DOI: 10.21088/ijmfnm.2455.8621.12225.1

Indian Journal of Maternal-Fetal & Neonatal Medicine
Volume 12 Number 2 July - December 2025

REVIEW ARTICLE

Role of Arginine in IUGR: Review

Alka Bhaurao Patil[1], Harshali Rajiv Tuknait[2], Tanvi Arun Punj[3], Sanskruti Radheshyam Rathod[4]

HOW TO CITE THIS ARTICLE:

Alka Bhaurao Patil, Harshali Rajiv Tuknait, Tanvi Arun Punj, *et al.* Role of Arginine in IUGR: Review. Indian Journal of Maternal-Fetal & Neonatal Medicine 2025; 12(2): 39-43.

ABSTRACT

L-arginine is a semi-essential amino acid that plays a critical role in various physiological processes, such as protein synthesis, wound healing, immune function, and cardiovascular regulation. The available data support the hypothesis that L-arginine or L-citrulline supplementation would be suitable for implementation in resource-constrained settings and will enhance placental vascular development and improve birth outcomes.

Oligohydromnios and IUGR are pregnancy complications affecting 7 percent of pregnancies.

This article explores their causes, focusing on amino acid transfer and placental function. The paradoxical effects of maternal protein supplementation are discussed, alongside the therapeutic potential of L-arginine and L-citrulline in improving fetal outcomes.

KEYWORDS:

• Oligohydromnios • IUGR • Nitrous Oxide • Vasodilation • Arginine • Amnioinfusion

AUTHOR'S AFFILIATION:

[1] Professor, Department of Obstetrics and Gynecology, ACPM Medical College, Dhule, Maharashtra, India.
[2] Junior Resident, Department of Obstetrics and Gynecology, ACPM Medical College, Dhule, Maharashtra, India.
[3] Junior Resident, Department of Obstetrics and Gynecology, ACPM Medical College, Dhule, Maharashtra, India.
[4] Junior Resident, Department of Obstetrics and Gynecology, ACPM Medical College, Dhule, Maharashtra, India.

CORRESPONDING AUTHOR:

Harshali Rajiv Tuknait, Junior Resident, Department of Obstetrics and Gynecology, ACPM Medical College, Dhule, Maharashtra, India.

E-mail: alkabpatil12@gmail.com

➢ **Received:** 16-06-2025 ➢ **Accepted:** 22-10-2025

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-Commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the Red Flower Publication and Open Access pages (https://rfppl.co.in)

INTRODUCTION

Seven percent of pregnancies are complicated by both quantitative and qualitative changes in the amniotic fluid. A single deepest pocket (SDP) of less than 2 cm, an amniotic fluid index (AFI) measurement of less than 5 cm, or less than the fifth centile for gestational age are the three ways to identify oligohydramnios, an obstetric issue.[1] Most cases of oligohydramnios are caused by premature membrane rupture; other reasons include chromosome abnormalities, drugs like NSAIDs, and fetal abnormalities such urinary system malformations.[2] Often, premature delivery and fetal development limitation are associated with mild oligohydramnios. Pulmonary hypoplasia, which can develop at rates ranging from 13 to 21%, has a major impact on neonatal survival in some oligohydramnios cases. The neonatal prognosis, which can occasionally be fatal in situations of severe oligohydramnios, may be improved by amnioinfusion, which restores an amniotic fluid volume sufficient to lessen the negative environmental impacts and, if feasible, prolong pregnancy.[3]

Reduced placental blood flow in industrialized countries and maternal undernutrition in underdeveloped countries are the two most frequent causes of IUGR. Nitric oxide (NO), a free radical vital to human physiology, aids in preserving the equilibrium of a number of functions. This chemical may play a significant role in the development of preeclampsia and intrauterine growth restriction; it is crucial for the physiology of labor and cervical ripening in obstetrics; and because it relaxes smooth muscles.

Additionally, arginine activates the mechanistic (mammalian) target of rapamycin cell signaling pathway, which promotes protein synthesis in the fetus, uterus, and placenta. Oral arginine supplementation has also been demonstrated to enhance fetal growth in mothers with IUGR. When everything is said and done, dietary arginine supplementation that enhances placental and uterine growth and function provides a workable means of boosting fetal and embryonic growth and survival.[4]

CAUSESOFFETALGROWTHRESTRICTION

Fetal growth restriction, or IUGR, can be caused by fetal, maternal, and placental causes.

