

REVIEW ARTICLE:**PREGNANT WOMEN STRUGGLING WITH HIGH BLOOD PRESSURE AND STRESS IN PREGNANCY AND ROLE OF NITRIC OXIDE SUPPLEMENTS L-ARGININE FOR PROLONG PERIOD**

Khalida Soomro¹, Muhammad Ali Soomro², Sadaf Memon³

¹ Department of Cardiology, Ziauddin University Hospital KDLB Branch Karachi.

²Department of Pathology , Bilawal Medical College for Boys LUMHS.

³Department of Pharmacology, Liaquat University of Medical & Health Sciences (LUMHS) Jamshoro

CORRESPONDENCE: DR. KHALIDA SOOMRO E.mail: prokhalidasoomro@hotmail.com

Submitted: October 19, 2023

Accepted: March 30, 2024

INTRODUCTION:

Mental stress can contribute to the exacerbation of hypertension in pregnant women and preeclampsia by the release of stress hormones such as adrenaline and cortisol level. Nitric oxide (NO) has an important role in stress, anxiety and hypertension. Less NO-dependent vasodilation and excess formation of reactive oxygen species could explain poor placenta perfusion already in Pregnancy-induced hypertension (PIH) and Preeclampsia due to impaired endothelial function. Studies have indicated that Nitric oxide supplement L-arginine can lead to beneficial effects on various cardiometabolic markers, including blood pressure and vascular function especially in pregnant mothers.

OBJECTIVE:

The primary objective of this meta-analysis study of placebo-controlled trials was to assess and ascertain the evidence of effectiveness of L-arginine and its use in enhancing nitric oxide synthesis to translate into tangible improvement in Hypertension and preeclampsia management, Nitric oxide supplement L-arginine's ubiquitous molecule's role is a subject of debate and research with focus on both systolic and diastolic values, pregnancy outcomes and understanding of its role in Hypertension resistant to currently available therapies.

METHODS:

In this study focused on role of L-arginine on high blood pressure during pregnancy, we did a thorough research, effective communication of information from relevant and up-to-date research articles, studies from reputable sources and great places of academic database like PubMed, Google Scholar, 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:

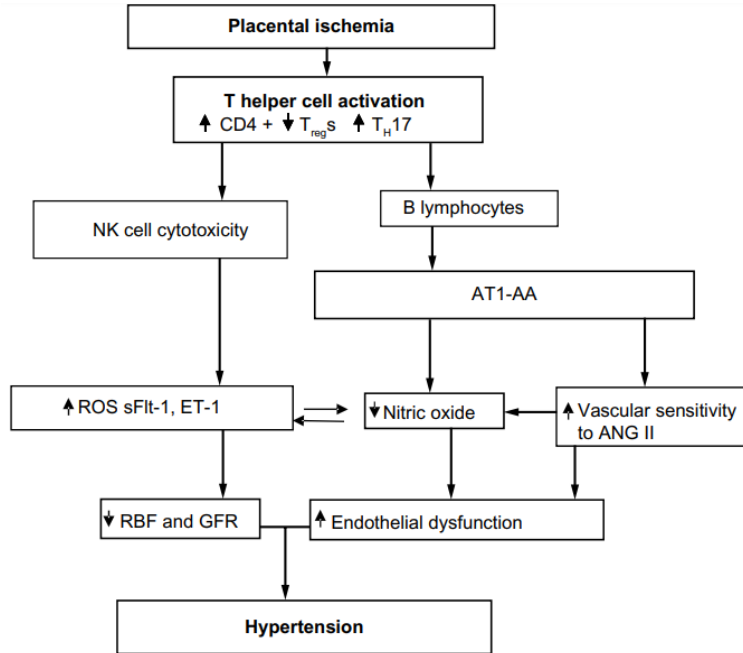
Result of this meta-analysis shows Nitric Oxide L-arginine supplementation showed a mean decrease in diastolic blood pressure and can lead to beneficial effect on blood pressure and vascular function especially in pregnant mothers with stress, mean increase up to 1.23 weeks ($p = 0.002$) for gestation period to delivery but did not showed reduction in systolic blood pressure as compared to placebo.

