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Role of Nitric Oxide Donor in Intrauterine Growth Restriction

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I. Introduction:

The growth of normal fetus is controlled by a delicate balance of genetic, placental and maternal factors. Any perturbations in this delicate balance may result in growth restriction or accelerated growth. Among the intrauterine environmental factors, nutrition plays the most decisive role in influencing placental and fetal growth.[1]Intrauterine Growth Restriction is considered when the fetal growth rate is below normal with respect to the growth potential of a specific infant for the respective race and gender of the foetus. IUGR is when the fetal weight is less than10th percentile of the average weight for its gestational age.[2]

It affects about 3-10% of all gestations.[3] It is associated with significant increase in morbidity and mortality in perinatal period and infancy. The incidence of stillbirth is increased nearly fourfold in fetal growth restriction pregnancies.[4] Out of 22 million small for gestational age infants in the world, 21 million belongs to developing countries and India's share is around 7-10 million constituting 30% of live births.[5] These infants are more likely to develop hypertension, atherosclerosis, type 2 diabetes and metabolic derangement in adult life compared to infants within normal birth weight[6].

Nitric oxide (NO) is produced by nitric oxide synthases (NOS) using the amino acid L-arginine

as substrate. It is synthesized in vascular endothelial wall, diffuses into adjacent vascular smooth muscle cells and increases the concentration of second-messenger cyclic guanosine monophosphate (cGMP), resulting in the relaxation of vascular smooth muscle. It increases the oxygen and nutrient supply to the fetus by vasodilatation of feto-placental circulation.

Reduced NO availability may have an important role in the pathophysiology of IUGR[7]; previous data suggest that IUGR could be induced by blocking NO synthesis.[8] Therefore, NO donor (glyceryltrinitrate and isosorbidemononitrate), precursors (L-arginine) and NO mediator (sildenafil citrate and vardenafil) may be possible therapeutic approaches for IUGR.

L-Arginine , a precursor of NO, may improve the fetal growth by the following mechanisms

a) Increasing utero- placental perfusion and fetal nutrient delivery by increasing local NO concentrations.
b) Arginine mediated stimulation of maternal growth hormone[9]
c) Enhancement of placental growth and development via promotion of polyamine synthesis
d) It is a potent fetal insulin secretagogue and insulin is a major anabolic hormone in the fetus[10]
e) Arginine has been shown to stimulate skeletal muscle protein synthesis.

Acknowledging the beneficial effects of L-arginine, the present study was designed to evaluate the role of L-arginine in women with IUGR and its effect on neonatal outcome. Moreover, there is paucity of data assessing the effect of L-Arginine in IUGR. Hence this study was conducted in a tertiary care centre, Manipur, a remote North- Eastern state of India.

II. Objective:

To study the effect of L- Arginine supplementation on fetal weight and neonatal outcome among the pregnant women between (24-36 weeks) diagnosed with IUGR in a tertiary care centre , Manipur.

III. Methods:

The study was a non randomized controlled interventional study conducted among pregnant women from 24-36 weeks with IUGR attending the Department of Obstetrics and Gynaecology in Regional Institute of Medical Sciences, Imphal, during a period of 18 months from Sept 2018 to August 2020. The study was approved by Research Ethics Board, RIMS. A total of 96 pregnant women were enrolled- divided into 2 groups: Group A supplemented with L- Arginine (3gm daily for 21 days) and group B without L- Arginine supplementation. Monitoring was done according to standard protocol of antenatal check up and ultrasonography with Doppler Velocimetry every 2 weeks.

IV. Results:

In the group treated with L- Arginine, we observed an increased in estimated fetal weight after 3 weeks of treatment (P < 0.001), decreased in S/D ratio of umbilical artery by a mean of 0.35 (P<0.001), more term deliveries (P=0.009) and higher APGAR score at 1 min (P=0.002). We also observed that there were higher low birth weight babies (P<0.005), NICU admission (P=0.004), resuscitation with endotracheal tube intubation (P=0.015) and newborn complications among the non treatment group.

