REVIEW ARTICLE

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WOMEN STRUGGLING WITH HYPERTENSION AND STRESS IN PREGNANCY AND THE ROLE OF PROLONGED USE OF NITRIC OXIDE SUPPLEMENTS: A META-ANALYSIS

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ABSTRACT

Mental stress can contribute to the exacerbation of hypertension in pregnant women and preeclampsia by releasing stress hormones such as adrenaline and cortisol. Nitric oxide (NO) has an important role in stress, anxiety, and hypertension.

OBJECTIVES

To provide an understanding of the impact of nitric oxide, particularly the effects of L-arginine supplementation on mental stress and blood pressure regulation in pregnant women, to discuss the emerging concepts related to the pathogenesis of hypertension and preeclampsia, and also to highlight the potential benefits of L-Arginine and L-Citrulline supplementation in improving birth outcomes and maternal health.

METHOD

In this study, we focused on the role of L-arginine on high blood pressure during pregnancy. We did thorough research and effective communication of information from relevant and up-to-date research articles, studies from reputable sources, and great academic databases like PubMed, Google Scholar, and medical journals. Around 16 trials were searched in Pub-Med and Google scholar. A total of six trials were included in this meta-analysis.

RESULTS

Nitric Oxide L-Arginine Supplementation showed a mean decrease in diastolic blood pressure and can lead to beneficial effects on blood pressure and vascular function, especially in pregnant mothers with stress, a mean increase up to 1.23 weeks ($p = 0.002$) for the gestation period to delivery, but did not show a reduction in systolic blood pressure as compared to placebo.

CONCLUSION

This meta-analysis study supports the notion that the availability of this substrate for NO synthesis prolongs the latency to the development of preeclampsia and decreases hypertension in a high-risk pregnant woman with hypertension and stress.

KEYWORDS

Arginine; Citrulline; Dietary Supplements; Hypertension; Maternal Health; Nitric Oxide; Pre-Eclampsia; Pregnancy; Stress.

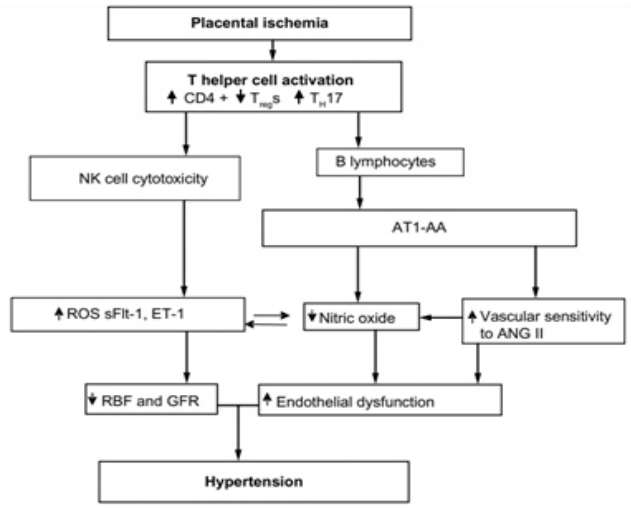
INTRODUCTION

High blood pressure during pregnancy is a significant health concern that can lead to various complications, posing risks to both the mother and the foetus. Hypertension and eclampsia occur relatively frequently, affecting approximately 1 in every 12 to 17 pregnancies among women aged 20 to 44, leading to more maternal mortality and the risk of 2.7-fold higher preterm birth in developing countries.[1] A cohort study conducted during the last century by Irgens et al. published the results of 626,272 live births in Norway between 1967 and 1992.[2] They found that women with preeclampsia had a 1.2-fold higher long-term risk of all-cause death than women who did not have this condition. Predisposing traditional factors like a positive family history, hypertension, diabetes, pre-existing renal disease, multiple pregnancies, and a poor obstetric history may play a role here. Yet the pathways involved in hypertension in pregnancy are still unknown. One risk may be mental stress, which does not directly cause hypertension and preeclampsia, but can exacerbate the condition by increasing blood pressure and potentially impacting overall health due to the activated "fight or flight" response of the body, which involves the release of stress hormones such as adrenaline and cortisol. In response, constricting blood vessels increases the heart rate and blood pressure. This stress-induced increase in blood pressure can be particularly concerning for a woman suffering from pregnancy induced hypertension (PIH).

