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ANALYSIS OF INOSITOL SUPPLEMENTATION FOR IMPROVING OVARIAN RESPONSE IN POOR RESPONDERS UNDERGOING IN VITRO FERTILIZATION: A RANDOMIZED CONTROLLED TRIAL

Original Article

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ABSTRACT

Background: Poor ovarian response remains a major challenge in assisted reproductive technology, often resulting in low oocyte yield and reduced pregnancy rates. Conventional stimulation strategies frequently fail to produce meaningful improvements, prompting interest in adjunct therapies that may enhance oocyte quality. Myo-inositol, a naturally occurring molecule involved in intracellular signaling, has shown potential benefits in ovarian physiology, yet evidence in poor responders remains limited.

Objective: To evaluate whether myo-inositol supplementation prior to ovarian stimulation improved the number of mature oocytes retrieved and clinical pregnancy rates in women with poor ovarian response undergoing in vitro fertilization.

Methods: A randomized controlled trial was conducted among women meeting established criteria for poor ovarian response. Participants were allocated to receive either myo-inositol with folic acid or folic acid alone for eight weeks before controlled ovarian stimulation using a standardized antagonist protocol. Ovarian response was monitored via transvaginal ultrasonography and hormonal assessment. Mature oocytes were identified morphologically at retrieval, embryo quality was graded on day 3, and clinical pregnancy was confirmed by ultrasound visualization of a gestational sac with cardiac activity. Statistical analysis included independent t-tests, chi-square tests, and Pearson correlation, with significance set at $p < 0.05$.

Results: Women receiving myo-inositol demonstrated a significantly higher mean number of mature oocytes compared with controls. Improved embryo quality and a higher clinical pregnancy rate were also observed in the intervention group. Positive correlations were found between inositol supplementation and markers of ovarian response, while age showed a negative association.

Conclusion: Myo-inositol supplementation was associated with enhanced ovarian responsiveness and improved clinical outcomes in poor responders undergoing in vitro fertilization, suggesting its value as a supportive adjunct to conventional stimulation protocols.

Keywords: Fertilization in Vitro; Infertility, Female; Myo-Inositol; Oocytes; Ovulation Induction; Pregnancy Rate; Reproductive Techniques, Assisted.

INTRODUCTION

Infertility affects millions of couples worldwide and carries profound emotional, social, and financial consequences. Assisted reproductive technologies, particularly in vitro fertilization, have transformed the management of many infertility conditions, yet outcomes remain highly variable across patient groups (1). One of the most challenging populations in reproductive medicine is women classified as poor ovarian responders, who exhibit diminished ovarian reserve and produce a limited number of oocytes despite controlled ovarian stimulation (2). These patients frequently experience cycle cancellations, low embryo yield, and reduced pregnancy rates, making treatment both physically and emotionally taxing. Improving ovarian response in this group remains a central priority in reproductive endocrinology (3).

Poor ovarian response is a multifactorial condition influenced by age, genetic background, environmental exposures, and metabolic status (4). Although advances in stimulation protocols and laboratory techniques have improved overall IVF success rates, the prognosis for poor responders has not progressed at the same pace. Standard interventions, such as increasing gonadotropin doses or modifying stimulation regimens, often result in higher treatment costs without consistently improving outcomes (5). As a result, attention has increasingly turned toward adjuvant therapies aimed at enhancing follicular competence and oocyte quality rather than merely increasing medication intensity (5, 6).

Inositols, particularly myo-inositol, have emerged as promising candidates in this regard. As naturally occurring carbocyclic polyols, inositols play an essential role in intracellular signaling pathways, including those involved in insulin regulation and follicle-stimulating hormone signaling within the ovary (7). These mechanisms are believed to influence oocyte maturation and follicular development (8). In clinical practice, inositol supplementation has been widely studied in women with polycystic ovary syndrome, where it has demonstrated benefits in improving metabolic parameters, restoring ovulation, and enhancing oocyte quality. The biological plausibility of its role in ovarian physiology has encouraged investigation beyond polycystic ovary syndrome into other forms of ovarian dysfunction (9).

