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Original Research Article

Evaluating combined therapy with myoinositol and D-chiro-inositol in infertility management across PCOS phenotypes: a comprehensive retrospective data analysis

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder affecting up to 20% of reproductive-aged women, often leading to infertility due to chronic anovulation. The condition has a multifactorial etiology involving genetic, hormonal, and metabolic factors, with insulin resistance being a key feature. The clinical presentation and therapeutic response can vary among different PCOS phenotypes. Myoinositol and D-chiro inositol has garnered attention as a potential insulin sensitizer with fertility-enhancing effects in women with PCOS. This study aimed to evaluate the impact of Myoinositol and D-chiro inositol treatment on fertility outcomes across different PCOS phenotypes, focusing on pregnancy rates and phenotype-specific responses.
Methods: A review of medical records from 200 women with PCOS treated at M2M Women's Clinic between 2018 and 2020 was conducted. Each woman took a sachet twice daily containing 2 g of Myo-Inositol and 50 mg of D-Chiro-Inositol in a 40:1 ratio. They were grouped into four types (A, B, C, D) based on the Rotterdam criteria. Data on treatment specifics, fertility outcomes, and follow-up results were analysed, and Chi-square tests were employed to compare pregnancy rates across the phenotypes.
Results: Out of the 200 participants, 143 (71.5%) completed follow-up. The overall pregnancy rate was 70.6%, with rates of 70.4% in Phenotype A and 69.1% in Phenotype D. Phenotypes B and C achieved 100% conception rates; however, these findings were constrained by small sample sizes.
Conclusions: Myoinositol, in combination with D-Chiro-Inositol in the physiological 40:1 ratio, appears effective in improving fertility outcomes, particularly in Phenotypes A and D. Further research with larger sample sizes is warranted to validate these findings across all PCOS phenotypes and refine phenotype-specific treatment protocols.

Keywords: Polycystic ovary syndrome, Myoinositol, D-chiro-inositol, Infertility, PCOS phenotypes, Pregnancy rates

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent and multifaceted endocrine disorders in women of reproductive age, with a global prevalence estimated to range between 6% and 20%, depending on the diagnostic criteria applied.[1] It represents a major cause of female infertility, primarily due to chronic anovulation and impaired follicular maturation. The disorder encompasses a wide spectrum of reproductive, metabolic, and psychological abnormalities, making it a significant clinical and public health concern. The etiology of PCOS is multifactorial and not yet fully elucidated. It is understood to arise from a complex interplay of genetic, hormonal, metabolic, and environmental factors, leading to heterogeneity in clinical presentation and therapeutic response.[1] Genetic predisposition, coupled with lifestyle and environmental influences such as diet, stress, and

exposure to endocrine-disrupting chemicals, plays a pivotal role in disease manifestation. The combination of these factors contributes to the dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis, insulin signalling, and androgen biosynthesis the three key pathways implicated in PCOS pathogenesis.

A defining characteristic of PCOS is hyperandrogenism, clinically manifested by hirsutism, acne, and androgenic alopecia.[1] Approximately 70% of affected women exhibit insulin resistance, which induces compensatory hyperinsulinemia. Elevated insulin levels, in turn, enhance ovarian androgen production by stimulating theca cells and suppressing hepatic synthesis of sex hormone-binding globulin (SHBG). This hormonal imbalance further aggravates hyperandrogenism, creating a vicious cycle that disrupts normal folliculogenesis, leading to follicular arrest and chronic anovulation the hallmark of infertility in PCOS.[2] Moreover, dysregulation of the gonadotropin-releasing hormone (GnRH) pulse frequency alters the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) ratio, further impairing ovulatory function.[1]

Globally, the prevalence and clinical presentation of PCOS vary considerably due to differences in diagnostic approaches (Rotterdam, NIH, AE-PCOS criteria), population characteristics, and ethnic background. For example, South Asian women tend to present with more severe insulin resistance and metabolic disturbances, while women of African descent often exhibit pronounced hyperandrogenic features.[2] These variations highlight the importance of adopting personalized diagnostic and therapeutic strategies rather than a uniform approach to PCOS management.

The reproductive and metabolic consequences of PCOS are profound. Beyond infertility and menstrual irregularities, women with PCOS are predisposed to a range of long-term health complications, including metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, and endometrial carcinoma.[2] Psychological morbidities such as anxiety, depression, and reduced quality of life are also frequently reported. Therefore, PCOS management requires a multidimensional approach addressing reproductive, metabolic, and psychosocial aspects.