Table 1. Distribution of the study participants by gestational age at the time of delivery (N=96)

Gestational age at the time of delivery (weeks)	**Intervention Group**		
	Group A n=48 n (%)	**Group B n=48 n (%)**	**p value**
Preterm (< 37 weeks)	10 (20.8)	22 (45.8)	**0.009**
Term (≥ 37 weeks)	38 (79.2)	26 (54.2)	

Table 1 shows that the period of gestation of less than 37 weeks at the time of delivery was significantly higher among the group who didn't receive arginine (45.8% vs 20.8%) and it was found to be statistically significant (p=0.009).

Table 2. Distribution of the study participants by the mode of delivery (N=96)

Mode of delivery	**Intervention Group**		
	Group A n=48 n (%)	**Group B n=48 n (%)**	**p value**
Normal vaginal delivery	39 (81.3)	34 (70.8)	0.232
Caesarean section	9 (18.7)	14 (29.2)	

Table 2 shows that caesarean delivery was more in the group without arginine therapy but it was not found to be statistically significant (p=0.232).

Table 3. Estimated fetal weight (pre-treatment and post-treatment) between the two groups (N=96)

Estimated fetal weight (grams)	**Group A n=48 Mean (SD)**	**Group B n=48 Mean (SD)**	**p value**
Pre-treatment **Mean (SD)**	1516.4 (314.5)	1520.0 (310.2)	0.954
Post-treatment **Mean (SD)**	1997.5 (305.7)	1786.9 (287.4)	0.001
Estimated fetal weight difference (grams)			
Estimated fetal weight difference (grams) **(post-treatment - pre-treatment) Mean (SD)**	481.1 (97.4)	266.9 (87.8)	**<0.001***

*** Difference in Difference (DID) analysis**

Table 3 shows that the mean pre-treatment estimated foetal weight was comparable between the two groups (p=0.954). The increase in estimated fetal weight after three weeks of intervention was higher among the group who received arginine (481.1 grams vs 266.9 grams) and they were found to be statistically significant (p<0.001).

Table 4. Mean umbilical artery S/D ratio (pre-treatment and post-treatment) between the two groups (N=96)

Mean umbilical artery S/D ratio	**Group A n=48 Mean (SD)**	**Group B n=48 Mean (SD)**	**p value**
Pre-treatment **Mean (SD)**	4.3 (0.2)	4.1 (0.3)	**<0.001**
Post-treatment **Mean (SD)**	3.9 (0.2)	4.5 (0.3)	-
Umbilical artery S/D ratio difference			
Umbilical artery S/D ratio difference **(post-treatment - pre-treatment) Mean (SD)**	-0.35	0.36	**<0.001**

*** Difference in Difference (DID) analysis**

Table 4shows that the mean umbilical artery S/D ratio was lower in the group without arginine treatment during pre-treatment and it was found to be statistically significant (p<0.001). There was a mean decrease of 0.35 in the umbilical artery S/D ratio among the pregnant women who were on arginine treatment when compared to the pregnant women who were not on arginine treatment, where there was an increase of S/D ratio of 0.36 and it was found to be statistically significant (p<0.001).

Table 5. Comparison of birth weight between the two groups (N=96)

Birth weight (grams)	**Intervention Group**		**PRR (95% CI)**	**p value**
	Group A n=48 n (%)	**Group B n=48 n (%)**		
1601-1800	3 (6.3)	8 (16.7)	14.5 (2.1-101.6)	**<0.001**
1801-2000	9 (18.8)	23 (47.9)	14.4 (2.1-98.3)	**<0.001**
2001-2200	17 (35.4)	16 (33.3)	9.6 (1.4-67.6)	**0.001**
2201-2400	19 (39.6)	1 (2.1)	**Reference**	

***PRR (Prevalence Risk Ratio)**

Table 5 shows that the pregnant women without arginine treatment were found to have low birth weight babies when compared to the pregnant women who were on arginine treatment for IUGR (p<0.05).

Table 6. Comparison of Apgar score between the two groups (N=94)

Apgar score	**Group A n=48 Mean (SD)**	**Group B n=46 Mean (SD)**	**p value**
Apgar score at 1 minute **Mean (SD)**	8.7 (0.5)	8.3 (0.6)	**0.002**
Apgar score at 5 minutes **Mean (SD)**	8.9 (0.3)	8.8 (0.4)	0.117

Table 6 shows that the Apgar score was significantly higher at 1 minute among the group who received arginine treatment (p=0.002). However, there was no significant difference in Apgar score at 5 minutes between the two groups (p=0.117).