Emerging evidence suggests that myo-inositol may improve ovarian responsiveness even in women without insulin resistance, potentially by optimizing intracellular calcium signaling and enhancing mitochondrial function within oocytes (10). Small clinical studies have reported improvements in oocyte maturity and embryo quality among women receiving inositol prior to IVF, yet findings have been inconsistent, and many studies have focused on broader infertility populations rather than specifically targeting poor responders. This distinction is important, as poor responders represent a physiologically distinct group with compromised follicular reserve, where subtle improvements in oocyte competence may translate into meaningful clinical gains.

Despite growing interest, there remains uncertainty regarding the magnitude of benefit that inositol supplementation may offer to women with diminished ovarian reserve undergoing IVF. Variability in study designs, dosing regimens, and patient selection has limited the ability to draw firm conclusions. Furthermore, many fertility centers continue to rely primarily on pharmacologic stimulation strategies without integrating metabolic or micronutrient-based adjuncts, partly due to the absence of clear, population-specific evidence. Generating data focused specifically on poor ovarian responders is therefore essential to inform clinical decision-making and provide patients with realistic expectations.

Beyond clinical outcomes, the potential advantages of inositol supplementation include its favorable safety profile, oral administration, and relatively low cost compared with advanced reproductive interventions. If shown to enhance oocyte yield or improve pregnancy rates, it could represent a simple and accessible adjunct to standard IVF protocols, particularly in resource-constrained settings where repeated cycles pose a significant burden.

In this context, the present study was designed to examine whether pre-treatment with myo-inositol prior to controlled ovarian stimulation improves ovarian response and reproductive outcomes in women identified as poor responders undergoing IVF. The primary objective was to determine whether supplementation increases the number of mature oocytes retrieved. A secondary objective was to evaluate its effect on clinical pregnancy rates, thereby assessing whether any improvement in ovarian response translates into meaningful clinical benefit.

METHODS

A parallel-group randomized controlled trial was conducted in the Urban Region of Sindh, a setting selected due to its concentration of tertiary fertility centers and diverse patient population seeking assisted reproductive services. Women presenting for in vitro fertilization (IVF) were screened consecutively. Eligible participants were aged 22–40 years and classified as poor ovarian responders according to the Bologna criteria, defined by at least two of the following: previous retrieval of ≤3 oocytes with standard stimulation, antral follicle count (AFC) <7, or anti-Müllerian hormone (AMH) <1.1 ng/mL. Exclusion criteria included polycystic ovary syndrome, untreated thyroid or prolactin disorders, severe endometriosis (stage III–IV), uterine anomalies, prior ovarian surgery within 6 months, and use of hormonal supplements in the preceding 8 weeks.

A total sample of 64 participants was determined, consistent with sample sizes used in comparable interventional fertility studies evaluating adjunct therapies in poor responders. Participants were randomly allocated in a 1:1 ratio using computer-generated block randomization with sealed opaque envelopes to receive either oral myo-inositol (2 g twice daily with 200 µg folic acid) for 8 weeks prior to ovarian stimulation or folic acid alone as control. Both groups subsequently underwent a standardized antagonist IVF protocol using recombinant follicle-stimulating hormone, with dose adjustments based on ovarian response monitored via transvaginal ultrasonography. The primary analysis was performed on a per-protocol basis, including only participants who completed the IVF cycle.

Baseline demographic and clinical data were recorded using structured case report forms. Ovarian reserve markers (AMH, day-3 FSH, and estradiol) were measured using chemiluminescent immunoassay. Follicular development was monitored through serial transvaginal ultrasound using a high-frequency probe, and trigger timing was standardized when at least two follicles reached ≥18 mm. Oocyte retrieval was performed 36 hours post-trigger under ultrasound guidance. Retrieved oocytes were assessed by experienced embryologists using standard morphological criteria to determine maturity (metaphase II stage). Fertilization was achieved via intracytoplasmic sperm injection, and embryo quality was graded on day 3 using established morphological scoring systems. Clinical pregnancy was confirmed by transvaginal ultrasound visualization of a gestational sac with cardiac activity at 6–7 weeks. Data were analyzed using SPSS version 26. Normality of continuous variables was assessed using the Shapiro–Wilk test. Independent sample t-tests compared mean numbers of mature oocytes and hormone levels between groups, while chi-square tests evaluated differences in clinical pregnancy rates. Pearson correlation analysis explored associations between inositol use and ovarian response markers. A p-value <0.05 was considered statistically significant. Institutional ethical approval was obtained prior to study commencement, and all participants provided written informed consent.