According to the Rotterdam criteria (2003), PCOS is classified into four distinct phenotypes, reflecting the heterogeneity of the disorder:[3] Phenotype A (Classic PCOS): Presence of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, Phenotype B (Hyperandrogenic Anovulation): Characterized by hyperandrogenism and ovulatory dysfunction without polycystic ovaries, Phenotype C (Ovulatory PCOS): Exhibits hyperandrogenism and polycystic ovarian morphology but with preserved ovulation, Phenotype D (Non-Hyperandrogenic PCOS): Demonstrates ovulatory dysfunction and polycystic ovaries in the absence of hyperandrogenism.

These phenotypes differ not only in clinical and biochemical presentation but also in their response to therapeutic interventions. For instance, Phenotypes A and B are often associated with severe insulin resistance and metabolic complications, whereas Phenotype D tends to show milder endocrine disturbances.

Among various therapeutic strategies, myoinositol, a naturally occurring polyol and insulin-sensitizing agent, has gained substantial attention for its role in PCOS management. Myoinositol functions as a precursor for inositol phosphoglycans (IPGs) key secondary messengers in insulin signal transduction thereby enhancing insulin sensitivity and glucose uptake.[1] By improving insulin responsiveness, myoinositol indirectly reduces hyperinsulinemia-induced androgen synthesis, leading to amelioration of hyperandrogenic symptoms and restoration of ovulatory function.

Clinical trials and meta-analyses have demonstrated that myoinositol supplementation significantly reduces fasting insulin levels, improves the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index, and normalizes menstrual cyclicity in women with PCOS.[1] Furthermore, it enhances spontaneous ovulation rates, oocyte quality, and clinical pregnancy outcomes, especially in women undergoing assisted reproductive technologies (ART) such as in vitro fertilization (IVF). Several studies have also reported reductions in serum testosterone and improvements in cutaneous manifestations like hirsutism and acne following myoinositol therapy.

Despite this growing body of evidence, a critical research gap persists, most existing studies treat PCOS as a homogeneous condition without accounting for phenotype-specific variations. The pathophysiological and metabolic heterogeneity across phenotypes suggests that the therapeutic efficacy of myoinositol may differ depending on the underlying endocrine and metabolic profiles.

Therefore, the present study seeks to explore the fertility outcomes associated with myoinositol therapy across distinct PCOS phenotypes, emphasizing its impact on ovulatory function, hormonal balance, and pregnancy outcomes. By examining phenotype-specific responses, this investigation aims to contribute to a more personalized approach in managing PCOS and optimizing reproductive outcomes.

METHODS

This retrospective study assessed the efficacy of myoinositol in enhancing fertility outcomes among women diagnosed with various PCOS phenotypes. The

primary objective was to evaluate the impact of myoinositol treatment on pregnancy rates.

Study population

A total of 200 women diagnosed with polycystic ovary syndrome (PCOS) who received myoinositol-based therapy were enrolled in the study. Each participant was administered a sachet containing 2 g of Myo-Inositol (MI) and 50 mg of D-Chiro-Inositol (DCI), maintaining a physiological 40:1 MI:DCI ratio. This formulation was taken orally twice daily. The sachet format ensured precise dosing and enhanced bioavailability, aligning with current clinical evidence that supports the 40:1 ratio for improving insulin sensitivity and reproductive health in women with PCOS, while DCI specifically contributes to enhanced ovarian steroidogenesis and improved ovulatory function.

Clinical data were retrospectively collected from patient records at M2M Women's Clinic, encompassing treatments provided between 2018 and 2020. The study applied the following inclusion and exclusion criteria:

Inclusion and exclusion criteria

The inclusion criteria for the study required female patients aged 18-35 years diagnosed with PCOS per the Rotterdam criteria, classified into one of the four phenotypes (A, B, C, D). Participants must have received myoinositol as part of their treatment regimen and had complete medical records available for analysis, including treatment history and follow-up data. Additionally, only those with infertility due to ovulatory dysfunction were included, while other reasons for infertility were excluded. The exclusion criteria eliminated patients with incomplete or missing treatment data, a diagnosis of PCOS not conforming to the Rotterdam criteria, or concurrent use of interventions that could confound results, such as additional fertility-affecting medications. Male factor infertility and other female infertility causes, such as tubal endometriosis or fibroids, were also excluded.