CONCLUSION:

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

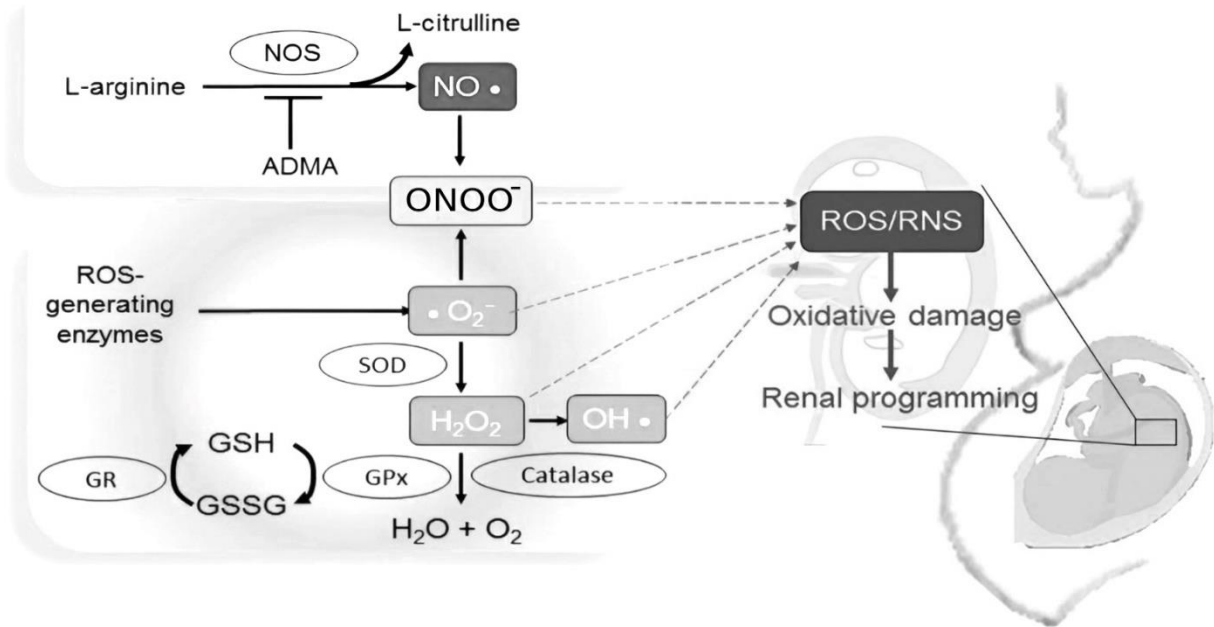
Introduction:

High blood pressure during pregnancy is a significant health concern that can lead to various complications posing risks to both the mother and the fetus. 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 during 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 role here. Yet pathway involved in hypertension in pregnancy are still unknown, one of the 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 activated "fight or flight" response of the bodies involves the release of stress hormones such as adrenaline and cortisol, in response constrict blood vessels increases the heart rate and blood pressure. This stress-induced increase in blood pressure can be particularly concern for a women suffering from PIH already. 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 counseling can help alleviate stress and contribute to better blood pressure control. Nitric-oxide (L-arginine) both play role in the management of hypertension in pregnant women and improve pregnancy outcomes. As Nitric oxide (NO) is a crucial signaling molecule intimately involved in the functions of the female reproductive tract by playing a vital role in blood flow through the fetoplacental circulation through regulating blood vessel tone, vasodilatation and adapting increased circulatory demands of fetal and placental growth during hypertension in pregnancy [3]. Thus, promotes intrauterine growth of the fetus by increasing bioavailability of endothelial nitric oxide (NO) production and improving the umbilical artery flow in pregnant women with PIH.



Lorena M Amaral et. al. (Figure no. 1) [4]

Nitric oxide synthases (NOSs) enzyme exists 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 No. 2) [5]



The production of NO can be inhibited competitively by analogues of L-arginine, including Nω-monomethyl-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].

