

World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/



ISSN: 2319-5622

Research Article

EFFECT OF L-ARGININE ON AMNIOTIC FLUID INDEX IN OLIGOHYDRAMNIOS IN THIRD TRIMESTER OF PREGNANCY

M. Madhu Babu *, M. Shalom, T. Ahalya and K. Sai Lakshmi

Department of pharmacology, Sir C R Reddy College of Pharmaceutical Sciences, Santhi Nagar, Eluru – 534007, INDIA.

Received on: 23-03-2019; Revised and Accepted on: 07-05-2019

ABSTRACT

 $m{T}$ he aim of this study is to assess the effectiveness of L- Arginine on Amniotic fluid index (AFI) levels in Oligohydramnios in third trimester of pregnancy. Oligohydramnios is an abnormal condition occurring during pregnancy resulting from lack of or reduced amniotic fluid. Oligohydramnios are associated with increased risk of birth defects. To decrease the birth defects due to Oligohydramnios and to avoid the complications of other treatment methods, we chose the treatment with L – Arginine. L- Arginine is a semi-essential amino acid acting as a substrate for synthesis of Nitric Oxide (NO). L- Arginine is converted into Nitric Oxide and molecular 02 by Nitric Oxide Synthase enzyme. Nitric Oxide diffuses into the underlying vascular smooth muscle cells and mediates vasodilatation and platelet stabilization by a cyclic GMP-dependant process, leads to increase in AFI. We have collected 60 cases of Oligohydramnios. AFI levels increased between 2cm to 10 cm after the usage of L-Arginine. The highest incidence of Oligohydramnios were noted in first pregnancies i.e. Gravida I. By using L- Arginine 43.3% of C- Sections are reduced. So oral use of L-arginine can be used as a cheap and feasible method.

KEYWORDS: Oligohydramnios, L- Arginine, AFI, Nitric Oxide (NO), C- Section.

INTRODUCTION

Vol. 8, Issue 5, 2019

Definition: It is an abnormal condition occurring during pregnancy resulting from lack of or reduced amniotic fluid. (Fluid surrounding the baby in the uterus)^[1].

Rupture of the membranes is the most common cause of Oligohydramnios; however, because the amniotic fluid is primarily foetal urine in the latter half of the pregnancy, the absence of foetal urine production or a blockage in the foetus urinary tract can also result in Oligohydramnios.

Normal range of amniotic fluid: 8 - 25cm

Types of Oligohydramnios:

Mild Oligohydramnios: If AFI levels are 5 – 8 cm Moderate Oligohydramnios: If AFI levels are < 5 cm. Sever Oligohydramnios: If AFI levels are < 2 cm.

Epidemiology ^[2]:

Oligohydramnios is a complication in approximately

* Corresponding author: M. Madhu Babu

Department of Pharmacology, Sir C R Reddy College of Pharmaceutical Sciences, Santhi Nagar, Eluru – 534007, INDIA. * E-Mail: tanetiahalva123@gmail.com

DOI: https://doi.org/10.5281/zenodo.2678002

4.5% of all pregnancies and severe Oligohydramnios is a complication in 0.7% of pregnancies. Oligohydramnios is more common in pregnancies beyond term, as the AFI normally decreases at term. It complicates as many as 12% of pregnancies that last beyond 41 weeks.

Role of amniotic fluid ^[3]:

1. Protecting the foetus: The AF acts as shock absorber and protects from external trauma.

2. *Temperature control:* The fluid insulates the baby keeping it warm and maintains the foetal body temperature.

3. Infection control: The amniotic fluid contains antibodies. It has bacteriostatic properties. It decreases potential for infections.

4. Pulmonary development: AF volume maintains AF pressure which reduces loss of lung liquid.

5. Muscle and bone development: As the baby floats inside the amniotic sac, it has the freedom to move about; giving muscles and bones the opportunity to develop properly.

6. Lubrication: Amniotic fluid prevents parts of the body such as the fingers and toes from growing together.

7. Umbilical cord support: Fluid in the uterus prevents the umbilical cord from being compressed. This cord transports food and oxygen from the placenta to the growing foetus.

