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Research Article

Effect of L-Arginine Supplementation in treatment of Intrauterine Fetal Growth Restriction

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Abstract

Background: Adult phenotypes may be significantly impacted by fetal development, which is a critical period in humans. The pathological growth restriction of the embryo within the uterus continues to be a significant public health concern known as intrauterine growth restriction (IUGR). Small for gestational age (SGA) and the aforementioned term are frequently employed interchangeably. **Aim and objectives;** to examine the impact of L-Arginine supplementation in treatment of Intra-uterine fetal Growth Restriction at Minia Maternity University Hospital. **Methodology:** This research was done on 60 pregnant females with IUGR in the Department of Obstetrics and Gynecology, MMUH, cases were separated into two groups: Group A: 30 pregnant women received L-Arginine and Group B: 30 pregnant women received placebo. **Results:** There was no significant variance in age, BMI, parity, gravidity & GA at assessment among both groups (P-value > 0.05). There was statistically significant higher post-treatment EFW in L-Arginine treated than placebo group (P-value < 0.05). **Conclusion**: L-Arginine may enhance neonatal outcome and fetal condition after delivery in expectant women with IUGR by extending the duration of pregnancy and increasing the likelihood of delivering a child with a greater birth weight, an improved Apgar score & a reduced incidence of cesarean sections. Nevertheless, these advantages must be validated through a larger, more-powered investigation utilizing a larger sample size.

Keywords: Intrauterine growth restriction (IUGR), L-Arginine. NO. Fetal outcome.

Introduction

The genetic potential of the fetus is limited by Fetal growth restriction (FGR)[1]. The estimated fetal weight (EFW) must be under the 10th percentile for the usual standard of gestational age in order to diagnose FGR [2]. Risk of adverse perinatal outcomes and long-term complications is increased with FGR, according to epidemiological research[4,5]

The primary endogenous vasodilator involved in controlling placental circulation is nitric oxide (NO)[5]. Placental trophoblast invasion and vascular tone and resistance regulation are both influenced by it [6].

Three different forms of nitric oxide synthase (NOS) are involved in the production of NO from L-Arginine: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). One of the primary roles of the NO generated by vascular endothelial cells—which is mostly caused by the action of eNOS—is to regulate blood perfusion and expand blood vessels [7].

One competitive inhibitor of NOS that decreases NO generation is asymmetric dimethylarginine, or ADMA. There are nine isoforms of the protein L-Arginine methyltransferase (PRMT), the most common of which is PRMT1, which is responsible for ADMA synthesis in humans[8].

Two isoforms of dimethylarginine dimethylaminohydrolase (DDAH)—DDAH1 and DDAH2—are responsible for ADMA degradation. The primary metabolic locations of ADMA are consistent with the extensive in vivo expression of DDAH1, while DDAH2 is mostly present in placental tissues. Endothelial dysfunction, participation in cardiovascular illnesses, pre-eclampsia (PE), and reduced vasodilation due to inhibited NOS activity are all outcomes of high ADMA levels [9]

Angiogenic factors, such as vascular endothelial growth factor (VEGF) and placental growth factor (PLGF), promote angiogenesis in the placenta and are essential for the development and maintenance of the placenta's function. In its role as angiogenesis regulator, NO promotes the production of VEGF and the proliferation of endothelial cells [10].
The aim of the research was to evaluate the impact of L-Arginine supplementation in treatment of Intra-uterine FGR at MMUH, Primary outcome improvement in growth velocity, Secondary outcome improvement in amniotic fluid or Doppler parameters if impaired.

Patients and Methods

This clinical research was done In the Department of Obstetrics and Gynecology, Minia Maternity University Hospital between January-December 2023 for 4 weeks after taking medical history, Clinical examination and informed written consent from all subjects and after being approved by the local ethical Committee; on cases with their fetal weight below 10th percentile for their gestational age with the following criteria:

Inclusion Criteria: Singleton pregnancy**,** Gestational age among ±28 Weeks and ± 34 weeks**,** Average liquor or reduced liquor and Normal or impaired Doppler indices
Exclusion criteria: Any maternal medical disorders e.g. (Hypertension, Diabetes, PE, Systemic lupus erythromatosis and etc.), pre-mature rupture of membrane and Presence of any congenital fetal mal-formation**.**

