To study the Efficacy of Sildenafil citrate V/s L-Arginine sachets on pregnancy and perinatal outcome in idiopathic borderline oligohydramnios

Dr. Siram Sreeja Reddy, Dr. Sushmitha Dindi, Dr. Varada Hasamnis

(Post graduate student)Kims & RF , Amalapuram, Andra Pradesh
(Post graduate student)KIMS &RF , Andra Pradesh , Amalapuram

(Senior Resident)Kims& RF , Amalapuram, Andra Pradesh

CORRESPONDING AUTHOR :DR. Varada Hasamnis
(Senior Resident)Kims& RF , Amalapuram, Andra Pradesh

Department of Obstetrics and Gynecology,
Konaseema institute of medical science and research foundation, Amalapuram, Andra Pradesh, India

Abstract: Borderline oligohydramnios always produce a dilemma of management and counseling among obstetricians. The purpose of this study was to assess the effects of L-arginine alone against sildenafil citrate on pregnancy outcomes and the improvement of AFI in pregnant women with idiopathic borderline oligohydramniosis. A well-known obstetric issue linked to fetal morbidity and death as well as surgical interferences is oligohydramnios. It has been proposed that giving sildenafil citrate to oligohydramnios will increase their amniotic fluid index (AFI).

Materials and methods: This Retrospective cohort study was conducted at Konaseema Institute of Medical Science & Research Foundation(KIMS&RF) from 2022 December to 2024 December. 120 women with idiopathic borderline oligohydramnios were allocated to two groups. Group 1 received sildenafil 25mg twice daily for 4 weeks and Group 2 received L-Argenine sachets twice daily for 4 weeks.AFI was measured at the time of randomization, 24 h after treatment, and then weekly for 4 weeks. After being assessed for all prenatal risk factors, the patients began taking two L-arginine sachets (3 grams, two sachets each day). The course of treatment was maintained until there was a noticeable improvement in the liquor. However, if the liquor level stayed below 5, patients were taken into consideration for delivery. Additionally, neonatal outcomes and the mean rise in AFI were examined. The two groups' variations in AFI, birth method, gestational age at delivery, and newborn outcomes were contrasted.

Results : In oligohydramnios cases, treatment with sildenafil showed significant increase in AFI score. Mean increase in AFI was statistically increased at 2nd and 4th week after treatment with Sildenafil compared to L Arginine. Incidence of fetal distress,Rates of Meconium stained amniotic fluid(MSAF) were lower and ,Birth weight ,Apgar score in 5th minute, Rates of NICU Admissions, Neonatal deaths were also significantly better with Sildenafil treatment.

Conclusion: The finding showed that Sildenafil supplementation in women with borderline idiopathic oligohydramnious is efficient in increasing the amniotic fluid content and extending pregnancy by an average of 2.4 weeks, which will improve neonatal prognosis by permitting fetal lung maturation.

Key Words: Oligohydramnios, Pregnancy Outcome, Sildenafil, l-arginine, Amniotic fluid index, fetal outcome

Introduction:

Through out pregnancy,fetus is surrounded by Amniotic fluid,a transparent liquid that is contained within the amniotic sac, and offers a supportive environment for healthy growth and development. Amniotic fluid volume abnormalities may reflect fetal or placental pathology. Abnormally decreased fluid volume is termed oligohydramnios. The amniotic fluid volume may decrease in 3-5% of pregnancies. A common