J Pharm Res, 2019;8(5):250-259

8. GIT development: Swallowing of AF enhances growth and development of GIT.



Fig. 1: Role of amniotic fluid

Aetiology:

Placental Causes: [4]

- *Placental Abruption:* Placental abnormalities, like a partial abruption, which causes the placenta to peel away from the inner uterus wall, may lead to amniotic fluid deficiency. Any irregularity in the placental blood and nutrient supply can prevent the baby from producing urine which may lead to serious complications.
- *Carrying Twins:* Women pregnant with twins or multiples are at a higher risk of low amniotic fluid levels. Twin-to-twin transfusion syndrome (a condition where one twin experiences severe amniotic fluid deficiency while the other has excessive amounts of fluid) can also cause Oligohydramnios.
- **Drug-Induced Cause:** Using NSAIDs like indomethacin ^[5] and certain ACE (angiotensin-converting enzyme) inhibitors ^[6] leads to obstruction in fetal urine production.
- *Birth defects:* Problems with the development of the kidneys or urinary tract which could cause little urine production, leading to low levels of amniotic fluid.
- *Leaking or rupture of membranes:* ^[7] This may be a gush of fluid or a slow constant trickle of fluid. This is due to a tear in the membrane. Premature rupture of membranes (PROM) can also result in low amniotic fluid levels.
- **Post Date Pregnancy:** A postdate pregnancy (one that goes over 42 weeks) can have low levels of amniotic fluid, which could be a result of declining placental function.

Signs and symptoms of Oligohydramnios: [8]

- Rapid growth of uterus.
- Measurements of size smaller than dates.
- Abdominal discomfort.
- Leaking of the amniotic fluid.
- Little or decreasing foetal movement.
- Uterine contractions.
- Abnormal findings on a foetal monitor including foetal distress.

- Baby is easy to feel when a health care provider touches the mother's abdomen.
- Slow heartbeat of the baby.

Complications of Oligohydramnios: [9]

Oligohydramnios occurring during the first and the second trimester is more likely to cause serious complications than when it occurs during the third trimester.

- *Birth Defects:* Malformation or complete absence of some external or internal organs in the new born (hip dysplasia, club foot)
- *Premature Birth:* Delivery before completing 37th week of pregnancy
- *Miscarriage:* Death of the baby in the uterus before twenty weeks of pregnancy
- *Stillbirth:* Death of the baby in the uterus after twenty weeks of pregnancy
- Death of the baby shortly after birth Oligohydramnios can lead to the following problems when occurring during the third trimester:
- *Foetal growth restrictions:* Complications like an umbilical cord compression during labour or at the time of birth (the umbilical cord is responsible for carrying oxygen and food to the foetus, so its compression prevents the baby from getting enough nutrition and oxygen)
- Caesarean delivery (a surgical method to bring the baby out through a cut in the mother's abdomen and uterus).

Diagnosis:

Oligohydramnios typically diagnosed through a combination of

- Physical examination
- Assessment of personal history
- AFI (amniotic fluid index) or deep pocket measurement
- Sterile Speculum Examination
- Maternal Blood Test
- Amniotic wrinkle

M. Madhu Babu, et al.

Amniotic fluid index: [10]

- Ultrasonic diagnosis of Oligohydramnios is performed by obtaining a measurement called the amniotic fluid index
- The amniotic fluid index is measured by dividing the uterus in to four imaginary quadrants.
- The linea nigra is used to divide the uterus in to right and left halves.
- The umbilicus serves as the dividing point for the upper and lower halves.
- The transducer is kept parallel to the patient's longitudinal axis and perpendicular to the floor.
- The deepest, unobstructed, vertical pocket of fluid is measured in each quadrant in centimetres.
- The four pocket measurements are then added to calculate the AFI.
- AFI between 10 to 18 cm considered as normal with a mean of 14 cm.
- AFI less than 10 cm considered as abnormal.
- An AFI is less than 8 cm indicates Oligohydramnios.



