e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2024; 14(2); 169-175

Original Research Article

A Study to Assess the Efficacy and Safety of Myoinositol in PCOS Management

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Received: 07-01-2024 / Revised: 25-01-2024 / Accepted: 02-02-2024

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Conflict of interest: Nil

Abstract

Background: Polycystic ovarian syndrome (PCOS), alternatively termed Stein-Leventhal syndrome, stands as one of the most widespread endocrine disorders. This syndrome presents as a multifaceted and intricate disorder marked by the presence of polycystic ovaries alongside a spectrum of symptoms. These symptoms include amenorrhea, oligomenorrhea, hirsutism, anovulation, and indications of androgen excess, such as acne and male-pattern baldness.

Methods: This study included women aged 18-40 years diagnosed with PCOS according to Rotterdam's criteria. Of 75 screened patients meeting Rotterdam's criteria, n=60 were recruited after obtaining informed consent. Participants were randomly assigned to three groups: control (n=20), Metformin (n=20), and Myoinositol (n=20). Clinical assessments, including medical history, anthropometric measurements, blood pressure, and ultrasonography, were conducted at baseline and periodically during the study.

Results: Group 1 (Control): Received no medication or specific intervention. Group 2 (Metformin): Received 500mg Metformin tablets twice a day. Group 3 (Myoinositol): Received 2gm Myoinositol tablets twice a day. Metformin treatment showed a consistent decrease in blood glucose levels compared to the control and Myoinositol groups. Both Metformin and Myoinositol showed reductions in LH levels compared to the control group, with Myoinositol having a more pronounced effect. Only Myoinositol showed a statistically significant decrease in FSH levels compared to the control and Metformin groups. Both Metformin and Myoinositol showed reductions in TSH levels compared to the control group, with Myoinositol having a larger decrease. Myoinositol showed a statistically significant decrease in prolactin levels compared to the control and Metformin groups, who had minimal changes.

Conclusion: Our findings suggest that myoinositol (MI), a non-hormonal drug, is effective in PCOS treatment by regulating menstrual cycles, inducing ovulation, and enhancing pregnancy success rates in cases of infertility. Notably, MI demonstrates a high degree of safety and effectiveness, with minimal to no observed side effects compared with both placebo and metformin.

Keywords: Myoinositol (MI), Metformin, Polycystic Ovarian Syndrome (PCOS), Infertility.

Introduction

Polycystic ovarian syndrome (PCOS), also known as Stein-Leventhal syndrome, is among the most prevalent endocrine disorders, affecting approximately 20% of women of reproductive age [1]. It manifests as a complex multidimensional disorder characterized by the presence of polycystic ovaries in conjunction with a cluster of symptoms, including amenorrhea, oligomenorrhea, hirsutism, anovulation, and signs of androgen excess, such as acne and crown pattern baldness [2]. The precise prevalence of PCOS remains uncertain due to the syndrome's lack of precise definition, although estimates suggest it affects 5-10% of women of reproductive age [3]. PCOS has garnered significant attention due to its high prevalence and potential reproductive, metabolic, and cardiovascular consequences. PCOS development is influenced by both environmental and genetic factors, with obesity exacerbated by poor dietary habits and physical inactivity exacerbating the condition in susceptible individuals. While the exact

role of other environmental modifiers such as infectious agents or toxins remains speculative, PCOS may have been advantageous in ancient times, contributing to smaller family sizes, reduced childbirth-related mortality, increased muscle mass, and enhanced energy storage capacity [4]. Genetic factors strongly contribute to the etiology of PCOS, with the condition inherited as a complex genetic trait. Certain genes such as CYP11A1 and CYP17A1 may render the ovary susceptible to insulin-stimulated androgen secretion while impeding follicular maturation [5, 6].

