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Effect of L-Arginine on Intrauterine Growth Restriction Fetuses Measured by Birth weight a Randomised Controlled Trial

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Abstract: Background An area of fetal medicine research interest is to determine whether the enhancement of NO productivity could boost fetal growth patterns. There are attempts to the treatment of IUGR pregnancies by L-Arginine but the results are still inadequate**. Objective:** This study investigate the effect of L-arginine supplementation on fetal growth and pregnancy outcome. **Methodology** A prospective interventional randomized controlled research trial, conducted at Ain Shams University Maternity Hospital. From 2017till 2018**,** 260 pregnant females as research study Categorized randomly into two equal numbered research groups, 12 cases were dropped out due to loss of contact with them. Finally249 pregnant women were diagnosed with IUGR and have been categorized into two groups according to the results: **Group I:**125 pregnant women with IUGR received 3g L_arginine and 75 mg of Acetyle salicylic daily. **Group II:** 124 pregnant women with IUGR received 75mg Acetylesalicylicic acid daily only. Both research groups were followed up by daily fetal movement counting, day after daycardiotocography (CTG), doppler twice weekly, Pelvic sonographic assessment weekly for: Head Circumference (HC), Abdominal circumference (AC), Femur Length (FL), Estimated fetal weight (EFW), Amniotic fluid index (AFI) or Mean Vertical Pocket**. Results** The Rate of estimated fetal weight increase, birth weight and Apgar score were statistically significantly higher among L-Arginine research group than among control group (p values<0.001). NICU admission and preterm delivery were statistically significantly less frequent among L-Arginine group than among control group (p value<0.001). **Conclusions L-arginine** seems to be useful management agent for improving asymmetrical mild IUGR fetuses viaraising nitric oxide levels which enhances the fetomaternal circulatory functional performance.

[Moustafa I. Ibrahim, Hayam F. Mohammad, Manar L. Younis Ch. **Effect of L-Arginine on Intrauterine Growth Restriction Fetuses Measured by Birth weight a Randomised Controlled Trial.** *Nat Sci* 2019;17(12):158-166]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 22. doi:10.7537/marsnsj171219.22.

Keywords: L-arginine, IUGR, nitric oxide.

1. Introduction

Intrauterine growth restriction is a crucial issue as regards perinatal care, causing perinatal mortality and morbiditysequlaeaffectingaround8% of pregnancies. IUGR is clinically defined as a fetal weight under the 10thcentile for gestational age. The probability of IUGR is higher among severe SGA infants**. 1,2,3.**

IUGR could be categorized into two main types according to the causative path physiological origin as non–placenta mediated growth restriction, e.g structural or chromosomal anomaly, inborn errors of metabolism and fetal infection; and placental-mediated growth restriction e.g due to Maternal issues pathologically affecting placental transfer function low pre-pregnancy weight, under nutrition, medical diseases affecting placental implantation and vasculature such as pre-eclampsia, autoimmune disease**.4,5,6.**

Furthermore IUGR is categorized into 2 types symmetrical when the fetus is small but well-proportioned and asymmetrical when the fetus abdominal growth is restricted. Different wide spectrum management approaches integrated with extensive research efforts are undertaken to avoid fetal restrictive growth issues. Prior research efforts and management protocols implemented the usage of aspirin to prevent placental insufficiency, however, there is insufficient evidence for such therapy to be routinely indicated for fetal growth restriction prevention**.7,8,9.**

Interestingly it was revealed and displayed at cellular and molecular levels that the maintainenece of the physiological Vascular tone is critical in maintenance of feto placental perfusion. It was observed by prior groups of investigators that Nitric Oxide synthesized from the placental vascular system is of cornerstone importance in maintenance adequate placental blood flow by decreasing the placental

vascular tone, decreased Nitric Oxide availability could have a critical role in the path physiological origin of IUGR. Consequently, nitric oxide donor segglyceryltrinitrate and isosorbidemononitrate precursors (L-arginine) and NO mediator as sildenafil citrate could be a valuable management protocol possible for IUGR issues**.10,11,12.**

An area of fetal medicine research interest is to determine whether the enhancement of NO productivity could boost fetal growth patterns. There are attempts to the treatment of IUGR pregnancies by L-Arginine but the results are still inadequate**.13,14,15.**

Aim

The current study was to investigate the effectiveness of L-Arginine in enhancement of clinical pregnancy outcomes in IUGR cases.

