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Intravenous L-arginine in Oligohydramnios

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Abstract

Background: Oligohydramnios is associated with increased maternal and fetal morbidity and mortality. Intravenous amino acid supplementation has emerged as a potential therapy to improve amniotic fluid levels and pregnancy outcomes. Previous studies suggest that L-arginine and branched-chain amino acids may enhance fetal growth and reduce preterm birth. This study aims to evaluate the effectiveness of an intravenous amino acid solution rich in L-arginine in pregnant women with oligohydramnios.

Methods: The prospective study was conducted in the Department of Obstetrics and Gynaecology at Asgar Ali Hospital, Dhaka, over two years, extending from March 2022 to January 2024, among 48 pregnant women with oligohydramnios. The participant received five (5) doses of IV amino acid supplementation during gestational weeks 28–34, under the supervision of a physician.

Results: The study's mean age of pregnant women was 28.19 ± 4.27 years, and the mean gestational age at diagnosis was 30.04 ± 1.89 weeks. Most cases of oligohydramnios with IUGR were identified at 28–30 weeks of gestation, accounting for 69.2% of the study population. Mean fetal weight before administration of the IV amino acid solution was 1424.04 ± 656.20 gm. After 3 weeks of treatment, the mean fetal weight increased to 2313.27 ± 528.16 gm, with an average fetal weight gain of 889.23 ± 716.72 gm, which was statistically significant ($P < 0.001$). Before administering the IV amino acid solution, the mean amniotic fluid index (AFI) was 5.00 ± 0.75 cm, which improved to 7.69 ± 0.84 cm after 3 weeks.

Conclusions: Intravenous supplementation of amino acids, particularly L-arginine and branched-chain amino acids, may offer potential benefits for pregnant women with oligohydramnios. These supplements could enhance uteroplacental blood flow and improve fetal nutrient delivery, potentially leading to better fetal growth outcomes.

Keywords: Oligohydramnios, AFI, amino acid infusion, L-arginine, BCAA, pregnant women, USG, ēSD, IUGR, BPD, HC, AC, FL

Introduction

Amniotic fluid fills the amniotic sac surrounding the developing fetus during pregnancy. It is a watery, alkaline fluid that nourishes and shields the developing fetus.[1] Oligohydramnios is defined as inadequate amniotic fluid for the gestational age.[2] The deepest fluid pocket in the amniotic sac can be measured to be less than 2 cm, or an amniotic fluid index of 5 cm or less can be reported.[3] Oligohydramnios is now typically defined as having an amniotic fluid index below the 5th percentile for the gestational age.[4] Long-term effects of decreased amniotic fluid include pulmonary hypoplasia, Potter's syndrome, club foot, club hand, and hip dislocation, fetal anomaly, increased cesarean section for fetal distress, fetal hypoxia and acidosis, stillbirth, and a high incidence of maternal and perinatal morbidity and mortality.[5] Oligohydramnios can

cause intrauterine growth retardation (IUGR) in pregnancy because of decreased renal perfusion and urine output.[1] IUGR is the rate of fetal growth that is less than normal compared to the infant's growth potential.[6] In newborns, IUGR is related to increased complications such as short stature, cardiovascular disease, insulin resistance, diabetes mellitus type 2, dyslipidemia, and end-stage renal disease in adulthood.[7] Neonatal death rates in both term and pre-term neonates are considerably higher in those diagnosed with IUGR antenatally.[8] Worldwide oligohydramnios is observed in nearly 7–8% of pregnancies, while IUGR affects nearly 5–10% of pregnancies.[1] IUGR is observed in 23.8% of newborns, and approximately 30 million babies globally suffer from it every year.[9] Around half of the preterm stillbirths and 25% of the term stillbirths were growth-retarded.[10] The developing countries contribute to 75% of the world's total IUGR.[11] In low and middle-income countries, each year 23.3 million infants are estimated to be born with IUGR, and Bangladesh ranks fourth among the countries with the highest burden of IUGR with a prevalence of 30.5%.[12] However, data regarding oligohydramnios associated with IUGR is still limited. To treat oligohydramnios, amino acid supplementation is often recommended, which can adequately provide for the carbon and nitrogen requirements of the growing fetus.[13] Many studies showed that prenatal intervention through the administration of amino acids and nutrients is effective in extending gestation and facilitating optimal fetal development.[14] Also, amino acid supplementation has a role in the weight gain of the fetus.[15] L-arginine is of utmost significance for achieving somatic growth by releasing growth hormone through stimulation of the growth hormone-releasing hormone and the subsequent rise in plasma growth hormone.[16] It is evident that given the branched-chain amino acid (BCAA) ability to independently stimulate muscle protein synthesis, it is considered for nutritional therapy to promote lean mass growth in the IUGR fetus during pregnancy.[17] However, there is no data in the context of Bangladesh on the effect of intravenous (IV) supplementation of amino acids, including L-arginine, in pregnant women with Oligohydramnios. This study aims to assess the effectiveness of this IV amino acid supplementation among pregnant women with oligohydramnios.