Fetal causes include

- chromosome abnormalities
- numerous pregnancies
- fetal diseases
- fetal morphological abnormalities

Maternal Causes include

- nutritional deficits, especially in the areas of vitamin C and vitamin E.
- maternal diseases, especially chronic conditions like tuberculosis and malaria. Diabetes mellitus, heart disease, chronic lung disease, hypertension, and anemia are among the mother's medical conditions. Oxidative stress is also found to be the cause of IUGR.[5]

The severity of IUGR correlates with the severity of decreased amino acid transfer. Decreased placental transfer of essential amino acids in cases of placental insufficiency might account for a lack of improved fetal growth.[6]

Maternal Amino Acid supplementation for IUGR

Excessive protein supplementation in the mother's diet decreases the perinatal mortality rate and the risk of preterm and SGA birth. The development of the placenta, the growth of the fetus, and the expansion of maternal tissues during pregnancy all depend on amino acids for protein accretion. One could argue that these several tissues are "competitors" for the same supply of amino acids, which is considered a "limited resource." When intrauterine growth restriction (IUGR) is present, the fetus is the "loser" in this conflict. Given this perspective, it would seem reasonable to assume that providing additional dietary protein to pregnant women will improve fetal growth, particularly for those who are at risk of giving birth to a child with IUGR. Protein malnutrition is more likely to result in reduced fetal growth than a pure protein deficiency due to additional complicating factors such vitamin shortages and the psychosocial environment. Conversely, there is a clear link between maternal calorie deficit and IUGR.[7]

Protein supplementation to Prevent or Treat IUGR

Human tests have shown that a higher maternal calorie intake without high dietary protein levels frequently results in

an improvement in fetal weight (albeit not necessarily lean mass) without creating noticeable negative effects. When more dietary protein is needed to supply this energy, poor fetal weight growth and adverse perinatal outcomes occur.[8] Supplements high in dietary protein may therefore be detrimental to the growing embryo. Trials of nutritional interventions related to pregnancy are challenging to assess and often do not provide a specific mechanistic interpretation of the observed outcomes. Normal pregnancies and high-risk pregnancies, such as IUGR, were often included due to different patient inclusion criteria.[9]

In addition to energy and protein, supplements differed from one trial to the next in terms of their fat, vitamin, and mineral makeup. Throughout the trials, there were variations in the supplement's protein source (and thus its amino acid composition) and when it was introduced during pregnancy. Last but not least, if the mother consumed fewer nutrients from other sources, either family members may have received the supplement or long-term therapeutic nutritional supplements could have replaced the nutrients in the ordinary diet. These studies preferred to concentrate on this cohort because to their greater incidence of IUGR, even if individuals with limited means are more likely to encounter these latter two problems.[10]

Probable Mechanism explaining fetal outcome with Protein intake

The mechanisms responsible for adverse fetal outcomes as a result of maternal high protein supplementation are unknown. Elucidation of these mechanisms has the potential to allow for the rational design of interventions which can safely promote intrauterine growth, decrease the incidence of indicated preterm delivery for IUGR, and prevent short and long term complications of this disease.[11] Three potential mechanisms for fetal amino acid toxicity that have been explored in animal models of normal human fetal growth and metabolism and animal models of IUGR: 1) competitive inhibition of transport among essential amino acids across the placenta, 2) mismatch of increased fetal amino acid supply with persistently low fetal anabolic hormone concentrations, and 3) preferential utilization of increased fetal amino acids for oxidative metabolism rather than protein synthesis and accretion. It should be emphasized that these potential mechanisms are not mutually exclusive and most likely interact to explain the observations made in the human clinical trials.[12]

L-Arginine and uteroplacental insufficiency

A versatile amino acid, L-arginine serves a variety of biological purposes. It functions as a precursor to both proteins and nitric oxide, which is known to be a calming factor derived from the endothelium.[13] Through nitric oxide-mediated artery dilatation, L-arginine enhances uteroplacental blood flow, which boosts the fetus's access to nutrients and promotes growth. L-arginine was found to be useful in cases of intrauterine growth restriction in a study conducted by Ropacka *et al.* Similarly, the use of L-arginine was linked to a lower rate of surgical births and higher Apgar scores at 1 and 5 minutes in another trial conducted by Dera *et al.* in patients who were growth restricted and pre-eclamptic.

