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# L-Arginine Supplementation during Intrauterine Growth Restriction and Its Correlation with Fetal Outcome

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## ABSTRACT

Intrauterine growth restriction (IUGR), a syndrome wherein the fetal development is pathologically limited in utero, continues to be a significant public health risk, because it impacts not only the newborn phase, but also the adult phenotype and quality of life. The amino acid L-Arginine, which is necessary for human nutrition, is the precursor of nitric oxide. It plays a crucial function in fetal nourishment oxygenation, resulting in an improvement of intrauterine growth restriction, an increase in birth weight, and a decrease in neonatal morbidity and death. A prospective observational study was conducted, with a sample size of 124 patients suffering from IUGR and prescribed with L-Arginine, during the period of 6 months from August to February in tertiary care hospital. The SPSS statistical tool, version 16.0, was used for the statistical analysis. The same number of study subjects were analyzed before and after treatment with L-Arginine. There was an increase in baby weight after supplementation of L-Arginine, with a good APGAR score, and there was a decrease in intrauterine deaths and there was also a decrease in cesarean section. Hence it can be concluded that there was an increase in the baby weight and also improve perinatal outcomes following administration of L-Arginine to IUGR-complicated pregnant women.

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

## INTRODUCTION

L-Arginine is a particular type of amino acid having numerous biological roles. The letter "L" indicates the left-handed orientation of the molecule. L-Arginine is a B category drug. For a wide variety of illnesses, the oral dose of L-Arginine is 6 to 30 g per day. (1) IUGR, a syndrome wherein the fetal development is pathologically limited in utero, continues to be a significant public health risk, because it impacts

not only the newborn phase, but also the adult phenotype and quality of life.

IUGR refers to fetal development which is lower than normal in comparison to the possibility of growth. It is also characterized as a variation from a normal fetal development pattern and is typically caused by a fetus's innately diminished growth potential or other harmful effects.

IUGR is the second major cause of perinatal deaths, behind preterm, and is linked to an increased risk of perinatal problems including hypoxemia, low APGAR scores, and cord blood acculturation, which may have severe implications on neonatal health. Studies have demonstrated that IUGR is related with a higher risk of preterm birth, decreased neonatal survivability, and long-term consequences such as impaired neurodevelopmental progress in infancy and insulin resistance in adulthood.

There is a substantial link between IUGR and an increase in perinatal and infant morbidity and mortality. One of the most concerning elements of IUGR is that the detrimental implications of fetal developmental restriction persist into childhood and into adulthood. [1]

### *Types of IUGR*

IUGR is classified into three different forms

- Asymmetrical IUGR: The most prevalent type of IUGR. Abnormal growth typically develops in the late second or third trimesters, following 28 weeks of gestation. It influences the hypertrophy phase of fetal development. It is caused by uteroplacental insufficiency, which results from a restriction in nutrient supply. [2,3]
- Symmetrical IUGR: It is caused by growth restriction in the initial stage of pregnancy, i.e., the hyperplastic stage. Every pathogenic insult reduces the quantity of fetal cells and their overall growth potential. All growth metrics are diminished in infants with symmetric growth restriction, including weight, length, and head circumference. In such circumstances, the difference between the head and chest circumferences will be less than 3cm. [2,3]
- Mixed IUGR: It is a combination of the two different forms. At the intermediate phase of development, fetal growth restriction affects hyperplasia and hypertrophy. It is particularly common when IUGR is triggered by placental factors in late pregnancy. It is indicative of both symmetrical and asymmetrical IUGR. Early in the second trimester, it is correlated with persistent hypertension, Lupus nephritis, and vascular disease. [2,3]

IUGR can be caused by maternal, placental, or fetal factors. [4]

Age of the mother (<16 years and >35 years), maternal hypoxia, and the use of drugs like those of warfarin, corticosteroids, antiepileptics, anticancer, anti-metabolites, and folic acid antagonists, previous SGA birth poor weight during pregnancy, moderate to physical work, maternal infection and parasite infestation are considered maternal factors. [5-11]

Placental factors include placental weight less than 350g, single umbilical artery, placental dysfunction, abruptio placenta, placental hemangioma, placental infection. [12-15]