RESULTS

All 78 women assessed for eligibility during the recruitment period were screened, of whom 64 met the inclusion criteria and consented to participate. They were randomized equally into the inositol supplementation group (n = 32) and the control group (n = 32). Four participants (two from each group) discontinued before oocyte retrieval due to poor follicular development or personal reasons, resulting in 60 women completing the IVF cycle and being included in the final analysis (response rate 93.8%). Participant flow is illustrated in Figure 1. No serious adverse events related to supplementation were reported.

The mean age of the participants was 33.8 ± 4.1 years, and the majority had a history of at least one prior failed IVF cycle. Baseline ovarian reserve markers, including AMH, AFC, and day-3 FSH levels, were comparable between groups, with no statistically significant differences observed. The demographic and clinical characteristics are summarized in Table 1, demonstrating homogeneity between the groups at baseline.

Women who received myo-inositol showed a significantly improved ovarian response compared with controls. The mean number of total oocytes retrieved was 6.1 ± 2.4 in the inositol group versus 4.2 ± 1.9 in the control group (p = 0.002). More importantly, the number of mature (metaphase II) oocytes was higher in the intervention group (4.8 ± 1.8) than in controls (3.1 ± 1.5), representing a statistically significant difference (p < 0.001). Estradiol levels on the day of trigger were also modestly higher in the inositol group (1,685 ± 412 pg/mL vs. 1,432 ± 395 pg/mL; p = 0.031), suggesting enhanced follicular activity. These outcomes are detailed in Table 2.

Fertilization rates per injected oocyte were slightly higher in the inositol group (68.4% ± 14.2) compared to the control group (61.7% ± 13.8), although this difference did not reach statistical significance (p = 0.087). However, the number of good-quality day-3 embryos was significantly greater among women receiving inositol (2.3 ± 1.1 vs. 1.5 ± 0.9; p = 0.004). Clinical pregnancy was achieved in 11 of

30 women (36.7%) in the inositol group compared to 6 of 30 (20.0%) in the control group, yielding a statistically significant difference ($\chi^2 = 4.02$, $p = 0.045$). Outcome comparisons by group are presented in Table 3.

Correlation analysis demonstrated a moderate positive association between duration of inositol supplementation and number of mature oocytes retrieved ($r = 0.41$, $p = 0.003$). AMH levels were also positively correlated with mature oocyte yield ($r = 0.52$, $p < 0.001$), while age showed a negative correlation ($r = –0.46$, $p = 0.001$). These relationships are summarized in Table 4. Overall, the findings indicated that pre-treatment with myo-inositol was associated with improved ovarian responsiveness and higher clinical pregnancy rates in poor responders undergoing IVF.

Table 1: Baseline Demographic and Clinical Characteristics of Participants (N = 64)

Variable	Total Sample Mean ± SD / n (%)
Age (years)	33.8 ± 4.1
BMI (kg/m²)	25.6 ± 3.2
Duration of infertility (years)	5.1 ± 2.3
Primary infertility	38 (59.4%)
Secondary infertility	26 (40.6%)
Previous failed IVF cycles (≥1)	49 (76.6%)
AMH (ng/mL)	0.92 ± 0.31
Antral Follicle Count	5.8 ± 1.4
Day-3 FSH (IU/L)	10.9 ± 2.8

