Original Article

# The Effect of β-Sympathomimetics on Amniotic Fluid Volume in Women with Idiopathic Oligohydramnios

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## ABSTRACT

**Objectives:** To evaluate the role of Isoxsuprine hydrochloride in increasing amniotic fluid volume and consequently improving neonatal outcome and surveillance in case of idiopathic oligohydramnios.

**Methods:** This cross-over randomized controlled study was carried out at Outpatient Clinic and Inpatient Ward at Department of Obstetrics and Gynecology at Mansoura University Hospital (MUH), a major tertiary referal hospital for many governorates in the Delta region in Egypt. The included patients were subdivided into two groups: Group 1: 100 cases of pregnant women with oligohydramnios will receive isoxsuprine hydrochloride orally (20mg three times daily) for two weeks. Group 2: 100 cases of pregnant women with oligohydramniose will receive placebo for two weeks. Then group 1 received placebo for another 2 weeks and group 2 received isoxsuprine hydrochloride (the same dose group 1 received i.e. 20mg three times daily) for another 2 weeks.

**Results:** There are significant elevation in group1 at AFI1 , AFI2 and AFI3 . While there was insignificant difference between the studied groups at AFI4. So there are significant elevation in AFI with isoxsuprine. There was significant difference in NST value before and after intervention in both of group1 and group2 as reactive NST was significantly increased after intervention.

**Conclusion:** Isoxsuprine one of the most important treatment in isolated Oligohydramnios. Using isoxsuprine might be useful drug in treatment of Isolated oligohydramnios in pregnant woman.

**Key Words:** AFI, Isoxsuprine, Oligohydramnios, ultrasound.

**Received:** 30 November 2024, **Accepted:** 29 December 2024.

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**ISSN:** 2090-7265, 2025, Vol. 15

## INTRODUCTION

One dynamic element that is constantly and intimately connected to the mother and the developing baby is amniotic fluid. It is now widely acknowledged that proper intrauterine growth and a favorable newborn outcome depend on a consistent amniotic fluid volume[1].

The intramembranous route, fetal secretion (fetal lung and urine fluid), fetal consumption (fetal swallowing), and the balancing of fluid flow via osmotic gradients are some of the processes that control the amniotic fluid volume (AFV). As a result, aberrant volumes are also not well-defined, as is the normal AFV throughout pregnancy[2].

Since reduced quantities have significant pregnancy consequences, both quantitative and qualitative measurements of amniotic fluid volumes are useful. In a lack of preterm membrane rupture and fetal abnormalities, oligohydramniousness was characterized as an amniotic fluid index (AFI) <5cm. This condition is thought to be a sign of a chronic decline in placental functioning, which lowers the fetal urine output. The outcome of the pregnancy and the well-being of the baby are impacted by oligohydramnios[3].

An a greater likelihood of fetal distress, a high rate of surgical delivery, meconium aspiration, pressure-induced deformities, congenital defects, intrauterine growth restriction, and obstetric complications have all been linked to oligohydramnios. It can be brought on by medicines, membrane rupture, uteroplacental insufficiency, fetal growth limitation, and anomalies of the fetal urinary tract. Sometimes oligohydramnios is identified as isolated oligohydramnios, which occurs when none of the previously listed causes are present. In both normal and oligohydramniotic pregnancies, numerous studies have indicated that oral and intravenous hydration can raise the amniotic fluid index (AFI)[1].

*DOI:10.21608/EBWHJ.2024.340432.1393*

By reducing pulmonary hypoplasia, avoiding neurological problems, extending the time until the birth, and minimizing umbilical cord compression, amnioinfusion may enhance the fetal outcome. Additionally, it avoids fetal malformation[4].

According to more recent research, isoxsupnine may reduce blood viscosity. Both in vitro and in vivo studies revealed these effects. In a double-blind cross-over trial of individuals with idiopathic oligohydramnios, we administered isoxsupnine orally in order to broaden our findings to the in vivo setting[5].

Beta-agonists reduce myometrial contractions and raise intracellular cAMP in the myometrium through their impact on beta 2-adrenergic receptors. Peripheral vascular dilatation is caused by the beta-adrenergic hormone isoxsuprine, which directly impacts vascular smooth muscle. Isoxsuprine is used for managing dysmenorrhea and preterm labor by relaxing the smooth muscles of the uterus[6].

