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# L-Arginine supplementation in iugr and its effect on fetal outcome: A randomised control trial

**Dr. Vinitha Padmini Mary, Dr. Hajee Arshiya Bareen and S Padmanaban**

**Abstract**
**Objective:** Intrauterine growth restriction (IUGR), a condition in which the foetal growth is restricted pathologically in utero, remains a serious health problem. The main aim of this study was to evaluate the effect of L-Arginine administration on the fetal outcome in pregnancies complicated by intra uterine growth restriction.
**Methods:** This randomized control study was undertaken in the Department of Obstetrics and Gynaecology at Government Kilpauk Medical College and Hospital, Chennai from March 2017 to August 2017. The study included 60 randomly chosen pregnant women diagnosed with intrauterine growth restriction (IUGR). 30 women received 3 g of L-Arginine daily as a supplement to standard therapy (case Group) and 30 women received only routine therapy (control group). The ultrasound and clinical examination were done on the first day of hospitalization and then every week in both the groups.
**Results:** In the group treated with L-Arginine, we observed higher Estimated fetal weight after 4 weeks of treatment ($p$ <0.05), higher birth weight at delivery ($p$ < 0.05), and Apgar score at 5 minutes ($p$ < 0.05) compared to control group. There were no significant differences in IUGR (at entry and at delivery) between two groups. We also observed that there was an improvement in the liquor status of the group treated with L-Arginine ($p$<0.05).
**Conclusion:** Our study demonstrated that L-Arginine administration to pregnant women with IUGR may improve fetal condition and neonatal outcome after delivery by prolonging pregnancy and delivering a child with higher birth weight, better Apgar score and decrease the rate of caesarean sections. However, these benefits require confirmation by larger, more-powered study.

**Keywords:** IUGR, L-Arginine, neonatal outcome, oligohydramnios

## Introduction
Foetal development represents a critical period in humans. The growth of a normal foetus is controlled by a delicate balance of genetic, maternal, placental and foetal factors.

- The genetic drive for the growth
- Environmental factors in uterus
- The supply of growth substrates to the foetus
- Potential of foetus per se to grow

Any alterations in Thea fore said factors may result in the restriction of growth of the foetus.
Among the intrauterine factors, nutrition plays the most important role in affecting placental and foetal growth. The supply of substrate to the foetus is regulated by maternal - placental factor.
The current view in embryology is that a foetus has an inherent potential to grow into a healthy appropriately sized new born. However, if there is an imbalance in one or more of these critical growth and development factors, the foetus may fail to achieve appropriate size & weight.

## Significance of Focussing on Iugr
Intrauterine growth restriction (IUGR), a condition in which the foetal growth is restricted pathologically in utero, remains a serious health problem; as it affects not only the neonatal period, but also the adult phenotype and quality of life.
IUGR has been defined as the foetal growth rate that is below normal with respect to the growth potential of a specific infant for the respective race and gender of the foetus. It can also be described as a deviation from an expected foetal growth pattern and is usually due to the result of innate reduced growth potential or other multiple adverse effects on the foetus. IUGR represents the second most common cause of perinatal mortality, after prematurity,

And it is related to an increased risk of perinatal complication as hypoxemia, low APGAR scores and cord blood academia, with possible negative effects on neonatal outcome. It has been proven by studies that there is an increased risk of premature birth, reduced survival of the neonate and long-term sequel like impairment of neuro-developmental progress in childhood and insulin-resistance in adulthood, associated with IUGR.

There has been significant association of IUGR with increase in morbidity and mortality in perinatal period and infancy as shown in figure-1. The adverse consequences of growth deprivation in utero extending beyond early years into later life is one of the most worrisome aspects of IUGR.

**Role of L-Arginine in Pregnancy and Foetal growth**

L-Arginine is a versatile amino acid with a wide range of biological functions. The "L" in the name refers to the left-handed configuration of the molecule. It serves as a precursor not only to proteins but also nitric oxide which has been identified as endothelium-derived relaxing factor.

