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UNVEILING THE NEXUS BETWEEN PREECLAMPSIA AND NUTRITION: A COMPREHENSIVE LITERATURE REVIEW ON MATERNAL HEALTH

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Abstract

Preeclampsia, a pregnancy-related syndrome impacting multiple organ systems, is a leading cause of maternal mortality, bleeding, and infection. The World Health Organization estimates that preeclampsia contributes to 70,000 maternal and 500,000 infant deaths annually worldwide. Recent research highlights the importance of optimal nutrition from preconception through childhood and adolescence. The novelty of this research is that it examines the relationship between preeclampsia and food: a comprehensive literature review of maternal health. This literature review collected and analyzed articles from online databases to explore the role of micronutrient supplementation in preventing preeclampsia. Findings emphasize the potential benefits of micronutrient supplementation, including L-arginine, vitamin D, and folic acid. Recommendations include daily vitamin D supplementation of 10-25 µg for pregnant women, oral administration of 3g per day of L-arginine for 3 weeks, and high-dose folic acid (4 mg/day) during the first trimester of pregnancy along with multivitamin supplementation. Micronutrient supplements and consuming nutrient-rich foods during pregnancy have been proposed to reduce the likelihood of developing preeclampsia. These approaches can potentially impact the formation of the placenta, oxidative stress levels, and the expression of angiogenic factors. This review underscores the importance of optimal nutrition throughout preconception, pregnancy, birth, and beyond for maternal and infant health. It highlights the need for further research and policy attention in this area. Implementing recommended micronutrient supplementation strategies during pregnancy may contribute to improved maternal and infant outcomes and should be considered as part of a comprehensive prenatal care program.

Keywords: L-arginine; Maternal mortality; Micronutrient supplementation; Preeclampsia; Vitamin D.

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1. INTRODUCTION

Preeclampsia is one of the leading causes of maternal mortality besides bleeding and infection (1)(2,3). It is best described as a syndrome that only occurs during pregnancy and can impact almost all organ systems (4,5). The conventional definition of preeclampsia, as outlined by the American College of Obstetrics and Gynecology (ACOG), involves the development of hypertension and the presence of protein in the urine after the 20th week of pregnancy in an individual who previously had normal blood pressure (6). Preeclampsia is thought to be directly responsible for 70,000 maternal fatalities worldwide, according to a recent WHO report. Preeclampsia also causes 500,000 infant deaths annually in addition to maternal mortality and morbidity. In Indonesia, preeclampsia-related maternal mortality is rising annually (7).

Eclampsia, a severe symptom of the disease, refers to the occurrence of convulsions and is linked to hypertensive disorders that occur during pregnancy (8,9). The presence of generalized tonic-clonic convulsions in cases of preeclampsia considerably raises the risk to both the mother and the fetus (4). Eclampsia is marked by the sudden onset of focal, multifocal, or tonic-clonic seizures, which occur in isolation without the presence of other associated conditions like epilepsy, cerebral ischemia and infarction, intracranial hemorrhage, or drug use (8). There are few reliable statistics describing the incidence of maternal mortalities caused by eclampsia globally. Estimates from 16 datasets put the case fatality rate at 8.3%, whereas the WHO survey showed 32 maternal mortalities and 3.7% of women with eclampsia (10).

Nutrition is a critical factor in pregnancy. In the past, the significance of optimal nutrition throughout the entire journey, from preconception to adolescence, has been overlooked by researchers, clinicians, and policy experts. However, there has been a recent change in this regard, with increased recognition of its importance. (11).

Micronutrient supplementation during pregnancy has been suggested to lower the risk of preeclampsia due to their impact on placentation, oxidative stress, and angiogenic factor expression (12). To implement this supplementation, individuals are advised to include in their diet foods that are abundant in calcium, vitamin C, vitamin D, vitamin E, folic acid, zinc, magnesium, dark chocolate, L-arginine, long-chain polyunsaturated fatty acids, as well as a diverse range of fruits and vegetables (12–14). This review of the literature will explore the role of dietary supplements, particularly L-arginine, vitamin D, and folic acid in the prevention of pre-eclampsia or eclampsia. The objective of this literature review is to provide an explanation regarding the role of micronutrient supplementation, specifically focusing on L-arginine, vitamin D, and folic acid, in the prevention of pre-eclampsia or eclampsia during pregnancy.

2. METHODS

The study design utilized in this research is a comprehensive literature review. The primary data sources for this literature review were online databases, including PubMed Database, Google Scholar, and Cochrane Library. These databases were systematically searched to identify relevant articles published in reputable sources, focusing on the role of micronutrient supplementation in preventing pre-eclampsia or eclampsia during pregnancy.

