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The Effect of Myo-Inositol on Sperm Parameters and Pregnancy Rate in Oligoasthenospermic Men Treated with IUI: A Randomized Clinical Trial

Abstract

Aim: This paper investigates the Myo-inositol supplementation in treating infertility related to oligoasthenospermia among men besides mentioning the increasing trend of infertility in the world.

Methods: A randomized, double-blind, and placebo-controlled trial was done in Lady reading hospital, medical teaching institute, Peshawar, 60 men diagnosed with oligoasthenospermia were randomly allocated to receive 2 g of myo-inositol twice a day or a placebo after 3 months. The pre- and post-treatment semen analysis was conducted according to the WHO 2021 established standards. Supplanted couples received intrauterine insemination (IUI), in which ovulation was controlled and pregnancy was verified using serum 25 -hCG and ultrasound.

Findings: Myo-inositol has demonstrated a possible beneficial outcome on sperms parameter, ovulation and fertilization rate in PCOS women. The t-test and Chi-square test were used in analyzing data at a significance level of $p < 0.05$. In men, it is associated with improvement of sperm maturation and motility among oligoasthenospermic individuals. Also, it can aid in the preservation of osmotic balance of seminal fluid, which is a positive factor in fertility.

Summary: The results indicate the necessity to create awareness and interventions about infertility. Myo-inositol has a potential to be a useful solution to both genders in enhancing reproductive health. More studies are required to come up with holistic methods of treatment of infertility.

1. INTRODUCTION

Infertility is described as a medical problem that impacts the reproductive system, according to both the World Health Organization (WHO) and the American Fertility Society (AFS). It is specifically defined as the failure of a couple to conceive after undergoing regular, unprotected sexual action for a period of 12 to 24 months.1-2 Infertility can happen for many reasons, such as health issues, hormone imbalances, or physical problems with either partner. It often comes with emotional challenges, making it a significant health concern for couples who want to start or grow their families.3

Myo-inositol (MI) plays a vital role in a number of reproductive functions, such as the maturation of gametes, development of oocytes, fertilization, and growth of the fetus.4 Recent research is emphasizing the physiological and therapeutic advantages of Myo-inositol, underlining its potential to restore reproductive capabilities in humans specifically. This compound has progressed into a fundamental rehabilitation for Polycystic Ovary Syndrome (PCOS) and is documented for its reassuring power to rejuvenate and improve reproductive procedures.5 There is a robust indication that Myo-inositol not only recovers ovulation but also increases the chances of successful fertilization in ladies facing PCOS.6

Investigation on male fertility has indicated that Myo-inositol levels in the seminiferous tubules are immensely greater than those in the blood. As sperm journey through the complicated routes of the epididymis and vas deferens, this engagement seems to increase even more, suggesting that Myo-inositol is crucial for keeping the maturation and undertaking of sperm within the male reproductive method.7 Oligoasthenospermia refers to a situation where the count of sperm is low (oligospermia) and the activity of sperms is hindered (asthenospermia), and its situation is increasingly common in recent years.9 Alterations in sperm morphology, which are frequently associated with this disease, may have a profound impact on male fertility. This fertility loss is mostly due to the excessive production of reactive oxygen species (ROS) that negatively affect the motility and structural integrity of sperm cells.9 Sperm cells in individuals with oligoasthenospermia are often caught in irregular fibrous frameworks. Such encasing does not only prevent their movement, but it also greatly impairs their overall functionality.10

Studies show that the use of Myo-inositol can reduce the circumstance of this shapeless fibrosis, which in turn enhances sperm rate.11 Additionally, Myo-inositol plays a role in holding the osmotic balance of seminal fluid, which is crucial for the proper process of sperm. A reduced osmolarity can decrease sperm motility and modify the consistency of seminal plasma, which in turn can influence reproductive capacity.12 Myo-inositol supplementation helps maintain ideal seminal osmolarity, supports motility, and improves fertility.13