Methods

This prospective study was conducted in the Department of Obstetrics and Gynaecology at Asgar Ali Hospital, Dhaka, over two years from March 2022 to January 2024. A total of 48 pregnant women aged 20–35 years were enrolled based on predefined inclusion and exclusion criteria. Eligible participants were those with singleton pregnancies between 24 and 34 weeks of gestation diagnosed with oligohydramnios, defined as an amniotic fluid index (AFI) of less than 5 cm. Women with severe maternal comorbidities such as uncontrolled diabetes or hypertension, known fetal anomalies, intrauterine infections, fetal distress at enrollment, or a history of hypersensitivity to amino acid preparations were excluded. All participants received intravenous L-arginine for three consecutive days. Baseline assessment included detailed medical history and ultrasonographic evaluation of estimated fetal weight (EFW) and AFI. A follow-up ultrasound was performed three weeks after the initial scan, following completion of therapy, to reassess EFW and AFI. Maternal weight gain and adverse events were also recorded during the intervention period, while neonatal outcomes such as Apgar scores, birth weight, and NICU admission were documented at delivery. Data were analysed using IBM SPSS Statistics version 21.0 and OpenEpi version 3.01. Descriptive statistics were used for demographic variables, while inferential analysis was performed using chi-square and Student's t-test. A *P*-value <0.05 with a 95% confidence interval was considered statistically significant.

Results

Figure 1 shows the age distribution of the study participants. The majority were aged 31–35 years (45.8%), followed by 26–30 years (33.3%), and 20–25 years (20.8%).

Figure 2 showing the BMI distribution of the study participants. The majority were overweight (41.7%), followed by morbid obesity category 1 (33.3%), morbid obesity category 2 (16.7%), and smaller proportions of normal weight (4.2%) and morbid obesity category 3 (4.2%).

Table 1 shows that multiparity was predominant (62.5%), and primiparity accounted for 37.5% of cases. Concerning the history of previous cesarean delivery, there was an even distribution where 50% did not have any history of previous cesarean delivery, 29.2% had one cesarean, and 20.8% had two cesareans. The prevalence of previous uterine scar is thus substantial among the subjects included. On the other hand, concerning maternal well-being, 50% were free from other diseases, 16.7% suffered from hypertension, and 16.6% were atopic.

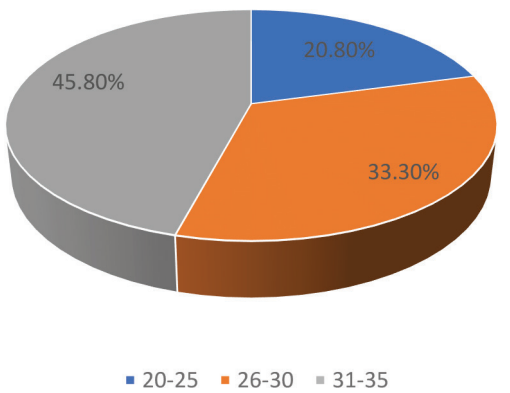

Figure 1: Age distribution of the participants.

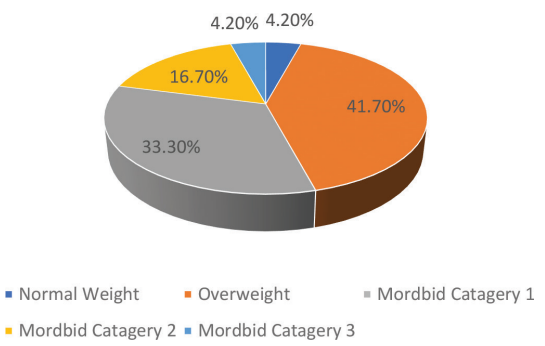

Figure 2: BMI category of the patients.