There are several proposed mechanisms by which Arginine supplementation might improve foetal growth.

a. Increasing utero placental perfusion and foetal nutrient delivery by increasing local nitric oxide (NO) concentrations.
b. A second mechanism is Arginine mediated stimulation of maternal growth hormone secretion.
c. A third potential mechanism is enhancement of placental growth and development via the promotion of polyamine synthesis.
d. Arginine, in modest to high amounts, is a potent foetal insulin secretagogue, and insulin is a major anabolic hormone in the foetus.
e. Finally, Arginine has been shown to stimulate skeletal muscle protein synthesis.

**FDA Category**

It is a category B drug.

**Recommended Dosage**

L-Arginine has been studied at oral doses of 6 to 30 g/day for a variety of conditions. Many formulations have been used.

**Objective**

The main aim of this study was to evaluate the effect of L-Arginine administration on the fetal outcome in pregnancies complicated by intra uterine growth restriction.

**Methods**

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**Results**

In the group treated with L-Arginine, we observed higher Estimated fetal weight after 4 weeks of treatment ($p$ <0.05), higher birth weight at delivery ($p$ < 0.05), and Apgar score at 5 minutes ($p$ < 0.05) compared to control group. There were no significant differences in IUGR (at entry and at delivery) between two groups. We also observed that there was an improvement in the liquor status of the group treated with L-Arginine ($p$<0.05).

**Results**

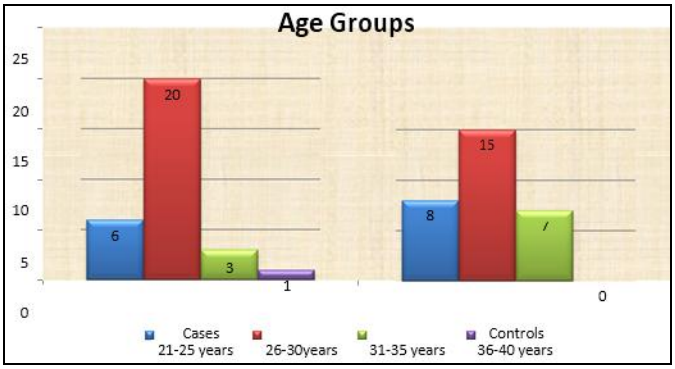


**Fig 1:** Age

**Table 1:** Pre-Treatment EFW (GMS)

| Pre-Treatment EFW (GMS) Groups | Cases | % | Controls | % |
|---|---|---|---|---|
| ≤ 1100 mgs | 3 | 10.00 | 3 | 10.00 |
| 1101-1300 GMS | 16 | 53.33 | 14 | 46.67 |
| 1301-1500 GMS | 6 | 20.00 | 7 | 23.33 |
| 1501-1700 GMS | 5 | 16.67 | 6 | 20.00 |
| Total | 30 | 100.00 | 30 | 100.00 |

**Table 2**

| Pre-Treatment EFW (GMS) Distribution | Cases | Controls |
|---|---|---|
| Mean | 1288.97 | 1291.57 |
| SD | 159.23 | 166.50 |
| P value (Unpaired t Test) | | 0.9509 |

The study subjects were distributed in 1101-1300 GMS pre-treatment EFW group in cases group (n=10, 53.33%) and same pre-treatment EFW group in control group (n=14, 46.67%) (p=0.9509, unpaired t test), p value being insignificant.

**Table 3:** Post Treatment EFW

| Post-Treatment EFW (GMS) Groups | Cases | % | Controls | % |
|---|---|---|---|---|
| ≤ 1500 GMS | 0 | 0.00 | 2 | 6.67 |
| 1501-1700 GMS | 5 | 16.67 | 15 | 50.00 |
| 1701-1900 GMS | 17 | 56.67 | 10 | 33.33 |
| 1901-2100 GMS | 6 | 20.00 | 3 | 10.00 |
| 2101-2300 GMS | 2 | 6.67 | 0 | 0.00 |
| Total | 30 | 100.00 | 30 | 100.00 |

**Table 4**

| Post-Treatment EFW (GMS) Distribution | Cases | Controls |
|---|---|---|
| Mean | 1848.17 | 1680.60 |
| SD | 157.05 | 156.59 |
| P value (Unpaired t Test) | | 0.0001 |

Cases group (n=17, 56.67%) 1701-1900 GMS and in control group 1501-1700GMS (n=15, 50.00%) (p=0.0001, unpaired t test). The difference in the mean post-treatment EFW in cases group (1848.17) and control group (1680.60) was found to be statistically significant ($p$ <0.05). The increased difference in the mean post-treatment EFW (167.57, 9% higher) was statistically significant ($p$ <0.05).