Chronic stress can contribute to overall poor health and potentially affect the progression and severity of preeclampsia. Addressing this issue is of paramount importance to ensure the well-being of pregnant women and their unborn children. Stress reduction techniques such as relaxation exercises, mindfulness, deep breathing, and counselling can help alleviate stress and contribute to better blood pressure control. Nitric-oxide (L-arginine) plays a role in the management of hypertension in pregnant women and improves pregnancy outcomes. Nitric oxide (NO) is a crucial signalling molecule that is intimately involved in the functions of the female reproductive tract by playing a vital role in blood flow through the fetoplacental circulation via regulating blood vessel tone, vasodilatation, and adapting to the increased circulatory demands of foetal and placental growth during hypertension in pregnancy.[3] Thus, it promotes intrauterine growth of the foetus by increasing the bioavailability of endothelial nitric oxide (NO) production, and improving the umbilical artery flow in pregnant women with PIH.

Figure 1

Role of Placental Ischemia and Vasoactive Factors in the Pathogenesis of CVD and Hypertension in Previously Preeclamptic Women. [4]

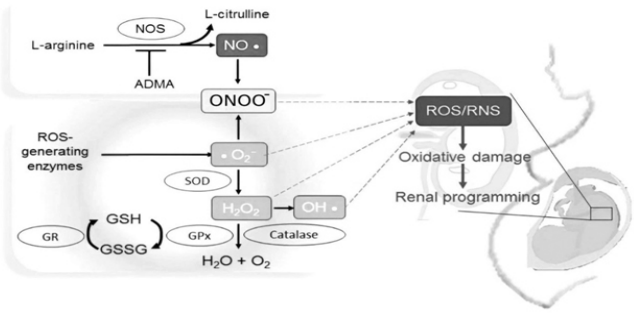


RBF= Renal blood flow; GFR= Glomerular filtration rate; CVD= Cardiovascular disease; ROS= Reactive oxygen species.

Nitric oxide synthases (NOSs) enzymes exist in three main forms. A constitutive, calcium-dependent form is found in endothelial cells (e-NOS) and neurons (b-NOS), while a calcium-independent, inducible form (i-NOS) is present in macrophages, neutrophils, and other cell types, including vascular smooth muscle. (Figure 2)[5]

Figure 2

Diagram illustrating the nitric oxide (NO) pathway, and antioxidant systems in a foetus. [5]



The overproduction of ROS or RNS under adverse intrauterine conditions overwhelms the antioxidant system, resulting in oxidative damage and, thereby, compromising renal development.

NOTE: NOS: nitric oxide synthase; ADMA: asymmetric dimethylarginine; ONOO−: peroxynitrite; SOD: superoxide dismutase; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: reduced glutathione; GSSH: oxidised glutathione; H2O2: hydrogen peroxide; OH: hydroxyl radical.[5]

The production of NO can be inhibited competitively by analogues of L-arginine, including Nωmonomethyl-L-Arginine (L-NMMA) and Nω-nitro-L-Arginine methyl ester (L-NAME), providing a powerful and specific tool to determine the role of NOS in physiology and pathology. L-arginine can be obtained from endogenous metabolism by nitric oxide synthase into nitric oxide and L-Citrulline, both of which play roles in regulating vascular tone, immune response, and cell growth.[6]

By delving into the latest research and conducting a comprehensive meta-analysis, we strive to shed light on the promising strategies for managing high blood pressure. We aim to provide a thorough understanding of the impact of nitric oxide, particularly the effects of L-arginine supplementation on mental stress and blood pressure regulation in pregnant women. We will discuss the emerging concepts related to the pathogenesis of hypertension and preeclampsia and also highlight the potential benefits of L-Arginine and L-Citrulline supplementation in improving birth outcomes and maternal health.