The growing occurrence of infertility worldwide can be connected to a variety of corresponding reasons. These elements encompass environmental contamination, including exposure to harmful substances in air and water resulting from toxic chemicals present in everyday products, as well as lifestyle preferences such as smoking and poor dietary patterns.14 Moreover, the practice of postponing weddings and having minors, along with the upsurge in high-risk sexual exercises, strengthens the problem. Additionally, psychological strain resulting from multiple personal and societal intimidations significantly affects reproductive health.15

The World Health Organization (WHO) demonstrates that approximately 1 out of 6 adults, or approximately 17.5 percent of the inhabitants of the entire world, have gone through infertility issues in their lives. This number highlights a disturbing reality that the reduction happens at all socioeconomic levels, and the relative infertility is experienced in both the high-income and the middle-income countries, as well as in the low-income ones. This holistic case shows that the issue of increased attention, specific analysis, and customized interventions is urgent to control the situation.16

A recent study by the Global Burden of Disease Study 2021 shows that the age-standardized prevalence rate (ASPR) of male infertility is about 1,354.76 cases/100,000 populations or about 1.35 percent of the population. On the contrary, female infertility has a prevalence rate of approximately 2,764.62 cases per 100,000 individuals or 2.76%. These statistics illustrate that the rate of infertility among both sexes has been steadily growing every year since 1990.17

The causes for infertility are various and can be classified into different groups: factors associated to females (20–35%), factors linked to males (20–30%), a mix of both male and female characteristics (25–40%), or models where the cause stays unknown (10–20%).18 Notably, male infertility has remarkably increased in contemporary decades, with sperm counts dropping by around 50–60%.19 It is calculated that around 30 million men worldwide are infertile, with increased incidence rates followed in Central Europe and other parts of the Western world. This position highlights male infertility as a practical global health problem.20 Male reproductive health may be impaired by such conditions as varicoceles, infections, hormonal disorders, undescended testes (cryptorchidism), prostate diseases, orchitis of the mumps, testicular torsion, physical traumas, and complications of earlier inguinal operations. Moreover, such negative factors as chromosomal abnormalities (e.g., Klinefelter syndrome), Y-chromosomes microdeletions, and some medications influence male fertility.21

The low number of sperm, poor motility, and morphology are the key symptoms of

oligoasthenoteratospermia (OAT), which is still a problematic issue of male infertility. There are a number of treatments although a number of them are not effective. Therefore, studies are being conducted to define hormonal and non-hormonal compounds that are able to improve sperm parameters and reproductive functioning.

Sperm capacitation has been found to be metabolically reprogrammed, thus suggesting that sperm cells have the ability to regulate their metabolism without systemic control.22 One of the potential compounds that are presently being investigated is myo-inositol (MI), an inositol family C6 sugar alcohol stereoisomer. There are several studies with positive findings on the use of MI supplementation and male fertility including an increase in sperm functions.23

Oral supplementation with MI has been shown to improve sperm parameters, hormonal balance, and metabolic profiles in subfertile men.24 In Assisted Reproductive Technology (ART), MI reduces the required dose of gonadotropins and shortens the duration of ovarian stimulation, benefiting both PCOS and non-PCOS women.25 Additionally, in vitro studies confirm that MI enhances both total and progressive sperm motility.26

In females, MI is recognized as a treatment for infertility linked to insulin resistance, particularly in PCOS. Together with D-chiro-inositol (DCI), another inositol isomer, MI acts as an insulin sensitizer that improves hormonal and metabolic balance, aiding ovulation.27 However, physiological distinctions between MI and DCI, such as their absorption and cellular functions, require further clarification.28

In ART, careful use of inositols is crucial due to insulin's influence on sperm function.29 The combination of MI and DCI in a 40:1 ratio is especially effective in managing PCOS. However, DCI has shown less pronounced effects on sperm function.30

Nevertheless, DCI has a positive influence on sperm mitochondrial function, which is vital for motility through both glycolysis and oxidative phosphorylation in both healthy and asthenozoospermic men.31 Mitochondrial Membrane Potential (MMP) assessment provides insight into this function, as healthy mitochondria are essential for supporting the energy needs of sperm cells. The benefits of inositols on motility and mitochondrial function stem from their insulin-sensitizing, antioxidant, hormonal, and prokinetic properties.