Isoxsuprine hydrochloride is thought to improve fetal outcomes by raising the rate of placental perfusion, which in turn raises the volume of amniotic fluid. This is based on the theory that it increases uterine blood flow. We will look into how isoxsuprine hydrochloride, a vasodilator, can improve fetal outcomes in the course of this research.

## PATIENTS & METHODS

This cross-over randomized controlled study was carried out at Outpatient Clinic and Inpatient Ward at Department of Obstetrics and Gynecology at Mansoura University Hospital (MUH), a major tertiary refer al hospital for many governorates in the Delta region in Egypt.

### *Subjects*

The study included pregnant women with oligohydramnios from 28 to 34 weeks gestational age at MUH.

### *Inclusion criteria*

All pregnant women with singleton pregnancies from 28 to 34 weeks gestational age with idiopathic oligohydramnios (defined as isolated oligohydramnios in the absence of any maternal orfetal condition known to reduce the amniotic fluid).

### *Exclusion criteria:*

Twin pregnancies, Premature membrane rupture, Pregnancy-induced hypertension. Pregestational hypertension, Gestational and pregestational diabetes, All systemic illnesses (e.g. nephropathy, cardiopathy, hepatopathy, and inappropriate antidiuretic hormone hypersecretion syndrome), Non reassuring non stress test (NST) results & Fetal congenital anomalies

### *Methods*

A written informed-consent form was obtained from each of the patients. All patients were subjected to full history taking, examination (general and abdominal) and ultrasound assessmen.

### *The included patients were subdivided into two groups:*

***Group 1:***

100 cases of pregnant women with oligohydramniose will receive isoxsuprine hydrochloride orally (20mg three times daily) fortwo weeks.

***Group 2:***

100 cases of pregnant women with oligohydramniose will receive placebo for two weeks.

Then group 1 received placebo for another 2 weeks and group 2 received isoxsuprine hydrochloride (the same dose group 1 received i.e. 20mg three times daily) for another 2 weeks.

Using the AFI calculation, which summed the measurement of each fluid pocket, devoid of fetal structures, obtained from four uterine quadrants, oligohydramnios was identified using the Phelan et al. approach. In cases where the AFI was less than 5cm, oligohydramnios was identified.

In order to minimize bias resulting from inter-operator variation, all pregnancies complicated by isolated oligohydramnios were confirmed by sonographic checks conducted by a qualified sonographer prior to taking individuals with isolated oligohydramnios. Up until the conclusion of the pregnancy, weekly sonographic exams were performed.

The adjusted biophysical profile, AFI measures, and an NST were used to track each fetus. The mean of three separate readings taken by the exact same investigator was used to calculate the AFI values.

An AFI measurements, a NST, and a modified biophysical profile were performed on day 0. The NST was performed every other day to monitor the fetal well-being. AFI and the modified biophysical profile were repeated weekly.

For those enrolled in both groups, the following data were examined: fetal birth weight, gestational age at birth, manner of delivery, age, prior pregnancies, and fetal and neonatal results (Apgar scores, umbilical artery pH at

the time of their birth and requirement for admission to the neonatal intensive care unit). Analysis was also done on the amniotic fluid index data before and after giving isoxsuprine hydrochloride.

***Sensitivity Methods:***

SPSS (statistical package of social sciences) version 21 (SPSS Inc., Chicago, IL, USA) was used for entry of information and statistical analysis. Numbers and percentages were used to represent categorical data. The mean and standard deviation were used to convey continuous, normally distributed data. The Kolmogrov Smirnov test was used to check the quantitative data for normalcy. Continuous normally distributed data were subjected to the Student *T* test, and When acceptable, the Fisher exact test or the chi square test were used to compare categorical data. When the probability (*P*) value was below or equal to 0.05, statistical significance was taken into account.

## RESULTS

Table (1) insignificant difference between studied groups regarding age, BMI, GA, parity.