**Table 5:** Birth Weight (GMS)

| Birth Weight (GMS) Groups | Cases | % | Controls | % |
|---|---|---|---|---|
| ≤ 1600 GMS | 0 | 0.00 | 7 | 23.33 |
| 1601-1800 GMS | 4 | 13.33 | 16 | 53.33 |
| 1801-2000 GMS | 17 | 56.67 | 5 | 16.67 |
| 2001-2200 GMS | 8 | 26.67 | 2 | 6.67 |
| 2201-2400 GMS | 1 | 3.33 | 0 | 0.00 |
| Total | 30 | 100.00 | 30 | 100.00 |

Cases group (n=17, 56.67%) 1801-2000 GMS and in control group 1501-1700GMS (n=16, 53.33%) (p=0.0001, unpaired t test).

**Table 6**

| Birth Weight (GMS) Distribution | Cases | Controls |
|---|---|---|
| Mean | 1946.93 | 1711.80 |
| SD | 120.07 | 145.22 |
| P value (Unpaired t Test) | | <0.0001 |

The difference in the mean Birth weight in cases group (1946.93) and control group (1711.80) was found to be statistically significant ($p$ <0.05).

**Table 7:** Resuscitation Type

| Resuscitation Type | Cases | % | Controls | % | P value Chi Squared Test |
|---|---|---|---|---|---|
| Routine Care | 21 | 77.78 | 16 | 64.00 | 0.2733 |
| Bag and Mask | 4 | 14.81 | 12 | 48.00 | 02114 |
| Endotracheal Intubation | 2 | 7.41 | 3 | 12.00 | 0.5752 |

The increased percentage difference in various resuscitation type in cases group and control group was found to be statistically insignificant ($p$ >0.05).

**Table 8:** NICU Admission

| NICU Admission | Cases | % | Controls | % |
|---|---|---|---|---|
| Yes | 8 | 29.63 | 8 | 32.00 |
| No | 19 | 70.37 | 17 | 68.00 |
| Total | 27 | 100.00 | 25 | 100.00 |
| P value (Chi Squared Test) | | | 0.9254 | |

The decreased percentage difference in NICU admission in cases group and control group (2.37, 7% lower) was found to be statistically insignificant ($p$>0.05).

**Table 9:** Complications

| Complications | Cases | % | Controls | % | P value Chi Squared Test |
|---|---|---|---|---|---|
| RD | 13 | 48.15 | 14 | 56.00 | 0.3712 |
| Hypoglycaemia | 5 | 18.52 | 9 | 36.00 | 0.1567 |
| Hypothermia | 4 | 14.81 | 6 | 24.00 | 0.4011 |
| VH, NEC | 1 | 3.70 | 3 | 12.00 | 0.2622 |

RD – Respiratory distress VH – Ventricular Haemorrhage
NEC – Necrotising entero colitis

The decreased percentage difference in complication status in cases group and control group (10.70, 33% lower) was found to be statistically insignificant ($p$ >0.05).

## Discussion

In my study, majority of the study subjects in cases group were distributed in 26-30 years age group (n=20,66.67%) and same age group in control group (n=15, 50.00%). The difference in the mean age of patients in cases group (27.77%) and control group (27.70%) was found to be statistically insignificant ($p$>0.05). In both the groups in the study, gestational age at entry was around 30 weeks, in case group (n=14, 46.67%) and in control group (n=14, 46.67%), with the difference in the mean gestational age at entry in cases group (30.60) and control group (30.60) being statistically insignificant ($p$ >0.05).