method for evaluating the volume of the amniotic fluid is to estimate the amniotic fluid index (AFI)using obstetric ultrasound examination (1). AFI evaluation is an essential component of every second or third-trimester sonogram. It is assessed by measuring either a single pocket or the amniotic fluid index (AFI). AFI is a quantitative estimate of amniotic fluid. An AFI of 8 or above is normal, while an AFI of 5-8 is considered borderline oligohydramnios (low normal) and an AFI below 5 indicates severe oligohydramnios. Oligohydramnios can be accompanied by a non-complicated pregnancy or a finding in a complicated pregnancy (with hypertensive disorders or fetal anomalies) (2). The pathophysiology of oligohydramnios is not clearly established, but when detected in the absence of rupture of membranes, could be a sign of chronic suboptimal placental function. Idiopathic types of oligohydramnios account for about 7% of all cases of oligohydramnios in pregnancy and are associated with adverse fetal outcomes (3).Sildenafil is also currently used to treat pulmonary arterial hypertension (4, 5). Using sildenafil leads to loosening the arterial wall, increasing uterine blood flow, and, uteroplacental perfusion as a consequence (6, 7). The purpose of the present study was to evaluate the benefits of sildenafil on volume of AFI in cases of borderline oligohydramnios.L-Arginine is a precursor to nitric oxide (NO), a key molecule in vasodilation, which enhances blood flow to the placenta and promotes fetal nourishment [8]. Nitric oxide's vasodilatory effects increase uteroplacental blood flow, improving the transfer of oxygen and nutrients to the fetus, which can directly impact AFI levels by enhancing amniotic fluid

production [9]. Borderline Oligohydramnios is associated with a higher rate of preterm delivery, cesarean delivery for non-reassuring Non-Stress Test (NST), fetal growth restriction, congenital anomalies, perinatal outcome. (10). There is no conclusive treatment for idiopathic oligohydramnios, however, there are some therapeutic methods in the literature such as maternal hydration (11-14) using desmopressin, nitric oxide donors or amnioinfusion (15-17), maternal resting in left lateral decubitus position (18), and usually, the effect of these methods continue for a short time.Recently Sildenafil is suggested for treatment of isolated oligohydramnios. Sildenafil is a class B drug that causes vascular relaxation and increases uterine blood flow. Several studies investigate sildenafil citrate's impact on fetal growth restriction and have some conflicting results and there are few studies that investigated the role of this drug on isolated oligohydramnios (19, 20)

MATERIALS and METHODS:

Place of study: The study was carried out in Department of Obstetrics and Gynecology at Konaseema Institute of Medical Sciences & Research Foundation, Amalapuram,
Dr.B.R.A Konaseema District, Andhra Pradesh, India
The study population of 120 women was selected according to inclusion and exclusion criteria.

The study was approved by the ethics committee.

Type of Study: Retrospective Cohort Study

Duration of study: A period of 24 months(December 2022 to December 2024) from the date of approval by the Institutional
Scientific and Ethical committee for data collection as well as
analysis and reporting.

Study tool:
A semi-structured proforma was used for data collection, it collected details such as efficacy of Sildenafil citrate V/s L-Arginine sachets in oligohydramnios, mode of delivery,rate of operative interference in cases of term pregnancy with borderline AFI,perinatal outcome in cases of term pregnancy with borderline AFI.

Inclusion Criteria :

1. Age of the mother 18-35 years
2. Gestational Age: 28-34 weeks
3. Singleton Gestation with cephalic presentation
4. AFI 5-8 cm &
5. Intact membranes
6. Early and late onset of fetal growth restriction suspected clinically and confirmed by USG

Exclusion Criteria :

1. Gestational Age >37 weeks
2. Gestational Age <28weeks
3. Associated fetal malformation
4. Ruptured membranes
5. Multiple Gestation
6. AFI <5 cm
7. Post-term> 42 weeks of gestation.
8. Mal presentation
9. High risk pregnancy
    a. Preeclampsia
    b. Diabetes
    c. Chronic renal disease
    d. Connective tissue disorder
    e. Uterine scar due to previous LSCS, myomectomy.
    f. Anemia

Statistical analysis :

The collected data were processed using SPSS version 22 (IBM Corp., Armonk, NY, USA).

Ethical Approval:

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee (IEC) of KIMS & RF, Amalapuram, prior to the commencement of the study.