PCOS arises from excessive luteinizing hormone (LH) secretion from the anterior pituitary gland coupled with elevated insulin levels and insulin resistance. It is a leading cause of female infertility and presents with symptoms such as anovulation, oligomenorrhea, amenorrhea, hirsutism, acne, and mood disorders [7]. The Rotterdam Criteria, established in 2003, is widely used for PCOS diagnosis, requiring the presence of at least two out of three criteria: oligo-or anovulation, hyperandrogenism, and polycystic ovaries on ultrasound, while ruling out other causes [8]. PCOS complications include reproductive issues, such as increased miscarriage rates, endometrial cancer, infertility, and cardiovascular concerns, including coronary artery disease, hypertension, and metabolic disorders such as obesity, insulin resistance, and type 2 diabetes [2]. Tailored treatment involves addressing patient concerns with options ranging from hormonal contraception to ovulation induction. Lifestyle modifications, including dietary and behavioral changes, are the initial approach. Medications such as oral contraceptives, antiandrogens, gonadotropin-releasing hormone agonists, and ovulation-inducing agents may be prescribed alongside hypoglycemic agents such as metformin. Surgical interventions, such as ovarian drilling, may also be considered [9]. Metformin, an insulin sensitizer, improves metabolic disorders associated with insulin resistance in PCOS but can cause gastrointestinal side effects and, rarely, lactic acidosis. Thiazolidinediones, another class of drugs, are associated with weight gain, cardiovascular events, fractures, and bladder cancer [10, 11]. Myoinositol (MI), a new insulin sensitizer, has recently emerged as a promising treatment for PCOS-related infertility. MI is a potential alternative to metformin because of its ability to enhance insulin sensitivity without associated side effects. Studies have shown that MI treatment effectively reduces hormonal, metabolic, and oxidative abnormalities in PCOS patients by ameliorating insulin resistance [12]. The motivation for conducting this study stems from limited research on myoinositol supplementation for PCOS treatment in India.

Material and Methods

This cross-sectional study was conducted in the Department of Pharmacology in coordination with the Department of Obstetrics and Gynecology. Institutional Ethical approval was obtained for the study. Written permission was obtained from all the participants of the study after explaining the nature of the study in the vernacular language. Those voluntarily willing to participate in the study were included.

Inclusion Criteria: This study included women aged 18-40 years diagnosed with PCOS according to Rotterdam's criteria.

Exclusion Criteria: Patients who had received hormonal infertility treatment in the past 6 months, those at risk of lactic acidosis, diabetic patients on insulin or insulin sensitizers, pregnant or lactating women, individuals with liver or renal failure, lung diseases, ischemic heart disease, or peripheral vascular disease were excluded.

Methodology:

This prospective, open-label, parallel-arm, randomized controlled study aimed to assess the efficacy and safety of Metformin versus MI in PCOS women over 24 weeks. Of 75 screened patients meeting Rotterdam's criteria, n=60 were recruited after obtaining informed consent. Participants were randomly assigned to three groups: control (n=20), Metformin (n=20), and Myoinositol (n=20). Clinical assessments, including medical history, anthropometric measurements, blood pressure, and ultrasonography, were conducted at baseline and periodically during the study. Patients were advised to maintain regular exercise and lifestyle modifications throughout the study. Group No of Subject descriptions Group I (n=20) Control -PCOS patient who delays specific treatment, Group II (n=20) PCOS subjects + Tab. Metformin 500mg twice a day Group III (n=20) PCOS subjects + Tab. Myoinositol 2 gm twice a day. Biochemical analysis included Blood Sugar-Fasting (FBS), Blood Sugar - Post-Prandial (PPBS), Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Thyroid Stimulating Hormone (TSH), Prolactin.

Statistical Analysis: All the available data was refined and uploaded to MS Excel and analyzed by SPSS statistical package version 21. The categorical variables were represented as mean, standard deviation, and percentage. The categorical variables were calculated by ANOVA analysis and p values were (<0.05).

Results

Out of the n=60 cases included in the study, the majority of women with PCOS in this study fall within the 26-30 age group (60%). This suggests that PCOS diagnosis might be most frequent in the 26-30 age group within the studied population (Figure 1). The mean age distribution in groups of the study population shows the mean age for Group

1 was 25.12 ± 3.19 years, for Group 2 was 25.91 ± 2.75 years, and for Group 3 was 24.29 ± 3.11 years.