Fig. 2: Amniotic fluid index

Treatment of Oligohydramnios:

- *Amnio infusion:* ^[11] In this treatment, the doctor infuses sodium chloride in amniotic sac through an intrauterine catheter, at room temperature. But it is associated with severe complications like umbilical cord prolapsed, preterm labour or prolongation of labour, chorio amniotic, infections etc.
- *Vesico-amniotic shunt:* ^[12] If the low amniotic fluid is due to baby not being able to pass urine, then the doctor will try to divert the baby's urine with the help of vesicos-amniotic shunt. While this procedure will take care of the low amniotic fluid in uterus, but it doesn't ensure the effective functioning of your baby's kidney or lungs.
- *Fluid Injections:* This is a temporary method of treating Oligohydramnios by injection fluid with the aid of amniocentesis.
- *Maternal Hydration:* Here, the doctor advises to drink lots of water and put in IV and oral fluids to increase the volume of amniotic fluid. This is applicable if dehydration causes Oligohydramnios.
- **Bed rest:** If there is mild Oligohydramnios, then doctor will keep under observation and advise complete bed rest. Proper hydration and complete bed rest can help to increase intravascular spaces ^[13], hence making more space for amniotic fluid.
- *Termination of pregnancy:* The worst of all may be the medical termination of pregnancy due to severe Oligohydramnios during the first trimester. But it is the as the baby may born with severe and multiple defects.

Except maternal hydration and bed rest all the above procedures are expensive, need medical supervision of health care professionals and hospitalisation. Maternal hydration and bed rest are not effective up to the mark.

Treatment with L- Arginine:

- L-arginine is a semi-essential amino acid acting as a substrate for synthesis of NO ^[13]. NO has a diverse role in obstetrics as it plays a vital role in labour, cervical ripening, preeclampsia, and intrauterine growth restriction. Nitric oxide (NO) is an important regulator of placental perfusion and plays an important role in placental vascular endothelial function. NO is synthesized from the physiologic precursor L-arginine by stereo specific enzyme Nitric Oxide Synthase (NOS) in what is called the L-arginine/NO pathway, and L-arginine is the only substrate for the NO ^[14]. NO diffuses into the underlying vascular smooth muscle cells and mediates vasodilatation and platelet stabilization by a cyclic GMP-dependant process ^[15].
- L-arginine promotes intrauterine growth of the fetus by increasing bioavailability of endothelial nitric oxide (NO) production and improving the umbilical artery flow in pregnant women.

L – Arginine <u>NOS</u> Nitric oxide (NO)^[16]

• L- Arginine is less expensive and it just requires good patient compliance.

METHODOLOGY

A prospective observational study was conducted in government general hospital (secondary care), Eluru consisting

M. Madhu Babu, et al.

of antenatal patients (sample size 60) diagnosed with Oligohydramnios (AFI <8cm) in third trimester.

This study was supported by Dr. M. Padma (Civil surgeon OBS and GYN), Dr. K. Shalini (Assistant Civil surgeon OBS and GYN) and Dr. Divya (OBS and GYN) under the guidance of M. Madhu Babu Sir (M. Pharm. Pharmacology).

The diagnostic test performed for the confirmation of Oligohydramnios is Ultra sonography of gravid uterus.

The patient were took under the consideration whose AFI is < 8cm.

Oligohydramnios are typically diagnosed through a combination of

- 1. Physical examination: The physical examination was done by the duty doctor present in the antenatal ward.
- 2. Assessment of personal history:
- 3. AFI (amniotic fluid index).
- 4. The patients were evaluated and were started on L-Arginine sachets (3g, 3 sachets per day with their preferred flavor).
- 5. The treatment was continued till an adequate improvement in liquor was noted.
- 6. Method for statistical analysis: T- test.
- 7. Sample size: 60

RESULTS

Table No. 1: Age group Vs No. of Patients

S. No.	Age group	No. of patients	Percentage
1	18 – 21	27	45
2	22 – 24	16	26.6
3	25 – 27	13	21.6
4	28 - 30	04	6.6

In our study the highest rate of Oligohydramnios is in the age group of 18 to 21 years and the least rate is in age group of 28 to 30.