Table 7. Comparison of type of resuscitation between the two groups (N=94)

Type of resuscitation	**Intervention Group**		**p value**
	Group A n=48 n (%)	**Group B n=46 n (%)**	
Routine care	33 (68.7)	21 (45.7)	**0.015**
Bag and mask ventilation	14 (29.2)	17 (37.0)	
Endotracheal intubation	1 (2.1)	8 (17.3)	

Table 7 shows that the babies of the mother who did not receive arginine treatment were found to be having higher chance of resuscitation by endotracheal tube intubation when compared to the babies of mothers who received arginine treatment (17.3% vs 2.1%) and it was found to be statistically significant (p=0.015).

Table 8. NICU admission between the two groups (N=94)

NICU admission	**Intervention Group**		**p value**
	Group A n=48 n (%)	**Group B n=46 n (%)**	
Yes	15 (31.3)	28 (60.9)	**0.004**
No	33 (68.8)	18 (39.1)	

Table 8 shows that NICU admission was significantly higher among the babies of pregnant women without arginine treatment (p=0.004).

Table 9.Comparison of complications of the new-born between the two groups (N=94)

Complications of the new-born	**Intervention Group**		**p value**
	Group A n=48 n (%)	**Group B n=46 n (%)**	
Yes	15 (31.3)	28 (60.9)	**0.004**
No	33 (68.8)	18 (39.1)	

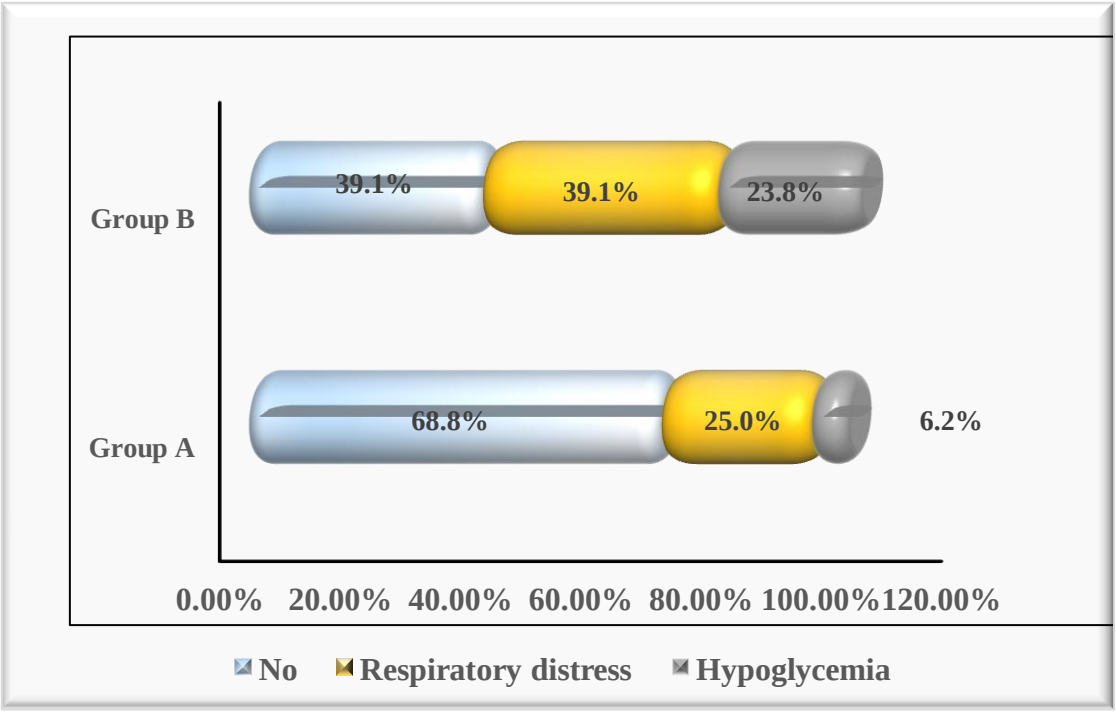

Figure 1. Distribution of new-borns by their complications (N=94)