A systematic and thorough search strategy was employed to identify relevant articles. The search terms used included keywords related to pre-eclampsia, micronutrient supplementation, L-arginine, vitamin D, and folic acid. Boolean operators such as "AND" and "OR" were used to combine the search terms effectively, and the search was limited to articles published in English. To be included in this literature review, articles had to meet the specified criteria: (1) focused on the role of micronutrient supplementation, specifically L-arginine, vitamin D, and folic acid, in preventing pre-eclampsia or eclampsia during pregnancy; (2) published in reputable sources such as peer-reviewed journals; (3) available in full text; and (4) published within the last 10 years to ensure currency of the literature. Articles were excluded if they were not relevant to the research topic or did not meet the inclusion criteria.

A standardized data extraction form was employed to gather data from the articles that met the inclusion criteria. The extracted data encompassed several aspects, including the authors' names, publication year, study design, sample size, details about the interventions used, observed outcomes, and conclusions relevant to the impact of micronutrient supplementation on preventing pre-eclampsia.. The findings from the included articles were synthesized and analyzed to identify patterns, trends, and consensus among the studies. The quality of the included articles was assessed using established criteria, such as the Joanna Briggs Institute Critical Appraisal Checklist for Systematic Reviews and Research Syntheses. To ensure meticulousness and precision, two independent reviewers conducted a quality assessment. The findings from the articles that met the inclusion criteria were analyzed using a narrative synthesis approach.

3. RESULT AND DISCUSSION

3.1 Overview of Preeclampsia

In the context of pregnancy, hypertension is identified by systolic blood pressure meeting or exceeding 140 mmHg and/or diastolic blood pressure meeting or exceeding 90 mmHg. Severe hypertension is defined as systolic blood pressure meeting or exceeding 150 mmHg and/or diastolic blood pressure meeting or exceeding 110 mmHg. (15). Pre-eclampsia is defined as the development of high blood pressure and protein in the urine, occurring after 20 weeks of pregnancy or in the postpartum period in women who previously had normal blood pressure. However, pre-eclampsia

can still be diagnosed even in the absence of protein in the urine if new-onset high blood pressure is accompanied by specific indications or symptoms of organ dysfunction (4,15).

The pregnancy complication preeclampsia has grave repercussions. Proteinuria and gestational hypertension are symptoms that help physicians to identify the illness. Two stages of preeclampsia are thought to develop or progress. Stage one implies a reduction in placental perfusion, which might cause an abnormal implantation to occur. Reduced vascularization at the placental site initiates a maternal inflammatory response in the second stage. This results in widespread endothelial dysfunction and excessive anti-angiogenic factor release into the maternal bloodstream, both of which cause hypertension. In pre-eclampsia, the placenta generates higher levels of a substance called soluble firms-like tyrosine kinase 1 (sFLT-1). This leads to an imbalanced vascular environment that disrupts the normal preservation of endothelial cells. sFLT-1 competes with vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) by binding to them, which affects the proper functioning of endothelial cells (as shown in Figure 1) (16,17).

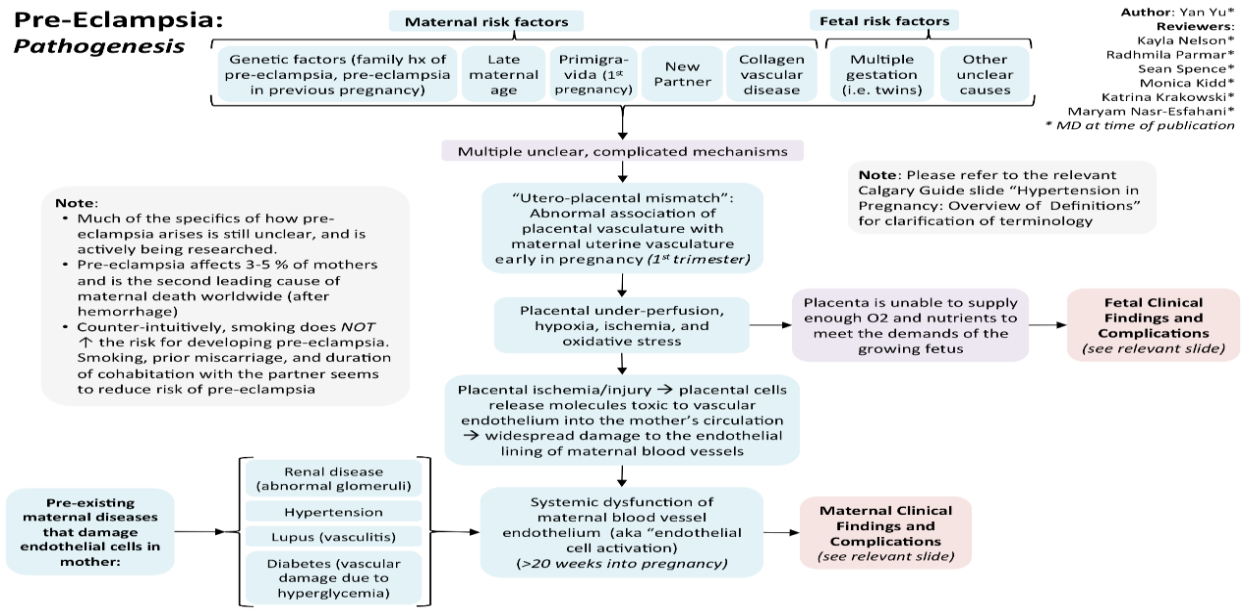

Figure 1. Pre-eclampsia Pathogenesis

Preeclampsia is a specific medical condition that exclusively occurs in pregnant women. It is characterized by the presence of protein in the urine, known as proteinuria, and elevated blood pressure. It develops after the first 20 weeks of pregnancy and accounts for 25% of all maternal deaths as well as perinatal morbidity and mortality. Preeclampsia occurs in approximately 2-10% of pregnancies, with a global average of 4-5%. While preeclampsia encompasses more than just high blood pressure and protein in the urine, the primary diagnostic