Fig. 3: Age group Vs No. of patients

Table No. 2: Stage of Oligohydramnios Vs No. of patients

1. Mild Oligohydramnios 6-8 27 45 2. Moderate Oligohydramnios 3-5 27 45 3. Severe Oligohydramnios <2	S. NO	Stage of Oligohydramnios	AFI (cm)	No. of patients	Percentage
2. Moderate Oligohydramnios 3-5 27 45 3. Severe Oligohydramnios <2	1.	Mild Oligohydramnios	6-8	27	45
3. Severe Oligohydramnios <2 06 10	2.	Moderate Oligohydramnios	3-5	27	45
· ·	3.	Severe Oligohydramnios	<2	06	10

This information states that the rates of mild and moderate Oligohydramnios share the equal distribution of incidence i.e. 45% and incidence of severe Oligohydramnios is 10%.



Fig. 4: Stage of Oligohydramnios Vs No. of patients

Table No. 3: Level of improvement

S. No.	Level of improvement	No. of patients	Percentage
1	Up to 2 cm	09	15
2	Up to 4 cm	18	30
3	Up to 6 cm	12	20
4	Up to 8 cm	03	5
5	Up to 10 cm	18	30





Fig. 5: Level of improvement

Table No. 4: Oligohydramnios Vs Gravida of pregnancy

S. No. Gravida of pregnancy	No. of patients	Percentage
1. Gravida I	35	58

J Pharm Res, 2019;8(5):250-259

2.	Gravida II	19	31.6
3.	Gravida III	5	8.3
4.	Gravida IV	0	0
5.	Gravida V	1	1.6

In our study the highest incidence of Oligohydramnios (more than 50% i.e. 58%) were noted in first pregnancies i.e. Gravida I.



Fig. 6: Oligohydramnios Vs Gravida of pregnancy

Table No. 5: Mode of delivery Vs No. of Patients

S. No.	Mode of delivery	No. of patients	Percentage
1.	Normal delivery	26	43.3
2.	C- Sections	34	56.5

Generally all Oligohydramnios patients were supposed to undergo C -Section if AFI is not increased. By using L- Arginine 43.3% of C- Sections are reduced. In all the patients AFI is increased but still C- Sections are due to some underlying cause like the Gravida I is C-Sections.



Fig. 7: Mode of delivery Vs No. of patients

Table No. 6: Side effects of L- Arginine

S. No.	Side effect	No. of patients	Percentage
1.	Pain abdomen	22	36.6
2.	Diarrhoea	5	13.3
3.	Vaginal bleeding	5	13.3
4.	Back ache	2	3.33
5.	Bloating	5	13.3
6.	None	33	55

In our study there is a significant increase in AFI by using L- Arginine with minor side effects like pain abdomen, diarrhoea; vaginal bleeding, back ache; bloating and more than 50% of patients have no side effects.



Fig. 8: Side effects of L -Arginine

AFI levels before and after using of L - Arginine:

Table No. 7: AFI Levels before and after using of L - Arginine

S. No.	AFI before use of	AFI after use of
	L-Arginine (cm)	L-Arginine (cm)
1	2	6
2	7	8
3	7.4	8.3
4	6	8.1
5	8	12
6	4	8
7	2	14
8	5	9
9	3	6
10	6	10
11	6	8
12	6.5	7
13	8	10
14	5.2	10
15	5.8	10.2
16	4	8
17	3	7.5
18	6	10
19	3	8.5
20	6	8
21	3.4	8
22	5	9
23	4	9.8
24	4	9.9
25	2	11.8
26	2	9.8
27	3	10
28	3	10
29	4	10
30	3	11
31	6.5	18
32	6	10.3
33	8	9

