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FEMARGIN SACHETS- Helps to prevent pre-eclampsia in high-risk pregnancy

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ABSTRACT

L-Arginine is a semi-essential amino acid involved in numerous areas of human physiology, including production of nitric oxide (NO) – a key messenger molecule involved in vascular regulation, immune activity, and endocrine function. Arginine is also involved in protein production, wound healing, erectile function, and fertility. Arginine is not considered essential because humans can synthesize it de novo from glutamine, glutamate, and proline. However, dietary intake remains the primary determinant of plasma arginine levels. The present paper reviews the role of femargin Sachetsdeveloped by R&D cell of Lactonova Nutripharm Pvt Ltd. Hyderabad for overall successful Pregnancy outcome.

Keywords: Semi-essential amino acid, nitric oxide (NO), L-Arginine, femargin sachets.

INTRODUCTION

Pre-eclampsia is a major cause of maternal mortality and morbidity, preterm birth, perinatal death, and intrauterine growth restriction1. Preeclampsia is when women have high blood pressure and possibly protein in urine during pregnancy or after delivery. Also having low clotting factors (platelets) in blood or indicators of kidney or liver trouble. Preeclampsia generally happens after the 20th week of pregnancy. However, in some cases it occurs earlier, or after delivery. Eclampsia is a severe progression of preeclampsia. With this condition, high blood pressure results in seizures. Like preeclampsia, eclampsia occurs during pregnancy or, rarely, after delivery. Circulating l-arginine is a substrate for nitric oxide synthesis during pregnancy; preliminary data suggest that supplemental l-arginine in the diet may lower the risk of pre-eclampsia during pregnancy by promoting vasodilatation through increased production of nitric oxide3.

What is Preeclampsia

Preeclampsia is when you have high blood pressure and possibly protein in your urine during pregnancy or after delivery. You may also have low clotting factors (platelets) in your blood or indicators of kidney or liver trouble. Preeclampsia generally happens after the 20th week of pregnancy. However, in some cases it occurs earlier, or after delivery. Eclampsia is a severe progression of preeclampsia. With this condition, high blood pressure results in seizures. Like

preeclampsia, eclampsia occurs during pregnancy or, rarely, after delivery.

Causes

- Genetic factors
- blood vessel problems
- Autoimmune disorders
- Being pregnant with multiple fetuses
- Being over the age of 35
- Being in your early teens
- Being pregnant for the first time
- Being obese
- Having a history of high blood pressure
- Having a history of diabetes
- Having a history of a kidney disorder

Symptoms of Preeclampsia

- Persistent headache
- Abnormal swelling in your hands and face
- Sudden weight gain
- Changes in your vision
- Pain in the right upper abdomen

During a physical exam, your doctor may find that your blood pressure is 140/90 mm Hg or higher. Urine and blood tests can also show protein in your urine, abnormal liver enzymes, and low platelet levels.

