

## L – Arginine Supplementation in Intrauterine Growth Retardation

R. Mittal<sup>1\*</sup>, K. Satwant<sup>2</sup> and N. Mittal<sup>1</sup>

<sup>1</sup>Department of Pharmacology, Pt B D Sharma Postgraduate Institute of Medical Sciences, Rohtak - 124001, Haryana, India.

<sup>2</sup>Department of Obstetrics & Gynaecology, M M Medical College, Kumarhatti, Solan, Himachal Pradesh, India.

### ABSTRACT

Intrauterine growth retardation (IUGR), defined as estimated birth weight below 10<sup>th</sup> percentile for gestational age, is very common in a developing economy like India. Various environmental and nutritional factors play a causative role in this condition. IUGR primarily occurs due to placental insufficiency because of placental ischemia. The deficiency of L-arginine has been postulated to cause IUGR by reducing nitric oxide synthesis leading consequently to impaired utero-placental perfusion. Numerous animal and human studies have recommended L-arginine supplementation in pregnancy to facilitate fetal growth. But there are some contradicting reports also. Hence, future well planned studies need to be conducted to improve knowledge on the role of this semi-essential amino acid in modulating fetal growth.

**Key words:** L-arginine, Intra- uterine growth retardation, Pregnancy, Placental perfusion

### INTRODUCTION

Pregnancy is a harmonious relation between a mother and fetus. Mother provides for the need of the developing fetus, while at the same time the fetus lends support to the mother as she experiences a myriad of physiological changes. The growth of a normal fetus is controlled by a delicate balance of genetic, placental and maternal factors i.e. the genetic drive for the growth, environmental factors in uterus and the supply of growth substrates to the fetus. Any perturbations in this balance may result in growth restriction or accelerated growth. Among intrauterine environmental factors, nutrition plays the most decisive role in influencing placental and fetal growth.<sup>1</sup> It should be noted that the supply of substrate to the fetus is regulated by maternal - placental factor. The prevailing view in embryology is that a fetus has an inherent growth potential and under normal circumstances it will develop into a healthy appropriately sized newborn.<sup>2</sup> However, if there is an imbalance in one or more of these critical growth and development factors, the baby may fail to attain appropriate size & weight.

### DETERMINANTS OF INTRAUTERINE GROWTH RETARDATION

The most widely used definition of intrauterine growth retardation (IUGR) is a fetus whose estimated weight is below the 10<sup>th</sup> percentile for its gestational age.<sup>3</sup> Infants born with IUGR are exposed to a number of pre-morbid conditions like hypertension, diabetes and

coronary artery diseases in adult life.<sup>4,5</sup> IUGR primarily occurs due to placental insufficiency because of placental ischemia<sup>6</sup>, which is caused by imbalance between vasopressors & vasodilators. Vasopressors include thromboxanes (TXA<sub>2</sub>), angiotensin II and endothelin 1 whereas prostacyclins (PGI<sub>2</sub>) and nitric oxide<sup>7</sup> act as vasodilators. Nitric oxide (NO) is synthesized in the vascular endothelium and syncytiotrophoblast from L – arginine. NO significantly relaxes vascular smooth muscle, inhibits platelet aggregation, prevents intravillous thrombosis and thus increases fetal blood supply by improving the uteroplacental circulation.<sup>8,9</sup> Impaired arginine transport into endothelial cells was observed in the umbilical endothelium from IUGR infants in a clinical study.<sup>10</sup>

### ROLE OF L-ARGININE IN PREGNANCY AND FETAL GROWTH

L arginine is a semi essential amino acid acting as a substrate for synthesis of NO.<sup>11</sup> NO has a diverse role in obstetrics as it plays a vital role in labour, cervical ripening, preeclampsia and intrauterine growth restriction.<sup>12</sup> L-Arginine is also reported to improve growth hormone releasing hormone secretion, and as a consequence increase in plasmatic growth hormone influencing somatic growth.<sup>13</sup> It is also suggested that it may play a significant role in fetal growth, by stimulating insulin secretion and as a precursor for both polyamine synthesis and NO production.<sup>14</sup> Thus decreases in nitric acid dependent vasodilatation and excess formation of

reactive oxygen species could explain poor placental perfusion.