In humans and the majority of other mammals (such as pigs, lambs, and rats), arginine (Arg) is produced through the intestinal-renal axis from glutamine, glutamate, and proline. Arginase, nitric-oxide synthase, arg:glycine amidinotransferase, and arg decarboxylase are the enzymes that start the many processes that lead to arg breakdown. Each of the compounds produced by these pathways nitric oxide, polyamines, proline, glutamate, creatine, and agmatine has a significant biological impact. The detoxification of ammonia, a highly toxic chemical for the central nervous system, also requires arg. There is strong evidence that Arg controls the metabolism of energy substrates between organs and the operation of several organs.[14]

ROLE OF PLACENTAL AMINO ACIDS IN IUGR

The placenta is an essential organ for fetal development because it serves as a barrier between the mother and the fetus, controlling the exchange of nutrients, gasses, water, ions, and waste products between the two. In addition, it can perform metabolic, immunologic, and endocrine functions.[15]

The hemochorial placenta in humans consists of the endothelium of the fetal capillaries, the connective tissue of the villous tree, the cytotrophoblast (a second

layer of mononucleated trophoblasts that discontinues as pregnancy goes on), and the syncytiotrophoblast (a continuous, uninterrupted, multinucleated surface that covers the villous tree). For the best fetal-maternal exchange, the placenta develops and matures its villi in terms of weight, volume, and villi type during pregnancy.

Amino acids, which are also vital building blocks for fetal growth and development as well as the synthesis of proteins, purine and pyrimidine nucleotides, neurotransmitters, and other chemicals, are among the primary nutrients for fetal life during pregnancy. The complex process of amino acid transport throughout the placenta is mediated by transporters present on the microvillous plasma membrane and the basement membrane of syncytiotrophoblasts.[16]

The concentration of most amino acids in the umbilical artery and vein of IUGR fetuses is significantly lower than that of newborns born normally. Small for gestational age fetuses have especially low levels of the essential branched chain amino acids valine, leucine, and isoleucine. Furthermore, the maternal content of the majority of essential amino acids is substantially lower in pregnancies with appropriate for gestational age (AGA) fetuses than in pregnancies with IUGR fetuses. A maladaptation to pregnancy with insufficient hormone production is probably the cause of this; this finding, together with the fact that intrauterine growth restriction lowers the quantities of fetal amino acids, leads to much smaller fetal-maternal disparities in these pregnancies.[17]

L- Citrulline as a substitute for L- Arginine

L-citrulline, a nonessential L-amino acid (NEAA), is produced endogenously in the small intestine by the conversion of proline and glutamine. Proteins do not contain it. Endogenous or exogenous L-citrulline appears in the peripheral circulation rather than entering the liver for absorption like L-arginine does. L-arginine is released into the bloodstream after being converted from L-citrulline by the kidney. Because oral L-citrulline treatment increases systemic L-arginine availability, it is comparable to intravenous L-arginine infusion. L-citrulline supplementation has been proposed as an alternative to L-arginine supplementation to improve vascular function or restore NO production. Furthermore, animal studies suggest that L-citrulline may have an independent protein anabolic effect in situations associated with undernutrition. L-citrulline was more effective than L-arginine or an isonitrogenous NEAA mix at improving nitrogen balance in older, enterectomized, and malnourished rats. L-citrulline also enhanced muscle protein synthesis in human volunteers who were on dietary protein restriction.[18]

CONCLUSION

Fetal protein synthesis depends on the supply of amino acids, and previous research indicates that IUGR is linked to a decrease in the transfer of amino acids from mother to fetus. Transport systems working against a concentration gradient are involved in this type of transfer. The fetal/maternal isotope enrichment ratio for leucine and phenylalanine was reduced after an infusion of labeled amino acids in pregnant women with IUGR, and the placenta of human pregnancies with IUGR exhibits decreased expression of transport system A.

REFERENCES

1. Volante E, Gramellini D, Moretti S, Kaihura C, Bevilacqua G. Alteration of the amniotic fluid and neonatal outcome. Acta Biomed. 2004;75 Suppl 1:71-5. PMID: 15301296.
2. Bourdon A, Hannigsberg J, Misbert E, Tran TN, Amarger V, Ferchaud-Roucher V, Winer N, Darmaun D. Maternal supplementation with citrulline or arginine during gestation impacts fetal amino acid availability in a model of intrauterine growth restriction (IUGR). Clin Nutr. 2020 Dec;39(12):3736-3743. doi: 10.1016/j.clnu.2020.03.036. Epub 2020 Apr 10. PMID: 32336525.
3. Wu G, Bazer FW, Satterfield MC, Li X, Wang X, Johnson GA, Burghardt RC, Dai Z, Wang J, Wu Z. Impacts of arginine nutrition on embryonic and fetal development in mammals. Amino Acids. 2013 Aug;45(2):241-56. doi: 10.1007/s00726-013-1515-z. Epub 2013 Jun 4. PMID: 23732998.
4. Ji Eun Song, Seok Joo Park & Keun Young Lee. (2016) Amniotic fluid total antioxidant capacity and nitric oxide in emergency cerclage. The Journal of Maternal-Fetal & Neonatal Medicine 29:20, pages 3364-3367.