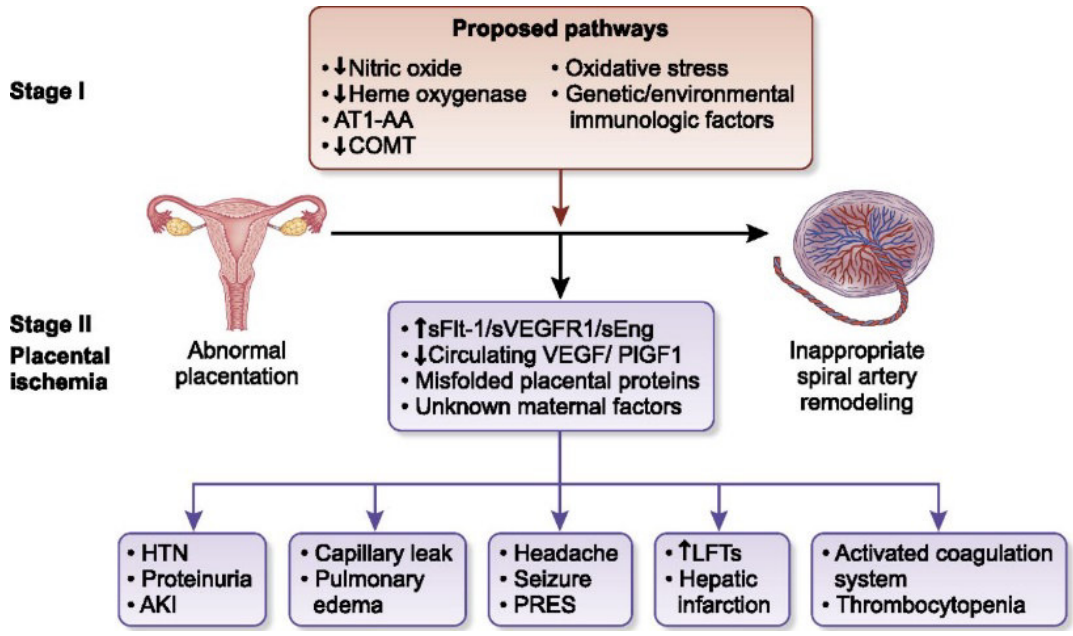
Complications of preeclampsia

Preeclampsia is a very serious condition. It can be life-threatening for both mother and child if left untreated. Other complications can include:

- Bleeding problems due to low platelet levels
- Placental abruption (breaking away of the placenta from the uterine wall)
- Damage to the liver
- Kidney failure
- Pulmonary edema
- Complications for the baby can also occur if they're born too early due to efforts to resolve preeclampsia.

Pathophysiology of Preeclampsia

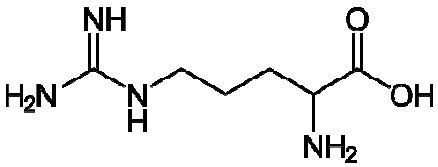
During implantation, placental trophoblasts invade the uterus and induce the spiral arteries to remodel, while obliterating the tunica media of the myometrial spiral arteries; this allows the arteries to accommodate increased blood flow independent of maternal vasomotor changes to nourish the developing fetus. Part of this remodeling requires that the trophoblasts adopt an endothelial phenotype and its various adhesion molecules. If this remodeling is impaired, the placenta is likely to be deprived of oxygen, which leads to a state of relative ischemia and an increase in oxidative stress during states of intermittent perfusion. This abnormal spiral artery remodeling was seen and described over five decades ago in pregnant women who were hypertensive. It has since been shown to be the central pathogenic factor in pregnancies complicated by intrauterine growth restriction, gestational hypertension, and preeclampsia. One limitation to this theory, hence, is that these findings are not specific to preeclampsia and may explain the difference in manifestations between placental preeclampsia and maternal preeclampsia.



Objective: This study aimed to estimate the effectiveness of L-arginine for preventing preeclampsia in high-risk pregnancy

L-Arginine Profile

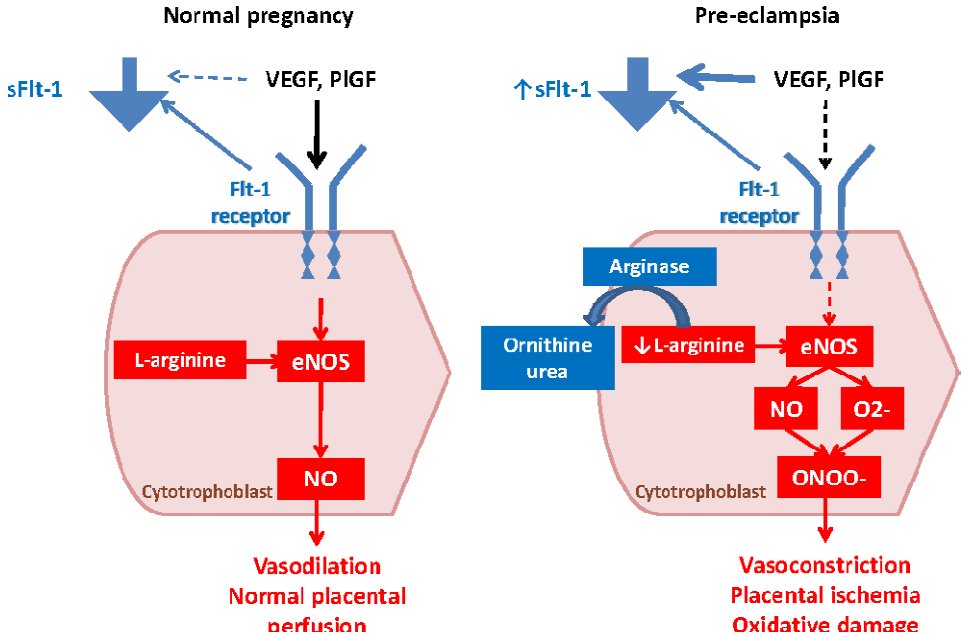
Arginine, also known as l-arginine (symbol Arg or R) is an α-amino acid that is used in the biosynthesis of proteins.L-arginine is converted in the body into a chemical called nitric oxide. Nitric oxide causes blood vessels to open wider for improved blood flow. L-arginine also stimulates the release of growth hormone, insulin, and other substances in the body5.