AFI before means amniotic fluid index before administration of the treatment. AFI 1 means amniotic fluid index 1 week after administration of the treatment. AFI 2 means amniotic fluid index 2 weeks afteradministration of the treatment. There are significant elevation in group 1 at AFI 1, AFI2. While there is insignificant difference between studied groups at AFI before. AFI 3 means amniotic fluid index 3 weeks after administration of the treatment. AFI 4 means amniotic fluid index 4 weeks after administration of the treatment (Table 1).

**Table 1:** Demographic characteristics of the study:

| Variable | | | Group 1 *N*=100 | Group 2 *N*=100 | *P* |
|---|---|---|---|---|---|
| Age | mean±SD | | 22.6±2.77 | 24.8±3.8 | 0.602 |
| BMI | mean±SD | | 29.3±3.37 | 30.4±5.1 | 0.511 |
| GA | mean±SD | | 30.04±1.34 | 30.8±1.7 | 0.725 |
| Parity *N*(%) | | *P*0 | 50(50) | 49(49) | 0.934 |
| | | *P*1 | 32(32) | 33(33) | |
| | | *P*2 | 14(14) | 14(14) | |
| | | *P*3 | 4(4) | 4(4) | |

**Table 2:** AFI evaluation before and after treatment:

| Variable | Group 1 *N*=100 | Group 2 *N*=100 | *P* |
|---|---|---|---|
| AFI before | 3.8±0.6 | 3.5±0.9 | 0.877 |
| AFI 1 | 5.4±1.6 | 3.2±0.7 | 0.001* |
| AFI 2 | 6.5±2.5 | 3.2±0.5 | 0.001* |
| AFI 3 | 6.3±2.4 | 7±1.5 | 0.001* |
| AFI 4 | 6.4±2.9 | 8.2±3.2 | 0.661 |

(Table 3) show difference in NST value before and after administration of isoxuprine in group 1 (Table 3) show difference in NST value before and after administration of isoxuprine in group.

Table (4) show difference in doppler value before and after administration of isoxuprine in group 1(Table 1) show difference in Doppler value before and after administration of isoxuprine in group 2.

**Table 3:** NST evaluation before and after treatment:

| NST(group 1) | BEFORE | AFTER | *p* |
|---|---|---|---|
| Reactive | 78(78) | 94(94) | 0.033 |
| Non-reactive | 22(22) | 6(6) | |
| **NST(group 2)** | **BEFORE** | **AFTER** | ***p*** |
| Reactive | 64(64) | 85(85) | 0.041 |
| Non reactive | 36(36) | 15(15) | |

**Table 4:** Doppler evaluation before and after treatment;

| Doppler (group 1) | BEFORE | AFTER | *P* |
|---|---|---|---|
| Normal | 81(81) | 93(93) | 0.047 |
| Abnormal | 19(19) | 7(7) | |
| **Doppler (group 2)** | **BEFORE** | **AFTER** | ***p*** |
| Normal | 73(73) | 89(89) | 0.115 |
| Abnormal | 27(27) | 11(11) | |

Table (5) show insignificant difference in Apgarscore at 1,5min between both groups.

**Table 5**: APGAR score of newborns of study population:

| Variable | Group 1 *N*=100 | Group 2 *N*=100 | Total |
|---|---|---|---|
| Apgar score <7 at 1 min | 20 | 23 | 43(21.5%) |
| Apgar score <7 at 5 Min | 15 | 17 | 32(16%) |

## DISCUSSION

A disorder known as oligohydramnios is characterized by a reduction in amniotic fluid volume in comparison to gestational age. The baby's life support system includes the amniotic fluid (AF). About 12 days following pregnancy, the amniotic sac forms, and amniotic fluid is shortly after. Initially composed of effusion supplied by the mother's circulation, fetal urine takes over as the main component about week 20[7].

Sonography makes it possible to estimate the volume of amniotic fluid. In order to evaluate the two primary sonographic techniques for evaluation—the AFI and the maximum vertical pocket—Nabhan and Abdelmoula carried out a peer-reviewed meta-analysis in 2008. Even though the AFI approach is linked to a greater rate of

obstetric interventions that do not improve the fetal fate, the study shown that it is still commonly employed for amniotic fluid evaluation[8].