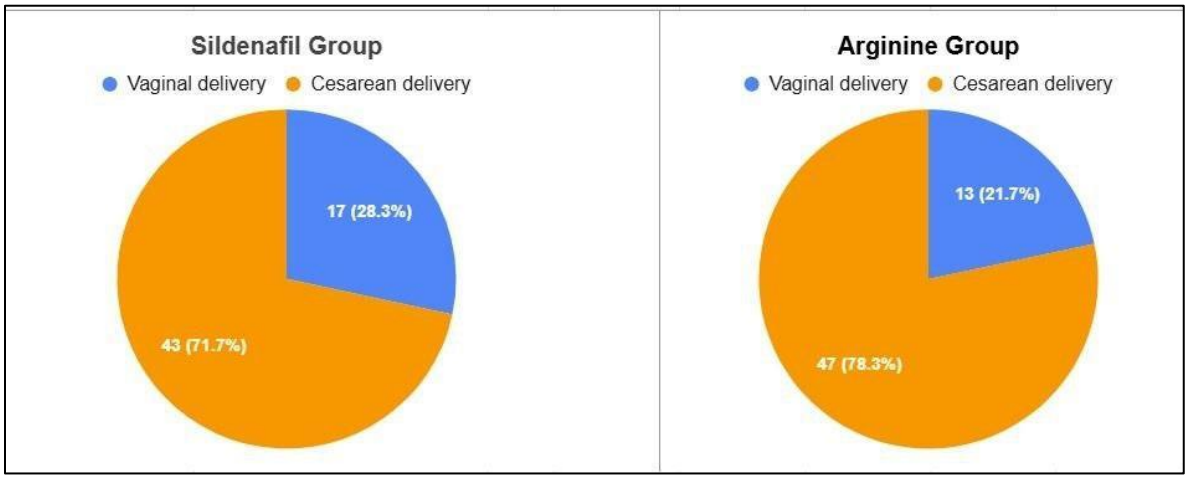
Objectives :

1. To study the mode of delivery/rate of operative interference in cases of term pregnancy with borderline AFI.
2. To study the perinatal outcome in cases of term pregnancy with borderline AFI. Perinatal outcomes assessed in terms of:
    a. Incidence of fetal distress
    b. Rates of Meconium stained amniotic fluid(MSAF)
    c. Birth weight< 2.5 kg
    d. Apgar score in 5th minute < 7,
    e. Rates of NICU Admissions, Neonatal deaths.

RESULTS AND DISCUSSION :

