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Original Research Article

Impact of Prolonged Oral L-Arginine Supplementation on Pregnancy Duration and Neonatal Outcomes in IUGR Fetuses with Abnormal Doppler Indices

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Abstract

Background: Intrauterine growth restriction (IUGR) with abnormal Doppler indices is associated with uteroplacental insufficiency, fetal hypoxia, preterm delivery, and increased perinatal morbidity and mortality. Nitric oxide–mediated vasodilatation plays a crucial role in improving placental perfusion. Oral L-arginine, a nitric oxide precursor, has been proposed as a therapeutic agent to enhance uteroplacental circulation, prolong pregnancy, and improve neonatal outcomes. However, evidence regarding prolonged supplementation in Doppler-compromised IUGR pregnancies remains limited.

Objective: To evaluate the effect of prolonged oral L-arginine supplementation on pregnancy duration, Doppler parameters, and neonatal outcomes in pregnancies complicated by IUGR with abnormal Doppler indices.

Methods: This randomized controlled study was conducted over one year, from 01.05.2020 to 30.04.2021, at Department of Obstetrics and Gynaecology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan. A total of 130 pregnant women with singleton pregnancies between 28 and 34 weeks of gestation, diagnosed with intrauterine growth restriction (IUGR) and abnormal umbilical artery Doppler indices, were enrolled in the study. Participants were randomly allocated into two groups: the intervention group (n = 65), which received oral L-arginine 3 g twice daily in addition to standard obstetric care, and the control group (n = 65), which received standard obstetric care alone. All participants were followed prospectively until delivery. Data were analyzed using independent t-test and chi-square test. A p value < 0.05 was considered statistically significant.

Results: Women receiving L-arginine demonstrated significantly greater pregnancy prolongation compared to controls. Improvement in umbilical artery resistance and cerebroplacental ratio was observed more frequently in the intervention group. Mean gestational age at delivery and mean birth weight were higher in the L-arginine group. NICU admissions and low Apgar scores were reduced among supplemented pregnancies, while perinatal survival improved.

Conclusion: Prolonged oral L-arginine supplementation in pregnancies complicated by IUGR with abnormal Doppler indices appears to improve uteroplacental perfusion, prolong gestation, and enhance neonatal outcomes. L-arginine may represent a useful adjunct therapy in the management of Doppler-compromised growth-restricted fetuses, particularly in settings where options for advanced fetal therapy are limited.

Keywords: Oral L-Arginine Supplementation, Pregnancy, Neonatal, Intrauterine growth restriction.

Introduction

Intrauterine growth restriction (IUGR) remains a major contributor to perinatal morbidity and mortality worldwide, particularly in developing countries where maternal nutritional deficiencies and placental insufficiency are prevalent. IUGR affects approximately 8–12% of pregnancies globally and is strongly associated with stillbirth, neonatal intensive care admission, and long-term

neurodevelopmental impairment [1,2]. According to the World Health Organization, placental insufficiency and uteroplacental vascular dysfunction are among the leading causes of fetal growth restriction and adverse perinatal outcomes [3]. Abnormal fetal Doppler indices, especially increased umbilical artery pulsatility index and reduced cerebroplacental ratio, are recognized markers of uteroplacental insufficiency and fetal hypoxia.

These Doppler abnormalities often precede clinical deterioration and are predictive of preterm delivery, operative birth, and perinatal mortality [4,5]. Management of Doppler-compromised IUGR remains challenging, as treatment options are limited and often focused on close surveillance and timely delivery rather than correction of the underlying placental dysfunction [6].

Nitric oxide (NO) plays a central role in regulating uteroplacental blood flow by mediating vascular smooth muscle relaxation and improving endothelial function. Reduced NO bioavailability has been implicated in the pathophysiology of placental insufficiency, leading to increased vascular resistance and impaired nutrient transfer to the fetus [7,8]. L-arginine, a semi-essential amino acid and precursor of nitric oxide, has therefore been proposed as a therapeutic agent capable of enhancing placental perfusion and improving fetal growth dynamics [9].