indicator for this condition is the presence of proteinuria. Proteinuria can be detected through various methods, including a 24-hour urine collection showing 300 mg or more of protein, a protein-creatinine ratio of 0.3 or higher, or consistent levels of protein in random urine samples (18).

3.2 Vitamin D

3.2.1 Vitamin D Deficiency and Physiology

Adequate vitamin D levels play a significant role in pregnancy due to the potential risks associated with low maternal vitamin D stores. Insufficient vitamin D during pregnancy can contribute to maternal health problems and increase the chances of delivering low birth weight infants or infants who are small for their gestational age. The prevalence of vitamin D deficiency varies across different countries, ranging from 18% to 84%. Factors influencing this variation include the country of residence, ethnicity, local dress codes, and dietary intake (16).

In recent research, it was discovered that a significant portion of women in the northeastern United States had insufficient levels of vitamin D. Specifically, around 54% of African-American women and 47% of Caucasian women were found to have serum 25(OH)D levels that indicated insufficient vitamin D. Furthermore, in pregnant women, approximately 30% of African-American women and 5% of Caucasian women had vitamin D levels that fell below the threshold for deficiency. Vitamin D deficiency was defined as having serum 25-hydroxyvitamin D levels below 37.5 nmol/L (18).

Micronutrient vitamin D3 was found to play a role in calcium metabolism and bone disorders. It is produced endogenously when UV-B radiation is exposed to the skin. Vitamin D3 affects gene regulation after being converted to 1,25-dihydroxy vitamin D3 (1,25(OH)D), which is the high-affinity ligand of the nuclear transcription factor vitamin D receptor (VDR). Once activated by ligands, the vitamin D receptor (VDR) binds to specific genomic sites near its target genes, thereby regulating their transcription. This process has the potential to influence the functioning of multiple organs. It is now widely acknowledged that vitamin D plays a crucial role in various organs, including the placenta, by modulating the expression of important genes involved in development. This is particularly relevant during pregnancy, as the concentrations of 1,25(OH)D, the active form of vitamin D, tend to naturally increase in the systemic circulation of the mother and within the placenta (18).

Pregnant women frequently have vitamin D deficiency, as determined by 25(OH)D serum levels. Numerous systematic reviews have indicated a strong correlation between vitamin D status and pre-eclampsia, with some demonstrating that serum vitamin D deficiency, defined as 25(OH)D 50 nmol/L, was a cut-off for increased risk and others finding that the cut-off was vitamin D insufficiency, defined as 75 nmol/L (13). Vitamin D

supplementation prescribed during the first trimester of pregnancy may help to prevent preeclampsia from recurring (p = 0.036) (16).

3.2.2 Vitamin D and Its Role in Pregnancy

There are three main functions for vitamin D during pregnancy. The initial stage involves enhancing the absorption of calcium, a crucial process for the fetus to accumulate bone minerals in the third trimester of pregnancy. Secondly, since the fetus is essentially a foreign graft during pregnancy, vitamin D aids in promoting its acceptance or tolerance by the mother's body. Thirdly, vitamin D plays a role in numerous transcriptional controls, contributing to various regulatory mechanisms (19).

Vitamin D modulates pro-inflammatory responses by promoting angiogenesis, lowering blood pressure, maintaining trophoblast survival potential, and maintaining immunological tolerance (13). This immunomodulatory effects and inflammation control are shown in the placenta. The provision of vitamin D supplements to individuals with a predisposition to preeclampsia lowers the levels of pro-inflammatory cytokines, which are responsible for regulating inflammatory reactions (12). The last point is that proteinuria appears to be related to renal vascular endothelial growth factor (VEGF). Vitamin D has the ability to regulate the angiogenic process by directly influencing the transcription of the VEGF gene (16,19).

Although vitamin D is often recommended as a preventive measure against preeclampsia, the guidelines from ESC, WHO, and ACOG suggest calcium supplementation for cases of pre-existing deficiency. Interestingly, there are several risk factors associated with vitamin D deficiency that contribute to endothelial dysfunction and impaired vascular health. Conversely, sufficient vitamin D intake can directly inhibit the proliferation of vascular smooth muscle cells and support calcium balance, which is inversely related to blood pressure levels. Vitamin D also plays a significant role as an endocrine inhibitor of renin biosynthesis, regulating the renin-angiotensin system crucial for maintaining blood pressure. Furthermore, vitamin D can influence the synthesis of adipokines, important for the health of endothelial and vascular functions (20,21).