Aims and Objectives: 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 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 also highlight the potential benefits of L-Arginine and L-Citrulline supplementation in improving birth outcomes and maternal health.

Material and Method

Literature Search

The present meta-analysis was performed in accordance with the Preferred Reporting items from 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 the retrieval methods.

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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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 enrollment at 29 weeks of gestation)	PE: L-arginine (30) or placebo (31)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • Increased foetal weight gain (during treatment) in the L-arginine-treated group • Increased newborn weight
Singh et al. [21]	3 Oral	21 d	FGR: women with FGR (60; 30 received L-arginine, 30 placebo) or AGA fetal growth (60)	<ul style="list-style-type: none"> • 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 labor: L-arginine (25) or placebo (20)	<ul style="list-style-type: none"> • 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)

Study Selection and Search Strategies

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

Our study followed articles with factors according to strict ACOG criteria 1996, the PICSO principle to establish in 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 20th week of pregnancy, with single stone pregnancies were included.

Exclusion Criteria:

Those studies with any of the following risk factors present as 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 metanalysis study.

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

Data Collection and Analysis:

The primary outcome of variables interest for this meta-analysis were the effects of L-arginine supplementation on maternal blood pressure, particularly focusing on systolic and diastolic BP, increase 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, mean increase in latency period and increase up to 1.23 weeks ($p = 0.002$) in gestational period up to delivery. Increased fetal birth weight in most studies with significantly lower values of SBP, DBP in the group taking L-arginine as compared with the controlled group. Importantly, treatment with exogenous L-arginine significantly elevated 24-h urinary excretion of NOx and 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 led to a meaningful reduction in blood pressure levels by L-arginine supplementation.

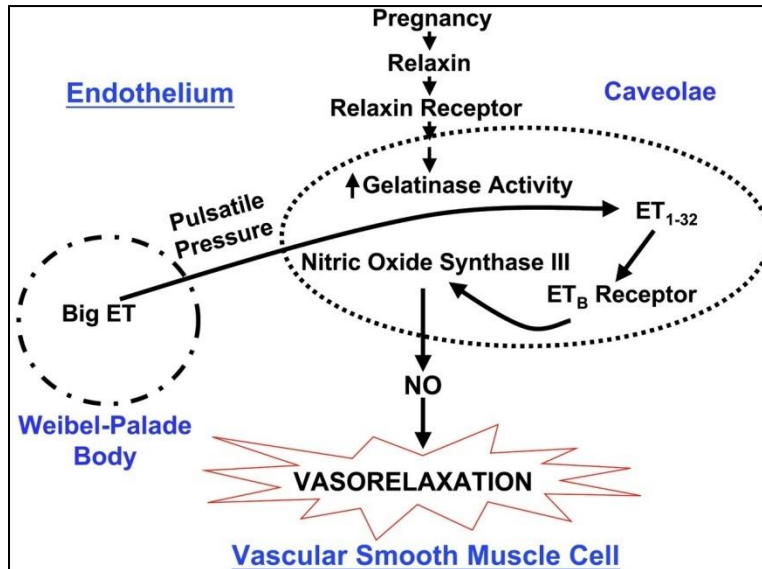
Discussion

Pregnancy is a transformative process involving in various challenges in metabolic, psychological and physiologic adaptations, one of the significant concerns is increase of high blood pressure during pregnancy due to stress, which poses a considerable risk to both maternal and fetal health [23].

Whereas Nitric oxide a molecule synthesized endogenously includes L-citrulline and L-arginine) not only plays a pivotal role in maintaining vascular homeostasis can relax blood vessels and reduce arterial stiffness hence reduce blood pressure in stress condition also and Improve carotid artery blood flow by enhancing blood flow, offers several heart boosting effects like improving performance in physical exertion activities, promote healing, enhance heart health, prevent 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 of 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].