Data collection

Data were retrospectively collected from medical records, covering key parameters such as the classification of PCOS phenotypes and the specifics of treatment, including the dosage and duration of myoinositol administration. Additionally, fertility outcomes were assessed, including pregnancy rates, time to conception, and any documented side effects. Follow-up data were also analysed to provide insights into treatment completion and ongoing outcomes.

Outcome measures

The primary outcome measure is the pregnancy rate, defined as the percentage of women who achieved a confirmed pregnancy during or after the administration of myoinositol treatment.

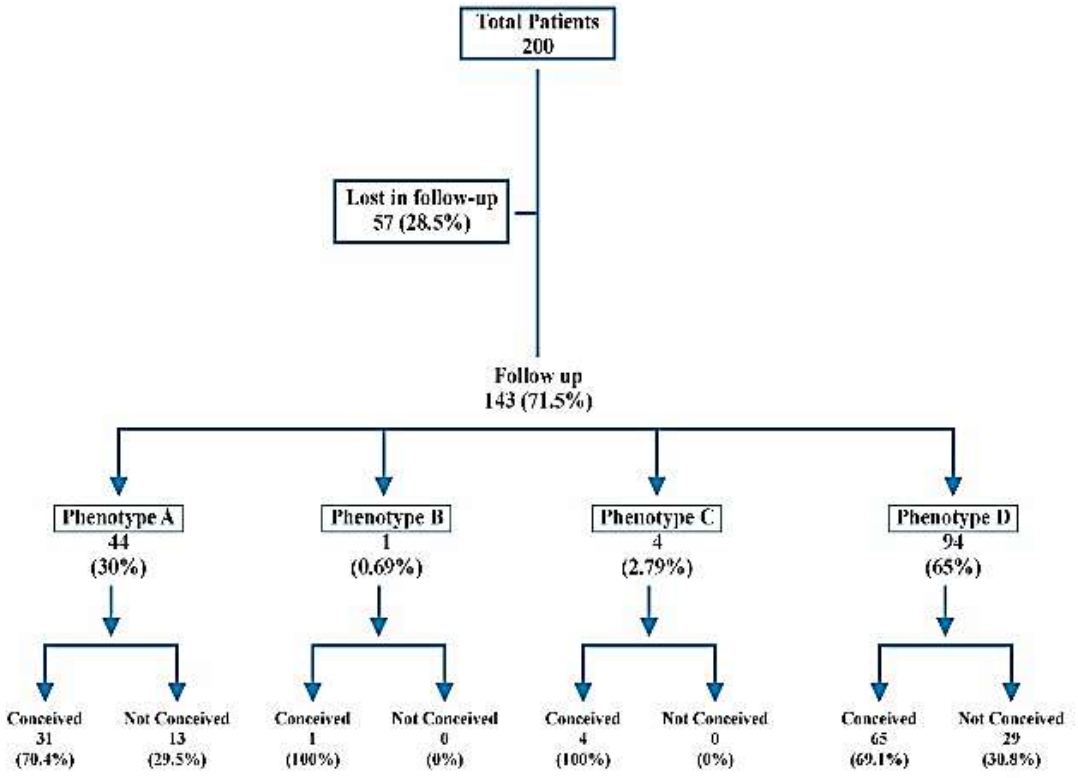

Figure 1: Distribution of PCOS phenotype and pregnancy outcomes among study participants.

Ethical considerations

Patient confidentiality was maintained by de-identifying personal information in the dataset. The study involved retrospective analysis of existing medical records, thus waiving the need for informed consent. General consent was taken from patients to use their data anonymously.

Statistical analysis

Descriptive statistics will summarize the clinical characteristics of the study population using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. For comparative analysis, pregnancy rates will be calculated and compared between PCOS phenotypes A, B, C and D. A Chi-Square test will be used to compare pregnancy rates and other categorical outcomes between these two phenotypes, with the analysis conducted using SPSS software.

RESULTS

The study included a total of 200 women diagnosed with PCOS, out of which 143 (71.5%) were successfully followed up for the assessment of fertility outcomes (Figure 1). The distribution of PCOS phenotypes among the participants was as follows: 30% were classified under Phenotype A, and 65% were identified as Phenotype D. The remaining 5% consisted of Phenotypes B and C, each with a minimal sample size (Table 1).

