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Is L-arginine supplementation has beneficial role in fetal outcome in patients of pre-ecclampsia?

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Abstract
Introduction: Preeclampsia is a multisystem complex disorder with an increased uterine arterial resistance due to deficiency of e-NOS, resulting in vasoconstriction. L-arginine is the substrate of nitric oxide (NO) and therefore we aimed to study the effect of its supplementation in preeclampsia patients.
Materials and Methods: The study was conducted in SN Medical College, Agra and included a total of 120 women out of which 60 were included in the study group and 60 in the placebo group, from 20 weeks of gestation onwards, complicated by Pregnancy induced hypertension and Doppler parameters were done serially at 4-6 weeks interval after supplementation of L-Arginine to see for the improvement.
Results: It was found that supplementation with Arginine significantly improved the fetal outcome in patients with Pre-eclampsia.
Conclusion: L-Arginine proved to be an efficient intervention to improve neonatal outcomes in patients with hypertensive disorders of pregnancy.

Keywords: L-arginine supplementation, beneficial role, pre-ecclampsia

Introduction
Preeclampsia is a multisystem complex disorder with an incidence of 3-7% for nullipara and 13% for multipara and is a major contributor of both fetal as well as maternal morbidity and mortality [1]. The pathophysiology behind this disorder needs to be elucidated more with the primary cause being abnormal placentation (there is defective invasion of the spiral arteries by the cytotrophoblast cell), resulting in increased uterine arterial resistance which results in increased sensitivity to vasoconstriction and finally establishment of chronic placental ischemia and oxidative stress [2, 3]. Endothelial nitric oxide synthase (e-NOS) promotes the synthesis of NO which dilates the arteriolar bed whereas in preeclampsia there is deficiency of e-NOS resulting in vasoconstriction of the placental vasculature as well as the vasculature of the other organs [4]. Moreover, inhibition of maternal synthesis of NO prevents embryo implantation [3].
Arginine is an essential amino acid, physiologically active in L-form, which is synthesized by endothelial cells and excreted with urine *in vivo*. It is a basic amino acid (AA) present in physiological fluids, with its high content in seafood, watermelon juice, nuts, seeds, algae, meats, rice protein concentrate, and soy protein isolate [5, 7] but low content in the milk of most mammals (including humans) [8, 9]. L-arginine is the substrate of nitric oxide (NO), a potent vasodilator, which may play a major role in regulating blood pressure. Its level in the blood during pregnancy is increased and its availability is very important to ensure proper and adequate synthesis of nitric oxide in endothelium and since there is increased destruction of NO in abnormal endothelium, the requirement of L-arginine increases. 4 Therefore, we aim to study the effect of supplementation of L-arginine in fetal as well as placental Doppler parameters in Preeclamptic patients. Hypertension, proteinuria, fetal growth retardation, and glomerular damage could be induced by blockade of NO synthesis, while hypertension induced by NO synthesis inhibition could be reversed by L-arginine supplementation [10].

Material and Methods
The present randomized placebo-controlled clinical trial designed to determine the effect of L-arginine therapy on Doppler parameters among the cases of Pregnancy induced hypertension (PIH) was conducted in the Department of Obstetrics and Gynaecology, S.N. Medical College, Agra and was approved by the Ethical Committee of the College after explaining the objectives of the study to each participant and taking their consent before including them.

Study group included the patients with Pregnancy induced hypertension (PIH) who received [3] gm L-Arginine twice a day and the Control group included the patients with Pregnancy induced hypertension (PIH) who received sachet containing multi vitamins twice a day.

L-arginine therapy

Cases with Pregnancy induced hypertension (PIH) were recommended to have 1 sachet of L-arginine dissolved in half glass of water twice a day.

Follow up visits

Participants were scheduled for clinical follow up after every [2] weeks until till delivery. Things to be followed during each visit (fortnightly)-

- Arterial blood pressure measurement
- Maternal weight gain evaluation
- Urine protein quantification

Colour doppler examination

Material: Doppler study was done on 'Micromax Turbo Sonosite Colour Doppler machine using Biconvex Abdominal Probe having low frequency (3.5 MHz). Doppler ultrasonography was done every [4] weeks with the mothers in semi- recumbent position, after few minutes rest without breathing movements. Measurements were repeated for at least [3] separate cardiac cycles.

Statistical analysis

All the analysis was carried out by using SPSS 16.0 version (Chicago, Inc., USA). The results are presented in mean±SD and percentages. The categorical variables were compared by Chi-square test. The Student unpaired and paired t-test were used to compared the continuous variables. The p-value<0.05 was considered significant.

Results

Table-1 presents the baseline characteristics of patients. The mean age of the study and placebo group was 25.73 (±3.71) and 25.70 (±3.31) years respectively. Majority of the patients in both the groups belonged to rural area and were illiterate. There was no significant (p>0.05) difference in the baseline characteristics of patients between the groups.