Table 9 shows that new-born complications were significantly higher among the babies of pregnant women without arginine treatment (p=0.004). Respiratory distress was present in 39.1% and hypoglycaemia 23.8% of the neonates in Group B and in Group A, respiratory distress was present in 25.0% and hypoglycaemia in only 6.2% of the neonates. **(Figure 1)**

V. Discussion:

Uteroplacental hemodynamics is important in pathophysiology of intra uterine growth restriction. Vascular tone is an essential target of the paracrine and endocrine regulations during pregnancy. NO synthesized in placental vasculature plays a crucial role in maintaining a low fetoplacental perfusion. Studies have shown varying levels of serum NO in third trimester of pregnancy.[11,12] However, the role of L-Arginine in the maintenance of endothelial vasculature and its role in feto-maternal circulation are less studied till date. Hence, it was imperative to look into the effects of L-Arginine in pregnant women with IUGR babies.

Influence of arginine therapy on Doppler indices in the umbilical artery was found to be favourable. In our study,there was a mean decrease of 0.35 in the umbilical artery S/D ratio among the pregnant women who were on arginine treatment when compared to the pregnant women who were not on arginine treatment, where there was an increase of S/D ratio of 0.36 and it was found to be statistically significant (P<0.001). Similar result was shown by a meta analysis conducted by Chen J et al[13.]

In the present study it was found that the mean birth weight of newborns, percentage of vaginal delivery and gestational age at delivery were higher in L-arginine group compared with the non treatment group. Similar results were reported by studies conducted by ShaliniS et al[14] and Xiao XM et al[15].

The increase in estimated fetal weight after three weeks of intervention was higher among the group who received arginine compared with non treatment group (481.1 grams vs 266.9 grams) and it was found to be statistically significant (p<0.001). Pregnant women without arginine treatment were found to have extremely low birth weight babies when compared to the pregnant women whowere on arginine treatment for IUGR (p<0.05). Similar results were shown bya meta-analysis conducted by Chen J et al[13]and also studies conducted by ShaliniS et al[14] Xiao Xm et al[15], Ropacka M et al [16] and Sieroszewski et al[17].

Apgar score was significantly higher at 1 minute among the group who received arginine treatment (p=0.002). NICU admission was significantly higher among the babies of pregnant women without arginine treatment (p=0.004). This is similar to various other studies conducted by different authors.[13,18] New-born complications were significantly higher among the babies of pregnant women without arginine treatment (p=0.004). Respiratory distress was present in 39.1% and hypoglycaemia 23.8% of the neonates in Group B and in Group A, respiratory distress was present in 25.0% and hypoglycaemia in 6.2% of the neonates. All these

evidences show that L-Arginine significantly improve the utero-placental flow and in turn birth weight and the maternal and fetal outcomes.

One of the major strengths of the present study is that a representative sample was chosen which in turn made the study generalizable to the similar kind of study population. One of the limitations which could have been taken care of is that the measurement of NO was not done, which could have increased the objective of our study finding.

VI. Conclusion:

A total of 96 pregnant women with IUGR were included in the study. The mean age of the participants was 26.3 years ± 1.4. Mean pre-treatment estimated foetal weight was comparable between the two groups. The increase in estimated fetal weight after three weeks of intervention was higher among the group who received arginine and was found to be statistically significant. There was a mean decrease of 0.35 in the umbilical artery S/D ratio among the pregnant women who were on arginine treatment when compared to the pregnant women who were not on arginine treatment, where there was an increase of S/D ratio of 0.36 and it was found to be statistically significant.

Pregnant women without arginine treatment were found to have more babies with low birth weight compared to those who were on arginine treatment. Apgar score was significantly higher at 1 minute among the group who received arginine treatment. NICU admission, newborn complications were significantly higher among the babies of pregnant women without arginine treatment. Hence, during antenatal care, all pregnant women and high risk cases should be screened to detect IUGR in earlier stages which will decrease perinatal morbidity and mortality. Apart from routine fetal surveillance in IUGR, Umbilical artery S/D ratio done by Doppler ultrasound helps in detecting increased resistance and monitoring a compromised fetus. IUGR cases should be supplemented with oral L- Arginine, a NO donor to reduce resistance in feto-placental circulation. Many of the adult diseases of foetal origin can also be decreased by treating pregnancies complicated with IUGR babies during antenatal period.