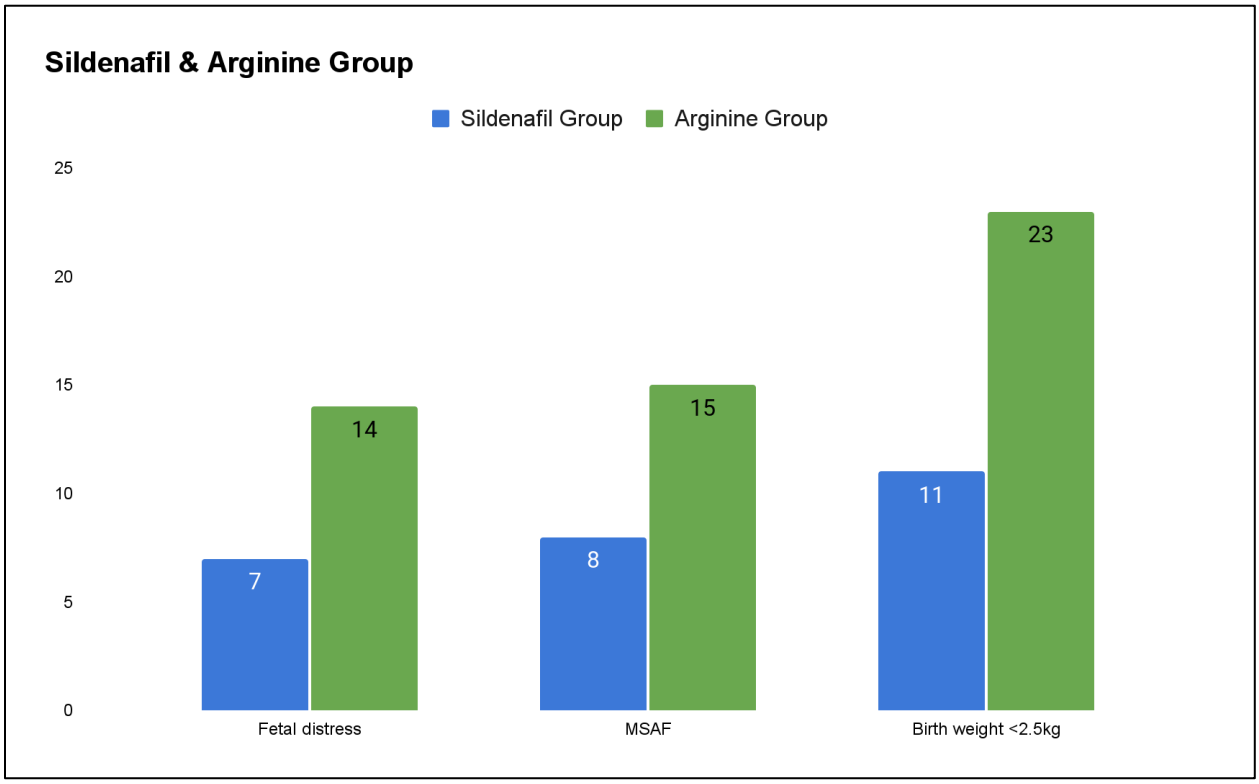
Distribution of cases according to mode of delivery and neonatal outcome in both groups (Table: 1)

	Sildenafil group	Arginine group
Mode of delivery		
1. Vaginal.	17(28.3%)	13(21.6%)
2. Cesarean.	43(71.6%)	47(78.3%)

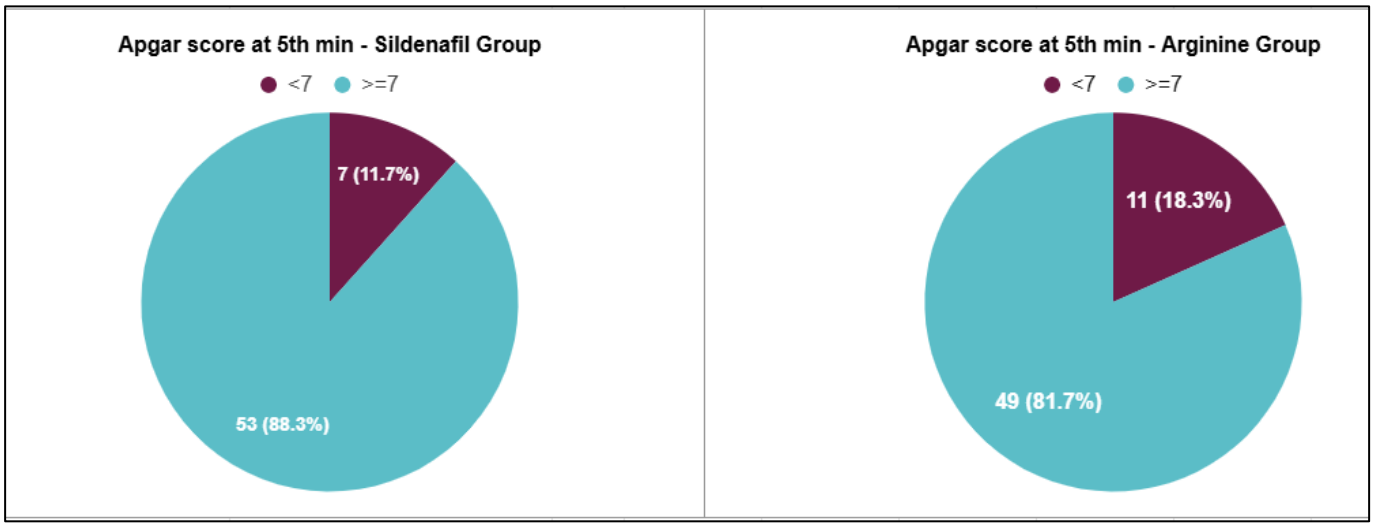


Distribution of cases according to neonatal outcome in both groups ((Table: 2)