Arginine plays an important role in cell division, wound healing, removing ammonia from the body, immune function, and the release of hormones. It is a precursor for the synthesis of nitric oxide (NO), making it important in the regulation of blood pressure

Mechanism of Action

Normal pregnancy leads to profound maternal hemodynamic changes, including increased blood volume and vasodilatation. Several vasodilator mediators are implicated, including prostaglandins, carbon monoxide and nitric oxide (NO). Pre-eclampsia (PE) affects 3–10 % of pregnancies and is associated with increased maternal and perinatal morbidity and mortality. Around 8 % of pregnancies are complicated by intra-uterine growth restriction (IUGR), also associated with increased perinatal mortality and morbidity. PE and IUGR often co-exist. NO is essential for the formation of healthy endothelium, and in pregnancy promotes endovascular invasion by the cytotrophoblast. As interstitial trophoblasts invade the maternal spiral arteries in the uterine wall, they produce NO which acts on artery walls to create a low-resistance, high-caliber uteroplacental unit. If this process fails, the result is a high-resistance uteroplacental circulation. The hypoperfused and ischemic placenta releases antiangiogenic factors which mediate generalized endothelial dysfunction, oxidative stress and inflammatory mediators. It is these mediators that are implicated in both the fetal and maternal syndromes of PE and IUGR. Studies of NO and its modulator amino acids, including the precursors arginine and homoarginine and the NO synthesis inhibitor asymmetric dimethylarginine (ADMA), have investigated their role in both normal and pathological pregnancies. Many studies of PE (and, to a lesser extent, IUGR) have investigated maternal circulating ADMA, arginine and homoarginine levels. This article reviews and discusses the role of these amino acids in pregnancy. The results have shed some light on their role in these pathologies, but some of the findings have been conflicting and more research is needed. 3



Literature Review:

HeldayantiSirenden, et al., (2019): **Objective:** The purpose of this study was to compare serum levels of l-arginine in normal pregnant women, severe preeclampsia, and severe preeclampsia with complications.**Methods:** It was an observational study with a cross-sectional design, 88 third trimester of pregnancy became the sample which consisted of 46 normal pregnant women, 30 severe preeclampsia, and 12 severe preeclampsia with complication. This study conducted in four hospitals in the city of Makassar: Dr. WahidinSudirohusodo hospital, education Hospital of Hasanuddin University, Fatimah, and Sitti Khadijah 1 Mothers and Children hospital. Serum blood samples were taken from the antecubital venous blood Assessment of serum l-arginine levels was carried out using the Human l-Arginine Assay Kit.**Results:** There were significant mean differences between normal, severe preeclampsia and severe preeclampsia with complications. The lowest serum levels of l-arginine were severe preeclampsia with complications (28.33ng/mL), then severe preeclampsia group (34.66ng/mL), and the highest was normal pregnant woman (60.91ng/mL).**Conclusion:** Severe preeclampsia with complications had the lowest l-arginine level. Role l-arginine level should be considered in the prevention and treatment of severe preeclampsia.

WorlanyoTashie, et al., (2020): **Background:** Preeclampsia is a major cause of maternal and neonatal morbidity and mortality in sub-Saharan Africa. Evidence indicates that endothelial dysfunction is central to the pathogenesis of preeclampsia. This study assessed the level of the components of the arginine-nitric oxide pathway to evaluate endothelial dysfunction in normotensive pregnancies and pregnancies complicated with preeclampsia.**Methods**: This case-control study was conducted among pregnant women who visited Comboni Hospital from January 2017 to May 2018. A total of 180 pregnant women comprising 88 preeclamptic women (PE) and 92 healthy normotensive pregnant women (NP) were recruited. Sociodemographic, clinical, and obstetric data were obtained using validated questionnaires. Blood pressure and anthropometrics were measured, and blood samples were collected for the estimation of nitric oxide (NO·), L-arginine, asymmetric dimethylarginine (ADMA), and 3-nitrotyrosine using an enzyme-linked immunosorbent assay technique.**Results**: The mean NO· ($p = 0.010$) and L-arginine/ADMA ratio ($p < 0.0001$) was significantly lower in PE compared to NP while mean L-arginine ($p = 0.034$), ADMA ($p < 0.0001$), and 3-nitrotyrosine ($p < 0.0001$) were significantly higher in PE than NP. ADMA showed a significant positive association with systolic blood pressure ($\beta = 0.454$, $p = 0.036$) in severe PE. Women with PE had significant intrauterine growth restriction ($p < 0.0001$) and low birth weight infants ($p < 0.0001$) when compared to NP.**Conclusion**: Preeclampsia is associated with reduced NO· bioavailability, L-arginine/ADMA ratio, and elevated levels of ADMA and 3-nitrotyrosine. Measurements of the levels of these parameters can help in the early prediction of endothelial dysfunction in

preeclampsia. Exogenous therapeutic supplementation with L-arginine during pregnancy to increase the L-arginine/ADMA ratio should be considered to improve endothelial function in preeclampsia and pregnant women at risk of developing preeclampsia.