Fetal factors include constitutionally minor (50-70% of SGA fetuses with fetal growth suitable for maternal size), chromosomal defects, multiple gestations, congenital infections (TORCH, Syphilis, congenital HIV). [16-18]

Genetic factors are classified as

- Placental Genes: Trophoblastic miRNA [19,20] overexpression, under-expression of placental growth factor (PIGF), [21] under-expression of placental insulin-like growth factor and over-expression of placental insulin-like growth factor. [22]
- Maternal Genes: Over-expression of Endothelin-1 (ET-1), Thrombophilia genes mutation [23]
- Fetal Genes: Genetic excision of IGF1 (insulin-like growth factor 1) [24] mutation of insulin-like growth factors 1 receptor. [25]

### *Fetal Growth and Development [4]*

Fetal development is a crucial period in humans. Normal prenatal growth is governed by a careful

balance of genetic, maternal, placental, and fetal variables. Sequential processes of tissue and organ growth, differentiation, and malnutrition characterize human fetal growth. The development of the fetus has been categorized into three phases.

- The Initial Phase: The period of hyperplasia occurring during the initial 4 months which is distinguished by the dramatic rise in cell count.
- The Second Phase: Involved are up to 8 months of gestation, during which both hyperplasia and hypertrophy occur.
- The Third Phase: Hypertrophy phase lasts 32 weeks. Fetal fat and glycogen are mostly deposited.

Fetuses whose estimated fetal weight is <10th percentile for their gestational age or two standard deviations under the mean of the population are regarded as growth restriction.

The APGAR test is conducted on a baby 1 minute and 5 minutes after birth. The 1-minute score indicates how well the infant withstood during the childbirth procedure. The 5 minutes score indicates how well the newborn is adjusting to life outside the womb to the healthcare professional. Appearance, Pulse, Grimace, Activity, and Respiration are the components of the APGAR scale. Each is graded on a scale from 0 to 2, with 2 being the highest score and 7, 8, or 9 being normal. The APGAR score indicates the state of a newborn infant immediately following birth.

### *Clinical examination*

- Fundal height estimation: A clear and concise technique for assessing foetal growth is serial fundal height estimation. Using tape, the measurement starts from the fundus and continues until the symphysis pubis. [26]
- Ultrasonography: Ultrasound measurements are head circumference, abdominal circumference. Measurements below the 10th percentile are highly suspicious of IUGR. [27]
- Amniocentesis: In this technique, a needle is inserted through the mother's skin and into her uterus to extract amniotic fluid for testing. The test may reveal infection or congenital anomalies which result in IUGR. [28]
- Doppler: Doppler scans are often utilized for evaluating placental blood supply, fetal umbilical blood flow, blood flow to heart and brain to ensure everything is normal [29, 30]

### *Prevention of IUGR*

- Keep all of the prenatal check-ups. Identifying potential issues as soon as possible.
- Pay attention to the baby's movements. A baby who does not move frequently or who stops moving could have a problem. Consult a doctor if any changes are noticed in the baby's movement.
- Double-check the medicines. A drug a mother is taking for another health concern might sometimes cause complications with her unborn baby.
- Develop healthy lifestyle practices. Stop drinking alcohol, taking drugs, or smoking.
- Take balanced energy protein, calcium supplements and multiple nutrient supplementations. [31-33]

### *Data And Method:*

### *Study Design And Tools*

This randomized prospective research was carried out at the obstetrics and gynecology department at Vijay Marie hospital, Khairtabad for a period of six months from September-February. The case was collected and analyzed. In this hospital-based trial, 124 pregnant women between the ages of 19 and 32 with fetal IUGR (intrauterine growth restriction weight <10th percentile for the gestational age measured sonographically) who received daily doses of L-arginine as an addition to usual treatment were included. Fig. 1 is a schematic illustration of the study design. The effect of L-Arginine in intrauterine growth restriction was analyzed using standard guidelines by referring journals and textbooks of obstetrics and gynecology by William Rayburn, textbook of obstetrics and gynecology by Gregory Fernandez and textbook of obstetrics and gynecology by Michael Belden.