Table 2: Ovarian Stimulation and Oocyte Retrieval Outcomes

Outcome Variable	Inositol Group Mean ± SD	Control Group Mean ± SD	p-value
Total oocytes retrieved	6.1 ± 2.4	4.2 ± 1.9	0.002
Mature (MII) oocytes	4.8 ± 1.8	3.1 ± 1.5	<0.001
Estradiol on trigger day (pg/mL)	1,685 ± 412	1,432 ± 395	0.031

Table 3: Embryological and Clinical Outcomes

Outcome	Inositol Group	Control Group	p-value
Fertilization rate (%)	68.4 ± 14.2	61.7 ± 13.8	0.087
Good-quality embryos (n)	2.3 ± 1.1	1.5 ± 0.9	0.004
Clinical pregnancy n (%)	11 (36.7%)	6 (20.0%)	0.045

Table 4: Pearson Correlation Between Clinical Variables and Mature Oocyte Yield

Variable	r	p-value
Duration of inositol use	0.41	0.003
AMH level	0.52	<0.001
Age	–0.46	0.001

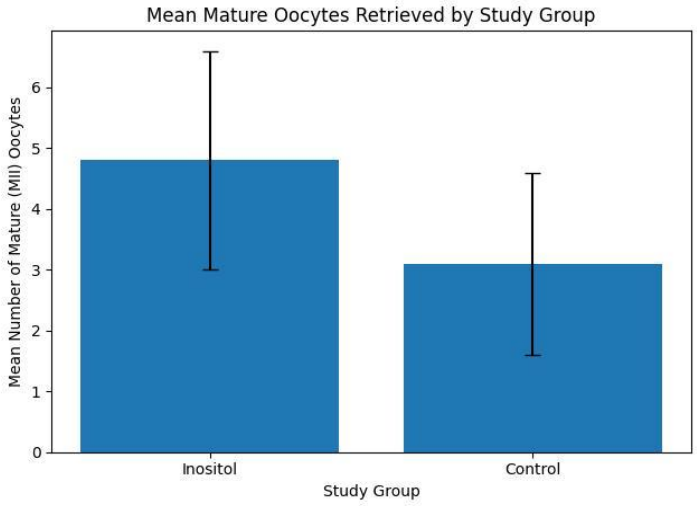

Figure 2 Mean Mature Oocytes Retrieved by Study Group

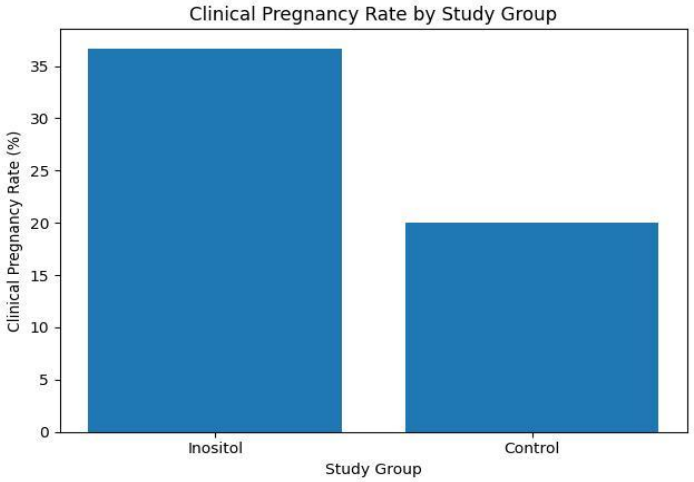

Figure 2 Clinical Pregnancy Rate by Study Group

DISCUSSION

The findings of this randomized controlled trial indicated that pre-treatment with myo-inositol was associated with a measurable improvement in ovarian responsiveness among women identified as poor responders undergoing in vitro fertilization (9, 11). Participants who received inositol produced a higher number of total and mature oocytes, along with a greater yield of good-quality embryos. Importantly, these laboratory improvements were accompanied by a higher clinical pregnancy rate, suggesting that the observed enhancement in ovarian performance translated into meaningful reproductive outcomes rather than representing only intermediate biological changes (12).