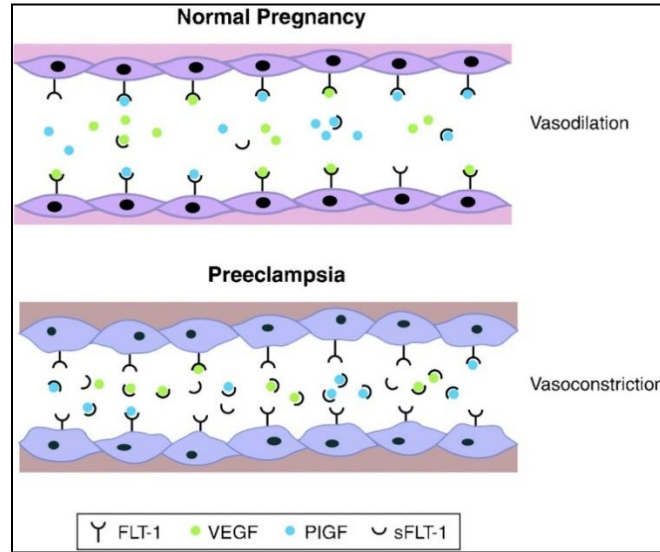
Evidence has accumulated which highlighted the role of Nitric oxide (NO) as a potent endothelial derived vasodilator implicated in gestational vasodilatation, by playing role in modulating myogenic tone and flow-mediated responses in vascular resistance in the peripheral and uterine circulation (11), 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 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 No. 3) [25, 26].



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

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 developing placenta is 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 the 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 no. 4). [25, 26]



(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.

Thus, during pregnancy, the role of NO, specially locally formed NO serves to maintain low vascular resistance besides attenuating the action of vasoconstrictors in facilitating vasodilation is crucial to adapt to the increased circulatory demands for the fetal and placental growth, L-arginine an amino acid, serves as a precursor for NO synthesis a family of enzymes [27]. especially in stress induce increase in hypertension due to the several functions which are related to protein synthesis and 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 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 metabolism of L-arginine into NO. The decline in blood pressure was greatest in women with preeclampsia [7].

Much of the older literature linking l-arginine deficient diet to preeclampsia has been shown to be erroneous, although some clinicians 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 level in maternal plasma specially in adolescent mother. 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 (27Trusted Source). Whereas due to 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 (14Trusted Source). Doses of L-arginine vary widely depending on what it's beneficial for patient. When used to treat preeclampsia, the dose typically ranges from 3–4 grams daily for up to 12 weeks, or until delivery under a doctor's supervision [28].

L-arginine administered intravenously to a pregnant mother with high blood pressure in 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 availability of the substrate for NO synthesis prolongs the latency to development of preeclampsia pregnant women with stress. The protective effect for pre-eclampsia was attained when L-arginine + antioxidant vitamins were supplemented before 24 weeks of gestation that may have value in reducing the risk of this lethal disease. (Figure No. 5) [29]