METHOD

Literature Search

The present meta-analysis was performed in accordance with the Preferred Reporting Items from the 16th database systemic reviews, which were independently searched, comprising PubMed/MEDLINE (PubMed.gov) and Google Scholar on this subject. The databases were searched within a time range from the earliest index to October 3, 2021, by using retrieval methods.

Table 1

Effects of L-arginine Supplementation on Pregnancy-Related Conditions-Summary of Studies

Study (ref.)	Dose g/d) Delivery form	Duration	Treatment groups (n)	Key findings
Facchinetti et al.[7]	30 I/V	Single dose	PE: uncomplicated pregnancy (12), PE (17)	• L-arginine–induced reduction in SBP and DBP in both groups, greater decrease of DBP in women with PE • Total L-citrulline production inversely related to baseline blood pressure, but not associated with birth outcomes
Zekiye Sultan Altun et al.[8]	14 Oral	≤28 d	PE: L-arginine (22) or placebo (23), and healthy gravid rates (22)	• Effects of oral L-arginine supplementation on blood pressure and asymmetric dimethylarginine in stress-induced preeclamptic
Staff et al.[9]	12 Oral	≤5 d	PE: L-arginine (15) or placebo (15)	• No change in DBP at 2 d post-intervention • No difference in latency to delivery, or mean birth weight
Vadillo-Ortega et al.[10]	6. 6 Oral	Duration of pregnancy (14–32 weeks of gestation)	PE: women with previous PE or high risk; placebo (L-arginine + antioxidant vitamins, antioxidants alone	• Plasma L-arginine (before treatment) lower in women who later developed PE • Increased circulating L-arginine and decreased SBP and DBP in L-arginine + vitamins group
Camarena Pulido et al.[11]	3 Oral (capsules)	Duration of pregnancy (20 weeks of gestation)	High risk of PE: L-arginine treated or placebo	• Increased incidence of PE, specifically severe PE, in placebo-treated women • Increased birth weight and decreased PTB in L-arginine–treated group • Decreased SBP and DBP and mean arterial pressure
Rytlewski et al.[12]	3 Oral	3 wk	PE: L-arginine (30) or placebo (31)	• Lower SBP, DBP, and mean arterial blood pressure in L-arginine–treated group • L-arginine increased 24-h urinary excretion of NOx and mean plasma L-citrulline
Rytlewski et al.[13]	3 Oral	Duration of pregnancy (average enrolment at 29 weeks of gestation)	PE: L-arginine (30) or placebo (31)	• Decreased antihypertensive dosage in patients receiving L-arginine • Lower rates of FGR, increased latency to delivery, and higher Apgar scores in L-arginine group