**Table 10**

| Characteristics | Group I | Group II | p value |
|---|---|---|---|
| Age | 27± 3 | 27±2.7 | >0.05 |
| BMI | 20±3 | 20±4 | >0.05 |
| Period of gestation | 30±1 | 30±1 | >0.05 |

Characteristics in study and control groups

Pre-treatment EFW was similar in both the groups between 1101-1300 GMS in case group (n=10, 53.33%) and in control group (n=14, 46.67%). The post- treatment EFW analysed in both the groups, after a period of 4 weeks, showed 1701-1900 GMS (n=17, 56.67%) in cases group and 1501-1700 GMS in control group (n=15, 50.00%). The difference in the mean in cases group (1848.17) and control group (1680.60) ($p$ <0.05) and the increased difference in mean post- treatment EFW in cases group compared to control group (167.57, 9% higher) was found to be statistically significant ($p$ <0.05). Similar results were by presented Sieroszewski at al. The ultrasound estimation of fetal weight at the start and at the end of the treatment showed a mean increase of 642 g. By comparison, within the control group a mean value increase of 395 g (SE 77 g) was found. There was a significant statistical difference when comparing the estimated fetal weight increase.

**Table 11**

| Characteristics | Group i | | Group ii | | p value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| Live births | 27 | 90 | 25 | 83.33 | >0.05 |
| IUD | 3 | 10 | 5 | 16.67 | >0.05 |
| Mean birth weight | 30 | 1.9±0.12 | 30 | 1.7±0.14 | <0.05 |
| GA at delivery | 30 | 35±0.7 | 30 | 34.9±0.94 | >0.05 |
| Vaginal delivery | 23 | 76.67 | 22 | 73.33 | >0.05 |
| LSCS rate | 7 | 23.33 | 8 | 26.67 | >0.05 |

Outcome in study and control groups

Percentage of live birth was found to be more in Arginine therapy group (90% in case group vs 83.33% in control group). In case group, intrauterine deaths were 3 (10%) and there were 5 in control group (16.67%) ($p$>0.05), difference being statistically insignificant. Of the above, there were 5 neonatal deaths in case group (18.52%) and 3 in control group (12%), with a statistically insignificant p value.

Though the gestational age at delivery was found to be more in Arginine therapy group around 35weeks whereas it was around 34 weeks in control group, the difference was statistically insignificant.

The mean birth weight of the neonates in case group was 1801-2000 GMS (56.67%) compared to 1601-1800GMS (53.33%) in control group($p$<0.05). This implies that the difference in the mean birth weight in cases group (1946.93GMS) and control group (1711.80GMS) and the increased difference in mean birth weight of 235.13GMS in cases group compared to control group (12% higher) was found to be statistically significant ($p$ <0.05). This outcome was comparable to the study done by Xiao XM *et al* in 2005. Their study showed a significantly higher mean birth weight in group supplemented with Arginine ($P$<0.05) than in

control group.

The incidence of vaginal delivery was 76.67% in cases group and 73.33% in control group. P value was found to be statistically insignificant ($p > 0.05$).

Postnatal assessment showed that Apgar score at 1st and 5th minute was higher in the L-Arginine group. However, the difference between the APGAR scores at 1st minute in neonates of both the groups was statistically insignificant. APGAR score at 5 minutes in the range of 7-10 was distributed as follows: in case group (81.48%) and in control group (76.00%). On analysing the difference in the mean APGAR score at 5 minutes in cases group (7.85) and control group (7.04), it was found to be statistically significant ($p < 0.05$). The increased difference in mean Apgar score at 5 minutes in cases group compared to control group (10% higher) was similar to the study done by Mariola Rapocka *et al* in 2007.

## Conclusion

The conclusion drawn from my study is that after oral administration of L- Arginine, in women where fetal wellbeing is good and no placental insufficiency as indicated by decreased Umblical Artery S/D ratio, there was increase in the birth weight of the baby, improved APGAR of the neonates and thereby good perinatal outcome. There was reduction in complications and need for NICU admissions. L-Arginine improves foetal weight more significantly in cases with idiopathic IUGR or where mother is nutritionally deficient rather than in those pregnancies affected by anemia or preeclampsia. Anemia should be corrected in the preconception stage to improve pregnancy outcome. Hence, during antenatal care all pregnant women and high risk cases should be screened to detect IUGR in earlier stages which will decrease perinatal mortality and morbidity. Apart from the routine fetal surveillance in IUGR, Umbilical Artery S/D ratio done by Doppler ultrasonography helps in detecting increased resistance and monitoring of a compromised fetus. The IUGR cases should be supplemented oral L-Arginine, a nitric oxide donor, to reduce the resistance in feto-placental circulation.

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