E ECamarena Pulido, et al., (2016):**Objective**: This study aimed to estimate the effectiveness of L-arginine for preventing preeclampsia in high-risk pregnancy.**Methods**: We performed a randomized, double-blind, placebo-controlled, clinical trial in patients with high-risk factors for preeclampsia. Fifty subjects received L-arginine, beginning from the 20th week of gestation. An additional 50 patients received homologated placebo.**Results**: The placebo group had a higher number of cases of preeclampsia (11/47) compared with the L-arginine group (3/49, P = 0.01). Birth weight was higher in the L-arginine group and there was a smaller number of preterm births (P = 0.03).**Conclusion**: L-arginine is effective for preventing preeclampsia.

DHA in Femargin

DHA (Docosahexaenoic acid, an omega-3 long chain polyunsaturated fatty acid) is found in every cell in our bodies. It is critical for brain, eye and central nervous system development and functioning. During pregnancy, developing babies rely on their mothers to get needed DHA. Since DHA is derived from the foods we eat, the content of DHA in a mother's diet determines the amount of DHA passed on to her developing baby. Unfortunately, the majority of pregnant womens fail to get the recommended amount of DHA in their diets and DHA is not found in most prenatal vitamins.The DHA intake from an average diet during pregnancy is only 80 mg DHA per day, based on a paper in the Journal of Nutrition, 2005 (Denomme et al. 135: 206-211).

A minimum 300 mg DHA daily is suggested, based on a 1999 NIH body of experts recommending needed levels to support fetal brain development and visual acuity benefits.

- A 2003 study published in the journal *Pediatrics* showed children whose mothers took a DHA supplement during pregnancy scored higher on intelligence tests at four years of age than children of mothers not taking DHA supplements.
- A 2004 study published in *Child Development* found that babies whose mothers had high blood levels of DHA at delivery had advanced attention spans into their second year of life. During the first six months of life these infants were two months ahead of babies whose mothers had lower DHA levels.
- Other research studies suggest breastfed babies have IQs of six to 10 points higher than formula-fed babies. Medical and nutritional experts attribute this difference to the DHA infants receive while nursing. *(Obstetrics & Gynecology, 2003)*.
- In a trial of women receiving DHA supplementation during the third trimester, the average length of gestation increased six days *(Obstetrics & Gynecology, 2003)*.
- Research has found low levels of DHA in mother's milk and in the red blood cells of women with postpartum depression. *(Journal of Affective Disorders, 2002)*. Some scientists believe increasing levels of maternal DHA may reduce the risk of postpartum depression.

The Benefits of DHA for Adult Health

DHA is important for brain, eye and heart health throughout life. In fact, a growing body of research continues to support the role that DHA plays throughout adulthood including Brain health. DHA is necessary for the development and maintenance of optimal structure and function of nerve cells in the brain and eyes.DHA plays a significant role in the maintenance of normal neurological function.A recently published large, randomized, placebo-controlled nutritional study published in *Journal of the Alzheimer's Association* has demonstrated the benefits of algal DHA in improving memory in older adults.

Heart Health

The American Heart Association (AHA) has established the following guide containing recommended intakes for omega-3 fatty acids.

Population	Recommendation
Patients without documented coronary heart disease (CHD)	Eat a variety of (preferably fatty) fish at least twice a week. Include oils and foods rich in alpha-linolenic acid (flaxseed, canola and soybean oils; flaxseed and walnuts).

Patients with documented CHD	Consume about 1 g of DHA per day.
Patients who need to lower triglycerides	2 to 4 grams of DHA per day provided as capsules under a physician's care.

Source: American Heart Association

In 2005, the USDA Dietary Guidelines recognized an association between the omega-3 fats and good cardiovascular health.

Proanthocyanidin in Femargin

Proanthocyanidin (PAorPAC), also known asprocyanidin, oligomeric proanthocyanidin (OPC), leukocyanidin, leucoanthocyanin and condensed tannins, is a class of flavanols. Proanthocyanidins are essentially polymer chains of flavonoids such as catechins.