In a study conducted by Hipponen et al., it was found that providing a daily supplement containing 400 IU of vitamin D resulted in a significant reduction in the risk of developing preeclampsia (OR= 0.66; 95% CI 0.52-0.83). Pregnant women diagnosed with preeclampsia experience a notable inflammatory response and heightened activity in their immune system within the placenta. These findings indicate that the immunomodulatory properties of vitamin D may potentially assist in facilitating placental implantation during pregnancy. A sufficient supply of vitamin D has an immunomodulatory effect and controls blood pressure. Other research has provided evidence that vitamin D levels are important for regulating early pregnancy risk factors for complications,

supporting fetal growth, and bone development (1).

In summary, role of vitamin D in preeclampsia may be supported by a number of plausible biological mechanisms. First, a flaw in placental implantation would result in less placental perfusion. Materials that would cause abnormal endothelial growth would be produced as a result of a weak placental perfusion. Second, vitamin D-regulated angiogenic processes plays a role in modulation of proteinuria by VEGF. Third, supplementation of additional vitamin D promotes enhanced flexibility, adaptability, and thickness of the media and intima within blood vessels. The renin-angiotensin-aldosterone system is an additional pathway through which insufficient vitamin D levels can potentially lead to elevated blood pressure (19).

3.2.3 Vitamin D Supplement Recommendation

The recommended daily intake of vitamin D for women and pregnant women is typically considered adequate at 15 µg (600 IU). A deficiency is indicated by a serum concentration of 25(OH)D below 50 nmol/L (>20 ng/mL) (13). To maintain a desirable plasma level of 25(OH) vitamin D (>32 ng/ml), a prescription for vitamin D supplementation of 4000 IU per day is found to be more effective (16). In everyday life, it is advisable for pregnant women to take a daily vitamin D supplement ranging from 10-25 µg (400-1000 IU) to ensure they do not experience deficiency. Vitamin D supplementation is often necessary during pregnancy to achieve the recommended sufficient status according to vitamin D guidelines. Since there is significant variability in vitamin D levels and response to supplementation among individuals, screening can be beneficial in determining the optimal dosage (13).

3.3 L-Arginine

3.3.1 Arginine Physiology

Prenatal oral supplements commonly include iron, folic acid, a range of micronutrients, and lipid-based nutrients to enhance the outcomes of childbirth. L-arginine has a crucial function in the production of nitric oxide, which acts as a mediator for vascular relaxation and prevents platelet adhesion (22). Providing this essential micronutrient to pregnant women has been suggested as a means to decrease the adverse birth outcomes for their fetuses (22–24).

Arginine serves as the exclusive nitrogen provider for nitric oxide synthase, an enzyme responsible for the primary pathway of nitric oxide synthesis, making it a key factor in the production of nitric oxide. Nitric oxide contributes to various physiological processes during pregnancy, such as the regulation of blood flow in the uterus and fetoplacental circulation, as well as maintaining uterine quiescence (24,25). Research indicates that in cases of malaria and bacterial infections, decreased arginine levels are directly associated with reduced bioavailable nitric oxide and

impaired microvascular function. However, restoring arginine levels has been shown to improve endothelial function (23,25).

Arginine has the ability to metabolize into ornithine and proline, which are amino acids involved in the production of polyamines by the placenta. These polyamines play a crucial role in facilitating cell proliferation, migration, vasculogenesis, angiogenesis, and blood vessel dilation. Insufficient availability of arginine can potentially disrupt these processes, leading to adverse outcomes in pregnancy. Research has shown that women who delivered infants with a small gestational age had lower levels of arginine in their bloodstream compared to women who delivered infants appropriate for their gestational age (24,25).

The body's need for arginine can be fulfilled through either dietary sources or internal production. However, situations that result in a substantial increase in arginine utilization do not lead to a corresponding increase in its synthesis within the body. Therefore, in such circumstances, an increased dietary intake becomes necessary to meet the elevated arginine requirements. Pregnancy is considered one such condition where the demand for arginine is heightened. It has been described as a state of relative arginine deficiency because pregnant women experience an increased synthesis of nitric oxide, which relies on arginine availability (25). The successful outcome of a pregnancy and delivery relies on the proper development of the placenta, ensuring its functionality and sufficient vascularization. Vasculogenesis, the creation of new blood vessels, and angiogenesis, the modification of existing blood vessels, are highly controlled processes crucial for the formation of vascularized tertiary villi in the placenta. These villi serve as the location for the exchange of nutrients between maternal and fetal blood (23).