Table 1: Sociodemographic characteristics of study and placebo group

	Study group (n=60)	Placebo group (n=60)	p-value
Age in years, mean ± Sd	25.73±3.71	25.70±3.31	0.82a
Place of residence, no. (%)			
Rural	43(71.7)	46 (76.7)	0.53b
Urban	17 (28.3)	14 (23.3)	
Education, no. (%)			
Illiterate	41(68.3)	39 (65.0)	0.69 b
Literate	19 (31.7)	21(35.0)	
Social class, no.(%)			
Upper class	3(5.0)	4(6.7)	0.70
Upper middle class	4(6.7)	2(3.3)	
Middle class	2(3.3)	5(8.3)	
Lower middle class	20(33.3)	20(33.3)	
Lower class	31(51.7)	29(48.3)	
Gravida, no. (%)			
Primi	33(55.0)	34(56.7)	0.85
Multi	27(45.0)	26(43.3)	
Gestational age in week, mean ± sd	26.25±2.42	26.27(2.16)	0.84
Blood pressure, mean ± sd			
Systolic B.P.(mm Hg)	156.90±6.87	155.80±7.05	0.39
Diastolic B.P.(mm Hg)	96.70±8.46	95.60±8.50	0.47

Table-2 shows the comparison of Doppler parameters between the study and the placebo groups from presentation (1st visit) to follow-ups.

There was no significant (that is p value was >0.05) difference in all the Doppler parameters at 1st visit between the groups. The mean change in AFI from 1st to 3rd visit was observed to be significant (p<0.01) in both the groups but it was higher in the Study group than Placebo group from 1st to 3rd visit. The estimated foetal weight was found to be significantly higher in the Study group compared to Placebo group at 2nd (p=0.005) and 3rd (p=0.04) visit (Table 2). The mean change in the PI of uterine artery, umbilical artery, MCA and the CP ratio from 1st to 3rd visit was observed to be significant (p=0.0001) in both the groups but it was higher in the Study group as compared to the Control group(Table 3).

Table 2: Comparison of estimated fetal weight and AFI

Doppler parameters	1st visit	2nd visit	3rd visit	Mean change from 1st visit to	
				2nd visit, p-value	3rd visit, p-value
AFI					
Study Group	9.06±0.80	9.16±0.83	13.12±0.84	0.10±1.20, 0.50	4.06±1.15, 0.0001*
Placebo group	8.60±0.80	9.47±0.66	12.23±1.43	0.87±0.68, 0.001*	3.63±1.61, 0.0001*
p-value	0.06	0.08	0.07	0.09	0.04
Fetal weight in grams					
Study Group	774.62±214.23	1597.67±188.38	2221.02±203.68	823.05±262.84, 0.0001*	1446.40±298.33, 0.0001*
Placebo group	759.52±220.2	1478.15±259.67	2139.52±2	718.63±379.28,	1388.00±298.59,

	3		44.03	0.0001*	0.0001*
p-value	0.70	0.005*	0.04*	0.001*	0.001*
Presence of NOTCH					
Study Group	39 (65.0)	2 (3.3)	0 (0.0)	0.0001*	-
Placebo group	34 (56.7)	3 (5.0)	0 (0.0)	0.0001*	-
p-value	0.35	0.64	-		
PI of Uterine artery					
Study Group	1.53±0.12	1.43±0.13	1.38±0.13	0.09±0.04, 0.0001*	0.14±0.04, 0.0001*
Placebo group	1.54±0.14	1.46±0.13	1.42±0.15	0.08±0.06, 0.0001*	0.12±0.08, 0.0001*
p-value	0.55	0.21	0.24	0.18	0.17

Table 3: Comparison on Doppler parameters from presentation (1st visit) to follow-ups

PI of Umbilical artery					
Study Group	1.29±0.10	1.19±0.10	1.14±0.12	0.10±0.04, 0.0001*	0.15±0.06, 0.0001*
Placebo group	1.27±0.11	1.20±0.11	1.16±0.11	0.07±0.03, 0.0001*	0.11±0.08, 0.0001*
p-value	0.28	0.86	0.41	0.16	0.15
PI of MCA					
Study Group	1.46±0.14	1.39±0.13	1.34±0.09	0.04±0.13, 0.01*	0.12±0.15, 0.0001*
Placebo group	1.49±0.09	1.46±0.10	1.43±0.10	0.03±0.12, 0.07	0.05±0.13, 0.002*
p-value	0.14	0.001*	0.0001*	0.41	0.02*
S/D ratio					
Study Group	4.09±0.97	3.72±0.78	3.45±0.87	0.36±1.25, 0.02*	0.63±1.20, 0.0001*
Placebo group	3.94±0.84	3.80±0.78	3.51±0.80	0.13±1.03, 0.32	0.42±1.10, 0.004*
p-value	0.37	0.56	0.70	0.002*	0.02*
CP ratio					
Study Group	1.13±0.16	1.11±0.14	1.04±0.20	0.02±0.21, 0.41	0.08±0.27, 0.01*
Placebo group	1.18±0.14	1.15±0.20	1.11±0.19	0.02±0.22, 0.39	0.06±0.21, 0.01*
p-value	0.10	0.18	0.07	0.99	0.22