5. Chen J, Gong X, Chen P, Luo K, Zhang X. Effect of L-arginine and sildenafil citrate on intrauterine growth restriction fetuses: a meta-analysis. BMC Pregnancy Childbirth. 2016 Aug 16;16:225. doi: 10.1186/s12884-016-1009-6. PMID: 27528012; PMCID: PMC4986189.

6. Kitsiou-Tzeli S, Tzetis M. Maternal epigenetics and fetal and neonatal growth. Curr Opin Endocrinol Diabetes Obes. 2017 Feb;24(1):43-46. doi: 10.1097/MED.0000000000000305. PMID: 27898587.

7. Wu G, Morris SM Jr. Arginine metabolism: nitric oxide and beyond. Biochem J. 1998 Nov 15;336 (Pt 1)(Pt 1):1-17. doi: 10.1042/bj3360001. PMID: 9806879; PMCID: PMC1219836.

8. Nabi F, Arain MA, Bhutto ZA, Shah QA, Bangulzai N, Ujjan NA, Fazlani SA. Effect of early feeding of L-arginine and L-threonine on hatchability and post-hatch performance of broiler chicken. Trop Anim Health Prod. 2022 Nov 12;54(6):380. doi: 10.1007/s11250-022-03378-2. PMID: 36370219.

9. Sreedharan, R., & Jajoo, S. (2016). Effect of L-arginine on amniotic fluid index in oligohydramnios. International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 2(1), 80–82. Retrieved from https://www.ijrcog.org/index.php/ijrcog/article/view/183

10. Paolini CL, Meschia G, Fennessey PV, *et al.* An in vivo study of ovine placental transport of essential amino acids. American Journal of Physiology: Endocrinology and Metabolism. 2001;280(1):E31–E39. doi: 10.1152/ajpendo.2001.280.1.E31

11. Philipps AF, Holzman IR, Teng C, Battaglia FC. Tissue concentrations of free amino acids in term human placentas. American Journal of Obstetrics and Gynecology. 1978;131(8):881–887. doi: 10.1016/s0002-9378(16)33136-2

12. Wu G, Bazer FW, Cudd TA, Jobgen WS, Kim SW, Lassala A, *et al.* Pharmacokinetics and safety of arginine supplementation in animals. J Nutr. 2007;137:1673S–80.

13. 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;6:202–7. doi: 10.1016/S1071-5576(99)00017-9.

14. Casanello P, Sobrevia L. Intrauterine growth retardation is associated with reduced activity and expression of the cationic amino acid transport systems yþ/hCAT-1 and yþ/hCAT-2B and lower activity of nitric oxide synthase in human umbilical vein endothelial cells. Circ Res. 2002;91:127–34. doi: 10.1161/01.RES.0000027813.55750.E7.

15. Dera A, Ropacka M, Kowalska J, Markwitz W, Nycz P, Breborowicz GH. The effect of L-arginine treatment on the neonatal outcome from pregnancies complicated by intrauterine growth restriction and gestational hypertension. Arch Perinat Med. 2007;13:35–9.

16. Benedtto C, Marozio L, Neri I, Giarola M, Vlope A, Facchinetti F. Increased l-citrulline/l-arginine plasma ratio in severe preeclampsia. Obstet Gynecol. 2000;96:395–9. doi: 10.1016/s0029-7844(00)00939-x

17. Neri I, Mazza V, Galassi MC, Volpe A, Facchinetti F. Effects of L-arginine on uteroplacental circulation in growth-retarded fetuses. Acta Obstet Gynecol Scand. 1996;75:208–12. doi: 10.3109/00016349609047088.

18. Aurélie Bourdon, Patricia Parnet, Christel Nowak, Nhat-Thang Tran, Norbert Winer, Dominique Darmaun, L-Citrulline Supplementation Enhances Fetal Growth and Protein Synthesis in Rats with Intrauterine Growth Restriction123,The Journal of Nutrition,Volume 146, Issue 3,2016, Pages 532-541.