Several clinical studies have suggested that L-arginine supplementation may improve fetal growth parameters, reduce vascular resistance in the uteroplacental circulation, and prolong pregnancy in cases of IUGR (10–12). Oral L-arginine is particularly attractive as an intervention because it is inexpensive, widely available, and associated with minimal adverse effects when used in pregnancy [13]. Some randomized trials have demonstrated improved amniotic fluid index, increased birth weight, and delayed need for delivery following supplementation [14,15]. However, evidence remains inconsistent, particularly in pregnancies complicated by abnormal Doppler indices, where placental vascular pathology is more advanced.

Furthermore, most available studies have evaluated short-term supplementation or heterogeneous populations of growth-restricted fetuses, limiting the generalizability of their findings. There is a relative paucity of data specifically assessing prolonged L-arginine supplementation in pregnancies with Doppler-confirmed placental insufficiency and its impact on clinically meaningful outcomes such as pregnancy prolongation, neonatal survival, and need for intensive care [16,17]. Given the substantial burden of IUGR-related complications and the limited therapeutic options currently available, exploring safe and affordable interventions that can improve uteroplacental circulation is of considerable clinical importance. Therefore, the present randomized controlled trial was designed to evaluate the impact of prolonged oral L-arginine supplementation on pregnancy duration, Doppler indices, and neonatal outcomes in pregnancies complicated by IUGR with abnormal Doppler findings.

Material and Methodology

Study Design and Setting: This randomized controlled study was conducted over one year, from 01.05.2020 to 30.04.2021, at Department of Obstetrics and Gynaecology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan. Institutional Ethics Committee approval was obtained prior to commencement of the study, and written informed consent was taken from all participants.

Study Population: Pregnant women diagnosed with intrauterine growth restriction (IUGR) with abnormal fetal Doppler indices in the third trimester were recruited from antenatal clinics and obstetric wards.

Inclusion Criteria

- Singleton pregnancy
- Gestational age between 28–34 weeks
- Ultrasound-confirmed IUGR (estimated fetal weight <10th percentile)
- Abnormal Doppler indices (umbilical artery PI >95th percentile and/or CPR <5th percentile)
- Maternal age 18–40 years

Exclusion Criteria

- Multiple gestation
- Major congenital fetal anomalies
- Pre-existing maternal hypertension, renal disease, or diabetes mellitus
- Placental abruption or placenta previa
- Known hypersensitivity to L-arginine

Sample Size Calculation

Sample size was calculated using the formula for comparison of two means:

$$n = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{d^2}$$

Where:

- $Z_{\alpha/2}$= 1.96 for 95% confidence interval
- Z_{β}= 0.84 for 95% study power
- σ= Standard deviation of pregnancy prolongation (assumed 2.5 weeks from previous studies)
- d= Minimum clinically significant difference in pregnancy duration (assumed 1 week)

$$n = \frac{2(1.96 + 0.84)^2(2.5)^2}{(1)^2} n = \frac{2(2.8)^2 \times 6.25}{1} n$$
$$= 2 \times 7.84 \times 6.25 = 98$$

Thus, the minimum required sample size was 98 participants (49 per group)**.**

After adjusting for 20% attrition/non-compliance, the final sample size required was approximately 130 participants (65 per group), which was considered adequate to maintain 95% statistical power and strong study validity.

Participants were randomly allocated into two groups:

- Group A (Intervention group) – Oral L-arginine supplementation
- Group B (Control group) – Standard obstetric management

Each group contained 65 patients.

Randomization and Allocation: Participants were randomized using computer-generated random numbers with sealed opaque envelope allocation. The investigator performing Doppler measurements was blinded to treatment allocation to minimize observer bias.

Intervention

Group A: Participants received oral L-arginine 3 g twice daily for a prolonged duration until delivery or up to 4 weeks, whichever occurred first, along with routine antenatal care.

Group B: Participants received standard antenatal management without L-arginine supplementation.

Both groups were monitored for maternal and fetal well-being.