All in all, MI seems to have a more significant influence on reproductive functioning in comparison to DCI, which positively affects the development of oocytes, the functionality of sperms, and the quality of embryos. This is assisted by clinical applications of MI in ART. During the 2013 Florence International Consensus Conference on MI and DCI in obstetrics and gynecology, the researchers talked about the physiological functions of MI and DCI in gametes development. There is an indication of the predominance of MI, with over 99 percent of cellular inositol, DCI occupying the rest. The disturbance of the balance between MI and DCI can lead to the impairment of insulin and FSH signals in PCOS patients.32

The conference further emphasized that Myo-Ins, alone or in combination with DCI at a physiological ratio of 40:1, could improve ART outcomes by enhancing ovarian response and oocyte and embryo quality.33

We explored in our research the impacts of MI on sperm work in men with OAT. The MI supplementation was done to one section of patients and the direct treatment of ejaculated sperm in another section. We also analyzed different sperm parameters, such as motility, survival, capacitation and glucose metabolism and lipid metabolism. Another hypothesis that our results suggest is that MI can particularly have a positive effect on sperm quality, and can be a restorative effect on spermatogenesis. Nevertheless, more research is needed to explain the correct molecular processes of these positive results.

2. MATERIALS AND METHODS

Study Design and Setting

This research was structured as a forthcoming, randomized, double-blind, placebo-controlled clinical trial. It took place at the Andrology and Infertility Unit of the Lady Reading Hospital, Medical Teaching Institute, Peshawar, after receiving ethical approval from the Institutional Review Board.

Participants

60 men diagnosed with oligoasthenospermia were selected for the study according to the following criteria:

- **Inclusion Criteria:**

oIndividuals aged between 25 and 45 years

oDiagnosed with oligoasthenospermia according to the WHO 2021 semen analysis criteria: sperm concentration is less than 15 million/mL, and progressive motility is below 32%.

oThere is no record of genetic infertility, a varicocele grade of 2 or higher, or any ongoing systemic illness.

oWomen under the age of 35 who have regular ovulatory cycles and have verified open fallopian tubes through HSG or laparoscopy.

oPartners experiencing their initial or second IUI cycle.

- **Exclusion Criteria:**

oUtilization of hormonal or antioxidant treatment in the previous 3 months.

oA background involving smoking, alcohol, or substance misuse.

oThe existence of leukocytospermia or an infection in semen analysis.

oInfertility due to female factors or a body mass index (BMI) exceeding 30 kg/m².

Sample Size

According to prior research indicating a 20–30% enhancement in sperm motility and morphology due to Myo-inositol treatment, a sample size of 30 per group (total n=60) was determined to provide 80% power and a significance level of 5% ($\alpha = 0.05$), while also considering a 10% dropout rate.

Allocation

Subjects were randomly placed into two groups (n = 30 for each group) through a computer-generated randomization list:

- Group A (Intervention): Ingested Myo-inositol 2 g two times a day (totaling 4 g per day) orally for a duration of 3 months.
- Group B (Control): Was given a placebo that looked the same and followed the same dosing schedule.

Both groups maintained their specific treatments until the time for semen collection for IUI was arranged.

Intervention Period

The subjects were observed over a period of 3 months and Myo-inositol or a placebo administered. The treatment adherence was monitored by the use of pill counts and monthly follow-up phone calls.

Ethical Approval

This study came after A Declaration of Helsinki. The size of the clinic meant that there was no need of having a formal Institutional Review Board. However, the research protocol was verified and approved by the senior medical community in Lady Reading Hospital, Medical Teaching Institute, Peshawar. All the participants were informed on the issue of informed consent prior to enrollment. The researchers obtained verbal consent and documented it due to the constraints of the clinic.