Recognizing L- Arginine's positive effects on vascular endothelium, the current study sought to assess the impact of L-Arginine supplementation in intrauterine growth restriction (IUGR) and its relationship to fetal response.

***Sample size***

Prospective observational research was conducted in a total of 124 patients for a time period of six months.

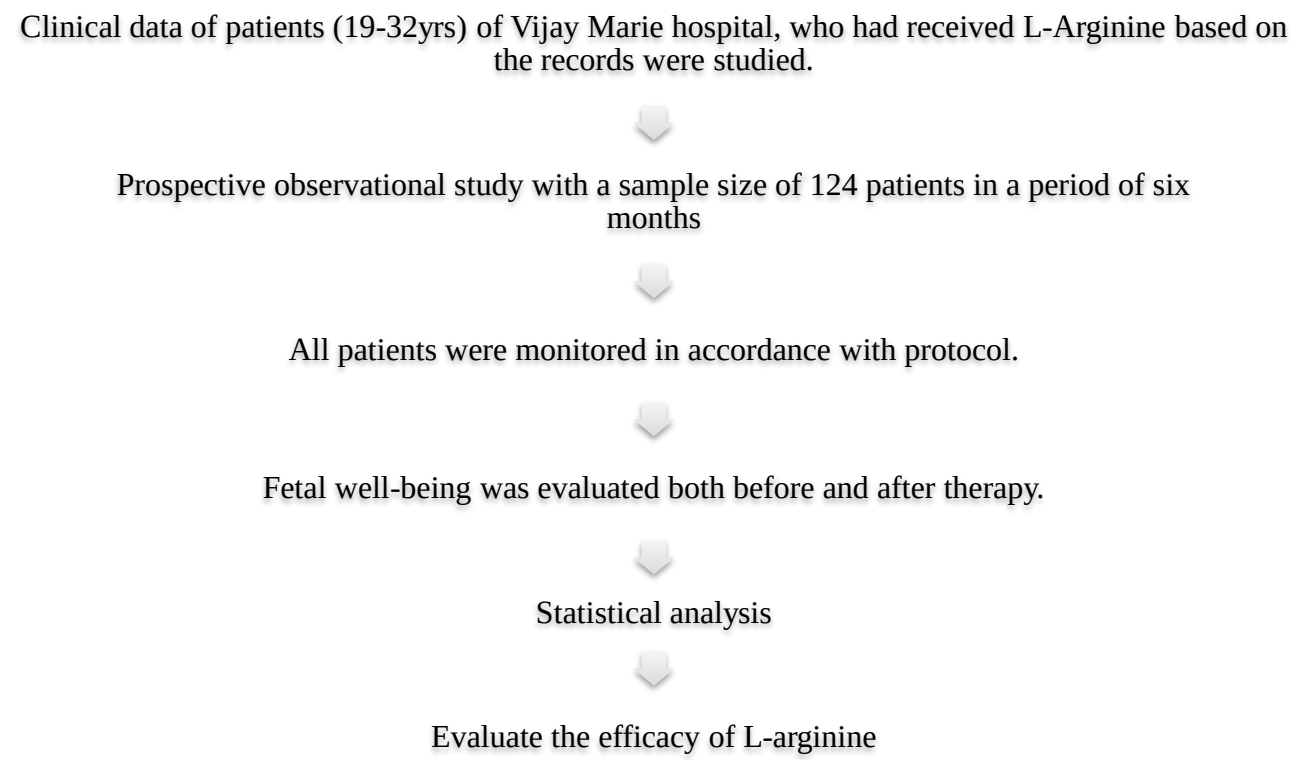


**FIG. 1:** Flow chart depicting the study design

***Sampling and Data Collection***

Prospective observational research involving 124 patients was conducted. In the research, pregnant women between the age of 19 and 32 who received L-Arginine participated. Women who do not meet the aforementioned criteria were excluded from the study. While data was still being collected, patients were informed about the trial using a format designed specifically for patient information. The demographic characteristics of the patient, such as age, comorbidities, and educational levels, were entered into the data entry form that was created specifically for this purpose.