Methodology

Aprospective interventional randomized controlled research trial, conducted at Ain Shams University Maternity Hospital. from 2017till 2018,260 pregnant females as research study Categorized randomly in to two equal numbered research groups inclusive research criteria Involved the following all pregnant women diagnosed with IUGR from 28 gestational weeks, singleton gestations, no maternal systemic disease, no congenital fetal malformation, estimated fetal weight below 10th centile**, exclusive research criteria** involved the following all pregnant woman diagnosed with IUGR before 28gestational weeks, multifetal gestations, maternal systemic disease, congenital fetal malformation. All recruited research study subjects have undergone full clinical history taking and examination full sonographic2 Dassessmente. g Bi-partial diameter, head circumference, abdominal circumference, femur length, estimated fetal weight estimated fetal weight percentile, amniotic fluid index Sonographic diagnosis of growth restricted fetuses have been on Hadlock formula for Estimated fetal weight (EFW) which is obtained by the ultrasound apparatus used in this study.

Hadlock 1: Log10BW=1.304+0.005251(AC) + 0.01938 (FL) 0.00004(Acx FL)

After obtaining a reliable gestational age and best estimate of the fetal weight (EFW), Hadlock fetal growth curve and table were be used to assign an EFW growth percentile. Fetuses with an EFW below the 10thcentile.

Cases within the first research group were administered oral L-arginine 3000mg/day (L-ARGININE 1000mg by PuRITAN'S PRIDE, INC.) till delivery and Acetylesalicylic acid 75mg once daily (Ezacard 75mg). Cases within the second research group were administered Acetylesalicylic acid 75mg once daily (Ezacard).

Both research groups were followed up by daily fetal movement counting, day after day CTG, doppler twice weekly, Pelvicsonographic assessment weekly for: HC, AC, FL, EFW, AFIor Mean Vertical Pocket**.**

The study was approved by Ethical committee of the Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges while qualitative variables were presented as number and percentages. The comparison between complicated and non complicated was done using Chi-square test and/or Fisher exact test for qualitative data and independent t-test for quantitative data. Logistic regression analysis univariate and multivariate by Backward (Wald) method was used to assess the most important predictors of complications. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant at the level of P-value < 0.05.

Results

A total of 260 pregnant women were diagnosed with IUGR after 28 weeks gestation were enrolled to the study and were divided into two groups.

Group A: received oral L-arginine 3000mg/day till delivery and Acetylsalicylic acid 75mg once daily. in this group 5 cases were missed.

Group B: received Acetylesalicylic acid 75mg once daily.6 cases were missed in this group.

12 cases were dropped out due to loss of contact with them. Finally249 pregnant women were diagnosed with IUGR and have been categorized into two groups according to the results: **Group I:** 125 pregnant women with IUGR. **Group II:** 124 pregnant women with IUGR.

3. Results

Table 1 revealed there was no statistical significant difference between L-Arginie and control research groups as regards demographic characteristics. b (age, BMI, parity, p values=0.713, 0.704, 0.448conseutively)

There was no statistical significant difference between L-Arginie and control research groups as regards basal Umbilical artery PI (p value =0.195). Umbilical artery PI significantly improved in both group (p value<0.001). Umbilical artery PI at delivery was statistically significantly lower among L-Arginine

research group than among control group (p value<0.001). Umbilical artery PI reduction was statistically significantly higher among L-Arginine research group than among control research group (p value <0.001). Table (2). There was no statistical significant difference between L-Arginie and control research groups as regards basal Umbilical artery RI (p value=0.164). Umbilical artery RI was statically significantly improved in both research groups (p value<0.001). Umbilical artery RI at delivery was statistically significantly lower among L-Arginine research group than among control research group (p value<0.001). Umbilical artery RI reduction was statistically significantly higher among L-Arginine research group than among control research group (p value<0.001). Table (3).