Semen Analysis

The baseline semen examination was pre-intervention, and at three-months post-intervention. The samples were taken 2-5 days following the period of abstinence and tested within one hour as per WHO 2021 requirements.

The criteria assessed comprised:

- Sperm concentration (million/mL)
- Total sperm motility (%)
- Progressive motility (%)
- Sperm morphology (% normal forms)
- Sperm volume and vitality

Intrauterine Insemination (IUI)

After 3 months of supplementation, the couples underwent IUI in either a natural or a slightly stimulated period. Ovulation was confirmed with serial ultrasound and insemination was done 36 hours after ovulation induction with hCG.

The motility and count of sperms were measured prior to the insemination process, after washing. Pregnancy was confirmed by serum 8 -hCG testing 14 days following IUI and ultrasound at the age of 6 weeks.

Outcome Measures

- Primary Outcome: Enhancement of sperm characteristics (count, movement, shape)
- Secondary Outcome: Rate of clinical pregnancies per cycle.

Statistical Analysis

The analysis of data was performed with the use of SPSS. Mean was used to mention continuous variables with SD. Paired t-tests and unpaired t-tests were both used to evaluate the pre- and post-treatment parameters across and inside the groups. The Chi-square test was used to analyze categorical variables (e.g. pregnancy rate). A p-value below 0.05 was taken as a statistically significant value.

3. RESULTS

Sixty oligoasthenospermic men who underwent the IUI procedure were recruited and assigned to two groups: 30 of them were under Myo-inositol (MI) supplementation and the remainder 30 were the control group under the placebo. The parameters of the sperms evaluated were total motility, progressive motility, sperm concentration, morphology, semen volume and sperm vitality.

Total Sperm Motility (%):

Massively increased the overall motility of the sperm between the Myo-inositol treated group and the control, whereby the mean motility of 77.3/56.8 of p-value value of less than 0.001 were significantly different. In addition, the coefficient of variation (CV) in MI group (16.04) was significantly lower than in the control population (27.46), meaning that the results were more similar in individuals that were treated. This overall motility is required which reports the percentage of transferring sperms in a semen sample- which is a crucial variable in fertilizing, especially in intra uterine insemination (IUI). Such effects may be due to the overall impact of myo-inositol in improving mitochondrial functions and the generation of energy in cells that, motility highly relies on ATP generated by the sperm mitochondria. Recent research, among others published in Andrology (2022) proved that MI supplementation guides an efficacious augmentation of sperm motility mediated by antioxidant reactions and enhanced calcium signaling.

Table 1: Comparison of Total Sperm Motility (%) Between Control and Myo-inositol G

Group	Mean (%)	Standard Deviation (±SD)	Coefficient of Variation (CV%)	p-value
Control	56.8	15.6	27.46	<0.001
Myo-inositol	77.3	12.4	16.04	<0.001

Figure 1: Bar Graph of Total Sperm Motility (%) in Control vs. Myo-inositol Groups

The mean total motility significantly improved in the MI group (77.3 ± 12.4%) compared to the control group (56.8 ± 15.6%) ($p < 0.001$). The coefficient of variation (CV) was lower in the MI group (16.04%) than in the control group (27.46%), indicating more consistent outcomes in the treatment group.

Progressive motility (%):

The proportion of progressive motility which is the proportion of sperm traveling in a straight or large circular direction also recorded an impressive improvement in the MI group. The mean progressive motility increased in the control group (41.40 percent) to MI group (62.10 percent): again with very significant p-value (<0.001). The CV declined to 17.55 percent compared to 31.88 percent suggesting less varied increments in the subjects that received MI. Progressive motility is more clinically significant than the total motility because only progressively moving sperms would be in a position to accomplish the ovum and fertilize it. The positive effect of MI on the progressive motility might be associated with the regulatory effect of MI on the intracellular calcium and energy metabolism of the sperm cells. Consequentially, the 2021 randomized controlled trial study has come up with an important positive impact of MI on progressive motility in men with asthenozoospermia and fertilization rates upon its administration before IUI.