***Statistical Analysis***

The SPSS statistical tool, version 16.0 (SPSS Inc., Chicago, IL, USA), was used for the statistical analysis, and all data are expressed as mean ± standard deviation (SD). P values <0.05 were regarded as significant. For data that were regularly distributed, the student t-test was applied.

## RESULTS

***Patient demographics***

Among the total number of cases, the number of cases observed was 19 among the age group between 19-20 yrs., 26 between the age group of 21-22 yrs., 29 between the age group of 23-24 yrs., 23 between the age group of 25-26 yrs., 12 between the age group of 27-28 yrs., 09 between

the age group of 29-30 yrs., and 06 between the age group of 31-32 yrs.

***IUGR Diagnosed at Different Gestation Age***

Cases prescribed with L-Arginine were collected based on the number of patients identified with IUGR and Oligohydramnios. Among them, 91 patients were diagnosed with IUGR and 33 patients with IUGR and Oligohydramnios.

***IUGR Diagnosed at Different Gestation Age***

IUGR diagnosed at 22nd week of gestation age included 18cases, 23rd week 09 cases, 24th week 35 cases, 25th week 29 cases, 26th week 25 cases, at 27th and 28th week 04 cases respectively.

***Fetal Weight Before and After L-Arginine Treatment (for a period of four weeks)***

Before treatment with L-Arginine, fetal weight between 351-400 grams were 19 cases, 401-450 grams were 05 cases, 451-500 grams were 05 cases, 501-550 grams were 14 cases, 551-600 grams were 31 cases, 601-650 grams were 23 cases, 651-700 grams were 13 cases, 701-750 grams were 08 cases, 751-800 grams and 801-850 grams were 03 cases respectively.

After treatment with L-Arginine for a period of four weeks, fetal weight between 700-800 grams were 18 cases, 801-900 grams were 09 cases, 901-1000 grams were 05 cases, 1001-1100 grams were 30 cases, 1101-1200 grams were 04 cases, 1201-1300 grams were 30 cases, 1301-1400 grams were 07 cases, 1401-1500 grams were 11 cases, 1501-1600 grams were 01 cases, 1601-17000 grams were 05 cases,1701-1800 grams were 04 cases.

***Birth Weight of Baby***

In patients prescribed with L-Arginine, baby weight immediately after delivery was found to be 2.1 kgs (01), 2.2 kgs (01), 2.4 kgs (03), 2.5 kgs (20), 2.6 kgs (03), 2.7 kgs (13), 2.9 kgs (01), 03 kgs (41), 3.1 kgs (13), 3.2 kgs (14), 3.3 kgs (05).

***Type of Delivery***

In patients prescribed with L-Arginine, full-term normal delivery (FTND) and lower segment cesarean section (LSCS) included 85 and 39 cases respectively.

***Live Births***

Among the total number of cases collected in patients prescribed with L-Arginine, live births included 120 cases and intrauterine death (IUD) was observed in 04 cases.

***APGAR Score of Baby***

Among the total number of cases collected in patients prescribed with L-Arginine, APGAR scores 7/8/9 were 102 cases, 6/7/8 were 18 cases.

***Comparison of various characteristics at different gestation age***

All patients diagnosed with IUGR between the 22nd and 28th week of gestation were compared before and after l-arginine administration. Prior to treatment, the fetal weight was below the 10th percentile of predicted weight; however, following four weeks of L-Arginine administration, the fetal weight increased. Table 1. Depicts the results obtained on fetal weight comparison between L-Arginine pre- and post-treatment at different gestation age.

**TABLE 1:** Comparison of Fetal Weight Between Pre and Post Treatment with L-Arginine From 22nd- 28th Week of Gestation Age

| S. No. | Week | Number of Patients | Pre- treatment | Post- treatment | p-value |
|---|---|---|---|---|---|
| | | | Mean± SD | Mean± SD | |
| **1** | 22nd | 18 | 388.88±5.17 | 767.88±4.18 | <0.0001 |
| **2** | 23rd | 09 | 436.22±20.8 | 867.33±4.05 | <0.0001 |
| **3** | 24th | 35 | 547.314±17.68 | 1058.06±32.22 | <0.0001 |
| **4** | 25th | 29 | 605.03±16.42 | 1251.13±29.48 | <0.0001 |