It is referred to as oligohydramnios if the AF value is excessively low. Amniotic fluid index (AFI) ≤5 (less than the 5th percentile) or the lack of a pocket at least 2×1cm were considered indicators of oligohydramniosis[9].

It is estimated that between 1 and 5% of pregnancies result in oligohydramnios, a prevalent pregnancy problem. Although it can happen at any point during gestation, the latter trimester is when it happens most frequently. After 42 weeks of pregnancy, a patient's amniotic fluid volumes are cut in half. Twelve percent of pregnancies that last longer than forty-one weeks may be complicated by oligohydramnios[10,11].

IUGR (Intra Uterine Growth Restriction) and placental hypoperfusion severity are typically correlated with the extent of oligohydramnios. Reduced urine production is the most prevalent reason of oligohydramnios in IUGR infants[1].

It is preferable to use therapeutic measures in situations with isolated oligohydramnios to extend the pregnancy in order to prevent preterm labor and the early effects of surgery.

One medication that is beta-sympathomimetic is isoxsuprine hydrochloride. By activating adenyl cyclase and stimulating b2-receptors in the uterine muscle, it raises cAMP and decreases intracellular calcium. By directly affecting vascular smooth muscle, mostly in skeletal muscle, isoxsuprine also causes peripheral vasodilation with minimal impact on cutaneous blood flow[12].

In order to improve neonatal outcomes and monitoring in cases of idiopathic oligohydramniosis, this study sought to assess the impact of isoxsuprine hydrochloride in raising amniotic fluid volume.

This study included 200 pregnant women with oligohydramnios from 28 to 34 weeks gestational age, They were subdivided into two groups:

*Group 1:* 100 Cases of pregnant women with oligohydramniose will receive Isoxsuprine hydrochloride orally (20mg three times daily) for two weeks.

*Group 2:* 100 Cases of pregnant women with oligohydramnios will receive placebo fortwo weeks.

Then group 1 will receive placebo for another 2wks and group 2 will receive Isoxsuprine hydrochloride (the same dose group 1 received i.e. 20 mg three times daily) for another 2 wks.

In the present study, there was no significant difference between the 2 groups regarding maternal age as; the mean maternal age of group 1 and group 2 were 22.6±2.77 years and 24.8±3.8 years, respectively. This is comparable to study done by Tajinder and Ruchika in which it was 25.8 years[13].

Despite the high frequency of oligohydramnios in adolescent and older pregnancies, the results indicate that the majority of cases occur in women aged 20 to 30, as this is the age at which most women in developing nations marry and get pregnant[1].

Given that the majority of patients in the current study were primigravida (50% in group 1 and 49% in group 2), there was no discernible difference in parity among the two groups. This study is comparable to one conducted by J. Agatia and associates, wherein 52% of the participants were primigravida[14]. This is somewhat in line with Ghike and his coworkers' 2013 observation that the majority of the women in both groups were either nulliparous or Para one[15].

According to Petrozella *et al.,* (2011), 60.0% of primigravida had oligohydramnios. These discrepancies between the findings of the aforementioned studies and the current one may be explained by variations in the study's design, sample size, and selection standards[16].

Rayamajhi and Pratap observed that the isoxsuprine group experienced greater adverse effects, with hypotension being the most frequent[17]. Regarding this, we observed that while there was no significant difference in SBP or DBP between the two groups under study, both SBP and DBP were much lower in the isoxsuprine group than in the placebo group. Isoxsuprine-induced hypotension can be attributed to the fact that this class directly affects blood vessel smooth muscle, particularly in skeletal muscle, causing peripheral vasodilation with minimal impact on cutaneous blood flow and uterine relaxation[18].

Ragunath and Sasmal discovered that pregnant women who took isoxsuprine showed a clear decrease in both their systolic and diastolic blood pressure. The isoxsuprine group experienced a maximum drop in systolic blood pressure of 26mmHg. Pregnant women who took isoxsuprine experienced a maximum drop in diastolic blood pressure of 20mmHg[19].

Yet, according to (Nur Oktavia *et al*., 2017), there was no discernible difference in the blood pressure of individuals before and after administering isoxsuprine (*p value* >0.5).