Table 1: Obstetric and clinical history of the patients

Obstetric and clinical history of the patients	Frequency	Per cent (%)
Para		
Primipara	18	37.5
Multipara	30	62.5
Previous cesarean sections		
0	24	50
1	14	29.2
2	10	20.8
Maternal comorbidities		
No comorbidities	24	50
Asthma	4	8.3
Atopy	6	16.6
DM	4	8.3
Dysmenorrhea	2	4.2
Hypertension	8	16.7
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Table 2 depicts that the mean age of patients was 28.17 ± 4.03 years, whereas the mean gestational age at presentation was 31.21 ± 4.25 weeks. The mean BMI was quite high (31.15 ± 5.13 kg/m²), which showed their predilection towards obesity. The mean blood pressure values were within upper limits; that is, systolic and diastolic pressures were measured to be 129.79 ± 15.07 mmHg and 77.08 ± 6.74 mmHg, respectively. The glycaemic state of patients was normal since their mean fasting blood sugar, post-prandial blood sugar, and HbA1c values were recorded to be 5.42 ± 0.99 mmol/L, 8.26 ± 1.69 mmol/L, and 5.05 ± 0.86%, respectively. Haemoglobin content in their serum had a mean value of 11.38 ± 0.66 g/dL, and hence borderline anaemia was detected in some cases, but there was no abnormality in their thyroid function because the mean TSH levels were 1.94 ± 0.88 mIU/L.

Table 2: The mean change of fetal parameters after administration of the IV amino acid solution

Clinical and biochemical presentation of the patients	Mean	SD
Age	28.17	4.03
Gestational age at presentation	31.21	4.25
BMI	31.15	5.13
Systolic blood pressure	129.79	15.07
Diastolic blood pressure	77.08	6.74
Body surface area	1.77	0.19
Fasting blood sugar	5.42	0.99
Post-prandial blood sugar	8.26	1.69
HbA1c	5.05	0.86
Hemoglobin	11.38	0.66
Thyroid-stimulating hormone	1.94	0.88

Table 3 presents a significant improvement in most of the biometric measurements of the fetus after administration of the IV amino acid solution. The average increase in biparietal diameter (BPD) is 1.44 ± 1.58 cm, whereas the increase in head circumference (HC) is 5.55 ± 5.65 cm; abdominal circumference (AC) has increased by 6.13 ± 5.48 cm, and the femur length (FL) has increased by 1.36 ± 1.31 cm, showing a highly significant *P*-value (<0.001). The increase in estimated fetal weight has been significantly high, as it has increased to 1042.50 ± 859.75 g ($P < 0.001$). However, the change in amniotic fluid index (AFI) was found to be 1.44 ± 4.71 cm, and this was not significant ($P = 0.156$).

Table 4 shows that the mean age of pregnant ladies in this research was 28.19 ± 4.27 years.

Table 3: The mean change of fetal parameters after administration of the IV amino acid solution

	Mean	Std. deviation	95% Confidence interval of the difference		*t*	Sig. (2-tailed)
			Lower	Upper		
Post intervention BPD - Pre intervention BPD	1.44	1.58	0.77	2.11	4.45	0
Post intervention HC - Pre intervention HC	5.55	5.65	3.16	7.93	4.81	0
Post intervention AC - Pre intervention AC	6.13	5.48	3.81	8.44	5.47	0
Post-intervention FL - Pre-intervention FL	1.36	1.31	0.81	1.91	5.1	0
Post-intervention weight - Pre-intervention weight (gm)	1042.5	859.75	679.46	1405.54	5.94	0
Post intervention AFI - Pre intervention AFI	1.44	4.71	−0.59	3.48	1.47	0.156

Mean gestational age at the time of detection of oligohydramnios and IUGR was 30.04 ± 1.89 weeks. The majority of patients were diagnosed between 28 and 30 weeks, constituting 69.2% of the total sample. This suggests that the most common gestational age during which babies with IUGR were found is 28–30 weeks.

Table 5 demonstrates a notable improvement in fetal weight following the use of the IV amino acid solution. Before treatment, the mean weight of the fetus was 1424.04 ± 656.20 grams, and after 3 weeks of using the IV amino acid solution, there was an increment in its weight to 2313.27 ± 528.16 grams. Thus, there was an average increase of 889.23 ± 716.72 grams in the weight of the fetus.

Table 4: Distribution of pregnant women according to their age and gestational age (weeks) at diagnosis.

Variable		f (%)	Mean ± SD
Age (Years)	17–25	12 (23.1)	
	26–30	22 (42.3)	28.19 ± 4.27
	31–35	18 (34.6)	
Gestational age (weeks)	28–30	36 (69.2)	
	31–32	10 (19.2)	30.04 ± 1.89
	33–34	6 (11.5)	

Table 6 shows a marked improvement in the level of the amniotic fluid index (AFI) after the use of the IV amino acid solution. Initially, before any therapy was provided, the AFI was found to be 5.00 ± 0.75 cm. After 3 weeks of therapy, the average AFI value became 7.69 ± 0.84 cm, with an AFI increase of 2.69 ± 0.47 cm. Thus, the improvement in AFI level was statistically significant ($P < 0.001$).