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|---|---|---|---|---|---|
| **5** | 26th | 25 | 689.12±31.03 | 1395.36±83.92 | <0.0001 |
| **6** | 27th | 04 | 703.5±61.05 | 1577.5±64.95 | <0.0004 |
| **7** | 28th | 04 | 840.5±33.12 | 1733±19.67 | <0.0001 |

All individuals diagnosed with IUGR between the 22nd and 28th week of gestation were compared before and after L-Arginine administration. Prior to treatment, the fetal weight was below the 10th percentile of predicted weight; after L-Arginine administration up to delivery, the baby's weight increased. Table 2. Depicts the results obtained on birth weight comparison between pre and post treatment of L-Arginine at different gestation age.

**TABLE 2:** Comparison of Birth Weight Between Pre and Post Treatment with L-Arginine From 22nd- 28th Week of Gestation Age

| S. No. | Week | Number of Patients | Pre- treatment | Post- treatment (At Delivery) | p-value |
|---|---|---|---|---|---|
| | | | Mean± SD | Mean± SD | |
| **1** | 22nd | 18 | 388.88±5.17 | 2994.44±158.01 | <0.0001 |
| **2** | 23rd | 09 | 436.22±20.80 | 2966.67±182.57 | <0.0001 |
| **3** | 24th | 34 | 547.08±17.89 | 2850±312.72 | <0.0001 |
| **4** | 25th | 27 | 604.22±17.05 | 2903.7±297.49 | <0.0001 |
| **5** | 26th | 24 | 688±31.17 | 2825±222.20 | <0.0001 |
| **6** | 27th | 04 | 703.5±61.02 | 2800±212.13 | <0.0006 |
| **7** | 28th | 04 | 840.5±33.124 | 2925±258.6 | <0.0007 |

In individuals identified with IUGR between the 22nd and 28th week of gestation, the fetal weight after four weeks of L-Arginine treatment was compared to the birth weight at the time of delivery. There was no IUD-related death. Table 3. Depicts the results obtained on birth weight comparison between pre and post treatment of L-Arginine at different gestation age and after delivery.

**TABLE 3:** Comparison of Birth Weight Between Post Treatment with L-Arginine From 22nd- 28th Week of Gestation Age and After Delivery

| S. No. | Week | Number of Patients | Pre- treatment | Post- treatment (At Delivery) | p-value |
|---|---|---|---|---|---|
| | | | Mean± SD | Mean± SD | |
| **1** | 22nd | 18 | 767.88±4.18 | 2994.44±158.01 | <0.0001 |
| **2** | 23rd | 09 | 864.33±4.05 | 2966.67±182.57 | <0.0001 |
| **3** | 24th | 34 | 1057.91±32.68 | 2850±312.72 | <0.0001 |
| **4** | 25th | 27 | 1253.11±29.05 | 2903.7±297.49 | <0.0001 |
| **5** | 26th | 24 | 1393.33±85.05 | 2825±222.204 | <0.0001 |
| **6** | 27th | 04 | 1577.5±64.95 | 2800±212.13 | <0.0022 |
| **7** | 28th | 04 | 1733±19.67 | 2925±258.6 | <0.0039 |

## DISCUSSION

Intrauterine growth restriction (IUGR) is characterized by a fetus with an estimated weight below the 10th percentile for its gestational age (4) and an abdominal circumference below the 2.5th percentile. There are two types of fetal growth restriction: symmetrical, in which the fetus is small but proportionate, and asymmetrical, in which abdominal growth is restricted. IUGR, a syndrome wherein the fetal development is pathologically limited in utero, continues to be a significant public health risk,

because it impacts not only the newborn phase, but also the adult phenotype and quality of life.

IUGR is the second major cause of perinatal deaths, behind preterm, and is linked to an increased risk of perinatal problems including hypoxemia, low APGAR scores, and cord blood acculturation, which may have severe implications on neonatal health. Studies have demonstrated that IUGR is related with a higher risk of preterm birth, decreased neonatal survivability, and long-term consequences such as impaired neurodevelopmental progress in infancy and insulin resistance in adulthood.