3.3.2 The L-Arginine-NO Biosynthetic Pathway

Nitric Oxide (NO-) is a potent signaling molecule that plays a vital role in maintaining the integrity of the endothelium by regulating processes such as vasodilation, leukocyte adhesion to blood vessels, and platelet aggregation. The production of NO occurs through an enzyme called nitric oxide synthase (NOS), which is present in all cell types. L-arginine serves as the initial component for the synthesis of NO- in all isoforms of NOS. However, the presence of asymmetric dimethylarginine (ADMA), a methylated form of L-arginine, naturally inhibits NOS isoforms, leading to a reduction in the formation of NO- from L-arginine. The balance between the substrate L-arginine and its inhibitor ADMA is represented by the L-arginine/ADMA ratio, which can significantly influence the function of NOS. Additionally, in vivo, NO can react with the superoxide anion (O2-) to produce peroxynitrite (ONOO-) (Figure 2) (23,26).

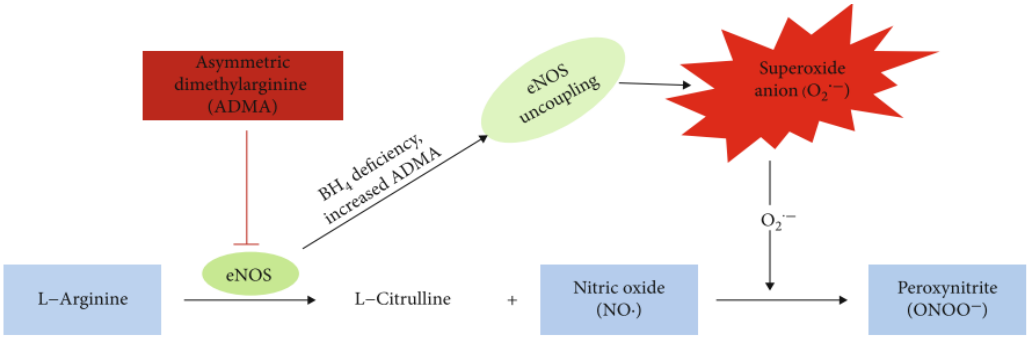

Figure 2. The L-arginine-Nitric Oxide Pathway

Nitric oxide (NO) are insufficiently produced in endothelial dysfunction. During pregnancies associated with preeclampsia, there is an elevation in the production of asymmetric dimethyl arginine (ADMA). This compound inhibits the activity of nitric oxide synthase (NOS), an endogenous enzyme responsible for the synthesis of nitric oxide (NO). NOS, specifically the isoform NOS3, is involved in the enzymatic conversion of L-arginine. In the presence of ADMA, there is a competition between L-arginine and ADMA for NOS3, resulting in increased levels of NO in individuals with higher ADMA levels (27). However, studies examining the levels of NO and ADMA in preeclampsia have provided conflicting reports. Some studies indicate that levels of NO and ADMA in maternal plasma, serum, or urine are comparable, higher, or lower in preeclampsia compared to pregnancies without hypertension (26).

The NOS enzymes are responsible for converting L-arginine into nitric oxide (NO). As a by-product of NO synthesis, L-citrulline is produced, which can also be obtained through dietary intake. L-citrulline can be recycled in a feedback loop to generate more arginine. The balance of arginine utilization in different metabolic pathways is influenced by various enzymes and competitive inhibitors, such as arginase, asymmetric dimethylarginine (ADMA), and symmetric dimethylarginine (SDMA), which also impact the availability of NO. SDMA inhibits the cellular uptake of L-arginine, indirectly inhibiting the conversion of L-arginine to NO. ADMA competitively inhibits NOS. The enzyme dimethylarginine dimethylaminohydrolase (DDAH) breaks down methylarginines, including ADMA. NO interacts with key mediators of angiogenesis at the placental trophoblast, such as PlGF, VEGF, and angiopoietins. The downstream activation of eNOS and the production of NO from L-arginine are necessary for the angiopoietin and VEGF proteins to induce angiogenesis. Moreover, NO signaling enhances the levels of VEGF and angiopoietin-1 (Ang-1) in endothelial cells through a positive feedback loop. Additionally, NO reduces inflammation-related endothelial activation by suppressing the expression of vascular adhesion molecules and proinflammatory cytokines (Figure 3) (23)

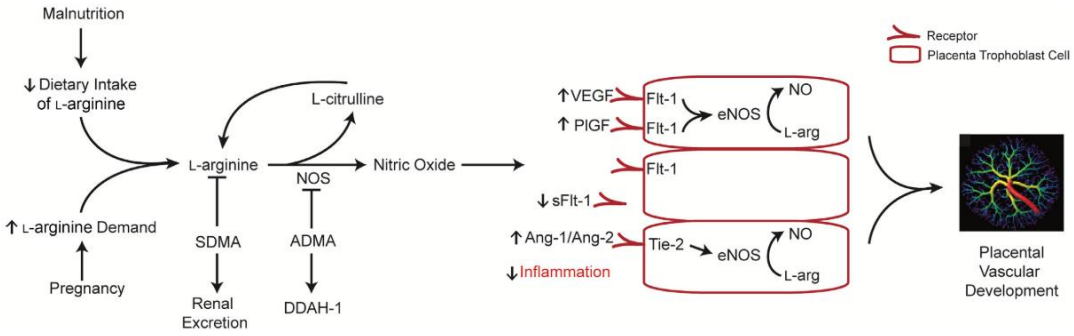

Figure 3. The L-Arginine-NO Biosynthetic Pathway Regulates Key Vasculogenic and Angiogenic Factors in Pregnancy

3.3.3 L-Arginine and Its Role in Pregnancy

During pregnancy, there is an elevated demand for L-arginine to accommodate the rapid growth of the fetus and placenta. Protein-rich foods, which are frequently absent from diets in environments with limited resources, are where L-arginine is found. Therefore, pregnant women may be at risk for arginine deficiency and decreased bioavailable NO due to reduced dietary intake and increased demand during pregnancy (24).

