

REVIEW ARTICLE

Role of Arginine in IUGR: Review

Alka Bhaurao Patil¹, Harshali Rajiv Tuknait²,
Tanvi Arun Punj³, Sanskruti Radheshyam Rathod⁴

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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

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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 as 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

CAUSES OF FETAL GROWTH RESTRICTION

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 as 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