The prevalence of IUGR in undeveloped countries is approximately six times than that of developed countries. The incidence of IUGR changes depending on country, community, and race, and it increases as gestational age decreases.

In Asia, a substantial percentage of infants are born with IUGR. The incidence of IUGR in India is second highest among south Asian nations. In prosperous countries, the prevalence of SGA births is around 10%. One-third of these instances are genuine IUGR.

The prevention of intrauterine growth restriction in newborns must be regarded as a top health care priority. A high risk of IUGR is cause for concern because it indicates not only a hazard of undernourishment and severe illness in women of childbearing age, but also a significant risk of malnutrition, morbidity, and mortality in the infant. Though much research had been made on the effectiveness of L-Arginine to pregnant women complicated by IUGR because of increased risk of IUGR and does not appear to reduce and also some researchers are expressing the doubt on the benefit of using L-Arginine in the treatment of IUGR. Hence this study was carried out to assess the effect of L-Arginine in patients with IUGR.

Therefore, we made this study to provide antenatal care to the fetuses and to decrease neonatal morbidity and to get healthy babies by using L-Arginine.

L-Arginine, an amino acid that is physiologically required for the fetus, is a precursor for the production of nitric oxide (NO), which helps sustain placental blood flow, fetal nutrition, and oxygenation. [34] Hence, it plays a crucial function in fetal nourishment oxygenation, resulting in an improvement of intrauterine growth restriction, an increase in birth weight, and a decrease in neonatal morbidity and death. [35]

In our prospective observational study, we have collected 124 patients suffering from IUGR and prescribed with L-Arginine, all of which comply with the inclusion and exclusion criteria. This study was conducted over the course of six months from August to February in a tertiary care hospital. A protocol was designed prior to the practical work followed by a literature survey. DCF-data collection forms: These are prepared based on our study design so that all data of each individual subject can be noted down at a place that makes follow up easy and serves as the main source for documentation. Then based on patients prescribed with L-Arginine cases were collected and analyzed.

The study subjects were distributed in 19-32 years of age groups, among these 91 subjects were diagnosed with IUGR and 33 subjects were diagnosed as IUGR with oligohydramnios.

We differentiated the IUGR patients according to their gestational age in weeks at 22nd week are 18 patients, at 23rd week are 9 patients, at 24th week are 35 patients, at 25th week are 29 patients, at 26th week are 25 patients, at 27th and 28th week are 04patients each.

These patients were evaluated prior to and following L-Arginine treatment. Before L-Arginine supplementation, the fetuses weight were less than 10th percentile and the fetuses weight between (351-400 grams) were 19 cases, (401-450 grams) were 5 cases, (451-500 grams) were 5 cases, (501-550 grams) were 14 cases, (551-600 grams) were 31 cases, (601-650 grams) were 23 cases, (651-700 grams) were 13 cases, (701-750 grams )were 8 cases, (751-800 grams) and (801-850 grams) were 3 cases each and we have compared the same patients after 04 weeks with L-Arginine treatment and their fetuses weight were increased according to their gestational age and fetuses weights were as follows (700-800 grams) were 18 cases,(801-900 grams) were 9 cases, (901-1000 grams) were 5 cases, (1001-1100 grams) were 30 cases, (1101-

1200 grams) were 4cases, (1201-1300 grams) were 30 cases, (1301-1400 grams) were 7 cases, (1401-1500 grams) were 11 cases, (1501-1600 grams) were 1 case,(1601-1700 grams) were 5 cases and (1701-1800 grams) were 4 cases.

Similarly, birth weight was also increased at the time of delivery that is 2.1 kg baby was 01, 2.2 kgs baby was 01, 2.4 kgs babies were 03, 2.5 kgs babies were 20, 2.6 kgs babies were 03, 2.7 kgs babies were 13, 2.9 kgs baby was 01, 3 kgs babies were 41, 3.1 kg babies were 13, 3.2 kgs babies were 14, 3.3 kgs babies were 05.

At 22nd week of gestational age, out of 18 cases, the mean weight of fetuses before L-Arginine treatment was 388.88±5.17 and after treatment for a period of four weeks, the mean weight of fetuses was 767.88±4.18 ($p < 0.0001$) and at the time of delivery the mean weight of babies was 2994.44±158.01 ($p< 0.0001$) and there was an appropriate increase in baby weight and there was no IUD death.