References:

[1]. Wu G, Bazer FW, Cudd TA, Meininger CJ, Spencer TE. Maternal nutrition and fetal development. J Nutr 2004; 134(9):2169-72.
[2]. Gilbert WM, Danielsen B. Pregnancy outcome associated with intrauterine growth restriction. Am J ObstetGynecol 2003;188(1):1596-9.
[3]. Divon MY, Hsu HW. Maternal and fetal blood flow velocity waveforms in intrauterine growth retardation. ClinObstetGynecol 1992; 35(1):156-71.
[4]. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ 2013; 346(1), 108-10.
[5]. Biswas R, Dasgupta A, Sinha RN, Chauduhri RN. An epidemiological study of low birth weight new-borns in the district of Puruliya, West Bengal. India J Public Health 2008; 52(2):65-71.
[6]. Barker DJ. Adult consequences of fetal growth restriction. Clin Obstet Gynecol2006 ; 49(1), 270-83.
[7]. Myatt L, Eis AL, Brockman DE, Greer IA, Lyall F. Endothelial nitric oxide synthase in placental villous tissue from normal, pre-eclamptic and intrauterine growth restricted pregnancies. Hum Reprod 1997; 12:167-72.
[8]. Diaz V, Lebras-Isabet MN, Denjean A. Effect of Nomega-nitro-L-arginine methyl ester-induced intrauterine growth restriction on postnatal lung growth in rats. Pediatr Res 2005; 58:557-61.
[9]. Neri I, Mazza V, Galassi MC, Volpe A, Facchinetti F. Effects of L-arginine on utero-placental circulation in growth retarded fetuses. ActaObstetGynecolScand 1996;75:208-12
[10]. Thureen PJ, Baron KA, Fennessey PV, Hay WW Jr. Ovine placental and fetal arginine and metabolism at normal and increased maternal plasma arginine concentrations. Peads Res 2002;51:464-71.
[11]. Schiessl B, Strasburger C, Bidlingmaier M, Mylonas I, Jeschke U, Kainer F, et al. Plasma and urine concentrations of nitrite/ nitrate and cyclic GMP in intrauterine growth restricted and preeclamptic pregnancies. Arch GynecolObstet 2006;274:150-4.
[12]. Lakhkar BN, Rajagopal KN, Gaurishankar PT. Doppler prediction of adverse perinatal outcome in PIH and IUGR. Indian J RadiolImag 2006;16(1):109-16.
[13]. Chen J, Gong X, Chen P, Luo K, Zhang X. Effect of L-arginine and sildenafil citrate on intrauterine growth restriction fetuses: a meta-analysis. BMC Pregnancy Childbirth 2016 Aug 16;16(1):225.
[14]. Singh S, Singh A, Sharma D, Singh A, Narula MK, Bhattacharjee J. Effect of l-Arginine on Nitric Oxide Levels in Intrauterine Growth Restriction and its Correlation with Fetal Outcome. Indian J ClinBiochem 2015 Jul;30(3):298-304.
[15]. Xiao XM, Li LP. L-Arginine treatment for asymmetric fetal growth restriction. Int J GynaecolObstet Off Organ Int Fed GynaecolObstet 2005 Jan;88(1):15-8.
[16]. Ropacka M, Kowalska J, Hepner K. The effect of L-arginine on fetal outcome in IUGR fetuses. Arch Perinat Med 2007;13(1):30-4.
[17]. Sieroszewski P, Suzin J, Karowicz-Bilińska A. Ultrasound evaluation of intrauterine growth restriction therapy by a nitric oxide donor (L-arginine). J Matern-Fetal Neonatal Med Off J EurAssocPerinat Med Fed Asia Ocean PerinatSocIntSocPerinatObstet 2004 Jun;15(6):363-6.
[18]. Lampariello C, De Blasio A, Merenda A, Graziano E, Michalopoulou A, Bruno P. Use of arginine in intruterine growth retardation (IUGR). Authors' experience. Minerva Ginecol 1997 Dec;49(12):577-81.

XXXXX, et. al. "Role of Nitric Oxide Donor in Intrauterine Growth Restriction."*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 20(05), 2021, pp. 17-21.