Data Collection

Baseline Assessment

- Maternal age, BMI, parity
- Gestational age at recruitment
- Blood pressure and hemoglobin
- Baseline ultrasound fetal biometry
- Amniotic fluid index
- Doppler indices (umbilical artery PI, middle cerebral artery PI, CPR)

Follow-up Parameters

- Weekly Doppler monitoring
- Fetal growth assessment
- Pregnancy prolongation (weeks gained after enrolment)
- Mode of delivery
- Birth weight
- APGAR score at 1 and 5 minutes
- NICU admission
- Perinatal morbidity and mortality

Outcome Measures

- Duration of pregnancy prolongation (weeks)
- Improvement in Doppler indices
- Birth weight and gestational age at delivery
- NICU admission rate
- Neonatal morbidity

Statistical Analysis: Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± SD, and categorical variables as percentages.

- Independent t-test was used for comparison of means
- Chi-square test was used for categorical variables
- Pearson correlation assessed association between Doppler changes and neonatal outcomes
- A p-value <0.05 was considered statistically significant

Results

A total of 130 pregnant women with IUGR and abnormal Doppler indices were enrolled and randomized into two groups:

- L-arginine group (n = 65)
- Control group (n = 65)

Both groups were comparable at baseline with respect to maternal age, parity, gestational age at recruitment, and Doppler indices ($p > 0.05$).

Table 1. Baseline Maternal and Obstetric Characteristics

Parameter	L-arginine Group (n=65)	Control Group (n=65)	p-value
Mean maternal age (years)	27.9 ± 4.1	28.3 ± 4.5	0.62
Primigravida (%)	38 (58.5%)	36 (55.4%)	0.71
Mean gestational age at recruitment (weeks)	32.4 ± 1.9	32.2 ± 2.1	0.58
Mean BMI (kg/m²)	24.6 ± 2.7	24.9 ± 2.9	0.64
Severe Doppler abnormality (%)	41 (63.1%)	39 (60.0%)	0.71

Baseline demographic and obstetric parameters were statistically comparable between groups, indicating proper randomization and minimizing confounding bias.

Table 2: Pregnancy Duration and Doppler Improvement

Outcome	L-arginine Group (n=65)	Control Group (n=65)	p-value
Mean pregnancy prolongation (weeks)	2.8 ± 1.2	1.6 ± 1.0	**0.001**
Doppler improvement (%)	39 (60.0%)	22 (33.8%)	**0.003**
Improvement in CPR (%)	42 (64.6%)	24 (36.9%)	**0.002**
AFI improvement (%)	36 (55.4%)	21 (32.3%)	**0.008**

The L-arginine group demonstrated:

- 75% longer pregnancy prolongation compared to controls
- ~26% higher Doppler improvement rates
- Significant improvement in placental perfusion indices

All findings were statistically significant ($p < 0.01$).

Table 3: Neonatal Outcomes

Neonatal Outcome	L-arginine Group (n=65)	Control Group (n=65)	p-value
Mean birth weight (kg)	2.18 ± 0.39	1.92 ± 0.41	**0.004**
Preterm delivery (%)	19 (29.2%)	31 (47.7%)	**0.03**
NICU admission (%)	17 (26.2%)	30 (46.2%)	**0.02**
Low APGAR at 5 min (%)	11 (16.9%)	23 (35.4%)	**0.01**
Perinatal mortality (%)	2 (3.1%)	6 (9.2%)	0.14

Neonates in the L-arginine group showed:

- 13% reduction in preterm delivery
- 20% lower NICU admission rate
- Significantly higher birth weight
- Improved immediate neonatal adaptation

Perinatal mortality was lower in the intervention group, though not statistically significant, possibly due to limited sample size.

Discussion

Intrauterine growth restriction (IUGR) associated with abnormal Doppler indices reflects placental insufficiency, impaired uteroplacental perfusion, and chronic fetal hypoxia. Reduced nitric-oxide–mediated vasodilatation in placental circulation is a key pathophysiological mechanism, leading to increased vascular resistance and compromised fetal nutrient delivery. L-arginine, a substrate for nitric oxide synthase, enhances nitric oxide production and improves endothelial function, thereby potentially improving placental perfusion and fetal growth.

Effect on Pregnancy Duration: In the present study, prolonged oral L-arginine supplementation resulted in a significant prolongation of pregnancy by approximately 1.2 weeks compared with controls (2.8 ± 1.2 vs 1.6 ± 1.0 weeks, $p = 0.001$). Similar prolongation has been observed in previous trials, where arginine therapy extended gestation by 1–2 weeks in pregnancies complicated by placental insufficiency and Doppler abnormalities [1,2].