At 23rd week of gestational age, out of 09 cases, the mean weight of fetuses before L-Arginine treatment was 436.22±20.8 and after treatment for a period of four weeks, the mean weight of fetuses was 867.33±4.05 ($p< 0.0001$) and at time of delivery the mean weight of babies was 2966.67±182.57 ($p< 0.0001$) and there was an appropriate increase in baby weight and there was no IUD death.

At 24th week of gestational age, from 35 cases, the mean weight of fetuses before L-Arginine treatment was 547.314±17.68 and after treatment for a period of four weeks, the mean weight of fetuses was 1058.06±32.22 ($p<0.0001$) and at time of delivery the mean weight of babies was 2850±312.72 ($p<0.0001$) and there was an appropriate increase in baby weight and there was one IUD death.

At 25th week of gestational age, from 29 cases, the mean weight of fetuses before L-Arginine treatment was 605.03±16.42 and after treatment for a period of four weeks, the mean weight of fetuses was 1251.13±29.48 ($p<0.0001$) and at time of delivery the mean weight of babies was 2903.7±297.49 ($p<0.0001$) and there was an appropriate increase in baby weight and there was two IUD death.

At 26th week of gestational age, from 25 cases, the mean weight of fetuses before L-Arginine treatment was 689.12±31.03 and after treatment for a period of four weeks, the mean weight of fetuses was 1395.36±83.92 ($p<0.0001$) and at time of delivery the mean weight of babies was 2825±222.20 ($p<0.0001$) and there was an appropriate increase in baby weight and there was one IUD death.

At 27th week of gestational age, from 4 cases, the mean weight of fetuses before L-Arginine treatment was 703.5±61.05 and after treatment for a period of four weeks, the mean weight of fetuses was 1577.5±64.95 ($p<0.0004$) and at time of delivery the mean weight of babies was 2800±212.13 ($p<0.0006$) and there was an appropriate increase in baby weight and there was no IUD death.

At 28th week of gestational age, from 4 cases, the mean weight of fetuses before L-Arginine treatment was 840.5±33.12 and after treatment for a period of four weeks the mean weight of fetuses was1733±19.67 ($p<0.0001$) and at time of delivery the mean weight of babies was 2925±258.6 ($p<0.0007$) and there was an appropriate increase in baby weight and there was no IUD death.

Our study showed that full-term normal delivery was 85, the lower segment cesarean section were 39 cases. Live births were 120, intrauterine death was 04 cases. APGAR score of the baby is 7/8/9 were 102 cases and 6/7/8 were 18 cases.

Hence among 124 patients, there was an increase in fetal weight and birth weight after supplementation of L-Arginine with a good APGAR score, there was a decrease in intrauterine deaths and also a decrease in cesarean section.

## CONCLUSION

Fetal weight and baby weight were analyzed before and after the treatment of l-arginine using standard guidelines. The outcome of our research is that, after oral administration of L-Arginine to pregnant women with a healthy fetal weight and no placental insufficiency, the infant's birth weight increased, and the neonates' APGAR ratings improved, indicating a positive perinatal

outcome. In situations of IUGR, L-Arginine boosts fetal weight more considerably. As a result, all pregnant women and high-risk cases should be evaluated for IUGR during antenatal care, which will reduce perinatal death and morbidity. To minimize resistance in feto-placental circulation and the risk of IUGR, IUGR cases should be supplemented with oral L-Arginine, a nitric oxide donor. Therefore, we have presented evidence that L-Arginine supplementation may enhance perinatal outcomes in women with IUGR-complicated pregnancies. Unfortunately, these data are insufficient to guide decisions regarding the use of L-arginine in pregnancies complicated by IUGR, as larger patient populations are necessary to examine the impact of L-Arginine on clinical outcomes and the number of studies may be minimal.

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### *Availability Of Data & Materials*

Not applicable.

### *Author's Contribution*

All authors contribute, read, and approve the final version of the manuscript.

### *Competing Interest*

The authors have no relevant financial or non-financial interests to disclose.

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