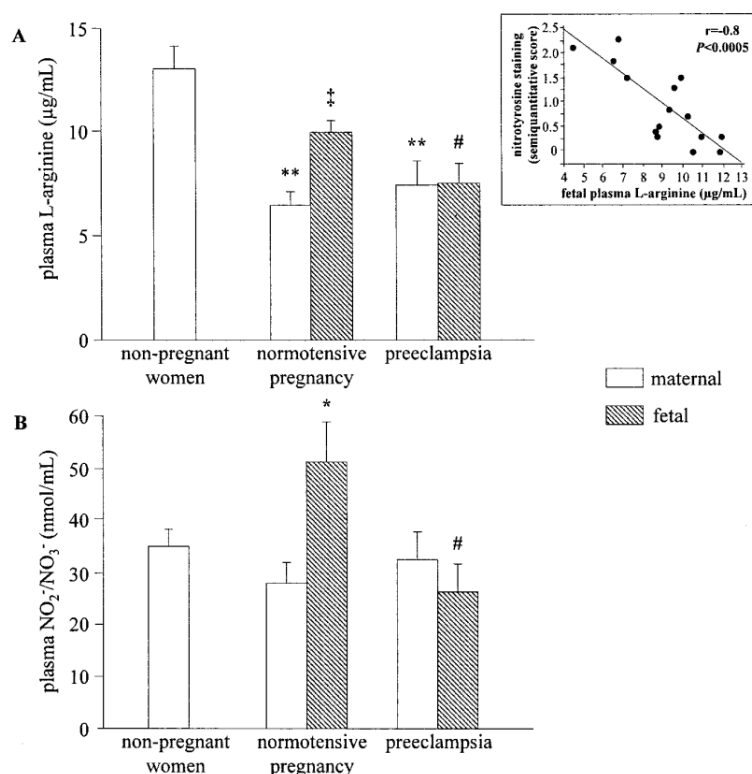


Figure 3. Plasma L-arginine (A) and NO₂⁻/NO₃⁻ (B) concentrations in maternal venous blood and fetal umbilical venous blood from NP (n=9) and preeclampsia (n=6) and in venous blood from nonpregnant women (n=6). Framed panel at upper right shows an inverse correlation between the semiquantitative score for nitrotyrosine staining in syncytiotrophoblasts and fetal plasma L-arginine concentration. Data are mean ± SEM. #P<0.05 versus fetal blood from NP; ‡P<0.0001; *P<0.05 versus maternal blood; **P<0.005 versus non-pregnant women.

In the third trimester of pregnancy, the main source of NO in the human uterus is probably: the vascular endothelium of large placental vessels and to limit 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 [30].

Safety & Consideration in Pregnancy.

As 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 of NO level and a decrease of arginase activity in the L-arginine-NO pathway. The supplementation with L-arginine during pregnancy results in significant reduction in stress induced hypertension and in new cases of pre-eclampsia. Studies have shown that L-arginine is safe and well tolerated and cost-effective therapy in pregnancy with hypertension as 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 [31]. Some patient may develop Anxious mood, Dehydration, 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 pre-eclampsia. 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 hypothesized 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 - 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 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 good source of L-arginine may also contain other substances such as antioxidant vitamins, omega 3, 6 and/or saturated fatty acids. "Vissek" estimated that the standard diet barely provides sufficient arginine for synthesis of the daily amount of creatinine excreted. Endogenous arginine synthesis is not markedly responsive to acute changes in arginine ingestion and in 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 package it 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 to prevent 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 suggested favourable effects of prenatal oral L-arginine on IUGR neonates, pre-term 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.

Limitation

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. Emphasis on short-term outcomes, lacking long-term data and some heterogeneities of results were evident with potential publication bias favouring positive outcomes. Ethical constraints on conducting randomized trials in pregnant women challenges in translating research findings into clinical practice. This paper provides some insight for future research.

Conclusions

This meta-analysis research aims to enrich the knowledge way for novel approaches in the care of pregnant women with hypertensive disorders with 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. With 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. 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 effectiveness of L-arginine is mixed, and its use in stress induced hypertension and preeclampsia management remains a subject of research and debate. Hopefully in future research will support more understanding of role of L-arginine supplementation's in managing gestational hypertension, its associated complications and prolonging gestation age in pregnancy. Mean while Parental, oral L-arginine in these w omen may be at least moderately recommended to improve birth outcomes, resulting in reduced rates of mortality and morbidity between neonatal and adult periods.