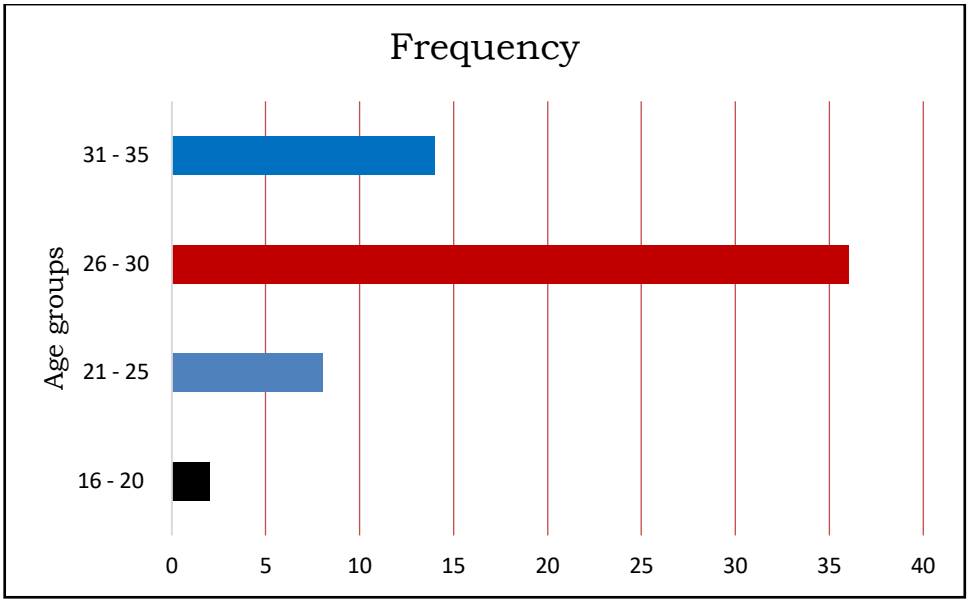

Figure 1: Showing the distribution of PCOS cases included in the study

Table 1 shows the distribution of 60 women diagnosed with Polycystic Ovary Syndrome (PCOS) according to their marital status and categorized into three groups. A higher proportion of women with PCOS are married (60%) compared to those who are unmarried (40%).

Table 1: Distribution of PCOS cases in the study

Age group	Married		Unmarried	
	Frequency	%	Frequency	%
Group 1 (n=20)	12	60	8	40
Group 2 (n=20)	11	55	9	45
Group 3 (n=20)	13	65	7	35
Total (n=60)	36	60	24	40

Table 2 shows the effects of Myoinositol (MI) supplementation on weight in 60 patients with Polycystic Ovary Syndrome (PCOS) across three groups and seven-time points. The table presents the mean weight (in kilograms) and standard deviation (SD) for each group at 0, 4, 8, 12, 16, 20, and 24 weeks. *Weight changes*: Group 1 (Control): Shows initial weight gain at week 4 (60.92 kg), followed by a gradual decrease reaching the lowest weight at week 12 (60.02 kg). The weight then fluctuates slightly but stays generally lower than baseline (week 0) throughout the remaining weeks. Group 2 (Tab Metformin): This shows a gradual increase in weight from week 0 (59.90 kg) to week 16 (62.16 kg), followed by a slight decrease in the remaining weeks. Group 3 (Myoinositol): Shows a similar gradual increase in weight from week 0 (62.12 kg) to week 16 (61.22 kg), with a slight increase in the final weeks. Myoinositol supplementation might be associated with initial weight gain followed by a potential weight-stabilizing or slight weight-reducing effect in women with PCOS. The initial weight gain could be due to various factors, such as fluid retention or improved insulin sensitivity leading to increased muscle mass.

Table 2: Effects on weight in n=60 PCOS patients at different intervals of time

Groups	Weight (in kg.)						
	0 week	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
Group 1 (Control)	62.12 ± 8.19	62.94 ± 8.90	62.39 ± 7.18	60.02 ± 8.58	61.22 ± 9.42	61.73 ± 6.67	62.33 ± 7.09
Group 2 (Metformin)	59.90 ± 5.62	60.12± 6.40	60.87 ± 7.01	61.27 ± 7.11	62.16 ± 9.45	61.92 ± 5.61	61.64 ± 6.71
Group 3 (Myoinositol)	60.15 ± 7.24	60.92 ± 7.81	59.97 ± 7.92	60.72 ± 8.48	60.02 ± 7.64	60.18 ± 7.36	60.89 ± 8.12

Table 3 shows the fasting blood glucose levels (in mg/dL) of women with polycystic ovary syndrome (PCOS) at seven different time points following their enrollment in a study. The women were divided into three groups: Baseline (0 weeks): All groups have an average fasting blood glucose level above the recommended normal range (typically below 100 mg/dL). Group 2 (Metformin) has the highest average baseline level (90.15 mg/dL). Over time: All groups show a gradual decrease in average fasting blood glucose levels throughout the 24 weeks. Group 2 (Metformin) consistently has the lowest average blood glucose levels across all time points. Group 3 (Myoinositol) and Group 1 (Control) have similar average blood glucose levels throughout the study. Metformin: The consistent decrease in blood glucose levels in the Metformin group (p=<0.001) suggests it might be effective in improving glycemic control in women with PCOS. Myoinositol and Control: The similar trends in these groups suggest that Myoinositol might not have a significant impact (P>0.05) on fasting blood glucose compared to the control group, and the observed decrease might be due to other factors or natural fluctuations.