Neri et al.[14]	20 I/V	Single dose	Mild to moderate gestational hypertension	• Acute L- arginine treatment reduced maternal SBP and DBP
Neri et al.[15]	20 I/V	5 d	Gestational hypertension: L-arginine (62) or placebo (61)	• Reduced SBP and DBP by both placebo and L-arginine, with greater decrease in L-arginine group
Facchinetti et al.[16]	20 I/V, 4 (oral) I/V + oral	5 d I/V, then 2 wk. oral	Gestational hypertension with or without proteinuria: placebo (35) or L-arginine (39)	• Increased latency (to delivery) in L-arginine–treated group. Reduced SBP and DBP 6 d post-I/V treatment • L-arginine attenuated evolution of PE, and reduced low birth weight in subset of patients without proteinuria
Neri et al.[17]	4 Oral	Duration of pregnancy (<16 weeks of gestation)	Mild chronic hypertension: L-arginine (39) or placebo (40)	• Increased gestational age, birth weight, and trend towards reduced neonatal complications in L-arginine group
Neri et al.[18]	30 I/V	Single dose	FGR: AGA (9), and FGR with (9) or without (9) increased utero-placental resistance	• L-arginine–induced decrease in resistance in FGR pregnancies with increased baseline resistance • Increased plasma NOx and growth hormone concentrations after L-arginine treatment in all groups
Winer et al.[19]	14 Oral	Duration of pregnancy (24–32 weeks of gestation)	Severe FGR: L-arginine (21) and placebo (22)	• No impact on outcomes in pregnancies with severe vascular growth restriction • No difference in serum NOx
Sieroszewski et al.[20]	3 Oral	20 d	FGR: L-arginine (78) or no treatment (30)	• Increased foetal weight gain (during treatment) in the L-arginine–treated group • Increased new-born weight
Singh et al.[21]	3 Oral	21 d	FGR: women with FGR (60; 30 received L-arginine, 30 placebo) or AGA foetal growth (60)	• Increased serum NO in L-arginine–treated FGR • Reduced umbilical artery resistance in L-arginine–treated FGR group • L-arginine increased live births, birth weight, and reduced neonatal complications (nonsignificant)
Rytlewski et al.[22]	3 Oral	Varied by participant (average of 3 wk)	Preterm labour: L-arginine (25) or placebo (20)	• L-arginine reduced pulsatility indexes in umbilical artery and increased pulsatility indexes in the middle cerebral artery, as well as increased cerebro-placental ratio values (MCA/UA)

I/V= Intravenous; SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure; PE= Preeclampsia; FGR= Fetal Growth Restriction; NOx= Nitric Oxide Metabolites; AGA= Appropriate for Gestational Age

Study Selection and Search Strategies

First, a preliminary screening was performed from all the retrieved literature, in which we removed duplicate studies and excluded those that did not meet the inclusion criteria. Excel format, including author, year, country, sample size, and disease. Nitric oxide supplements L-arginine for the prolong period method were considered. Intervention measures, frequency, duration, and outcome indicators were evaluated and noted. We reviewed the entire articles in the secondary screening.

Our study followed articles with factors according to strict ACOG criteria 1996 and the PICSO principle to establish inclusion criteria for participants, interventions, comparisons, results, and research design.

Participants Characteristics

The participants in the studies had a diverse range of maternal ages, spanning from 20 to 45 years, with a mean age of 30. 2 years. Several clinical parameters were assessed of each participant, including their systolic and diastolic blood pressure values, proteinuria levels, mental stress level and gestational age. All patients with onset of hypertension during late gestation with systolic (>140) or diastolic (>90) mmHg pressure on at least two occasions and preeclampsia with urinary protein excretion greater than 300 mg/24 hr after the 20th week of pregnancy and singleton pregnancies were included.

Exclusion Criteria

Those studies with any of the following risk factors present: smoking, chronic illnesses such as hypertension, coronary heart disease, renal disease, diabetes mellitus, prophylactic treatments with low-dose aspirin, severe foetal malformations detected by ultrasound examination were not included in this meta-analysis study.

Studies with a control group treated with conventional drug therapy and intervention type with L-Arginine plus conventional medicine were included. Studies included RCTs (blinded, non-blinded or placebo).

Data Collection and Analysis

The primary outcome variables of interest for this meta-analysis were the effects of L-Arginine supplementation on maternal blood pressure, particularly focusing on systolic and diastolic BP, increases in values due to stress, and pregnancy outcomes. The collected data from studies were subjected to meticulous analysis using appropriate statistical methods to determine the statistical significance of these effects.

Used the GRADE evidence for quality grading scoring methods currently formulated by a widely representative group of international guidelines, including 5 reasons that may reduce the quality of evidence and 3 possible reasons for improving the quality of evidence.