This randomized control research was done in the Department of Obstetrics and Gynecology Minia University. The research involved 60 randomly selected pregnant women identified as having IUGR.
Group (A): 30 cases received L-Arginine (BLUE OX® GINSENG fortified with ZINC. Dietary Supplement. Vanillin Taste. – Red Ginseng – L-Arginine – Wheat Germ Oil – Lecithin – Zinc Gluconate, Manuf. By: Nutrixia For: NEW CHAPTER, Sole Agent: MARVEL, Made in Egypt). Dose: 300 mg. 3 times Per day (case group)
Group (B): 30 cases received only Placebo (control group)

Methods:
Patients of both groups were subjected to the following: Complete history taking (Personal history, Past medical history and Obstetric history), Complete clinical examination (General examination, Estimation of gestational age) and Laboratory Investigations (CBC, Random blood sugar, Kidney functions test, Liver function tests and Coagulation profile)
The follow-up of both groups include: Weekly Obstetric ultrasound and Colour Doppler Blood Flow.
After birth neonates were evaluated: Birth weight [Time Frame: 15 min] and Apgar score [Time Frame: at one and five minutes after birth]

Ethical considerations: The procedure for utilizing L-Arginine was approved by the Institutional Ethical Committee. During enrollment, all subjects provided complete informed consent in straightforward language.

Statistical Analysis

The statistical analysis was done utilizing the SPSS statistical software, version 16.0 (SPSS Inc., Chicago, IL, USA). All of the data were reported as mean ± standard. A P value that was less than 0.05 was considered significant. For the data that were normally distributed, the student t-test was utilized.

Results

Table (1): Comparison of demographic and obstetric data the studied groups

		L-Arginine (N = 30)		placebo (N = 30)		independent student t-test/chi-square test	
		Mean	**SD**	**Mean**	**SD**	**t/x2**	**P-value**
Age (year)		26.70	3.96	27.87	3.88	-1.152	0.254
BMI		24.90	2.16	25.13	1.98	-0.437	0.664
GA at assessment(wk)		32.13	0.78	32.10	0.80	0.163	0.871
Gravidity	**PG**	2	6.7%	1	3.3%	0.642	0.887
	G1	9	30%	8	26.7%		
	G2	12	40%	12	40%		
	G3	7	23.3%	9	30%		
Parity	**P0**	11	36.7%	9	30%	0.450	0.799
	P1	12	40%	12	40%		
	P2	7	23.3%	9	30%		

There was no significant variance in age, BMI, parity, gravidity & GA at assessment among both groups.

Table (2): Comparison of Pre and Post Treatment EFW (gm) distribution of the studied groups.

	L-Arginine (N = 30)		Placebo (N = 30)		chi square test	
Pre-treatment EFW	**N**	**%**	**N**	**%**	**X^2**	**P-value**
≤ 1100 (gm)	3	10	3	10	0.301	0.960
1101-1300 (gm)	14	46.7	16	53.3		
1301-1500 (gm)	7	23.3	6	20		
1501-1700 (gm)	6	20	5	16.7		
Total	30	100	30	100		
Post-treatment EFW	**N**	**%**	**N**	**%**	**X^2**	**P-value**
≤ 1500 (gm)	0	0	2	6.7	13.223	0.010
1501-1700 (gm)	5	16.7	16	53.3		
1701-1900 (gm)	17	56.7	9	30		
1901-2100 (gm)	6	20	3	10		
2101-2300 (gm)	2	6.7	0	0		
Total	30	100	30	100		

There is statistically insignificant variance among L-Arginine treated and placebo groups in pre-treatment FEW distributions that showed 10% in each group were ≤ 1100 gm, 46.7% vs 53.3% were 1101-1300 gm, 23.3% vs 20% were 1301-1500 gm, 20% vs 16.7% were 1501-1700 gm. There is statistically significant greater EFW in L-Arginine treated than placebo groups in post-treatment EFW distributions that showed 16.7% vs 53.3% were 1501-1700 gm, 56.7% vs 30% were 1701-1900 gm, 20% vs 10% were 1901-2100 gm, 6.7% vs 0% were 2101-2300 gm while those with FEW ≤ 1500 were 6.7% in placebo group vs none in L-Arginine treated group.