These results aligned with the growing body of literature suggesting that inositol plays a supportive role in oocyte maturation and follicular competence (13). While much of the earlier research focused on women with polycystic ovary syndrome, where metabolic modulation is central, the present findings contributed to the view that inositol may exert benefits beyond insulin sensitization (14). The improvement in mature oocyte yield observed in this study was consistent with reports describing enhanced cytoplasmic maturation and better meiotic competence in oocytes exposed to favorable intracellular signaling environments (15). The modest but significant rise in estradiol levels on the day of trigger further supported the possibility of improved follicular activity in response to supplementation (16).

The increase in clinical pregnancy rate, though moderate in absolute terms, was clinically relevant in a population traditionally characterized by limited success. Poor responders often experience repeated cycles with low embryo numbers and diminished implantation potential (17). In this context, even incremental improvements in oocyte maturity and embryo quality may carry disproportionate value (18). The present findings supported the concept that optimizing oocyte competence, rather than solely intensifying gonadotropin stimulation, may represent a more physiologically sound strategy in this subgroup (19). This perspective contributed to an ongoing debate in reproductive medicine regarding the balance between pharmacologic escalation and metabolic or micronutrient-based adjuncts (20).

Several methodological strengths reinforced the credibility of these observations. The randomized controlled design minimized allocation bias, and the use of a standardized stimulation protocol reduced variability in ovarian management. Objective outcome measures, including ultrasound-monitored follicular development and embryologist-assessed oocyte maturity, enhanced the reliability of the data. The study also focused on a clearly defined population using established criteria for poor ovarian response, improving the clinical relevance of the findings.

At the same time, certain limitations warranted consideration. The sample size, although consistent with comparable interventional fertility studies, remained relatively small and limited the statistical power to detect differences in some secondary outcomes, such as fertilization rate. The study was conducted in a single regional setting, which may have influenced generalizability due to variations in patient demographics, environmental factors, and clinical practices. In addition, the duration of supplementation was limited to the pre-stimulation period, and longer-term effects on cumulative live birth rates were not assessed. Laboratory endpoints such as mitochondrial function or markers of oxidative stress, which could have clarified underlying mechanisms, were not measured.

Another important consideration involved the multifactorial nature of poor ovarian response. While inositol appeared to improve certain aspects of ovarian performance, it did not fully overcome the intrinsic limitations associated with diminished reserve. The observed benefits should therefore be interpreted as supportive rather than transformative. Overstating the effect of any single adjunct in this complex clinical scenario would not reflect the biological reality faced by patients and clinicians.

Future research would benefit from larger, multicenter trials to confirm these findings across diverse populations and clinical settings. Studies incorporating longer follow-up periods and reporting cumulative live birth rates would provide a more comprehensive understanding of clinical benefit. Mechanistic investigations exploring mitochondrial activity, oxidative balance, and gene expression within granulosa cells could further clarify how inositol influences follicular physiology. Comparative studies evaluating different doses or combinations with other adjuvants might also help refine treatment protocols.

Overall, the study contributed evidence that myo-inositol supplementation was associated with improved ovarian response and a higher likelihood of clinical pregnancy in poor responders undergoing IVF. While not a definitive solution for this challenging population, it represented a promising, low-risk adjunct that complemented existing stimulation strategies and supported a more integrative approach to reproductive care.

CONCLUSION

Pre-treatment with myo-inositol was associated with improved ovarian response and higher clinical pregnancy rates in women with poor ovarian reserve undergoing in vitro fertilization. The supplementation appeared to enhance mature oocyte yield and embryo quality, suggesting a beneficial effect on oocyte competence. As a safe, accessible adjunct, myo-inositol may represent a valuable supportive strategy in this challenging patient group, complementing conventional stimulation protocols and contributing to more individualized fertility care.

AUTHOR CONTRIBUTIONS

Author	Contribution
Aisha Ali*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Muniba Ali	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Naila Fatima	Substantial Contribution to acquisition and interpretation of Data

Author	Contribution
	Has given Final Approval of the version to be published
Lubna Farooq	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Farhat R. Malik*	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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