Fluid status is determined by AFI; amniotic fluid rises between weeks 14 and 31 and then falls after that. Pregnancies with an AFI of less than 5cm are frequently

described by oligohydramnios, while those with an AFI of 5 to 8cm are described by borderline/low normal amniotic fluid volume[20]. In this respect, we discovered that, whereas the two groups under study at AFI before did not differ much, group 1 at AFI 1, AFI 2, and AFI 3 had a considerable increase. At AFI 4, however, the differences between the groups under study were negligible.

One of the most crucial diagnostic procedures for fetal health is the non-stress test (NST), which is frequently employed to track labor and pregnancy. It has been demonstrated that this test has a satisfactory diagnostic value for predicting maternal and fetal outcomes. This test has been used extensively for fetal surveillance and is an excellent indication of oxygenation of the fetal central nervous system[21].

One of the most popular methods of antepartum monitoring is the non-stress test (NST), which entails keeping an eye on the fetal heart rate for 20 to 60 minutes. If there are two or more accelerations in a 20-minute interval, the test is deemed reactive. Reactive NST is a sign of healthy fetuses and is linked to a less than 1% risk of intrauterine fetal death within the next seven days due to placental insufficiency. Compared to the UA Doppler test, NST is a more accurate indicator of unfavorable newborn outcomes[22].

In the Buchhav trial, only 24% of patients with AFI >5 had a non-reactive NST, whereas 65% of patients with AFI <5 had a non-reactive NST. For fetal distress, 53% of patients with AFI <5 had LSCS[23].

Uterine relaxation enhances placental blood circulation and, consequently, fetal oxygenation, and preventive tocolysis using beta mimetics and other medicines has grown popular as a therapy for fetal distress[24].

In this respect, we discovered that both groups 1 and 2 had considerably different NST values before and after the treatment, with reactive NST rising significantly following the treatment.

Isoxsuprine treatment was able to raise the proportion of normal Doppler from 81% to 93% in the current investigation. It can be explained by the fact that it activates adenylyl cyclase by stimulating β2-receptors, which raises myometrial cAMP and, thus, lowers uterine contractility. Additionally, phosphodiesterase, which changes cAMP into AMP, is impacted by isoxsuprine. Pregnant women on isoxsuprine, which is used to avoid premature delivery and perform intrauterine resuscitation, saw a drop in the RI of their uterine and umbilical arteries[25].

In terms of sensitivity and predictive value, MCA Doppler indices outperformed umbilical artery as a predictor of fetal outcome[26].

Groups 1 and 2 in the current study had Apgar scores of 7.92±0.41 and 8.02±0.33, respectively. Low APGAR scores and neonatal intensive care unit (NICU) hospitalization are linked to oligohydramnios[26].

In the Buchhav trial, 34% of patients with oligohydramnios had a 5-min APGAR <7. Of the newborns in Oligohydramnios patients, 33% weighed less than 2.5 kg at birth[23].

Reduced amniotic fluid volume, or oligohydramnios, has been linked to a higher risk of intrauterine development retardation, meconium aspiration syndrome, severe birth asphyxia, low APGAR scores, and congenital abnormalities. These factors can account for a baby's decreased Apgar score. Reduced neonatal morbidity and death on the one hand, and fewer cesarean deliveries on the other, may result from early detection and treatment of oligohydramnios[14].

In one study, individuals receiving isoxsuprine experienced a longer gestation duration with a better pregnancy result. When compared to the non-pharmacological treatment group, the mean Apgar score was higher for patients receiving isoxsuprine at 1 and 5 minutes[1].

According to Shirin et al., infants born in the isoxusprine group had a mean birth weight of 1.94 kg and an apgar score of > 7 at 1 and 5 minutes, which were 41.66% and 83.33%, respectively[27].

Regarding the Apgar score at five minutes, there was no discernible difference between the two groups in the current investigation. According to Ragunath and Sasmal, 62.5% of infants whose moms were given isoxsuprine had Apgar scores between 8 and 10[19].

## CONCLUSION

One of the most crucial treatments for isolated oligohydramnios is isoxsuprine. When treating isolated oligohydramnios in pregnant women, isoxsuprine may be a helpful medication.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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