Studies show that proanthocyanidins antioxidant capabilities are 20 times more powerful than vitamin C and 50 times more potent than vitamin E .OPCs may help protect against the effects of internal and environmental stresses as well as supporting normal body metabolic processes. The effects may include depressing blood fat, emolliating blood vessels, lowering blood pressure, preventing blood vessel scleroses, dropping blood viscidity and preventing thrombus formation. Proanthocyanidins suppress production of a protein endothelin-1 that constricts blood vessels.

Methylcobolamin in femargin

Methylcobalamin is one of the two coenzyme forms of vitamin B12 (the other being adenosylcobalamin). It is a cofactor in the enzyme methionine synthase which functions to transfer methyl groups for the regeneration of methionine from homocysteine.

Clinical Applications

Homocysteinemia: Elevated levels of homocysteine can be a metabolic indication of decreasedlevels of the methylcobalamin form of vitamin B12. Therefore, it is not surprising that elevated homocysteine levels were reduced from a mean value of 14.7 to 10.2 nmol/ml following parenteral treatment with methylcobalamin.

Dosage

The dosage for clinical effect is 1500-6000 mcg per day. No significant therapeutic advantageappears to occur from dosages exceeding this maximum dose. Methylcobalamin has been administeredorally, intramuscularly, and intravenously; however, positive clinical results have been reported irrespective of the method of administration. It is not clear whether any therapeutic advantage is gainedfrom the non-oral methods of administration.

- Safety, Toxicity, and Side Effects
- Methylcobalamin has excellent tolerability and no known toxicity.

Folic acid in femargin

Folic acid (also known as vitamin B_9, vitamin $B_c$or folacin) and folate (the naturally occurring form), as well as pteroyl-L-glutamic acid, pteroyl-L-glutamate, and pteroylmonoglutamic acid are forms of the water-soluble vitamin B_9. Folic acid is itself not biologically active, but its biological importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in the liver. Adequate folate intake during the periconception period, the time right before and just after a woman becomes pregnant, helps protect against a number of congenital malformations, including neural tube defects (which are the most notable birth defects that occur from folate deficiency). Neural tube defects produce malformations of the spine, skull, and brain including spina bifida and anencephaly. The risk of neural tube defects is significantly reduced when supplemental folic acid is consumed in addition to a healthy diet prior to and during the first month following conception. Supplementation with folic acid has also been shown to reduce the risk of congenital heart defects,limb defects, and urinary tract anomalies. Folate deficiency during pregnancy may also increase the risk of preterm delivery, infant low birth weight and fetal growth retardation, as well as increasing homocysteine level in the blood, which may lead to spontaneous abortion and pregnancy complications, such as placental abruption and pre-eclampsia. The RDA for folate equivalents for pregnant women is 600–800 micrograms, twice the normal RDA of 400 micrograms for women who are not pregnant.

Fertility

Folate is necessary for fertility in both men and women. In men, it contributes to spermatogenesis. In women, on the other hand, it contributes to oocyte maturation, implantation, placentation, in

addition to the general effects of folic acid and pregnancy. Therefore, it is necessary to receive sufficient amounts through the diet to avoid subfertility.

Vitamin B6 in Femargin

Vitamin B_6 is a water-soluble vitamin and is part of thevitamin B complex group. Several forms of the vitamin are known, but pyridoxal phosphate (PLP) is the active form and is a cofactor in many reactions of amino acidmetabolism, including transamination, deamination, and decarboxylation. PLP also is necessary for the enzymatic reaction governing the release of glucose from glycogen.Vitamin B_6 has been used to treat nausea and vomiting in early pregnancy for decades. The intake of vitamin B_6, from either diet or supplements, could cut the risk of Parkinson's disease by half.

Vitamin B_6 has long been publicized as a cure for premenstrual syndrome (PMS). Study results conflict as to which symptoms are eased, but most of the studies confirm that women who take B_6supplements have reductions in bloating, breast pain, and premenstrual acne flare, a condition in which pimples break out about a week before a woman's period begins. There is strong evidence that pyridoxine supplementation, starting ten days before the menstrual period, prevents most pimples from forming. This effect is due to the vitamin's role in hormone and prostaglandin regulation. Skin blemishes are typically caused by a hormone imbalance, which vitamin B_6 helps to regulate. It is also suggested that ingestion of vitamin B_6 can alleviate some of the many symptoms of an alcoholic hangover and morning sickness from pregnancy. This might be due to B_6's mild diuretic effect.

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