*Significant

Discussion

The present study was conducted in the Department of Obstetrics and Gynaecology, S.N. Medical College, Agra. A total of 60 pregnant women were included in the study group and 60 women in placebo group. The main objective of this study was to assess the effect of supplementation of L-Arginine on various Doppler parameters in patients of preeclampsia.

In our study, there were no significant (p>0.05) difference in the age between the groups which was similar to studies conducted by Odibo *et al.* where the mean age was 28 years and Lakhkar *et al.* where the mean age was 27 years whereas in a study conducted by Zavala-Coca *et al.*, the mean age was 35 years [10-12]. The mean age of the patients in most of the studies is 27-28 years because this is the peak reproductive age group. Majority of the women in both the Study (71.7%) and the Placebo (76.7%) groups were from rural area, belonged to Hindu community, illiterate, housewives and belonged to the lower socio-economic status. Despite various efforts by the government to ensure proper coverage and care of the antenatal patients in the rural areas, still the pregnant females lack a good antenatal checkup and therefore the magnitude of the problem crops up in such patients. Majority of the women were primigravida, which was similar to the study conducted by Lakhkar *et al.*, because the incidence is more in primi as compared to multi [12].

In our study, the mean change in AFI from 1st to 3rd visit was observed to be significant (p<0.01) in both the groups and was higher in the Study group as compared to the Placebo group from 1st to 3rd visit, similar to the studies conducted by Hebbar *et al.*13 and Rinoy & Shubhada [14].

In our study, the estimated foetal weight was found to be significantly higher in the Study group as compared to the Placebo group at 2nd (p=0.005) and 3rd (p=0.04) visit. The intravenous administration of Arg-HCl (3 × 27 mg/kg body weight per day) enhanced fetal growth in ovine models of both undernutrition-induced and naturally-occurring IUGR15. It has also been seen that daily intravenous infusion of Arg (20 g/day) for [7] days to women with unknown causes of IUGR increased birth weight at term by 6.4% during later weeks of gestation. [17].

These findings provide a strong experimental basis for the use of Arg to prevent and treat IUGR in humans Lerman *et al.* studied the effects of long-term oral supplementation of L-arginine on coronary vessels and observed an improved blood flow in these vessels which was considerably higher as compared to the placebo group (rise by 9 ± 20% vs 6 ± 9%) [17]. In another study conducted by Neri *et al.*, they examined the effect of L-arginine on utero-placental circulation in pregnancy complicated by intrauterine growth restriction in the third trimester and observed an enhanced level of nitrates/nitrites and the growth hormone. They also observed significant changes in various other Doppler parameters and improved fetal outcome [18].

It was observed that after the supplementation of L-Arginine, there were significant changes in the mean values of various Doppler parameters from 1st to 3rd visit which were higher in the study group as compared to the placebo group. Lalthantluanga *et al.* showed that fetuses with Umbilical Artery Systolic/Diastolic (SD) ratio >3 were associated with poor perinatal outcome (89.65%) with sensitivity and specificity of 80.00% and 82.86% respectively. 19 Fetuses with cerebro-placental index (CPI) ≤1 have poor perinatal outcome in 95.74% with higher specificity (93.94%) and positive predictive value (95.74%). Uma *et al.* found that abnormal Umbilical Artery– PI

and the ratio of MCA-PI/Umbilical Artery PI (ratio <1.1) was significantly associated with operative intervention and poor perinatal outcome but abnormal MCA – PI was only significantly associated with operative intervention and not with perinatal complications.20 A wide range of interventions (Hyper-alimentation, Ca, Vit-D and Vit-E supplementation) have been suggested for the prevention and treatment of hypertensive disorders of pregnancy but none have proved to be beneficial. The mainstay of treatment in these patients is strict control of blood pressure using anti-hypertensive drugs and strict fetal and maternal monitoring.

Therefore, in our study it has been seen that treatment with exogenous Arginine increases fetal and neonatal outcome as well as improvements in Doppler parameters also helps in prolonging the pregnancy, but larger studies are required to further validate effects of L-Arginine.