### MOLECULAR BASIS OF L-ARGININE DEFICIENCY IN IUGR

Morris et al (2004) reported that gene expression and protein tissue content of arginase II (enzyme that degrades arginine to ornithine) were found to be higher in pre-eclamptic villi than in normotensive pregnancy.<sup>15</sup> Therefore a lower than normal L arginine concentration caused by arginase II over expression redirects endothelial isoform of nitric oxide synthase towards peroxynitrite. The interaction of NO and superoxide produces peroxynitrate anion, a strong long lived oxidant with pronounced deleterious effects that causes vascular damage. Peroxynitrite is a cytotoxic anion that inhibits mitochondrial electron transport, oxidizes proteins, and initiates lipid peroxidation and nitrates aromatic amino acid. Peroxynitrite by causing vascular damage contributes to the increased placental vascular resistance<sup>(16)</sup>. The combination of a deficiency of NO and increase in peroxynitrite can directly or indirectly initiate a vast majority of physiological & serological changes associated with placental dysfunction, increased thromboxanes and endothelin 1 and decrease in prostacyclins. Therefore, studies recommend the supplementation of L arginine and antioxidant in pregnancy to maintain the levels of NO so as to facilitate the required vasodilatation and have a beneficial role in the fetal growth.

### STUDIES ON L-ARGININE IN IUGR

Various studies have supported the use of L arginine in intra-uterine growth retardation. Vosatka et al (1998) conducted an experimental study to evaluate the effect of dietary supplementation with L – arginine preventing fetal growth retardation in rats and they concluded that L- arginine ameliorates maternal hypoxia induced fetal growth restriction in the rats.<sup>17</sup> Facchinelli et al (1999) investigated the biochemical and cardiovascular effects of L- arginine administration by infusion in normotensive pregnancy and women with pre-eclampsia. They observed that L- arginine infusion was associated with significant reduction of blood pressure in both groups. The investigator concluded that L- arginine loading in pregnant women is associated with increase in NO production i.e. vasodilatation leading to decrease in blood pressure and increase in utero-placental blood flow.<sup>18</sup> Rytlewski et al (2005) investigated the influence of dietary

supplementation with L- arginine on blood pressure and biochemical measures of NO production. The results of their study showed that after 3 weeks of treatment the values of systolic, diastolic and mean arterial blood pressure were significantly lower in group consuming L- arginine as compared with that of the placebo group. The decrease in blood pressure is through increased endothelial synthesis of NO.<sup>19</sup> Alexander et al (2004) concluded that supplementation with L – arginine decreases blood pressure in cases with reduced uterine perfusion pressure, and thus increases maternoplacental circulation.<sup>20</sup> Another trial carried out in pregnancy with IUGR showed that L-arginine increased maternal radicals of NO<sub>2</sub>, NO<sub>3</sub> level and infant birth weight.<sup>13</sup> In another study, treatment with L-arginine increased the availability of nutrients to the conceptus to support fetal growth and concentrations of several essential and conditionally essential amino acids methionine, isoleucine, leucine, and cysteine were increased.<sup>21</sup>

However, there also have been some contradicting reports in this field. One of the clinical studies clarifies that the efficacy of L arginine on IUGR depends on many factors like the degree of severity of IUGR, the route and timing of NO donor administration, and the capacity to enhance arginine availability and NOS or arginase activity. Norbert et al<sup>22</sup> observed that L-arginine supplementation relatively late in the course of gestation (28 week) caused fetal growth below the 3rd percentile and mean infant birth weight was much lower (1042 ± 476 gms) thus limiting enthusiasm for the use of arginine supplementation in pregnancies with severe IUGR. The failure of L arginine might be because of poor arginine bioavailability, poor conversion of arginine to NO, or a lack of effect of NO on placental vascular bed. Orally administered arginine presumably undergoes first pass uptake and degradation in liver,<sup>23,24</sup> hence, poor arginine availability in systemic blood may limit the efficacy of this amino acid. Another study also reviewed that clinical use of nitric oxide donors and L-arginine have less beneficial effect in the vascular complications of pregnancy, either as prophylactic or therapeutic agents.<sup>25</sup>

### CONCLUSION

Many studies reported the beneficial role of supplementation of L- arginine in the IUGR by increasing the synthesis of NO thus causing vasodilatation and improving placental ischemia leading to increase in the supply of substrates to the fetus. It has significant effect

on the improvement of uteroplacental microcirculation, which, obviously, can improve the placental oxygen-supplying function. It is tempting to speculate that supplementary treatment with L- arginine may represent a new, safe and efficient strategy to improve the function of the endothelium and might provide an attractive alternative or complement to conventional growth retardation therapy. However, keeping in view the contradicting reports, further studies need to be conducted to improve our knowledge and understanding about the vital role of specific amino acids like L arginine in the modulation of fetal growth.

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