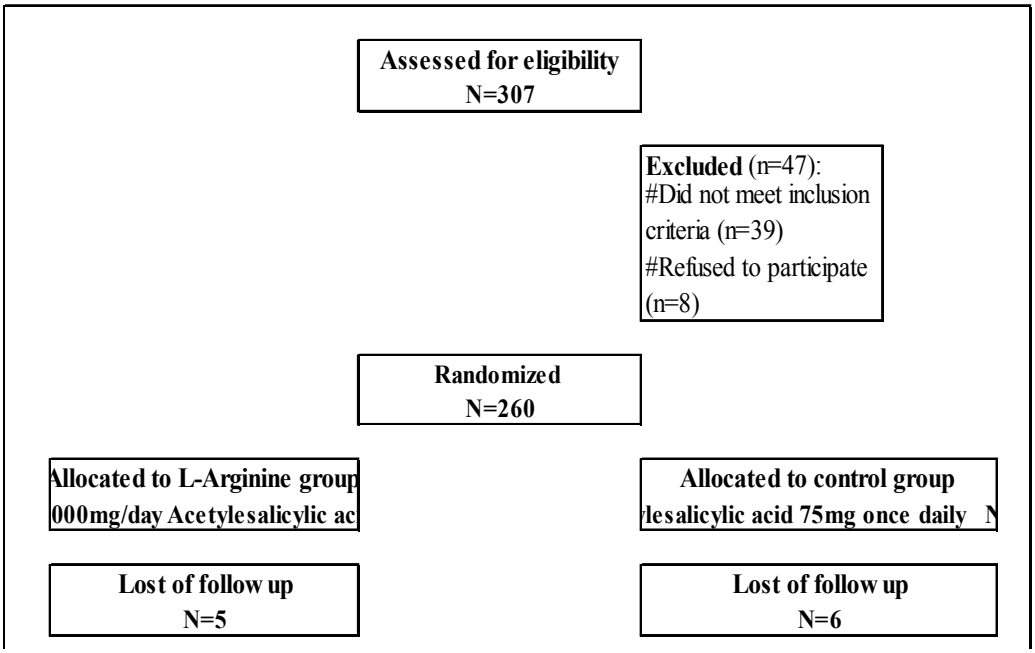

Figure (1): Flow chart of the studied cases

There was no statistical significant difference between L-Arginine and control research groups as regards basal Umbilical artery SD (p value=0.160). Umbilical artery SD statistically significantly improved in both research groups (p value<0.001). Umbilical artery SD at delivery was statistically significantly lower among L-Arginine group than among control research group (p value<0.001). Umbilical artery SD reduction was statistically significantly higher among L-Arginine research group than among control group (p value<0.001). Table (4).

There was no statistical significant difference between L-Arginine and control research groups as regards basal AFI (p value=0.829). AFI statistically significantly improved in both research group (p value<0.001). AFI at delivery and AFI elevation have been statistically significantly higher among L-Arginine research group than among control group (p value<0.001). Table (5).

There was no statistical significant difference between L-Arginine and control groups as regards basal GA (p value=0.103). GA statistically significantly increased in both research group (p value<0.001). GA at delivery and GA prolongation have been statistically significantly higher among L-Arginine research group than among control group (p value <0.001). Table (6).

There was no statistical significant difference between L-Arginine and control research groups as regards basal fetal weight (p value=0.203). Fetal weight statistically significantly increased in both research group (p value<0.001). Fetal weight at delivery and fetal weight increase were significantly higher among L-Arginine group than among control group (p value<0.001). Table (7).

The Rate of estimated fetal weight increase was statistically significantly higher among L-Arginine research group than among control group (p values<0.001) Table (8).

Apgar scores were statistically significantly higher among L-Arginine research group than among control research group (p value<0.001). NICU admission and preterm delivery were statistically significantly less frequent among L-Arginine group than among control group (p value<0.001). Table (9).

Table (1): Demographic characteristics among the studied groups

Variables	Measures	L-Arginie (N=125)	Control (N=124)	P
Age (years)	Mean±SD	29.0±3.0	29.1±3.2	^0.713
	Range	21.0–38.0	21.0–36.0	
BMI (kg/m^2)	Mean±SD	26.9±2.5	26.8±2.3	^0.704
	Range	21.0–31.9	21.6–32.3	
Parity (n, %)	Primi	30 (24.0%)	35 (28.2%)	#0.448
	Multi	95 (76.0%)	89 (71.8%)	

^Independent t-test, #Chi square test

Table (2): Umbilical artery PI among the studied groups

Time	Measures	L-Arginine (N=125)	Control (N=124)	P
Level				
Before	Mean±SD	1.23±0.21	1.26±0.17	0.195
	Range	0.66–1.74	0.89–1.59	
Delivery	Mean±SD	0.94±0.17	1.04±0.19	<0.001*
	Range	0.53–1.31	0.67–1.49	
Reduction	Mean±SD	0.30±0.11	0.23±0.11	<0.001*
	Range	0.03–0.64	0.01–0.48	
Reduction grades	0.00–	18 (14.4%)	33 (26.6%)	& <0.001*
	0.20–	89 (71.2%)	87 (70.2%)	
	≥0.40	18 (14.4%)	4 (3.2%)	
#P		<0.001*	<0.001*	
Value of L-Arginine in decreasing PI				
Items		Mean±SD	95% CI	
Reduction		0.07±0.01	0.04–0.10	
Value of L-Arginine in decreasing PI ≥0.20				
		Value	95% CI	
Rate elevation		12.2%	1.4%–21.8%	
Efficacy		16.6%	1.8%–31.7%	
Relative Rate		1.166	1.02–1.32	
Number needed to treat		8.2	4.6–72.0	