Table 1: Patient demographics.

Parameter	Details
Successfully followed up (%)	143 (71.5)
Age (Years)	21–45
Phenotype A, %	30
Phenotype D, %	65
Phenotype B, %	5
Phenotype C, %	5
Total participants	200

Pregnancy outcomes

Among the 143 patients who completed follow-up, the overall pregnancy rate was 70.6%, with 101 patients achieving pregnancy and 42 remaining non-pregnant. The outcomes varied by PCOS phenotype, as shown in Figure 1. For Phenotype A, 31 out of 44 patients (70.4%) conceived, while 13 (29.5%) did not. Phenotype B included only one patient, who achieved pregnancy, resulting in a 100% conception rate. Similarly, all 4 patients with Phenotype C achieved pregnancy, also yielding a 100% conception rate. In Phenotype D, 65 out of 94 patients (69.1%) conceived, while 29 (30.8%) did not.

To evaluate pregnancy outcomes across different PCOS phenotypes (A, B, C, and D), a Chi-square test for independence was performed to compare conception rates among the groups. The analysis yielded a Chi-square statistic of 2.18, with a p-value of 0.536 and 3 degrees of freedom. The expected frequencies for each phenotype were as follows: Phenotype A [31.08, 12.92], Phenotype B [0.71, 0.29], Phenotype C [2.83, 1.17], and Phenotype D [66.39, 27.61]. As the p-value is greater than the conventional significance level of 0.05, the results indicate that there is no statistically significant association between PCOS phenotypes and pregnancy outcomes in this dataset. This suggests that the rates of conception are similar across the different phenotypes.

DISCUSSION

The findings of this study highlight the differential effectiveness of myoinositol in treating various PCOS phenotypes, reinforcing the importance of phenotype-specific therapeutic strategies. Myoinositol has demonstrated notable efficacy in managing PCOS phenotypes A, B, and C, which are characterized by hyperandrogenism and insulin resistance. Given its well-established role in enhancing insulin sensitivity and regulating follicular development via FSH signalling, it is not surprising that patients with these phenotypes experienced significant metabolic and endocrine improvements. Clinical data supporting myoinositol's benefits in these subgroups include reductions in BMI, insulin resistance (HOMA index), glycaemic levels, LH/FSH ratios, and testosterone levels, ultimately leading to improved ovulation and pregnancy outcomes.

These observations are consistent with previous meta-analyses and systematic reviews, which have reported that myoinositol significantly reduces fasting insulin, HOMA-IR, and serum testosterone levels, while improving menstrual cyclicity, ovulation, and clinical pregnancy rates in women with PCOS.[4,5] Mechanistically, myoinositol functions as a secondary messenger in FSH signalling pathways, enhancing follicular maturation and oocyte quality, which likely explains its pronounced efficacy in hyperandrogenic and insulin-resistant phenotypes.[4-6]

In our cohort, phenotypes B and C achieved 100% conception rates, while phenotype A showed 70.4%, supporting myoinositol's fertility-enhancing potential within metabolically active PCOS subtypes. Although prior meta-analyses demonstrate that myoinositol improves ovulation and overall clinical pregnancy rates in PCOS, few studies report conception rates stratified by Rotterdam phenotypes A-D.[4,5] Existing evidence suggests that while the supplement exerts consistent metabolic benefits, reproductive outcomes vary among phenotypes, with the most pronounced effects seen in insulin-resistant and hyperandrogenic groups.[8]

Among ART-based studies, reported clinical pregnancy rates following myoinositol supplementation range from

approximately 40% to 63%, depending on study design, dose, and concomitant treatments.[7,9] None, however, have documented 100% conception in specific phenotype subgroups, suggesting that our findings may represent either a phenotype-specific effect unique to this population or a reflection of small subgroup sizes. Consequently, the high conception rates in phenotypes B and C should be interpreted as promising yet exploratory results, warranting replication in larger, stratified cohorts.