Table (3): Comparison of mean value of pre- and post-treatment EFW (gm) among both groups

	L-Arginine (N = 30)		Placebo (N = 30)		independent student t-test	
	Mean	**SD**	**Mean**	**SD**	**T**	**P-value**
Pre-treatment EFW (gm)	1324.18	177.04	1296.12	156.27	0.651	0.518
Post-treatment EFW (gm)	1821.73	153.85	1645.17	160.49	4.350	<0.0001

There was no statistically significant variance in Pre-treatment EFW among both groups (1324.18±177.04 vs 1296.12±156.27; P-value > 0.05). There is statistically significant higher post-treatment FEW in L-Arginine treated than placebo groups (1821.73±153.85 vs 1645.17±160.49; P-value < 0.05).

Table (4): Comparison of birth weight (gm) distribution amongst the studied groups.

	L-Arginine (N = 30)		Placebo (N = 30)		chi-square test	
	N	**%**	**N**	**%**	**X^2**	**P-value**
≤ 1600 (gm)	0	0	5	16.7	20.943	<0.0001
1601-1800 (gm)	4	13.3	15	50		
1801-2000 (gm)	12	40	5	16.7		
2001-2200 (gm)	8	26.7	5	16.7		
2201-2400 (gm)	6	20	0	0		
Total	30	100	30	100		

There is statistically significant higher birth weight in L-Arginine treated than placebo groups that showed 13.3% vs 50% were 1601-1800 gm, 40% vs 16.7% were 1801-2000 gm, 26.7% vs 16.7% were 2001-2200 gm, 20% vs 0% were 2201-2400 gm while those with birth weight ≤ 1600 were 16.7% in placebo group vs none in L-Arginine treated group.

Table (5): Comparison of birth weight mean value between the studied groups

	L-Arginine (N = 30)		Placebo (N = 30)		independent student t-test	
	Mean	**SD**	**Mean**	**SD**	**t**	**P-value**
Birth weight (gm)	2021.10	158.62	1789.70	176.29	5.137	0.0001

There is a statistically significant higher birth weight in L-Arginine treated than placebo group (2021.10±158.62vs 1789.70±176.29; P-value < 0.05).

Table (6): Comparison of pregnancy outcome between the studied groups

		L-Arginine (N = 30)		Placebo (N = 30)		chi-square test	
		N	%	N	%	x2	P value
Delivery	**NVD**	11	36.7%	10	33.3%	0.073	0.787
	CS	19	63.3%	20	66.7%		
IUFD	**No**	30	100%	27	90%	3.158	0.076
	Yes	0	0%	3	10%		
NICU admission	**No**	20	66.7%	16	53.3%	1.111	0.292
	Yes	10	33.3%	14	46.7%		
neonatal sex	**Male**	16	53.3%	20	66.7%	1.111	0.292
	Female	14	46.7%	10	33.3%		

Despite that NICU admission frequency in females who did not receive L-Arginine than those who received L-Arginine (33.3% vs 46.7%) but the variation was statistically insignificant. Also, IUFD was higher in females who did not receive L-Arginine than those who received L-Arginine but the distinction was statistically insignificant. there was a statistically insignificant distinction in a mode of delivery and fetal sex between females who did not receive L-Arginine and those who received L-Arginine.

Discussion

With its effects extending beyond the newborn phase to include the adult phenotype and quality of life, IUGR, a syndrome characterized by pathological limitations on fetal development in utero, remains a significant public health concern [11].

IUGR is a term utilized to describe the rate at which a fetus develops in relation to its potential growth for a foetus of a particular race and gender. [12].

In the current thesis demographic characteristics of thestudied groups showed that, there was no significant differencein age, BMI, parity, gravidity and GA at assessment between both groups (P-value > 0.05). In Patients of group A mean age was 26.70 ± 3.96 years, mean BMI was 24.90±2.16 Kg/m^2, the mean GA was 32.13±0.78 week. While, in group B mean age was 27.87±3.88 years, mean BMI was 25.13±1.98 Kg/m^2, the mean GA was 32.10±0.80 week.

In agreement was a randomized control study by Mary et al., sought to assess how administering L-Arginine affected the outcome for the foetus in pregnancies impacted by IUGR. A total of sixty pregnant cases with IUGR were selected at random for the research. The case group consisted of 30 women who had conventional therapy plus 3 g of L-Arginine daily, whereas the control group involved 30 cases who received only routine therapy. There was not a significant distinction among the two groups concerning age, BMI, or gestational period. [13].