^Independent t-test, #Paired t-test, & Chi square test. *Significant. CI: Confidence interval

Table (3): Umbilical artery RI among the studied groups

Time	Measures	L-Arginie (N=125)	Control (N=124)	P
Level				
Before	Mean±SD	0.74±0.05	0.75±0.03	0.164
	Range	0.62–0.83	0.66–0.81	
Delivery	Mean±SD	0.60±0.07	0.69±0.05	<0.001*
	Range	0.47–0.77	0.59–0.80	
Reduction	Mean±SD	0.14±0.07	0.05±0.04	<0.001*
	Range	0.01–0.32	0.01–0.17	
Reduction grades	0.00–	28 (22.4%)	102 (82.3%)	& <0.001*
	0.10–	81 (64.8%)	22 (17.7%)	
	≥0.20	16 (12.8%)	0 (0.0%)	
#P		<0.001*	<0.001*	
Value of L-Arginie in decreasing RI				
Item		Mean±SD	95% CI	
Reduction		0.09±0.01	0.07–0.10	
Value of L-Arginie in decreasing RI ≥0.10				
		Value	95% CI	
Rate elevation		59.9%	48.2%–69.5%	
Efficacy		337.4%	204.3%–538.7%	
Relative Rate		4.374	3.04–6.39	
Number needed to treat		1.7	1.4–2.1	

^Independent t-test, #Paired t-test, & Chi square test. *Significant. CI: Confidence interval

Table (4): Umbilical artery SD among the studied groups

Time	Measures	L-Arginie (N=125)	Control (N=124)	P
Level				
Before	**Mean±SD**	3.86±0.28	3.90±0.21	0.160
	Range	3.43–4.63	3.49–4.36	
Delivery	**Mean±SD**	3.31±0.11	3.69±0.15	**<0.001***
	Range	3.05–3.60	3.41–4.05	
Reduction	**Mean±SD**	0.55±0.29	0.21±0.19	**<0.001***
	Range	0.03–1.32	0.02–0.71	
Reduction grades	**0.00–**	63 (50.4%)	105 (84.7%)	**&**
	0.05–	53 (42.4%)	19 (15.3%)	**<0.001***
	≥0.10	9 (7.2%)	0 (0.0%)	
#P		**<0.001***	**<0.001***	
Value of L-Arginie in decreasing SD				
Item		**Mean±SE**	**95% CI**	
Reduction		0.33±0.03	0.27–0.39	
Value of L-Arginie in decreasing SD ≥0.05				
		Value	**95% CI**	
Rate elevation		34.3%	22.4%–44.2%	
Efficacy		223.7%	105.1%–427.4%	
Relative Rate		3.237	2.05–5.27	
Number needed to treat		2.9	2.3–4.5	

^Independent t-test, #Paired t-test, & Chi square test. *Significant. CI: Confidence interval

Table (5): AFI among the studied groups

Time	Measures	L-Arginie (N=125)	Control (N=124)	P
Level				
Before	**Mean±SD**	4.0±1.7	3.9±1.6	0.829
	Range	0.5–7.1	0.6–7.0	
Delivery	**Mean±SD**	10.1±1.6	9.3±1.7	**<0.001***
	Range	5.7–12.8	5.6–12.3	
Elevation	**Mean±SD**	2.4±0.6	1.7±0.6	**<0.001***
	Range	1.2–3.8	0.1–3.0	
Elevation grades	**0.00–**	11 (8.8%)	41 (33.1%)	**&**
	0.15–	91 (72.8%)	81 (65.3%)	**<0.001***
	≥0.30	23 (18.4%)	2 (1.6%)	
#P		**<0.001***	**<0.001***	
Value of L-Arginie in elevating AFI				
Item		**Mean±SD**	**95% CI**	
Reduction		0.7±0.1	0.6–0.9	
Value of L-Arginie inelevating AFI ≥0.15				
		Value	**95% CI**	
Rate elevation		24.3%	13.8%–32.0%	
Efficacy		36.3%	19.1%–50.8%	
Relative Rate		1.363	1.19–1.51	
Number needed to treat		4.1	3.1–7.2	