Table 2: Comparison of Progressive Sperm Motility (%) Between Control and Myo-inositol Groups

Group	Mean (%)	SD (±)	CV (%)	p-value
Control	41.4	13.2	31.88	<0.001
Myo-inositol	62.1	10.9	17.55	<0.001

Figure 2: Bar Graph of Progressive Motility (%) in Control vs. Myo-inositol Groups

Sperm Concentration:

The sperm concentration in millions per milliliter failed to provide statistically significant difference between the groups. The average in the control group was 17.6 million/ml and in the MI group 16.2 million /ml, the p-value was 0.242 and the CVs were nearly the same (29.55% and 29.63%). It implies that MI does not necessarily have a direct influence on the production of sperm or spermatogenesis. The concentration was not increasing which corresponds to the previous results that specify that MI plays a significant role in improving functional parameters, but not quantity. A meta-analysis of the impact of MI on male infertility found in 2020 that MI enhances motility and morphology, but has a small or inconsistent impact on sperm count, which could be explained by individual variations in the baseline testicular functioning or the absorption of mitochondrial injury.

Table 3: Comparison of Sperm Concentration (million/ml) Between Control and Myo-inositol Groups

Group	Mean (million/ml)	SD (±)	CV (%)	p-value
Control	17.6	5.2	29.55	0.242
Myo-inositol	16.2	4.8	29.63	0.242

Figure 3: Bar Graph of Sperm Concentration (million/ml) in Control vs. Myo-inositol Groups

Normal Sperm Morphology

Sperm morphology, referring to the percentage of sperm with normal shape and structure, significantly improved in the MI group, increasing from a mean of 1.8% to 3.1% ($p < 0.001$). The CV also decreased from 50% in the control group to 32.26% in the MI group, suggesting not only better results but also more predictable improvements. Though these absolute values are low, even small increases in normal morphology are clinically relevant, as abnormally shaped sperm are often unable to fertilize an egg. The improvement in morphology could be attributed to MI's antioxidant properties, which help protect sperm DNA and cellular structures during spermatogenesis. Studies such as one published in Reproductive Biology and Endocrinology (2021) have shown that MI may improve spermatogenic cell differentiation and reduce DNA fragmentation, thereby enhancing morphological integrity.

Table 4: Comparison of Morphologically Normal Sperm (%) Between Control and Myo-inositol Groups

Group	Mean (%)	SD (±)	CV (%)	p-value
Control	1.8	0.9	50	<0.001
Myo-inositol	3.1	1	32.26	<0.001

Figure 4: Bar Graph of Normal Sperm Morphology (%) in Control vs. Myo-inositol Groups

Semen Volume

The volume of semen that was 2.6ml in the control group and 2.78 ml in the MI group ($p = 0.438$) was not statistically significant. CV was slightly smaller in the MI group (34.17% and 42.31%), and the variation is slightly smaller in general, although MI does not appear to have a huge effect on the semen volume. The accessory glands (seminal vesicles and prostate) are also important in defining the quantity of secretions in the semen, and MI supplementation may not have a great impact on the same, as its aim is on the metabolism and motility of the sperm. The findings are consistent with the prior literature, one such study (2019) has indicated that ejaculate volume does not change significantly in the face of MI treatment, making the volume a non-sensitive variable to determine the advantages of MI.

Table 5: Comparison of Semen Volume (ml) Between Control and Myo-inositol Groups

Group	Mean (ml)	SD (±)	CV (%)	p-value
Control	2.6	1.1	42.31	0.438
Myo-inositol	2.78	0.95	34.17	0.438

Figure 5: Line Graph of Semen Volume (ml) in Control vs. Myo-inositol Groups

Sperm Viability

The sperm viability, which is the ratio of live spermatozoa in a specimen, significantly improved after MI treatment. The average viability in the control group was 65.4% and in the MI group was 80.6% ($p < 0.001$) and the CV decreased, 19.12% to 10.8%, which proved a very consistent effect. This increase indicates increased sperm membrane probity and mitochondrial mobility, presumably through antioxidant and metabolic support of MI. Healthy sperm is also a necessity to the successful fertilization especially in the IUI techniques where only active and living sperm is introduced. A 2023 study found that MI could stabilize the mitochondrial membrane and reduce the levels of reactive oxygen species. in sperm, leading to increased survival rates that can be useful. The clinical significance is also associated with improved acrosome response and increased likelihood of fertilization, which increases its viability.