References

1. Soomro, Khalida. PS-C30-8: PREGNANT WOMEN WITH STRUGGLING WITH HIGH BLOOD PRESSURE IN PREGNANCY AND ROLE OF NITRIC OXIDE SUPPLEMENTS L-ARGININE FOR PROLONG PERIOD. *Journal of Hypertension* 41 (Suppl 1): p e465, January 2023. | DOI: 10.1097/01. hjh. 0000917648. 77238.
2. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ*. 2001 Nov 24;323(7323):1213-7. doi: 10.1136/bmj. 323. 7323. 1213.
3. Krause BJ, Hanson MA, Casanello P. Role of nitric oxide in placental vascular development and function. *Placenta*. 2011 Nov; 32(11):797-805. doi: 10.1016/j. placenta. 2011. 06. 025. Epub 2011 Jul 27.
4. Amaral LM, Cunningham MW Jr, Cornelius DC, LaMarca B. Preeclampsia: long-term consequences for vascular health. *Vasc Health Risk Manag*. 2015 Jul 15;11: 403-15. doi: 10.2147/VHRM. S64798.
5. Tain YL, Hsu CN. Perinatal Oxidative Stress and Kidney Health6. *Antioxidants (Basel)*. 2022 Dec 21;12 (1):13. doi: 10.3390/antiox12010013.
6. Wu G, Bazer FW, Davis TA, Kim SW, Li P, Marc Rhoads J, Carey Satterfield M, Smith SB, Spencer TE, Yin Y. Arginine metabolism and nutrition in growth, health and disease. *Amino Acids*. 2009 May;37(1):153-68. doi: 10.1007/s00726-008-0210-y. Epub 2008 Nov 23.
7. Facchinetti F, Longo M, Piccinini F, Neri I, Volpe A. L-arginine infusion reduces blood pressure in preeclamptic women through nitric oxide release. *J Soc Gynecol Investig*. 1999;6(4):202-7.
8. Altun ZS, Uysal S, Guner G, Yilmaz O, Posaci C. Effects of oral L-arginine supplementation on blood pressure and asymmetric dimethylarginine in stress-induced preeclamptic rats. *Cell Biochem Funct*. 2008 Sep-Oct;26(5):648-53. doi: 10.1002/cbf. 1491. PMID: 18521818.
9. Staff AC, Berge L, Haugen G, Lorentzen B, Mikkelsen B, Henriksen T. Dietary supplementation with L-arginine or placebo in women with pre-eclampsia. *Acta Obstet Gynecol Scand*. 2004;83(1):103-7.
10. Vadillo-Ortega F, Perichart-Perera O, Espino S, Avila-Vergara MA, Ibarra I, Ahued R, Godines M, Parry S, Macones G, Strauss JF. Effect of supplementation during pregnancy with L-arginine and antioxidant vitamins in medical food on pre-eclampsia in high risk population: randomised controlled trial. *BMJ*. 2011;342:d2901.
11. Camarena Pulido EE, García Benavides L, Panduro Barón JG, Pascoe Gonzalez S, Madrigal Saray AJ, García Padilla FE, Totsuka Sutto SE. Efficacy of L-arginine for preventing preeclampsia in high-risk pregnancies: a double-blind, randomized, clinical trial. *Hypertens Pregnancy*. 2016;35(2):217-25.
12. Rytlewski K, Olszanecki R, Korbut R, Zdebski Z. Effects of prolonged oral supplementation with l-arginine on blood pressure and nitric oxide synthesis in preeclampsia. *Eur J Clin Invest*. 2005;35(1):32-7.
13. Rytlewski K, Olszanecki R, Lauterbach R, Grzyb A, Basta A. Effects of oral L-arginine on the foetal condition and neonatal outcome in preeclampsia: a preliminary report. *Basic Clin Pharmacol Toxicol*. 2006;99 (2):146-52.
14. Neri I, Blasi I, Facchinetti F. Effects of acute L-arginine infusion on non-stress test in hypertensive pregnant women. *J Matern Fetal Neonatal Med*. 2004;16 (1):23-6.