^Independent t-test, #Paired t-test, & Chi square test. *Significant. CI: Confidence interval

Table (6): Fetal GA (weeks) among the studied groups

Time	Measures	L-Arginie (N=125)	Control (N=124)	P
Level				
Before	**Mean±SD**	31.9±1.9	31.5±1.6	0.103
	Range	28.0–35.0	28.0–35.0	
Delivery	**Mean±SD**	35.8±1.0	33.7±1.8	**<0.001***
	Range	33.0–38.0	31.0–39.0	
Prolong-ation	**Mean±SD**	4.0±2.0	2.2±1.9	**<0.001***
	Range	1.0–9.0	1.0–8.0	
Prolong-ation grades	**1.0–**	53 (42.4%)	106 (85.5%)	**&** **<0.001***
	4.0–	64 (51.2%)	9 (7.3%)	
	≥7. 0	8 (6.4%)	9 (7.3%)	
#P		**<0.001***	**<0.001***	
Value of L-Arginie in prolonging pregnancy				
Item		**Mean±SE**	**95% CI**	
Prolongation		1.8±0.3	1.3–2.3	
Value of L-Arginie in prolonging pregnancy≥4. 0				
		Value	**95% CI**	
Rate elevation		43.1%	31.3%–52.7%	
Efficacy		296.8%	152.8%–545.5%	
Relative Rate		3.968	2.53–6.46	
Number needed to treat		2.3	1.9–3.2	

^Independent t-test, #Paired t-test, & Chi square test. *Significant. CI: Confidence interval

Table (7): Estimated fetal weight (gm) among the studied groups

Time	Measures	L-Arginie (N=125)	Control (N=124)	P
Level				
Before	**Mean±SD**	1889.5±264.7	1849.4±230.4	0.203
	Range	1347.0–2335.0	1289.0–2336.0	
Delivery	**Mean±SD**	2321.9±160.6	2037.0±234.8	**<0.001***
	Range	1907.0–2625.0	1558.0–2464.0	
Increase	**Mean±SD**	432.7±157.9	187.6±150.9	**<0.001***
	Range	203.0–1072.0	15.0–734.0	
Increase grades	**0.000–**	17 (13.6%)	107 (86.3%)	**&** **<0.001***
	0.250–	70 (56.0%)	8 (6.5%)	
	≥0.500	38 (30.4%)	9 (7.3%)	
#P		**<0.001***	**<0.001***	
Value of L-Arginie in decreasing SD				
Item		**Mean±SE**	**95% CI**	
Increase		245.1±19.6	206.5–283.6	
Value of L-Arginie in decreasing SD ≥0.250				
		Value	**95% CI**	
Rate elevation		72.7%	62.2%–80.8%	
Efficacy		530.2%	327.2%–838.8%	
Relative Rate		6.302	4.27–9.39	
Number needed to treat		1.4	1.2–1.6	

^Independent t-test, #Paired t-test, & Chi square test. *Significant. CI: Confidence interval

Table (8): Rate of estimated fetal weight increase (gm/week) among the studied groups

Time	Measures	L-Arginie (N=125)	Control (N=124)	P
Increase	**Mean±SD**	127.0±46.4	98.9±43.4	**<0.001***
	Range	84.3–248.0	15.0–192.0	
Increase grades	**0.000–**	47 (37.6%)	77 (62.1%)	**& <0.001***
	0.100–	61 (48.8%)	47 (37.9%)	
	≥0.200	17 (13.6%)	0 (0.0%)	
Value of L-Arginie in increasing the rate				
Item		**Mean±SE**	**95% CI**	
Increase		28.0±5.7	16.8–39.3	
Value of L-Arginie in increasing the rate ≥0.100				
		Value	**95% CI**	
Rate elevation		24.5%	11.4%–36.8%	
Efficacy		64.6%	25.5%–116.2%	
Relative Rate		1.646	1.26–2.16	
Number needed to treat		4.1	2.7–8.8	