Several studies have investigated the role of L-arginine in the prevention of pre-eclampsia. Goto et al. found that oral supplementation of L-arginine was associated with an increase in APGAR score in women at high risk of pre-eclampsia, as well as those with pre-eclampsia, gestational hypertension, or mild chronic hypertension (22). Tashie et al. reported a significant decrease in nitric oxide (NO) levels along with a significant increase in L-arginine, asymmetric dimethylarginine (ADMA), and 3-nitrotyrosine levels in pregnant women with preeclampsia compared to those with normotensive pregnancies. While both L-arginine and ADMA levels were higher in preeclampsia compared to normotensive pregnancies, the ratio of L-arginine to ADMA was significantly lower in preeclamptic women. The study suggested that the reduced levels of NO observed in preeclampsia could be attributed to the endogenous inhibition of endothelial nitric oxide synthase (eNOS) by ADMA. Elevated ADMA in hypertension may be a consequence of high blood pressure, as increased shear stress triggers the synthesis of ADMA (26).

In a study conducted by Pulido et al., it was demonstrated that supplementation with L-arginine can reduce the risk of pre-eclampsia by approximately 26%, with an efficacy rate of 74%. L-arginine supplementation was found to decrease systolic, diastolic, and mean blood pressure. Lower doses of L-arginine were found to be effective because they compensate for arginine loss, enhance its metabolic utilization through pathways independent of nitric oxide (NO), and compete with ADMA for the enzyme NOS3 when ADMA levels are elevated. This

mechanism allows L-arginine to prevent an increase in blood pressure in patients with high risk factors for pre-eclampsia. The use of lower doses of L-arginine provides the advantage of maintaining a similar level of effectiveness while avoiding the adverse effects reported in several other studies (27).

Human preeclamptic pregnant women have lower plasma levels of arginine and placental eNOS abundance than healthy pregnant women. Arginine deficiency in the preeclampsia placenta decreased NO and increased superoxide formation, leading to NO deficiency and excessive peroxynitrite formation, according to evidence from animal models. Additionally, it was discovered that preeclamptic pregnant women's ADMA levels rose even before preeclampsia manifested itself. These findings imply that pregnant women who have elevated ADMA concentrations have a higher risk of developing preeclampsia (24).

3.3.4 L-Arginine Supplement Recommendation

Arginine is regarded as being abundant in protein-rich foods like meats, dairy products, nuts, seeds, soy, and pulses. Between 3% and 15% of different proteins contain arginine relative to other amino acids. Only 3-4% of the low amount of protein in most cereals comes from arginine, making them arginine deficient. Fruits and vegetables have very little protein, which means they have very little arginine (23).

L-arginine is more expensive than aspirin. L-arginine has preeclampsia prevention benefits that outweigh the expense of its treatment. When given to patients at 19–20 weeks of pregnancy, L-arginine produced positive results (27). Moreover, other study concluded that oral arginine supplementation may be given from admission until delivery in preeclamptic women (24). Preeclampsia in high-risk patients can be prevented and/or treated significantly better with oral administration of 3 g of L-arginine per day for 3 weeks, as demonstrated in literature study (23,24,27).

3.4 Folic Acid

3.4.1 Folic Acid Deficiency

Hyperhomocysteinemia occurs in about 20–30% of patients with peripheral vascular disease and coronary artery disease. Homocysteine is easily oxidized to form homocysteine compounds when the level of the amino acid rises. At the same time, hydrogen peroxide and superoxide ion radicals are produced, which damages the vascular endothelial cells and results in a variety of vascular damage. Homocysteine is one of the factors that contributes to the development of hypertensive disorders during pregnancy (28).

The main contributor to acquired homocysteine is nutritional folic acid (FA) deficiency. FA, also referred to as pteroyl glutamic acid, is a water-soluble B vitamin found in the human body as FH4. It affects the growth and division of fetal neural tube cells as well as the metabolism of proteins and fats. FA is a crucial coenzyme for the synthesis of cell DNA and is essential for the development of the

fetus as well as the production of placenta (28). Human cytotrophoblast cells may also undergo apoptosis as a result of folate deficiency, which could have an impact on trophoblast invasion and placental development (29).

A sufficient amount of FA could promote fetal growth and development, widen placental blood vessels, and boost placental blood supply in addition to lowering the incidence of megaloblastic anemia and abortion. There is growing proof that long-term or high-dose use of FA supplements can successfully prevent pre-eclampsia (12).