	Sildenafil group	Arginine group
Perinatal outcome		
1. Fetal distress.	7	14
2 . Meconium stained amniotic fluid (MSAF)	8	15
3 . Birth weight <2.5 kg.	11	23



(Table -3)	Sildenafil group	Arginine group
4. Apgar score at 5th min		
< 7.	7(11.6%)	11(18.3%)
>=7.	53(88.3%)	49(81.6%)

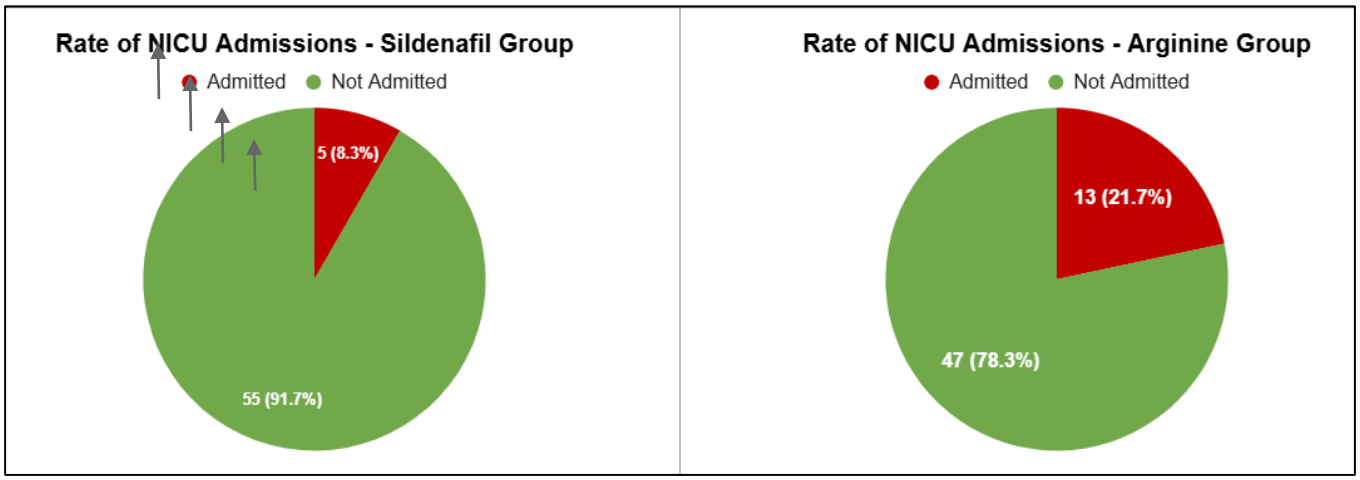


(Table: 4) Sildenafil group Arginine group

5. **Rate of NICU Admissions**

Yes.	5(8.3%)	13(21.6%)
No.	55(91.6%)	47(78.3%)