Table 4: Baseline characteristics of patients

	Study group (n=60)	**Placebo group (n=60)**	**p-value**
Age in years, mean±sd	25.73±3.71	25.70±3.31	0.82a
Place of residence, no. (%)			
Rural	43(71.7)	46 (76.7)	0.53b
Urban	17 (28.3)	14 (23.3)	
Education, no. (%)			
Illiterate	41(68.3)	39 (65.0)	0.69 b
Literate	19 (31.7)	21(35.0)	
Occupation, no. (%)			
Housewife	33 (78.3)	33(83.3)	0.48 b
Working	11 (21.7)	12 (16.7)	
Social class, no. (%)			
Upper class	3 (5.0)	4 (6.7)	0.70 b
Upper middle class	4 (6.7)	2 (3.3)	
Middle class	2 (3.3)	5 (8.3)	
Lower middle class	20 (33.3)	20 (33.3)	
Lower class	31 (51.7)	29 (48.3)	
Gravida, no. (%)			
Prima	33(55.0)	34 (56.7)	0.85 b
Multi	27 (45.0)	26 (43.3)	
Gestational age in week, mean ± Sd	26.25±2.42	26.27±2.16	0.84 a
Blood pressure, mean ± Sd			
Systolic mmHG	156.90±6.87	155.80±7.05	0.39 a
Distolic blood pressure mmHG	96.70±8.46	95.60±8.50	0.47 a
Sign of Protodiastolic notch in the uterine artery (Notch-UTA), no. (%)			
Present	39 (65.0)	34 (56.7)	0.35 b
Absent	21(35.0)	26 (43.3)	

A Unpaired t-test, B Chi-square test

Table 5: Comparison on Doppler parameters from presentation (1st visit) to follow-ups

Doppler parameters	**1st visit**	**2nd visit**	**3rd visit**	**Mean change from 1st visit to**	
				2nd visit, p-value	**3rd visit, p-value**
AFI					
Study Group	9.06±0.80	9.16±0.83	13.12±0.84	0.10±1.20, 0.50	4.06±1.15, 0.0001*
Placebo group	8.60±0.80	9.47±0.66	12.23±1.43	0.87±0.68, 0.001*	3.63±1.61, 0.0001*
p-value	0.06	0.08	0.07	0.09	0.04
Fetal weight in grams					
Study Group	774.62±214.23	1597.67±188.38	2221.02±203.68	823.05±262.84, 0.0001*	1446.40±298.33, 0.0001*
Placebo group	759.52±220.23	1478.15±259.67	2139.52±244.03	718.63±379.28, 0.0001*	1388.00±298.59, 0.0001*
p-value	0.70	0.005*	0.04*	0.001*	0.001*
Presence of NOTCH					
Study Group	39 (65.0)	2 (3.3)	0 (0.0)	0.0001*	-
Placebo group	34 (56.7)	3 (5.0)	0 (0.0)	0.0001*	-
p-value	0.35	0.64	-		
PI of Uterine artery					
Study Group	1.53±0.12	1.43±0.13	1.38±0.13	0.09±0.04, 0.0001*	0.14±0.04, 0.0001*
Placebo group	1.54±0.14	1.46±0.13	1.42±0.15	0.08±0.06, 0.0001*	0.12±0.08, 0.0001*
p-value	0.55	0.21	0.24	0.18	0.17
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Placebo group	1.27±0.11	1.20±0.11	1.16±0.11	0.07±0.03, 0.0001*	0.11±0.08, 0.0001*
p-value	0.28	0.86	0.41	0.16	0.15
PI of MCA					
Study Group	1.46±0.14	1.39±0.13	1.34±0.09	0.04±0.13, 0.01*	0.12±0.15, 0.0001*
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p-value	0.14	0.001*	0.0001*	0.41	0.02*

S/D ratio					
Study Group	4.09±0.97	3.72±0.78	3.45±0.87	0.36±1.25, 0.02*	0.63±1.20, 0.0001*
Placebo group	3.94±0.84	3.80±0.78	3.51±0.80	0.13±1.03, 0.32	0.42±1.10, 0.004*
p-value	0.37	0.56	0.70	0.002*	0.02*
CP ratio					
Study Group	1.13±0.16	1.11±0.14	1.04±0.20	0.02±0.21, 0.41	0.08±0.27, 0.01*
Placebo group	1.18±0.14	1.15±0.20	1.11±0.19	0.02±0.22, 0.39	0.06±0.21, 0.01*
p-value	0.10	0.18	0.07	0.99	0.22

*Significant

Conclusion

By examining the maternal and fetal vessels using Doppler ultrasound it is possible to determine, the risk of complications developing in the course of pregnancy long before clinical signs of preeclampsia as well as it helps in adequate fetal monitoring so that preventive and therapeutic measures can be undertaken early. L-Arginine proved to be an efficient intervention to improve the fetal and neonatal outcomes in patients with hypertensive disorders of pregnancy.

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