A randomized study by Sieroszewski et al. reported that arginine therapy prolonged pregnancy in IUGR cases by nearly 10% compared with placebo, attributed to improved uteroplacental blood flow and reduction in fetal hypoxic stress [3]. Likewise, Rytlewski et al. showed improvement in uterine artery resistance indices following supplementation, which allowed pregnancies to continue longer with reduced emergency deliveries [4].

The prolongation of gestation observed in our study likely resulted from improved fetoplacental circulation, stabilization of Doppler abnormalities, and delayed onset of fetal compromise.

Effect on Doppler Indices and Placental Perfusion: In this study, 60.0% of fetuses in the intervention group demonstrated Doppler improvement compared with 33.8% in the control group ($p = 0.003$). These findings align with prior reports demonstrating improvement in umbilical artery pulsatility index and cerebroplacental ratio following arginine therapy [5,6].

Nitric oxide derived from L-arginine enhances placental vasodilatation, decreases vascular resistance, and improves oxygen delivery to the fetus. Clinical studies indicate that arginine supplementation reduces uterine artery resistance by approximately 15–25%, thereby improving fetoplacental circulation [7].

Improved Doppler indices in our study support the hypothesis that L-arginine acts primarily through endothelial and vascular mechanisms.

Effect on Birth Weight and Neonatal Outcomes: NICU admission was significantly lower in the L-arginine group (26.2% vs 46.2%, $p = 0.02$). Preterm delivery was also reduced (29.2% vs 47.7%, $p = 0.03$), and mean birth weight was significantly higher (2.18 ± 0.39 kg vs 1.92 ± 0.41 kg, $p = 0.004$).

These improvements mirror findings from previous studies. Lucotti et al. observed a 15–20% increase in birth weight among IUGR fetuses receiving arginine supplementation [8].

Another controlled study reported higher Apgar scores and reduced NICU admissions among treated pregnancies, suggesting improved fetal oxygenation and metabolic stability [9].

Arginine supplementation has also been shown to improve placental amino-acid transport and fetal protein synthesis, contributing to enhanced growth and neonatal health [10].

Comparison with Previous Literature: Overall, our findings are consistent with available literature supporting the role of L-arginine in improving outcomes in placental insufficiency. Meta-analyses indicate that arginine therapy:

- Improves birth weight in 60–70% of IUGR pregnancies
- Improves Doppler parameters in 50–75%
- Reduces preterm delivery rates by 10–20%
- Improves neonatal survival by 5–10%

These percentages are comparable to those observed in our study, reinforcing the reproducibility of the intervention's benefits [11–13].

Mechanistic Interpretation

The beneficial effects observed in our study can be explained by several mechanisms:

1. Enhanced nitric oxide production, causing vasodilatation of placental vessels
2. Improved endothelial function, reducing uteroplacental resistance
3. Enhanced nutrient and oxygen transport to the fetus
4. Reduction of fetal hypoxia-induced stress response
5. Improved placental metabolism and amino-acid transport

These physiological mechanisms collectively improve fetal growth potential and delay delivery necessitated by fetal distress.

Strengths of the Study

- Prospective design with adequate sample size (n = 130)
- One-year recruitment minimizing seasonal bias
- Inclusion of Doppler-confirmed placental insufficiency
- Evaluation of both maternal and neonatal outcomes
- Statistically robust findings with significant p-values

Limitations

- Single-center study
- Lack of biochemical nitric-oxide measurement
- No long-term neurodevelopmental follow-up
- Possible dietary variations influencing arginine metabolism

Future multicenter randomized trials with long-term neonatal follow-up are recommended.

Conclusion

Prolonged oral L-arginine supplementation in pregnancies complicated by IUGR with abnormal Doppler indices significantly improves uteroplacental circulation, prolongs pregnancy duration, enhances birth weight, and reduces adverse neonatal outcomes.

The therapy appears safe, inexpensive, and physiologically targeted, making it a promising adjunctive intervention in the management of placental insufficiency. Routine use in carefully selected high-risk pregnancies may contribute to improved perinatal outcomes, although larger randomized trials are needed to establish standardized treatment protocols.

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