6. **Neonatal deaths.** 1 4



BASELINE CHARACTERISTICS OF TWO GROUPS

Start

|

| |

Sildenafil L-arginine

| |

After 24 hours After 24 hours

Mean AFI: 4.2 cm Mean AFI: 3.5 cm

| |

After 2 weeks After 2 weeks

Mean AFI:6.5cm Mean AFI: 5.0 cm

| |

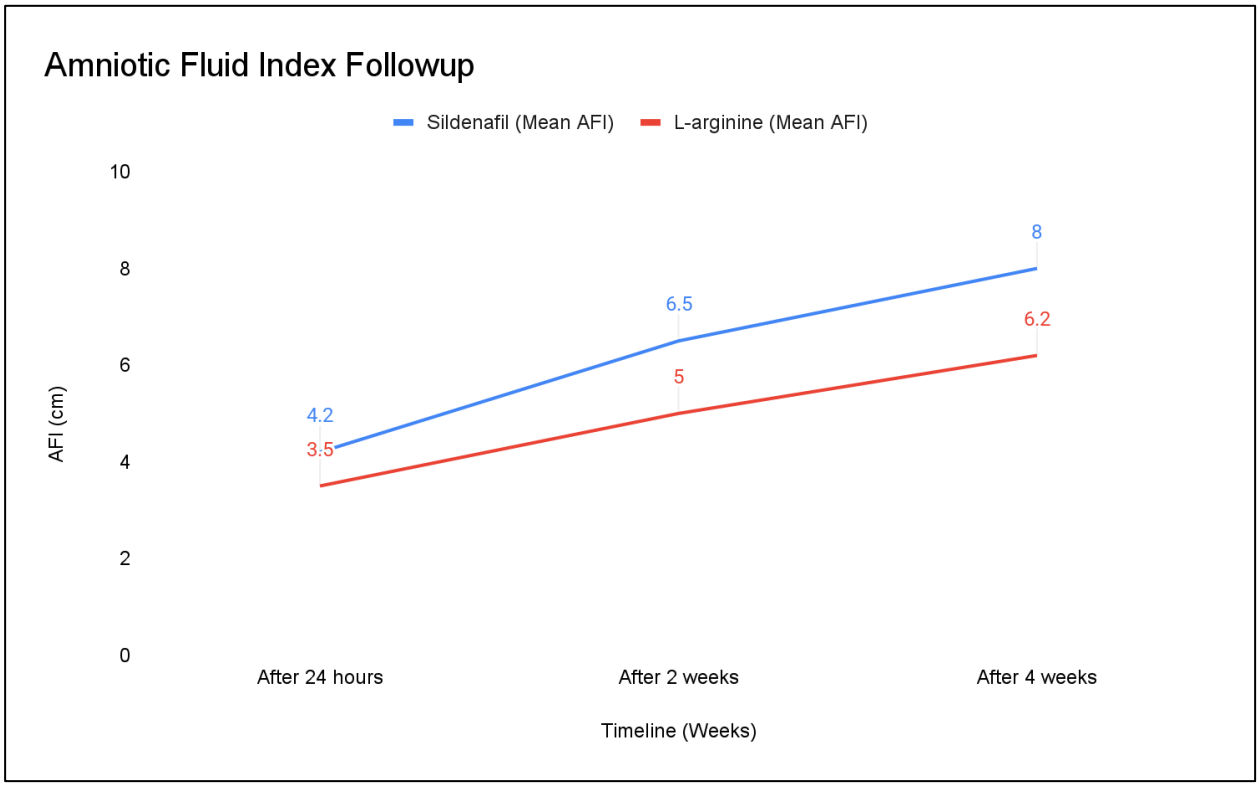
After 4 weeks After 4 weeks

Mean AFI: 8.0 cm Mean AFI: 6.2 cm

| |

Statistically Significant Statistically Significant

(p-value < 0.05) (p-value < 0.05)



The exact cause of isolated oligohydramnios is still unknown but the chronic suboptimal placental function is one among the probable reasons (20).Few studies have evaluated the efficacy of sildenafil in pregnancies complicated by oligohydramnios, and most of the participants in these studies were pregnant women with early and late onset fetal growth restriction (FGR). The results of these studies are conflicting (18). Sildenafil inhibits phosphodiesterase type 1 enzyme and increases the effect of nitric oxide by inhibiting phosphodiesterase type 5 and disrupting cyclic guanosine monophosphate degradation.