In the same line Winer et al., Data were gathered from 43 cases whose fetuses were found to have severe vascular IUGR below the third percentile. Of these patients, 21 were assigned to the L-Arginine group & 22 to the placebo group. The average ages of the two groups were 28.2±5.9 and 29.3±4.2 years, correspondingly; additionally, the average gestational age was 28.0±2.0 weeks, contrasted with 27.7±2.1 weeks, correspondingly. There was no significant variance among L-Arginine and the placebo group in demographic and obstetric data (P > 0.05) [14].

EFW after receiving L-Arginine treatment was statistically significantly higher than before treatment. Regarding EFW distributions, most pre-treatment cases (80 %) have EFW ≤1500gm while after treatment most cases (83.3%) have EFW more than 1700gm.

In agreement was several studies Bhargavi et al.,[11], Lampariello et al.,[15], Hegda et al.,[16], and Zhu et al.,[17] demonstrated that EFW after receiving L-Arginine treatment was significantly higher than before treatment.

In the current study, Post-treatment EFW was statistically significantly higher than pre-treatment EFW in L-Arginine treated (1324.18±177.04 vs 1821.73±153.85; P-value < 0.05). Also, in placebo group (1296.12±156.27vs 1645.17±160.49; P-value > 0.05).

These results were closed to those obtained by Chen et al.,[12] who found that there were statistically significant higher in Post-treatment EFW when compared with pre-treatment EFW in L-Arginine-treated patients.

The current data displayed that, there was statistically significant higher post-treatment EFW in L-Arginine treated than placebo group (1821.73±153.85 vs 1645.17±160.49; P-value < 0.05).

Similar findings were stated by Lampariello et al.,[15] Nevertheless, in another research Winer et al.,[14] stated no significance variance amongst the group received an L-Arginine supplement contrasted with control group.
Our results detected that, there was statistically significant greater birth weight in L-Arginine treated than placebo groups.

Neonatal weights in group II A were 1.90 ± 0.3 kg, while in group II B they were 1.77 ± 0.53 kg (P (0.05)). The L-Arginine treatment group had a greater gestational age at birth (35.68 ± 2.80 in group II A contrasted with 34.0 ± 3.50 in group II B). The newborn clinical characteristics of the population under study were comparable in the L-Arginine and placebo groups at birth, as stated by Winer et al.,[14]. Groups did not differ in terms of birth weight.

Results for baby weight immediately after birth in patients given L-Arginine were as follows: 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).

Despite that NICU admission frequency in females who did not receive L-Arginine than those who received L-Arginine (33.3% vs 46.7%) but the difference was statistically insignificant. Also, IUFD was higher in females who did not receive L-Arginine than those who received L-L-Arginine but the difference was statistically insignificant. there was statistically insignificant variance in mode of delivery and fetal sex between females who did not receive L-Arginine and those who received L-Arginine.

Singh et al.,[18] reported that, In the control group, a greater number of neo-nates essential resuscitation and venti-lating than in the L-Arginine group. NICU hospitalization was necessary for 30.76 and 33.33% of newborns in the L-Arginine group and control trial, with hospital stays of 9.75 ± 6.0 and 11.38 ± 8.5 days, correspondingly, with no statistically significant distinction. The rate of neonatal death was lower in cases with IUGR treated with L-Arginine (15.3% vs 12.5%). In accordance, Mary et al.,**[13]** found that the prevalence of vaginal delivery was 76.67 percent in the case group and 73.33 percent in the control group. The P value was judged to be statistically insignificant (p>0.05).

In another investigation, Bhargavi et al.,**[11]** displayed that Out of the total of 124 instances where L-Arginine was admini-stered, 85(69%) resulted in full-term deliveries while 39(31%) resulted in lower segment cesarean section.

Conclusion

In conclusion, L-Arginine given to pregnant women with IUGR may enhance fetal condition and neonatal prognosis following delivery by extending preg-nancy, resulting in a child with a greater birth weight, a greater Apgar score & and a lower risk of caesarean sections. Nevertheless, these advantages must be confirmed by a larger, more powerful investigation with a larger sample size.

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