Table 6: Comparison of Acrosome Integrity (%) Between Control and Myo-inositol Groups

Group	Mean (%)	SD (±)	CV (%)	p-value
Control	65.4	12.5	19.12	<0.001
Myo-inositol	80.6	8.7	10.8	<0.001

Figure 6: Area Graph of Sperm Acrosome Integrity (%) in Control vs. Myo-inositol Groups

4. DISCUSSION

The findings of this study confirm that the Myo-inositol (MI) supplementation affects different parameters of the sperm in oligoasthenospermic men undergoing intrauterine insemination (IUI) in a positive way. The total sperm motility and the progressive sperm motility improvement was one of the most important ones. The motility rate in the men who received MI was significantly greater than in the control group and even the variability of the motility rate was also low which points to the fact that it was not only less variable in its results, but also more uniform in its responses. These novel motility advances can be associated with known motility functions of MI in enhancing mitochondrial motion, ATP production, and calcium transport in spermatozoa and hence in eliciting the flagellar action and forward motion. These findings are not new given that other literature sources such as Condorelli et al. (2012) and Unfer et al. (2011) also established that similar increases in the sperm motility parameters following MI therapy.

Moreover, MI also had much better sperm morphology. Despite the fact that the percentages of the two groups were lower than the WHO reference range of percentages of mean morphologies, the percentages of normal forms were significantly higher in the MI group suggesting that MI has a protective impact on spermic structural defects. It can be attributed to the antioxidant mechanism of MI that is feasible in eliminating the reactive oxygen species (ROS), which is well known as the damages sperm membranes and DNA. Both Mancini et al. (2022) and Graziano et al. (2021) explain that MI enhances cellular health that raises membrane potential and reduces the oxidative stress, which is an important cause of inappropriate sperm morphology and functionality.

The acrosome integrity which is highly essential in fertilization was also boosted in the MI group. This helps in justifying the therapeutic worth of MI to enhance the fertilization capacity due to the stability of membranes and enzymatic activity that is required to penetrate zona pellucida. This parameter has not been extensively investigated in the previous literature, however, the most recent findings, such as the one by Colacurci et al. (2023), confirm our results that MI enhances acrosomal integrity through its antioxidant effect, as well as through mitochondrial preservation.

Surprisingly, a considerable difference was not observed in the volume of semen and sperm concentration in the two groups. This implies that MI can positively influence the functional rate of the sperm but not necessarily in short term effects of the testicular spermatogenesis and secretory activity of accessory glands. These statements can be compared to the findings of Palmelli et al. (2020) who also did not identify significant differences in these parameters in the case of MI therapy. The fact that the coefficient of variation in the MI group of these parameters is slightly smaller could however be indicative of more stable ejaculate characteristics that may be useful in the long term or when used in combination with other forms of treatment.

5. CONCLUSION

Summing up, the Myo-inositol supplementation has a beneficial impact on some of the most important sperm quality parameters in oligoasthenospermic men receiving IUI (total motility, progressive motility, normal morphology, and acrosomal integrity). These improvements, which do not involve any negative effect on semen volume or concentration, indicate that MI may first act by modulating the functionality of sperm and their ability to fuse with a female oocyte and not necessarily spermatogenesis. The findings are in line with an ever-increasing body of literature that MI is a safe and effective adjunctive treatment of male infertility. Since it has a positive effect on motility and morphology, which are essential predictors of a successful fertilization process, MI can be regarded as a valuable addition that can be used to enhance the outcomes of IUI in men with oligoasthenospermia. It is suggested that future large-scale, multicenter trials and longitudinal studies be done to validate those results and determine the effect of MI on pregnancy and live birth rates.

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