15. Neri I, Jasonni VM, Gori GF, Blasi I, Facchinetti F. Effect of l-arginine on blood pressure in pregnancy-induced hypertension: a randomized placebo-controlled trial. *J Matern Fetal Neonatal Med.* 2006;19(5):277–81.
16. Facchinetti F, Saade GR, Neri I, Pizzi C, Longo M, Volpe A. L-arginine supplementation in patients with gestational hypertension: a pilot study. *Hypertens Pregnancy.* 2007;26(1):121–30.
17. Neri I, Monari F, Sgarbi L, Berardi A, Masellis G, Facchinetti F. L-arginine supplementation in women with chronic hypertension: impact on blood pressure and maternal and neonatal complications. *J Matern Fetal Neonatal Med.* 2010;23 (12):1456–60.
18. Neri I, Mazza V, Galassi MC, Volpe A, Facchinetti F. Effects of L-arginine on utero-placental circulation in growth-retarded fetuses. *Acta Obstet Gynecol Scand.* 1996;75(3):208–12.
19. Winer N, Branger B, Azria E, Tsatsaris V, Philippe HJ, Roze JC, Descamps P, Boog G, Cynober L, Darmaun D. l-arginine treatment for severe vascular fetal intrauterine growth restriction: a randomized double-blind controlled trial. *Clin Nutr.* 2009;28(3):243–8.
20. Sieroszewski P, Suzin J, Karowicz-Bilińska A. Ultrasound evaluation of intrauterine growth restriction therapy by a nitric oxide donor (L-arginine). *J Matern Fetal Neonatal Med.* 2004;15(6):363–6.
21. Singh S, Singh A, Sharma D, Singh A, Narula MK, Bhattacharjee J. Effect of l-arginine on nitric oxide levels in intrauterine growth restriction and its correlation with fetal outcome. *Indian J Clin Biochem.* 2015;30(3):298–304.
22. Rytlewski K, Olszanecki R, Lauterbach R, Grzyb A, Kiec-Wilk B, Dembinska-Kiec A, Basta A. Effects of oral L-arginine on the pulsatility indices of umbilical artery and middle cerebral artery in preterm labor. *Eur J Obstet Gynecol Reprod Biol.* 2008;138(1):23–8.
23. Kiani AK, Bonetti G, Medori MC, Caruso P, Manganotti P, Fioretti F, Nodari S, Connelly ST, Bertelli M. Dietary supplements for improving nitric-oxide synthesis. *J Prev Med Hyg.* 2022 Oct 17;63 (2 Suppl 3):E239-E245. doi: 10.15167/2421-4248/jpmh2022.63.2S3.2766.
24. Gambardella J, Khondkar W, Morelli MB, Wang X, Santulli G, Trimarco V. Arginine and Endothelial Function. *Biomedicines.* 2020 Aug 6;8(8):277. doi: 10.3390/biomedicines8080277.
25. Jeyabalan A, Novak J, Danielson LA, Kerchner LJ, Opett SL, Conrad KP. Essential role for vascular gelatinase activity in relaxin-induced renal vasodilation, hyperfiltration, and reduced myogenic reactivity of small arteries. *Circ Res.* 2003 Dec 12;93 (12):1249-57. doi: 10.1161/01.RES.0000104086.43830.6C.
26. Davison JM, Homuth V, Jeyabalan A, Conrad KP, Karumanchi SA, Quaggin S, Dechend R, Luft FC. New aspects in the pathophysiology of preeclampsia. *J Am Soc Nephrol.* 2004 Sep;15 (9):2440-8. doi: 10.1097/01.ASN.0000135975.90889.60.
27. Castillo-Castrejon, Marisol & Migoya-Graue (2011). The role of L-arginine in human pregnancy. *Agro Food Industry Hi-Tech.* 22. 26-28.
28. Weckman AM, McDonald CR, Baxter JB, Fawzi WW, Conroy AL, Kain KC. Perspective: L-arginine and L-citrulline Supplementation in Pregnancy: A Potential Strategy to Improve Birth Outcomes in Low-Resource Settings. *Adv Nutr.* 2019 Sep 1;10(5):765-777.
29. Noris M, Todeschini M, Cassis P, Pasta F, Cappellini A, Bonazzola S, Macconi D, Maucci R, Porrati F, Benigni A, Picciolo C, Remuzzi G. L-arginine depletion in preeclampsia orients nitric oxide synthase toward oxidant species. *Hypertension.* 2004 Mar;43(3):614-22. doi: 10.1161/01.HYP.0000116220.39793.c9. Epub 2004 Jan 26.
30. Norman JE, Cameron IT. Nitric oxide in the human uterus. *Rev Reprod.* 1996 Jan; 1(1):61-8. doi: 10.1530/ror.0.0010061.

31. Possomato-Vieira JS, Khalil RA. Mechanisms of Endothelial Dysfunction in Hypertensive Pregnancy and Preeclampsia. *Adv Pharmacol.* 2016; 77: 361-431.