RESULTS

Statistical analysis of studies revealed significant reductions in both systolic and diastolic blood pressure values in the L-arginine group compared to the placebo group. After 4 to 32 weeks of treatment, the mean increase in latency period increased to 1.23 weeks ($p = 0.002$) in the gestational period up to delivery. Increased foetal birth weight in most studies, with significantly lower values of SBP, and DBP in the group taking L-arginine as compared with the controlled group. Importantly, treatment with exogenous L-arginine significantly elevated the 24-hour urinary excretion of NOx and the mean plasma levels of L-Citrulline. The effect of L-arginine on reducing blood pressure was particularly pronounced for systolic values ($F = 7.40$, $p < 0.004$) and diastolic values ($F = 2.54$, $p < 0.001$), showing a meaningful reduction in blood pressure levels by L-arginine supplementation.

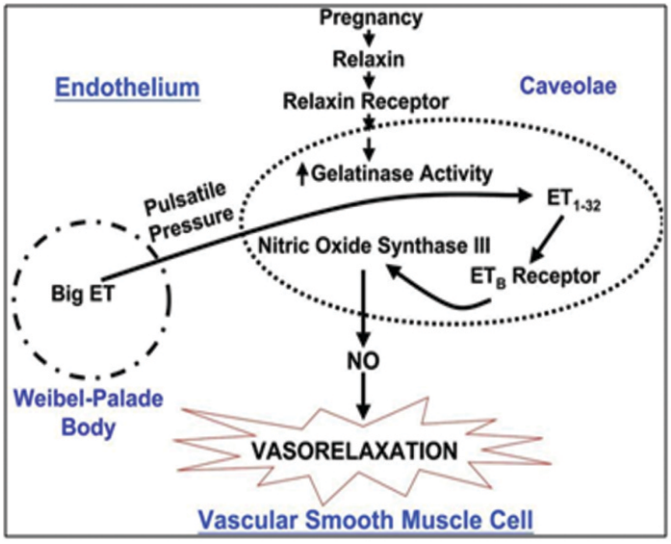
DISCUSSION

Pregnancy is a transformative process involving various challenges in metabolic, psychological, and physiologic adaptations. One of the significant concerns is the increase in high blood pressure during pregnancy due to stress, which poses a considerable risk to both maternal and foetal health [23]. Nitric oxide, a molecule synthesised endogenously by L-Citrulline and L-Arginine, not only plays a pivotal role in maintaining vascular homeostasis but can also relax blood vessels and reduce arterial stiffness, hence reducing blood pressure in stressful conditions. Improve carotid artery blood flow by enhancing blood flow. It offers several heart-boosting effects, like improving performance in physical exertion activities, promoting healing, enhancing heart health, and preventing PIH and preeclampsia. Its precursor, L-arginine, exerts excellent anti-stress effects on stress-induced shortened lifespan, cognitive decline, and depression, partly due to its protein-building ability. L-arginine can cross the blood-brain barrier and reach the brain tissues and

hypothalamus—something that most other medications and supplements cannot do. L-arginine increases dopamine transporter activity, and it can improve dopamine levels. as well as provide many other potential benefits by stimulating the release of certain hormones, such as insulin and human growth hormone.[24]