Discussion

Oligohydramnios poses a major risk to both mother and fetus, increasing perinatal death and morbidity. The main result is a lack of effective weight gain during pregnancy, which can lead to IUGR.[1] Ultrasonography has made it easier to diagnose oligohydramnios and IUGR. This allows us to be more careful and anticipate issues, particularly during labour. L-arginine is a versatile amino acid with diverse biological activities. It is a precursor to both proteins and nitric oxide, a relaxing agent produced by endothelial cells. L-arginine boosts uteroplacental blood flow by causing nitric oxide-mediated artery dilation. This enhances the nutrient supply to the fetus, promoting growth.[18] An Indian study found that the intravenous amino acid infusion was an effective modality for treating

Table 5: Fetal weight before treatment and 3 weeks after administration of the IV amino acid solution

Fetal weight (gram)	Mean ± SD	Average fetal weight gain	*P*-value
Before treatment (gm)	1424.04 ± 656.20	889.23 ± 716.72	**<0.001**
3 weeks after treatment (gm)	2313.27 ± 528.16		

Intravenous infusion containing L-arginine at a dose of 10.72 g used as the treatment.

Table 6: AFI before and after IV amino acid therapy

Amniotic fluid index (cm)	Mean ± SD	Average AFI gain	*P*-value
At 28–34 weeks	5.00 ± 0.75	2.69 ± 0.47	**<0.001**
3 weeks after administration of the IV amino acid solution	7.69 ± 0.84		

oligohydramnios associated with IUGR, with a strong positive impact on the amniotic fluid index.[1] In a study by Ropacka et al, L-arginine was found to be effective in cases of Intrauterine growth restriction.[19] Another study also revealed that intravenous infusion of amino acids, if given as a weekly regimen on alternate days, increases short-term AFI and also improves fetal weight and thus has a beneficial effect on both mother and fetus in the case of oligohydramnios.[15] In this study, five (5) doses of IV amino acid supplementation, consisting of BCAA and L-arginine, were administered to 28–34 weeks pregnant women who were diagnosed with oligohydramnios and IUGR by ultrasonography. The average age of the pregnant women was found to be 28.19 ± 4.271 in this study, indicating that women in our nation were pregnant at a very young age. Comparable results were discovered in an Indian investigation, where the average age was 24.15 ± 3.38 years.[18] Additionally, in the present study, the mean gestational age at diagnosis was 30.04 ± 1.89 weeks, and most cases, 69.2%, were identified between 28 and 30 weeks of gestation. This suggests that IUGR associated with oligohydramnios became most commonly apparent during this period in our cohort. Another study reported a mean gestational age of 32.73 ± 2.21 weeks.[1] A different study indicated that the mean gestational age was 32.3 weeks.[20] This study found that the mean amniotic fluid index was 5.00 ± 0.748 cm, indicating oligohydramnios when Aminosteril N Hepa 8% was given. However, after three weeks, it rose to 7.69 ± 0.838 cm with an average gain of 2.69 ± 0.47. Similar to our investigation, another study indicated that the average A.F.I. progress was 2.57 ± 0.68 cm.[15] According to an additional study, women's AFI changed on average by 2.03 cm ± 0.39 cm.[18] According to all the research, L-arginine may help with oligohydramnios. Mean fetal weight increased from 1424.04 ± 656.20 gm before treatment to 2313.27 ± 528.16 gm after 3 weeks, with an average gain of 889.23 ± 716.72 gm. In another study, the average growth in fetal weight was reported to be 150.0 grams, with a standard deviation of ± 37.8 grams.[15] According to another study, fetal weight was 1661.46 ± 361.85 g when amino acids were administered, but it increased to 2000.19 ± 376.70 g 5 weeks later.[1] Therefore, the important message of the present study is the short-term fetal growth response after intravenous amino acid therapy rather than week-wise presentation across 28–34 weeks. This unique study will assist clinicians in lowering the rate of fetal death. However, this study had many drawbacks. To start, the sample size was extremely small. Second, the fetal outcome was not noted. Thirdly, it was done at a single tertiary care centre.

Limitations of the Study

The study was limited by a small sample size, a single-centre design, the absence of a control group, and a short follow-up duration. Confounding factors were not fully controlled, and detailed maternal, neonatal, and long-term safety outcomes were not comprehensively evaluated.

Conclusions

The results showed that most IUGR cases were identified between 28 and 30 weeks of gestation, and fetal weight improved significantly 3 weeks after treatment. AFI also improved after therapy. Nevertheless, to solidify its position as a highly effective treatment for oligohydramnios, comprehensive long-term trials are needed to show not only its effectiveness but also its impact on maternal and perinatal outcomes. With a controlled group, more experimental research is required.

Recommendations

Intravenous amino acid therapy may be considered as an adjunct treatment for oligohydramnios

with IUGR under specialist supervision. Larger randomised controlled studies in Bangladesh are recommended to confirm efficacy, safety, optimal dosing, and long-term maternal-neonatal outcomes.

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