© 2012, JPR. All Rights Reserved

http://www.worldinventiapublishers.com/

34	7.8	8.8
35	5	17
36	7.8	10
37	6	7.8
38	6	8.9
39	6.8	9
40	5	7
41	6.4	7
42	5.7	10
43	5	8
44	2	5
45	2	8.3
46	5	8
47	5	12.7
48	7.8	10
49	4	9.8
50	4	10.2
51	4	8.2
52	5	13
53	6	11
54	7.5	9.2
55	6.4	10
56	7.9	9.5
57	5	8.3
58	5	11
59	3	16
60	4	7

Test for Analysis: t- Test:

Table No. 8: t-Test Two-Sample Assuming Equal Variances

	Variable 1	Variable 2
Mean	5.048333	9.565
Variance	3.223556	5.794517
Observations	60	60
Pooled Variance	4.509037	
Hypothesized Mean Difference	0	
DF	118	
t Stat	-11.6503	
P(T<=t) one-tail	1.2E-21	
t Critical one-tail	1.65787	
P(T<=t) two-tail	2.4E-21	
t Critical two-tail	1.980272	
t Critical two-tail	1.980272	

DISCUSSION

Amniotic fluid has major role in development of foetal lungs, and early severe Oligohydramnios leads to pulmonary hypoplasia. Oligohydramnios are associated with increased risk of birth defects. To decrease the birth defects due to Oligohydramnios and to avoid the complications of other treatment methods, we chose the treatment with L – Arginine. In our study there is significant increase in AFI (at least 1-3cm) with L-arginine.

L-arginine is a semi-essential amino acid acting as a substrate for synthesis of NO. NO has a diverse role in obstetrics as it plays a vital role in labour, cervical ripening, preeclampsia, and intrauterine growth restriction. Nitric oxide (NO) is an important regulator of placental perfusion and plays an important role in placental vascular endothelial function. NO is synthesized from the physiologic precursor L-arginine by stereo specific enzyme NO synthase in what is called the L-arginine/NO pathway, and L-arginine is the only substrate for the NO. NO diffuses into the underlying vascular smooth muscle cells and mediates Vasodilation and platelet stabilization by a cyclic GMP-dependant process.

We have collected 60 cases of Oligohydramnios, based on Inclusion and Exclusion criteria. In our study the highest rate of Oligohydramnios is in the age group of 18 to 21 years and the least rate is in age group of 28 to 30.The rates of mild and

http://www.worldinventiapublishers.com/

M. Madhu Babu, et al.

10%. AFI levels increased between 2cm to 10 cm after the usage of L- Arginine. The highest incidence of Oligohydramnios (more than 50% i.e. 58%) were noted in first pregnancies i.e. Gravida I. Generally all Oligohydramnios patients were supposed to undergo C -Section if AFI is not increased. By using L- Arginine 43.3% of C- Sections are reduced. In all the patients AFI is increased but still C- Sections are due to some underlying cause like the Gravida I is C-Section. In our study there is a significant increase in AFI by using L- Arginine with minor side effects like pain abdomen, diarrhoea; vaginal bleeding, back-ache; bloating and more than 50% of patients have no side effects. So oral treatment of L-arginine can be used as a cheap and feasible method.

CONCLUSION

 \mathbf{O} ligohydramnios are associated with increased risk of birth defects. To decrease the birth defects due to oligohydramnios and to avoid the complications of other treatment methods, we chose the treatment with L – Arginine.

Our study concludes that there is a significant increase in AFI (at least by 1-3 cm) with the use of L-Arginine in oligohydramnios. We observed that incidence rate of oligohydramnios is greater in primary pregnancy i.e. in Gravida I when compared to other Gravidas of pregnancy. With the use of L – Arginine 43.3% of C- Sections are reduced in our study. By using this drug there are minor side effects like pain abdomen, diarrhoea, back ache, vaginal bleeding. The most commonly occurred side effect is pain abdomen and 50% of patients have no side effects. By this study we are concluding that treatment with L-Arginine is safe, efficacious and cost effective method of treatment for oligohydramnios.