Interestingly, phenotype D, which lacks hyperandrogenism and significant metabolic abnormalities, also exhibited a favourable pregnancy rate (69.1%), comparable to that of phenotype A (70.4%). This finding contrasts with earlier studies that suggested limited benefit of myoinositol in non-insulin-resistant PCOS phenotypes, implying that alternative mechanisms may contribute to its efficacy in this subgroup.[8] Possible pathways include modulation of the GH-IGF1 axis, improvement of endometrial receptivity, or enhancement of oocyte competence through oxidative-stress reduction and intracellular inositol signalling.[4,7]

The absence of statistically significant differences in conception rates across phenotypes (p=0.536) indicates that, while myoinositol may beneficially modulate metabolic and endocrine profiles, pregnancy success likely depends on additional reproductive and endometrial factors. These may include oocyte quality, luteal support, and uterine environment, which collectively influence implantation and early pregnancy maintenance.[5,7,9]

Taken together, our findings underscore the necessity of individualized treatment approaches for PCOS patients, considering the heterogeneity of the disorder. While myoinositol serves as a cornerstone therapy for metabolically dysregulated phenotypes, its unexpected efficacy in phenotype D highlights the need for further research into its broader mechanisms of action. Future investigations should explore interventions tailored to phenotype D's unique pathophysiology, including treatments targeting ovarian and endometrial factors. Refining diagnostic criteria and expanding investigations into the underlying mechanisms of each PCOS phenotype will enhance personalized therapeutic strategies, ultimately optimizing reproductive outcomes across the PCOS spectrum.

Clinical implications and future research

Our study reinforces the therapeutic potential of myoinositol in improving fertility outcomes across different PCOS phenotypes, with particularly notable efficacy in Phenotypes A and D. While previous literature has primarily linked myoinositol's benefits to insulin-resistant phenotypes (A, B, and C), our findings that Phenotype D achieved a comparable pregnancy rate (69.1%) suggest that myoinositol may exert beneficial effects beyond insulin modulation.[4,5] These may involve improvements in oocyte competence, follicular dynamics, or endometrial receptivity, which collectively enhance conception potential.

Despite the encouraging results observed in phenotypes B and C, the small sample sizes in these groups limit the generalizability of our findings. Clinicians may consider integrating myoinositol into fertility treatment regimens particularly for phenotypes A and D while exercising caution when interpreting results for phenotypes B and C due to limited representation.

Limitations of the study

Selection Bias: Potential biases inherent in retrospective studies, including incomplete data and selection bias based on available records.

Sample Size for Phenotypes B and C: Small sample sizes for these phenotypes limit the ability to perform meaningful analyses for these groups.

Confounding Factors: The presence of other treatments or interventions not accounted for in the analysis. Unexplained infertility couldn't be excluded.

CONCLUSION

The study demonstrates the therapeutic efficacy of myoinositol in enhancing fertility outcomes among women with PCOS, particularly in Phenotypes A and D, with conception rates of 70.4% and 69.1%, respectively. The overall pregnancy rate of 70.6% aligns with previous reports (65–75%) following myoinositol therapy in ovulation induction or assisted reproduction, reinforcing its role as a safe and effective insulin-sensitizing and reproductive modulator.

While earlier studies emphasized benefits mainly in insulin-resistant and hyperandrogenic phenotypes (A and B), the favourable outcomes in Phenotype D suggest that myoinositol's effects may extend beyond metabolic regulation. Improvements in oocyte competence, mitochondrial activity, and calcium signalling could explain enhanced follicular development and endometrial receptivity in this subgroup.

Although Phenotypes B and C showed 100% conception, limited sample sizes restrict firm conclusions. The absence of significant inter-phenotypic differences in conception rates likely reflects sample size constraints rather than a lack of effect. Nonetheless, the positive trends support a broader efficacy across PCOS phenotypes.

Future research should include larger, phenotype-stratified cohorts and evaluate live birth rates, oocyte quality, and embryonic outcomes to clarify the mechanisms underlying myoinositol's reproductive benefits. By emphasizing phenotype-specific responses, these findings advance personalized fertility management and expand myoinositol's therapeutic scope beyond metabolic

correction to encompass improved oocyte and endometrial function.

Recommendations

Future research should prioritize: large-scale, phenotype-stratified randomized controlled trials to validate efficacy across all PCOS subgroups. Mechanistic studies to elucidate myoinositol's role in ovarian physiology and endometrial function in non-insulin-resistant phenotypes. Long-term evaluations of safety, optimal dosing, and sustainability of therapeutic benefits; and ntegration of molecular profiling (genomics, metabolomics, proteomics) to refine PCOS phenotyping and identify predictors of treatment response.

Such efforts will clarify whether the observed phenotype-specific conception rates reflect true biological differences or study-specific effects, thereby enhancing precision medicine approaches in the management of PCOS.

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