properties, which means it helps neutralize harmful molecules called reactive oxygen species (ROS) or free radicals. These molecules can cause oxidative stress, a condition characterized by an imbalance between antioxidants and free radicals. The author have found an oxidative imbalance in the Placental expressions as well as maternal/ fetal blood of Gestational Diabetes Mellitus and preeclampsia which are correlated well with the neurodegenerative changes in the newborn dyads of preeclampsia mother(11–14). Oxidative stress damages the endothelium, impairing its ability to regulate blood flow and increasing the risk of vascular diseases (11,13–16). By reducing oxidative stress, folic acid helps maintain the integrity of the endothelium and supports healthy blood vessels which may be vital during pregnancy.(7,17)

3. Homocysteine Metabolism: Elevated levels of homocysteine, an amino acid, have been associated with endothelial dysfunction and increased cardiovascular risk. Folic acid is involved in the conversion of homocysteine to methionine, a process known as Trans methylation. Adequate folic acid levels help to keep homocysteine levels in check, reducing the risk of endothelial damage and vascular issues.(18) Folic acid is a key player in the metabolism of homocysteine, an amino acid derived from the breakdown of proteins. Elevated levels of homocysteine have been associated with endothelial dysfunction (impaired blood vessel function) and oxidative stress, both of which are implicated in the development of preeclampsia. Improved homocysteine metabolism may contribute to a lower risk of preeclampsia.(10,19)

8. Inflammation Regulation: Chronic inflammation is a contributing factor to endothelial dysfunction and the development of atherosclerosis (hardening and narrowing of arteries). Folic acid has been shown to have anti-inflammatory effects, which can help mitigate inflammation-related damage to the endothelium and blood vessels.(20) Inflammation and oxidative stress are interconnected processes that play significant roles in various health conditions, including cardiovascular diseases, autoimmune disorders, and neurodegenerative diseases.(21) The author also has found an association with the inflammatory mediators and their association with the oxidative stress in the placenta of a pregnancy disorder (16). Folic acid has been found to modulate inflammatory pathways by regulating the production of pro-inflammatory cytokines (signaling molecules) and inhibiting the activation of nuclear factor-kappa B (NF-κB) (22), a key regulator of inflammatory responses.

9. Methylation and Epigenetic Regulation: Folic acid is involved in DNA methylation, a process that can influence gene expression patterns. Epigenetic modifications like DNA methylation play a role in regulating inflammation-related genes.(23) By modulating DNA methylation, folic acid may indirectly affect inflammation pathways. Altered DNA methylation patterns have been observed in women with preeclampsia. It's possible that folic acid's role in DNA methylation could influence the expression of genes involved in blood vessel function, immune response, and other factors relevant to preeclampsia development.(24,25)

10. Placental Development: Healthy placental development is crucial for a successful pregnancy. Folic acid is known to support placental growth and function. Abnormal placental development is believed to contribute to preeclampsia. Folic acid's impact on placental health could indirectly influence the risk of preeclampsia.(17,26)

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11. Overview of the Observational Studies Investigating Folic Acid and Preeclampsia

Many Observational studies have aimed to explore the potential association between folic acid status and the risk of developing preeclampsia during pregnancy. These studies examine whether there is a link between maternal folic acid intake, blood levels of folate, or folate supplementation and the incidence of preeclampsia. While such studies can provide valuable insights, it's important to note that observational studies cannot establish causation, but they can suggest potential relationships. Several population-based on the observational studies have investigated the association between folic acid and preeclampsia risk. A study with higher folic acid intake through diet or supplements may be associated with a reduced risk of preeclampsia. These studies often rely on self-reported dietary assessments, which can be subject to recall bias. Nevertheless, they generally indicate a trend toward a protective effect. However, results are not always consistent across different populations. Research examining blood levels of folate (serum folate) and its relation to preeclampsia risk has yielded mixed results (27). Some studies have found an inverse association between higher blood folate levels and reduced preeclampsia risk, while others have not consistently replicated this link. It is believed that various factors such as maternal age, socioeconomic status, preexisting health conditions, and overall diet could influence both folic acid intake and preeclampsia risk. Moreover, findings from one population might not reflect to other populations due to genetic, cultural, and environmental differences. Randomized controlled trials (RCTs) are considered the gold standard in medical research as they involve random assignment of participants to different interventions, allowing for the evaluation of causality. Several RCTs have investigated the effects of folic acid supplementation on preeclampsia incidence. These trials have explored variations in dosages, timing of supplementation, and the populations studied. To gain a comprehensive understanding of the collective evidence, meta-analyses and systematic reviews have been conducted to synthesize the findings of multiple RCTs. These analyses aim to provide more robust conclusions by pooling data from various studies. It has been observed in meta-analysis that a trend toward a protective effect of preeclampsia associated with folic acid supplementation although it is not always consistent with all studies. A pre-conceptional supplementation might influence the on better out come in terms of preventing preeclampsia especially among women with higher risk. On the other hand, some author propose a that higher folic acid intake might mask the vitamin B12 deficiency implicating an adverse outcome for both mother and baby.

12. Practical Considerations for Healthcare Providers Regarding Folic Acid Supplementation Recommendations

Healthcare providers play a critical role in guiding pregnant women towards optimal folic acid intake. It is advised that the an awareness about folic acid supplementation well before conception with their medical history, dietary habits, and risk factors for preeclampsia for a tailor recommendations to meet the specific needs of each pregnant woman. A balanced diet rich in folate-containing foods like leafy greens, citrus fruits, beans, and fortified grains as a complement combined with other associated vitamins and minerals is essential for better outcome.

13. Future Directions for Research and Potential Therapies

Future research could explore personalized approaches based on genetics and other risk factors. Identifying individuals with specific genetic variations could help tailor supplementation strategies more effectively. Researchers might need to investigate the benefits of combined interventions, such as folic acid supplementation along with other nutrients, to address multiple pathways associated with preeclampsia. In the recent years the concept of nutrigenomics and epigenetic modifications exploring the impact of folic acid on DNA methylation and gene expression could provide insights into novel therapeutic avenues. Developing early biomarkers for preeclampsia risk could help identify women who could benefit the most from targeted interventions.

14. Study Limitation:

This review did not discuss the in depth analysis of the molecular role of folate and their possible association with the diagnostic and treatment modalities in relation to the multi-omic studies.

15. Conclusion:

Preeclampsia, a serious pregnancy disorders that affects both maternal and foetal health needs early detection and management. Folic acid which is necessary for the foetal neural developments and healthier pregnancy for both mother and baby works by influencing homocysteine metabolism, endothelial function, antioxidant activity, methylation processes and placental development and may prevent the risk of preeclampsia. The molecular mechanisms by which folic acid may impact preeclampsia are interconnected and involve pathways related to homocysteine

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metabolism, nitric oxide production, placental development, epigenetic regulation, and antioxidant defense. Although folic acid may help mitigate oxidative stress, reduce inflammation, and support various cellular processes, it's important to note that its effects can vary based on individual health conditions and genetic factors. Future research holds promise for more targeted approaches and novel therapies that could further improve maternal and fetal health outcomes.

Ethical approval: This review does not include datas derived from any studies with human participants analysed by any of the authors.

Conflict of interest: The authors do not report a potential conflict of interest.

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