^Independent t-test, *Significant. & Chi square test. CI: Confidence interval

Table (9): Neonatal condition among the studied groups

Variables		L-Arginie (N=125)	Control (N=124)	P	RR (95% CI)
APGAR 1	**Mean±SD**	5.2±1.7	3.9±1.4	^ **<0.001***	--
	Range	3.0–8.0	3.0–7.0		
APGAR 5	**Mean±SD**	5.7±1.9	4.0±1.6	^ **<0.001***	--
	Range	3.0–9.0	3.0–8.0		
Preterm (n, %)		95 (76.0%)	113 (91.1%)	# **0.001***	0.83 (0.75–0.93)
NICU (n, %)		56 (44.8%)	108 (87.1%)	# **0.001***	0.51 (0.42–0.63)

^Independent t-test, & Chi square test, #Fisher's Exact test, RR: Relative risk, **CI:** Confidence interval

4. Discussion

The current research study was investigating and comparing two research categorial groups **Group A** in which pregnant females received L_arginine 3000mg/day orally and aspirin 75 mg /day and **Group B** pregnant females in this group received only aspirin 7 mg/day. Improvements in clinical outcomes was observed in both research groups however group A had shown statistical significant improvement various research outcomes were assessed such as birth weight umbilical artery Doppler indices, Apgar scoring level, amniotic fluid index, preterm labour and NICU admission. Concerning birth weight **fetal weight statistically** significantly increased in both research groups. **Fetal weight** at delivery and **fetal weight** increase was statistically significantly higher among L-Arginine research group than among control research group. The explanation of increase of birth weight due to L-arginine which acts as precursors of No which improve fetomaternal circulation via vasodilation. Also L-arginine has anti platelet aggregation effect. As a result of those actions the blood flow increase in fetomaternal circulation which lead to increase in fetal weight**.1,4.**

Umbilical artery Doppler improved in both groups, but improved significantly in L-arginine group. We observed a statistically significant reduction in perfusion index of umbilical artery and resistance index too. Amniotic fluid in our study was measured by MVP or AFI. It showed statistically significantly increase in liquor in L-arginine research group. Apgar scoring also showed statistically significantly improvement in L-arginine research group. we thought that happen because of increase in pregnancy weeks so it promotes maturation of fetuses**.2,5,9.**

Preterm labor was 76.0% among L-arginine research group and 91.1% in the control group. NICU administration was statically significantly lower in L-arginine research group. The current study findings didn't observed any adverse effects of L-arginine, that is justified by the fact that the research team used the minimum therapeutic dose of oral L-arginine furthermore the long term. impact of L-arginine in neonates wasn't investigated**.10,13.**

Chen J et al. [14]study a meta-analysis showed that L-arginine increased birth weight and prolonged gestational age at labor of IUGR fetuses and these findings are compatible with our findings.

Also In agreement with our study Soni *et al.*[15]found that l-arginine supplementation is improving volume of amniotic fluid in cases of oligohydramnios and prolonging pregnancy, allowing fetal lung maturation thus benefiting the neonatal outcome.

Mary *et al.* [16] study noticed that L-Arginine improves foetal weight more significantly in cases with idiopathic IUGR which computable with our study.

Jurisic *et al.*[17] found that L-arginine diminished umbilical artery resistance significantly and allowed pregnancy to continue which agree with our study.

Bansal et al. [18]proved that l-arginine increase amniotic fluid index in cases of oligohyramnios which agree with our study.

Another prior research study in harmony with the current study findings have revealed and displayed that the oral administration of l-arginine improved pregnancy clinical outcome (The mean birth weight of newborns, and gestational age at delivery was found to be higher amongl-arginine research group)**.7,19,20.**

Another prior research group of investigators conducted a study similar to the current study in approach and methodology have observed interestingly an improvement in Apgar scoringanda decrease in NICU admission that shows great harmony to the current study findings**.21,22,23.**

Investigators in previous studies have denoted that L-arginine promote intrauterine growth of the fetus by increasing NO productivity therefore consequently improving the umbilical artery flow in pregnant women with pregnancy-induced hypertension and fetal growth restriction**.12.**

A prior research group observed there was no statistical significant difference in birth weight and Apgar scoring in between group treated with L-Arginine IN comparison to placebo research group in severe IUGR, but the current study investigated only moderate degrees of IUGR. **8,24,25**

Conclusions and recommendations for future research

L-arginine seems to be a useful management agent for improving asymmetrical mild IUGR fetuses viaraisingnitric oxide levels which enhances the fetomaternal circulatory functional performance. Future research efforts are required to verify the impact and role of oral L-arginine in improve outcome of sever IUGR fetuses in a multicenric fashion putting in consideration long-term safety profile of the drug and cost effectiveness of the course of management.

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9/25/2019