Table 3: Fasting blood glucose in n=60 PCOS patients at different intervals

Groups	0 week	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
Group 1 (Control)	84.9 ± 7.62	85.19 ± 8.91	84.72 ± 8.03	83.90 ± 7.67	82.92 ± 7.71	83.99 ± 9.32	83.28 ± 6.71
Group 2 (Metformin)	90.15 ± 10.37	88.12 ± 7.28	87.11 ± 7.17	86.33 ± 7.34	85.11 ± 8.17	83.62 ± 7.64	82.55 ± 5.05
Group 3 (Myoinositol)	84.22 ± 7.32	83.66 ± 9.14	83.46 ± 8.37	82.29 ± 7.34	82.91 ± 8.70	82.66 ± 9.81	82.32 ± 6.17

Table 4 shows the levels of Luteinizing Hormone (LH) in IU/L (international units per liter) at seven different time points for women with polycystic ovary syndrome (PCOS) Baseline (0 weeks): All groups have similar average LH levels. Over time: Group 1 (Control): Shows slight fluctuations in LH levels throughout the study, with no statistically significant change (p-value = 0.125). Group 2 (Metformin): Shows a gradual decrease in LH levels over time, reaching a statistically significant reduction compared to baseline at week 24 (p-value = 0.034). Group 3 (Myoinositol): Shows the largest decrease in LH levels, reaching a statistically significant reduction compared to baseline at week 12 and remaining lower throughout the study (p-value = 0.0012). The observed decrease in LH levels in the Metformin group suggests it might have a moderate suppressive effect on LH secretion, potentially contributing to improved hormonal balance in PCOS. Myoinositol: The significant decrease in LH levels in the Myoinositol group suggests it might have a stronger suppressive effect compared to Metformin, potentially influencing LH production and ovulation regulation in PCOS. Control: The slight fluctuations in the control group might be due to natural variations in LH levels or other factors not controlled for in the study.

Table 4: LH levels in n=60 PCOS patients

Groups	LH (IU/L)							P values
	0 week	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks	
Group 1 (Control)	12.05± 1.09	12.92± 1.01	11.05± 1.11	11.82± 1.37	11.33± 1.05	10.89± 1.03	11.01± 1.64	0.125
Group 2 (Metformin)	12.40± 1.63	12.08± 1.32	11.50± 1.01	10.83± 0.97	9.84 ± 0.98	9.75± 1.01	9.35± 1.03	0.034
Group 3 (Myoinositol)	11.92± 1.01	10.97± 0.67	9.57± 1.33	8.05 ± 1.02	7.95± 1.31	8.50± 1.37	8.19± 0.54	0.0012

Table 5 shows the Follicle-Stimulating Hormone (FSH) levels in IU/L (international units per liter) at seven different time points for women with polycystic ovary syndrome (PCOS) categorized into three groups: Baseline (0 weeks): All groups have similar average FSH levels. Over time: Group 1 (Control): Shows slight fluctuations in FSH levels throughout the study, with no statistically significant change (p-value = 0.185). Group 2 (Metformin): Shows minor variations in FSH levels, with no statistically significant change (p-value = 0.331). Group 3 (Myoinositol): Shows a gradual decrease in FSH levels, reaching a statistically significant reduction compared to baseline at week 12 and remaining lower throughout the study (p-value = 0.042). Metformin: The lack of significant change in FSH levels in the Metformin group suggests it might have minimal to no effect on FSH levels in PCOS. Myoinositol: The significant decrease in FSH levels in the Myoinositol group suggests it might influence FSH production, potentially contributing to improved follicular development and ovulation in PCOS. Control: The slight fluctuations in the control group might be due to natural variations in FSH levels or other factors not controlled for in the study.

Table 5: FSH levels in n=60 PCOS patients

Groups	FSH (IU/L)							P values
	0 week	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks	
Group 1 (Control)	4.90 ± 0.94	4.93 ± 0.97	4.95± 1.04	5.18 ± 1.28	5.08 ± 1.36	4.01± 2.13	4.16±1.95	0.185
Group 2 (Metformin)	5.13 ± 0.67	5.15± 0.49	5.25 ± 0.57	5.40 ± 0.61	4.90 ± 0.64	4.82 ± 0.57	453±0.33	0.331
Group 3 (Myoinositol)	4.99 ± 0.55	4.78 ± 0.39	4.50 ± 0.49	4.01 ± 0.51	4.21 ± 0.60	4.02 ± 0.37	3.92±0.39	0.042