3.4.2 Folic Acid and Its Role in Pregnancy

The rapid cell division of the fetus and increased urinary losses during pregnancy result in increased folate requirements. For a healthy placentation, proper fetal growth and development, and the prevention of neural tube defects, pregnant women need to consume enough folate through their diets (supplemented as folic acid). Folate is involved in mechanisms that lower blood pressure, reduce oxidative stress, and restore endothelial function, so it may have protective effects in pre-eclampsia (13,30). One of the main theories for the development of pre-eclampsia is placental insufficiency and the vascular discrepancy that results from rising homocysteine levels (Hcy) (31). The methylation pathway, which is used to synthesize methionine again, is a significant metabolic pathway of homocysteine in living organisms. N5,10-methylenetetrahydrofolate reductase (MTHFR) is needed to catalyze the conversion of 5,10-methylenetetrahydrofolate to 5-methyl-tetrahydrofolate in this reaction. FA serves as a cofactor for this enzyme and acts as a methyl donor to regenerate methionine. FA may therefore play a significant role in both the development and progression of pre-eclampsia. Pregnant women with hyperhomocysteinemia and low folate status are at an increased risk of pre-eclampsia compared to the control group, research has shown (28).

Patients with severe pre-eclampsia prior to delivery have higher serum homocysteine concentrations than healthy late-pregnancy women, those who deliver 3 days later, and those who deliver 42 days later. When compared to 3 days after delivery, serum homocysteine levels in patients with severe pre-eclampsia were significantly lower at 42 days. Serum homocysteine concentrations in patients with severe pre-eclampsia were seen to decrease after delivery, and this decrease grew as the postpartum period lasted longer and the patient's condition improved. Severe pre-eclampsia has been correlated to an increase in serum homocysteine levels in pregnant women, and its severity has been correlated to the concentration of homocysteine in the blood. High dose FA administration were shown to further decrease plasma homocysteine levels (Figure 4) (28,32–34).

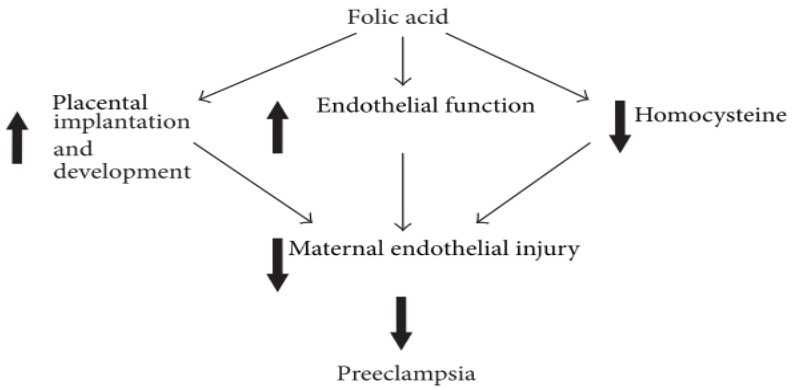

Figure 4. Schematic of Different Proposed Mechanisms of Action by which Folic Acid Decreases the Risk of Developing Pre-eclampsia.

Liu et al. demonstrated that supplementation of multivitamins containing folic acid significantly decreased the risk of preeclampsia (RR=0.70, 95% CI 0.53-0.93, p=0.01), while folic acid alone had no significant effects on preeclampsia risk (RR-0.97, 95% CI 0.80-1.17, p=0.73) (29). Sayyah-

3.4.3 Folic Acid Supplement Recommendation

Melli et al. demonstrated that daily folic acid intake with either doses od 0.5 mg or 5 mg throughout the pregnancy significantly reduced the plasma levels of Hcy. The higher dose of folic acid caused a greater reduction in plasma Hcy levels (Table 1) (31).

Table 1. Laboratory Parameters of Pregnant Women Before and After Receiving Low Dose or High Dose of Folic Acid Supplementation

Parameters	Low dose (n = 200)	High dose (n = 210)
Hcy (mcmol/l)Baseline	10.31(3.54)	13.17(3.89)
Hcy (mcmol/l)Endpoint	8.46(3.35)	7.20(3.35)
Plasma creatinine (mg/dl) Baseline	0.74(0.10)	0.71(0.10)
Plasma creatinine (mg/dl) Endpoint	0.70(0.09)	0.67(0.08)
Urine creatinine (mg/dl) Baseline	0.91(0.18)	0.91(0.19)
Urine creatinine (mg/dl) Endpoint	0.88(0.15)	0.88(0.53)
LDH (U/L)Baseline	292.84(86.65)	292.10(82.80)
LDH (U/L)Endpoint	293.23(90.38)	307.72(84.12)
Urea (mg/dl)Baseline	23.08(6.33)	21.20(7.83)
Urea (mg/dl)Endpoint	21.81(6.17)	21.05(6.36)
Uric acid (mg/dl) Baseline	3.84(0.72)	3.69(0.75)
Uric acid (mg/dl)Endpoint	4.30(1.15)	3.94(0.70)
BP (systolic) (mmHg)Baseline	118.92 (8.11)	116.31 (9.52)
BP (systolic) (mmHg)Endpoint	120.59 (10.61)	117.36 (9.51)
BP (diastolic) (mmHg) Baseline	76.50 (5.87)	74.57 (7.53)
BP (diastolic) (mmHg) Endpoint	78.07 (7.18)	74.73 (7.44)