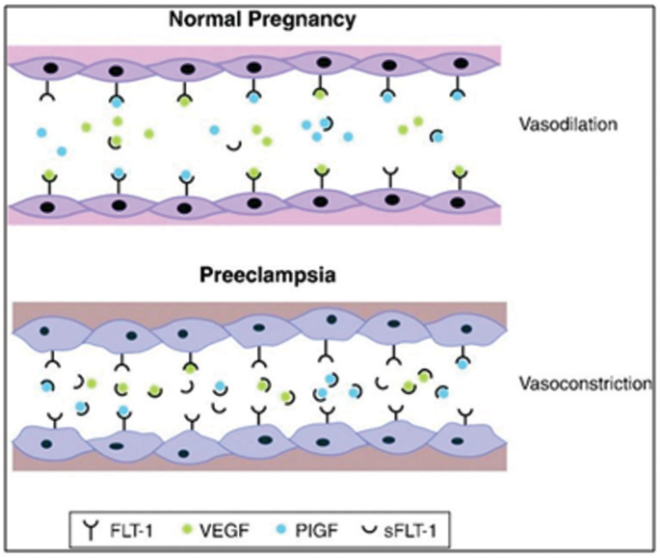
Evidence has accumulated that highlights the role of nitric oxide (NO) as a potent endothelial-derived vasodilator implicated in gestational vasodilatation by playing a role in modulating myogenic tone and flow-mediated responses in vascular resistance in the peripheral and uterine circulation (11), during pregnancy. Relaxin is produced by the corpus luteum of the ovary, circulates in the luteal phase of the menstrual cycle, and rises early in gestation due to human chorionic gonadotrophin produced by the placenta, which is a major stimulus for relaxin secretion. Jeyabalan et al demonstrated an essential role for vascular gelatinase in the relaxin-mediated, renal circulatory changes of pregnancy. However, whether circulating relaxin bioactivity may be deficient during the disease is uncertain (Figure 3).[25,26]

Figure 3
Proposed scheme of cellular mechanisms underlying pregnancy and relaxin-induced renal vasodilation and hyperfiltration and reduced myogenic reactivity of small renal arteries.[26]



The demand for NO increases to accommodate the expanded circulatory volume and augmented uteroplacental perfusion. NO may be instrumental to endovascular invasion and vessel remodelling of the developing placenta, as suggested by a number of experimental findings. First, NO release is coupled to VEGF and hepatocyte growth factor (HGF)-induced trophoblast invasion and motility. Second, in trophoblast cells, NO upregulates the expression and activity of the matrix-degrading proteases MMP-2 and MMP-9, which are required for invasion during embryo implantation. Finally, NO causes dilation of the uteroplacental arteries, which is another prerequisite for trophoblast invasion and remodelling of the endothelium (Figure 4).[25,26]

FIGURE 4
(Top) Flt1 on endothelial cells with few sFlt1 in the circulation. Agonists VEGF and PlGF can occupy Flt1. (Bottom) Vessel from preeclamptic patient with abundant sFlt1 that are able to catch VEGF and PlGF so that the growth factors cannot occupy Flt1 on the cell surface.



NOTE: soluble fms-like tyrosine kinase 1 (sFlt1); vascular endothelial growth factor (VEGF); placental growth factor (PlGF).

Thus, during pregnancy, the role of NO, especially locally formed NO, is to maintain low vascular resistance. Besides attenuating the action of vasoconstrictors in facilitating vasodilation, it is crucial to adapt to the increased circulatory demands for foetal and placental growth. L-arginine, an amino acid, serves as a precursor for NO synthesis, a family of enzymes.[27] stress-induced increase in hypertension due to the several functions that are related to protein synthesis and the removal of ammonia via the urea cycle. It is the source of amidino groups for creatinine synthesis. The existing literature suggests that L-arginine supplements have direct effects on the blood pressure of pregnant subjects.

Facchinetti and colleagues found that the intravenous infusion of L-arginine reduced blood pressure in pregnant women in association with increased L-citrulline levels, indicative of the metabolism of L-arginine into NO. The decline in blood pressure was greatest in women with preeclampsia.[7]

Much of the older literature linking an L-arginine-deficient diet to preeclampsia has been shown to be erroneous, although some clinicians have mentioned that preeclampsia is a disease of maternal malnutrition and recommend nutritional supplementation, citing the observation that preeclampsia is associated with low protein and low arginine levels in maternal plasma, especially in adolescent mothers. For example, a short period of food deprivation in pregnant adolescent women cannot maintain arginine production, especially when compared to adult pregnant women.[27] Placental growth and increased need may not be met through diet, especially in women living in low-resource settings without access to protein-rich foods. Due to the elusive pathogenesis of preeclampsia, prevention through routine supplementations with calcium, magnesium, omega-3 fatty acids, or antioxidant vitamins are found ineffective.[28]