As a result, high levels of guanosine monophosphate cause vascular relaxation and increase the uterine blood flow (15). Some studies found that sildenafil citrate increased the fetoplacental

perfusion in fetal growth restricted pregnancies and significantly improved the umbilical and middle cerebral artery Doppler velocimetry (19)

Outcome was in terms of Improvement in Amniotic fluid volume, Delivery mode,Weight at birth, Rate of Meconium stained Amniotic Fluid, Fetal distress, APGAR score, admission to neonatal intensive care unit (NICU).

CONCLUSION

In conclusion, sildenafil supplementation demonstrated significant efficacy in improving the volume of Amniotic fluid among pregnant women diagnosed with oligohydramnios as compared to L- Argenine . The intervention resulted in a statistically significant increase in AFI, which contributed to better neonatal outcomes, including reduced instances of low birth weight and NICU admissions. Additionally, Sildenafil enhance uteroplacental circulation and prolong pregnancy provides a promising,

approach to addressing complications related to low AFI.In cases of asymmetric IUGR, sildenafil citrate therapy may present a novel chance to enhance perinatal outcomes. Future randomized trials are required to confirm the usage and safety of sildenafil citrate in pregnancies complicated by early-onset IUGR, as these data are insufficient to firmly guide decision-making in this regard.According to our research, sildenafil works just as well as L-arginine to treat FGR. Both the mean fetal weight and color Doppler indices significantly improved when sildenafil citrate was used.The APGAR score was improved along with less NICU admission rates in the sildenafil-treated group

Refrences:

1. Rosati P, Guariglia L, Cavaliere AF, Ciliberti P, Buongiorno S, Ciardulli A et al. A comparison between amniotic fluid index and the single deepest vertical pocket technique in predicting adverse outcome in prolonged pregnancy. J Prenat Med 2015; 9: 12-5.

2. Rabie N, Magann E, Steelman S, Ounpraseuth Oligohydramnios in complicated and uncomplicated pregnancy: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2017; 49: 442-9 .

3. HalaAbd El-fttah A, AliSabahRamadan HA. The effect of oral versus intravenous fluid therapy on maternal and neonatal outcomes for women with oligohydramnios. Egyptian Nursing Jouurnal 2018; 15: 228 .

4. Ala M, Mohammad Jafari R, Dehpour AR. Sildenafil beyond erectile dysfunction and pulmonary arterial hypertension: Thinking about new indications. Fundam Clin Pharmacol. 2021 Apr;35(2):235-259.

5.Mohamed NA, Abou-Saleh H, Kameno Y, Marei I, de Nucci G, Ahmetaj-Shala B, et al. Studies on metal-organic framework (MOF) nanomedicine preparations of sildenafil for the future treatment of pulmonary arterial hypertension. Sci Rep. 2021 Feb 22;11(1):4336

6. Maher MA, Sayyed TM, Elkhouly N. Sildenafil Citrate Therapy for Oligohydramnios: A Randomized Controlled Trial. Obstetrics & Gynecology. 2017;129(4):615-20.