ACKNOWLEDGEMENTS

We take this opportunity to express our deep sense of gratitude and respect to our esteemed teacher and sir Guide M. Madhu Babu Assistant Professor, Sir C.R. Reddy College of Pharmaceutical Sciences, Eluru. for giving us a unique opportunity to work on such an important topic. We would like to thank our Principal Dr. I. Sudheer babu, of Sir C.R. Reddy College of Pharmaceutical Sciences, for proving help and support throughout the Project.

REFERENCES:

1. Larsen, William J. Human embryology. publisher: Churchill Livingstone. **2001**;3:490.

- Luton D, Alran S, Fourchotte V, et al. Paris heat wave and Oligohydramnios. Am J Obstet Gynecol 2004;191(6): 2103-5.
- Nicolini U, Fisk NM, Rodeck CH, Talbert DG, Wigglesworth JS. Low amniotic pressure in oligohydramnios is this the cause of pulmonary hypoplasia?. Am J Obstet Gynecol 1989;161(5):1098– 101.
- 4. Atrash HK. Koonin LM, Lawson FII, V, et al. Matemal mortality in the United States, 7979-1986. Obstet Gynecol **7990**;76:1055-60.
- Goldenberg RL, Davis RO, Baker RC. Indomethacininduced oligohydramnios. Am J Obstet Gynecol 1989; 160:1196-1197.
- 6. Hendricks SK, Smith JR, Moore DE, Brown ZA. Oligohydramnios associated with prostaglandin synthetase inhibitors in preterm labour. Brit J Obstetrics & Gynaecol **1990**. [Pubmed]
- 7. Caughey AB, Robinson JN, Norwitz ER. contempoary diagnosis and management of preterm premature rupture of membranes. Reviews in Obstetrics & Gynecol **2008**;1(1):11-22.
- 8. Asgharnia M, Faraji R, Salamat F, Ashrafkhani B, Dalil Heirati SF & Naimian. Perinatal outcomes of pregnancies with borderline versus normal amniotic fluid index. Iran J Reprod Med **2013**;11(9):705-10.
- 9. Wolff F, Schaefer R. Oligohydramnios- perinatal complications and disease in mother and child. Geburtshilfe und Frauenheilkunde **1994**;54(3):139-43.
- Magann EF, Chauhan SP, Bofill JA, Martin JN, Jr. Comparability of the amniotic fluid index and single deepest pocket measurement in clinical practice. Aust N Z J Obstet Gynaecol 2003;43(1):75-7.
- 11. Deboshree Bhattacharjee, et al. Low Amniotic Fluid (Oligohydramnios) during Pregnancy. July 31, **2018**.
- 12. Biard JM, Johnson MP, Carr MC, et al. Long-term outcomes in children treated by prenatal vesicoamniotic shunting for lower urinary tract obstruction. Obstet Gynecol **2005**;106(3):503-8.
- 13. Mittal R, Satwant K, Mittal N, et al. L-arginine supplementation in intrauterine growth retardation. Int J Pharm Chem Sci. **2013**;2(3):1569–72.
- 14. Viviana DP, Giuseppe C, Fabio F. Clinical use of nitric oxide donors and L-arginines in obstetric. J Mater Fetal Neonat Med **2007**;20(8):569–79.
- 15. Lampariello C, De Blasio A, Merenda A, et al. Use of Larginine in intrauterine growth retardation (IUGR): authors' experience. Minerva Ginecol. 1997; 49:577–81.
- 16. HL Sharma, KL Sharma, Principles of Pharmacology 2nd edition, **2011 2015**;247-248.

How to cite this article:

M. Madhu Babu, et al. EFFECT OF L-ARGININE ON AMNIOTIC FLUID INDEX IN OLIGOHYDRAMNIOS IN THIRD TRIMESTER OF PREGNANCY. J Pharm Res 2019;8(5):250-259. **DOI:** <u>https://doi.org/10.5281/zenodo.2678002</u>

Conflict of interest: The authors have declared that no conflict of interest exists. Source of support: Nil