Nitric oxide supplementation, including L-citrulline and L-arginine, to decrease diastolic BP also stimulates the release of certain hormones like stress hormones, e.g., adrenaline, cortisol, insulin, and human growth hormone. Overall, research has shown that L-arginine is safe and generally well tolerated in supplement form, when taken daily over long periods of 1 year or more.[29] Doses of L-arginine vary widely depending on what it's beneficial for the patient. When used to treat preeclampsia, the dose typically ranges from 3 to 4 grams daily for up to 12 weeks, or until delivery under a doctor's supervision. on.[28]

L-arginine administered intravenously to a pregnant mother with high blood pressure in a clinical setting consistently demonstrates an enhanced nitric oxide and growth hormone response in a dose-dependent manner, from 6.0 to 30 mg. Moreover, a secondary finding in one of these studies was that the L-arginine supplementation resulted in a significant reduction in the risk of indicated preterm birth, which supports the notion that the availability of the substrate for NO synthesis prolongs the latency to the development of preeclampsia in pregnant women with stress. The protective effect for preeclampsia was attained when L-arginine + antioxidant vitamins were supplemented before 24 weeks of gestation, which may have value in reducing the risk of this lethal disease. (Figure 5).[30]

In the third trimester of pregnancy, the main source of NO in the human uterus is probably the vascular endothelium of large placental vessels, which limits platelet aggregation at the interface between maternal and foetal circulations. Regular placental blood flow suppresses contractions of the underlying myometrium, as NO is a powerful dilator of the fetoplacental circulation. An accumulating body of evidence suggests that NO production may be augmented by oestrogens and that induction by oestrogen could account for some of the increase in NO production observed during pregnancy.[31]

Safety & Consideration in Pregnancy

Hypertensive disorders are related to endothelial damage in pregnancy, and Antihypertensive drugs, which may reverse the dysfunction of the endothelium, cannot be used in pregnancy either because they are teratogenic, like ACE inhibitors, or because their adverse effects are augmented when administered in combination with magnesium sulphate, such as calcium-channel blockers. Treatment with hydralazine, a drug used to treat hypertension in pregnancy, increases plasma cGMP levels. Flow-induced shear stress is a potent stimulus to vasodilatation in arteries during pregnancy. On the other hand, flow-induced vasodilatation has been reported to be reduced in arteries of women with preeclampsia[27] The results of studies indicate that psychological stress causes an increase in NO level and a decrease in arginase activity in the L-arginine-NO pathway. Supplementation with L-arginine during pregnancy results in a significant reduction in stress-induced hypertension and in new cases of pre-eclampsia. Studies have shown that L-arginine is safe, well-tolerated and cost-effective therapy in pregnancy with hypertension. In this sample, none of the patients reported adverse effects requiring study interruption.

Even though they have a strong safety profile, arginine supplements should be avoided by pregnant women with asthma, cirrhosis of the liver, kidney disease, low blood pressure, and guanidinoacetate methyltransferase deficiency, an inherited disorder that affects arginine metabolism, due to the potential for adverse effects.[32] Some patients may develop an anxious mood, dehydration, a depressed mood, and irritability with L-arginine. Antidepressants, like SSRIs or SNRIs, and Hydroxyzine should be first-choice options for managing anxiety in pregnancy only when anxiety symptoms in patients are at their worst.