All values are mean (SD)

Folic acid is frequently prescribed during pregnancy to prevent neural tube defects (0.4 mg/day), and this poses a significant research challenge in industrialized nations (12). The low dose (0.4 mg/day) and high dose (4 mg/day) of FA were adopted for the dosage selection from previously published protocols (28). When pregnancy is unplanned, the use of this supplement should begin as soon as possible and last at least the first trimester of the pregnancy (13). In summary, factors that reduce the risk of pre-eclampsia are shown in Table 2 (13).

Table 2. Factors Implicated in Reducing Risk of Pre-Eclampsia (Recommended Dietary Allowance (RDA)).

Factor	Recommendation	Further relevant advice
Maternal weight	Excessive weight gain during pregnancy and between pregnancies should be avoided. Women should ideally be of a healthy body weight (BMI) prior to conception. Recommendations are that underweight women (BMI ≤18.5) should put on between 13 and 18 kg; normal-weight women (BMI 18.5–24.9) should put on between 11.5 and 16 kg; overweight women (BMI 25–29.9) should put on between 7 and 11.5 kg and obese women (BMI ≥30) should put on no more than 5–9 kg.	A woman aiming to reduce her BMI prior to pregnancy should do so safely preferably with the help of a suitable healthcare professional.
Fibre	A high-fibre diet is recommended for pregnant women and those at risk of pre-eclampsia. Women should aim for a fibre intake of 25–30 g/day to reduce the risk of pre-eclampsia.	Higher fibre intake can reduce blood cholesterol, blood pressure and inflammation and may also aid in weight management.
Prebiotics and probiotics	Consume milk-based probiotics where possible as part of a normal diet.	Further research is required to determine the quantity, timing and efficacy of probiotics to reduce pre-eclampsia risk.
Dietary patterns	Pregnant women should aim to consume ≥400 g of fruits and vegetables per day and ≥250 mg/day of docosahexaenoic/ eicosapentaenoic acid by consuming ~230 g (8 ounces) of mixed seafood per week. High fat, salt, sugar foods and red and processed meats should be limited.	Avoid raw fish and fish with a high mercury content (shark, swordfish, king mackerel, tilefish, marlin, orange roughy, bigeye tuna) during pregnancy.
Vitamin D RDA 15 µg/day	Daily vitamin D supplement of 10–25 µg (400–1000 IU); stay well away from the upper limit of 100 µg (4000 IU).	A woman's current vitamin D status can be measured and may be helpful in defining optimum dosage.
Calcium RDA 1000 mg/ day	All pregnant women to be supplemented with 1 g calcium per day from 20 weeks' gestation to delivery. Women at heightened risk of pre-eclampsia and/or with a low dietary calcium intake should take a calcium supplement of 1–2 g/day during pregnancy.	Calcium supplement, for example, carbonate or citrate. Women are likely to have low dietary calcium intake if they do not consume dairy products which are a major calcium source.
Selenium RDA 60 µg/day	Women who are likely to have low selenium status (eg, in the UK), should increase their intake of selenium-rich foods, such as fish/shellfish. Alternatively, they should take a multivitamin/ multimineral containing selenium as soon as they know they are pregnant and preferably when planning pregnancy.	Brazil nuts are a good source of selenium but the dose can be very high, so it is a risky way of supplementing selenium. Keep intake down to four per week if taking regularly.
Multivitamins/ multiminerals	Women should take a multivitamin/multimineral supplement containing folic acid, vitamin D (unless taking separately) and selenium (if status is low) if they are planning on becoming pregnant. If pregnancy is unplanned, the woman should start the supplement as soon as possible. The supplement should be taken for at least the first trimester.	This supplement may be of particular importance for those who are overweight. Iodine is important for fetal brain development and should be included for a woman who does not eat dairy products or fish in a country that does not have iodised salt. The usual dose in pregnancy is 150 µg/day, usually as potassium iodide. Avoid taking a kelp supplement.

BMI, body mass index.

4. CONCLUSION

Nutrition plays a pivotal role in pregnancy especially in preventing pre-eclampsia or eclampsia. Micronutrient supplementation during pregnancy has been suggested to lower the risk of preeclampsia due to their impact on placentation, oxidative stress, and angiogenic factor expression. These micronutrients include vitamin D, L-arginine, and folic acid. Daily vitamin D supplement of 10-25 µg (400-1000 IU) is needed for pregnant women to prevent pre-eclampsia. Oral administration of L-arginine supplementation of 3 g per day for 3 weeks is suggested to prevent pre-eclampsia. High dose folic acid (4 mg/day) during first trimester of pregnancy with multivitamins supplementation has proven beneficial in preventing pre-eclampsia.

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