7. Mol BW , Walker SP. Sildenafil Citrate Therapy for Oligohydramnios: A Randomized Controlled Trial. Obstet Gynecol . 2017 Nov;130(5):1157.
8.Xiao, X. M., & Li, L. P. (2005). L-Arginine
treatment for asymmetric fetal growth restriction.
International Journal of Gynecology & Obstetrics,
88(1), 15-18.
9. Sharma, A., Dashora, S., Sharma, R., Chandra, K.,
& Gunawat, M. S. (2017). To study the effect of Larginine
in oligohydramnios to improve perinatal
outcome. IOSR Journal of Dental and Medical
Sciences (IOSR-JDMS), 16(4), 16-19. Available
10.Yadav P, Basnet T, Yadav SP. Maternal and perinatal outcome in borderline oligohydramnios: a hospital-based studY. International Journal of Medical Science And Diagnosis. 2021;5:19–21. [Google Scholar]
11. Ghafarnejad M, Tehrani MB, Anaraki FB, Mood NI, Nasehi L. Oral hydration therapy in oligohydramnios. J Obstet Gynaecol Res. 2009;35:895–900. [Abstract] [Google Scholar]
12. Gizzo S, Noventa M, Vitagliano A, Dall'Asta A, D'Antona D, Aldrich CJ, et al. An update on maternal hydration strategies for amniotic fluid improvement in isolated oligohydramnios and normohydramnios: evidence from a systematic review of literature and meta-analysis. PloS one. 2015;10:e0144334. [Europe PMC free article] [Abstract] [Google Scholar]
13. Malhotra B, Deka D. Duration of the increase in amniotic fluid index (AFI) after acute maternal hydration. Arch Gynecol Obstet. 2004;269:173–5. [Abstract] [Google Scholar]
14. Wolman I, Groutz A, Gull I, Gordon D, Geva E, Lessing JB, et al. Is amniotic fluid volume influenced by a 24-hour fast? The Journal of reproductive medicine. 2000;45:685–7. [Abstract] [Google Scholar]
15. Ross MG, Cedars L, Nijland MJ, Ogundipe A. Treatment of oligohydramnios with maternal 1-deamino-[8-D-arginine] vasopressin–induced plasma hypoosmolality. Am J Obstet Gynecol. 1996;174:1608–13. [Abstract] [Google Scholar]
16. Morad AWA, Abdelhamid AA. Nitric oxide donors for treatment of isolated oligohydramnios: A randomized controlled trial. Middle East Fertility Society Journal. 2018;23:310–4. [Google Scholar]
17. Fisk NM, Ronderos-Dumit D, Soliani A, Nicolini U, Vaughan J, Rodeck CH. Diagnostic and therapeutic transabdominal amnioinfusion in oligohydramnios. Obstet Gynecol. 1991;78:270–8. [Abstract] [Google Scholar]
18. Ülker K, Çiçek M. Effect of maternal hydration on the amniotic fluid volume during maternal rest in the left lateral decubitus position: a randomized prospective study. J Ultrasound Med. 2013;32:955–61. [Abstract] [Google Scholar]
19. da Silva Ferreira RD, Negrini R, Bernardo WM, Simoes R, Piato S. The effects of sildenafil in maternal and fetal outcomes in pregnancy: A systematic review and meta-analysis. PloS one. 2019;14:e0219732. [Europe PMC free article] [Abstract] [Google Scholar] Retracted
20. Choudhary R, Desai K, Parekh H, Ganla K. Sildenafil citrate for the management of fetal growth restriction and oligohydramnios. Int J Womens Health. 2016;8:367–72. [Europe PMC free article] [Abstract] [Google Scholar]

Discussion reference

20.Underwood MA, Gilbert WM, Sherman MP. Amniotic fluid: not just fetal urine anymore. J Perinatol. 2005;25:341–8. doi: 10.1038/sj.jp.7211290. [DOI] [PubMed] [Google Scholar]

18.Sharp A, Cornforth C, Jackson R, Harrold J, Turner MA, Kenny LC et al. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. Lancet Child Adolesc Health. 2018;2:93–102. doi: 10.1016/S2352-4642(17)30173-6. [DOI] [PubMed] [Google Scholar]

15.Wareing M, Myers JE, O'Hara M, Baker PN. Sildenafil citrate (Viagra) enhances vasodilatation in fetal growth restriction. J Clin Endocrinol Metab. 2005;90:2550–5. doi: 10.1210/jc.2004-1831. [DOI] [PubMed] [Google Scholar]

19.Dastjerdi MV, Hosseini S, Bayani L. Sildenafil citrate and uteroplacental perfusion in fetal growth restriction. J Res Med Sci. 2012;17:632–6. [PMC free article] [PubMed] [Google Scholar]