In summary

There is strong evidence available that supplementation with L-arginine during pregnancy results in significant reduction of hypertension and preeclampsia. Studies have demonstrated that in women with gestational hypertension and preeclampsia, prolonged dietary supplementation with L-arginine significantly decreased blood pressure through increased synthesis and/or bioavailability of NO. The increased formation of NO has been hypothesised to contribute to the maternal vasodilatation associated with gestation, which may raise requirements for L-arginine in addition to the foetal demands for this amino acid. There are no established nutritional guidelines for daily arginine intake; however, some authors have suggested that the mean daily arginine recommended intake is 3. 8 to 4. 0 g for the American adult. L-arginine is naturally found in dairy products, poultry, fish, nuts, legumes, and watermelon are the major source of these amino acids. L-arginine's availability is influenced by its dietary intake and endogenous production. Concentrations are maintained in plasma by protein or by synthesis from other amino acids. Foods that are a good source of L-arginine may also contain other substances such as antioxidant vitamins, omega-3,6 fatty acids, and/or saturated fatty acids. “Visek” estimated that the standard diet barely provides sufficient arginine for the synthesis of the daily amount of creatinine excreted. Endogenous arginine synthesis is not markedly responsive to acute changes in arginine ingestion, and in a normal adult's whole body, arginine homeostasis is thought to be achieved largely through dietary intake and modulation of the rate of arginine degradation. Manufacturers have made L-arginine and L-citrulline in a laboratory and packaged them as a pill or powder.[12]

Reducing stress can have several potential benefits for pregnant women with hypertension and preeclampsia, including Lowering blood pressure: Cognitive-behavioural therapy (CBT) and counselling may be beneficial for some patients to address the emotional and psychological aspects of stress during pregnancy. In severe cases, early delivery of the baby prevents further complications. Enhanced coping skills: Stress management strategies can empower women to better cope with the challenges of managing a high-risk pregnancy. Mental stress management and nutritional supplementation, such as L-arginine, may be considered as complementary measures but should not replace standard medical care. On the other hand, at least medium- or high-quality evidence suggests favourable effects of prenatal oral L-arginine in IUGR neonates, preterm birth, RDS, birthweight, and gestational age in women with stress and a history of poor pregnancy outcomes, and on Apgar score in women or with gestational or

mild chronic hypertension at high risk of pre-eclampsia. It's important to note that L-arginine should not be used as a standard treatment for preeclampsia, and any use should be under the supervision of a healthcare provider. It is tempting to speculate that the supplementary treatment with L-arginine may represent a new, safe and efficient strategy to improve the function of the endothelium in hypertension and preeclampsia.

Limitations

This study also had some limitations. Limited high-quality studies with variability in L-arginine dosage and administration protocols in pregnant women with high blood pressure in varying backgrounds of population and gestational stages. The emphasis on short-term outcomes, the lack of long-term data, and some heterogeneities of results were evident, with potential publication bias favouring positive outcomes. Ethical constraints on conducting randomised trials in pregnant women challenge translating research findings into clinical practice. This paper provides some insight for future research.

CONCLUSION

This meta-analysis research aims to enrich the knowledge of novel approaches in the care of pregnant women with hypertensive disorders and mental stress. Nitric oxide may play an important part in uterine physiology and pathology. Shows that deficiencies in NO production or bioavailability can disrupt this finely tuned equilibrium, potentially leading to abnormal blood vessel function and hypertension in pregnant women. IV infusion of L-arginine followed by prolonged dietary supplementation with L-arginine significantly decreased blood pressure through increased endothelial synthesis and bioavailability of NO.

The foreseeable future is likely to herald major advances in the understanding of the role of this ubiquitous molecule for these common conditions resistant to currently available therapies. The evidence of the effectiveness of L-arginine is mixed, and its use in stress-induced hypertension and preeclampsia management remains a subject of research and debate. Hopefully, future research will support a greater understanding of the role of L-arginine supplementation in managing gestational hypertension, its associated complications, and prolonging gestational age in pregnancy. Meanwhile, parenteral and oral L-arginine in these women may be at least moderately recommended to improve birth outcomes, resulting in reduced rates of mortality and morbidity between the neonatal and adult periods.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in preparing this manuscript.

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