Table 6 shows the Thyroid-Stimulating Hormone (TSH) levels in mIU/L (at seven different time points for women with polycystic ovary syndrome (PCOS) categorized into three groups: Baseline (0 weeks): All groups have similar average TSH levels. Over time: Group 1 (Control): Shows slight fluctuations in TSH levels, with no statistically significant change (p-value = 0.177). Group 2 (Metformin): Shows a gradual decrease in TSH levels, reaching a statistically significant reduction compared to baseline at week 24 (p-value = 0.043). Group 3 (Myoinositol): Shows the largest decrease in TSH levels, reaching a statistically significant reduction compared to baseline at week 12 and remaining lower throughout the study (p-value = 0.001). Metformin: The observed decrease in TSH levels in the Metformin group suggests it might have a mild suppressive effect on TSH production, potentially influencing thyroid function in some individuals with PCOS. Myoinositol: The significant decrease in TSH levels in the Myoinositol group is significant.

Table 6: TSH levels in n=60 PCOS patients

Groups	TSH (mIU/L)							P values
	0 week	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks	
Group 1 (Control)	4.01 ± 0.66	3.91 ±0.62	3.99 ±0.98	3.86 ±0.33	3.75 ±0.64	3.69 ±0.67	3.25 ±0.37	0.177
Group 2 (Metformin)	3.94 ± 0.63	3.51 ±0.53	3.64 ±0.67	3.29 ±0.83	3.10 ±0.61	3.06 ±0.55	3.01 ±0.57	0.043
Group 3 (Myoinositol)	4.05 ± 0.92	3.92 ±0.71	3.83 ±0.73	3.64 ±0.81	3.50 ±0.83	3.19 ±1.01	2.94 ±0.62	0.001

Table 7 shows the prolactin levels in ng/mL (nanograms per milliliter) at seven different time points for women with polycystic ovary syndrome (PCOS) Baseline (0 weeks): Group 3 (Myoinositol): Has the highest average prolactin level compared to the other groups. All groups have prolactin levels within the generally accepted normal range. Over time: Group 1 (Control): Shows minimal fluctuations in prolactin levels, with no statistically significant change (p-value = 0.984). Group 2 (Metformin): Shows minor decreases in prolactin levels, but not statistically significant (p-value = 0.101). Group 3 (Myoinositol): Shows the largest decrease in prolactin levels, reaching a statistically significant reduction compared to baseline at week 24 (p-value = 0.001). This table suggests that Myoinositol, but not Metformin, might be associated with a decrease in prolactin levels in women with PCOS.

Table 7: Prolactin levels in n=60 PCOS patients

Groups	Prolactin (ng/mL)							P values
	0 week	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks	
Group 1 (Control)	11.75 ± 2.29	11.45 ± 2.00	11.25 ± 2.11	11.34 ± 2.19	11.51 ± 2.34	11.60 ± 2.57	11.64 ± 1.98	0.984
Group 2 (Metformin)	10.99 ± 2.17	10.57 ± 2.11	10.21 ± 1.91	10.19 ± 1.33	10.09 ± 2.15	10.10 ± 1.97	10.06 ± 1.84	0.101
Group 3 (Myoinositol)	12.98 ±3.21	12.53 ±2.09	12.04 ± 2.66	11.83 ± 1.91	11.51 ± 1.83	10.88 ± 1.51	9.95 ± 1.08	0.001

Adverse effects: In our study 3 out of 20 patients treated with metformin showed mild GIT disturbance with predominantly diarrhea and stomach upset but there were no drop out. MI treated group did not show any adverse events.

Discussion

Polycystic ovarian syndrome (PCOS) is a multifaceted clinical condition typified by hyperandrogenism and chronic oligo/anovulation. Various factors contribute to the manifestation of PCOS, including genetic predisposition, elevated insulin levels, obesity, excess androgen production, abnormalities in the hypothalamic-pituitary-gonadal axis, environmental pollutants, food contaminants, and chronic inflammation [13]. In this study, we aimed to assess the effectiveness of Myoinositol (MI) in 20 PCOS patients compared with placebo

(20 patients) and metformin (20 patients) over 24 weeks. We observed a significant decrease in the fasting insulin levels in the metformin-treated group. Similar studies conducted previously by Genazzani et al. [14] and Unfer V et al. [15] also corroborate our findings. Our study demonstrated a notable reduction in LH levels starting from the 4th week and a decrease in the LH/FSH ratio from the 8th week onwards in the MI group. This finding aligns with prior research conducted by Genazzani et al. [14] Martino M. Zacchi et al. [16] and Antonio Simone Laganà et al. [17]. Additionally, our research revealed a significant decrease in prolactin levels from the 8th week onwards in the MI-treated group compared to the placebo and metformin groups. This observation is consistent with the results of similar studies by Genazzani et al. [14]. By the 12th week of treatment, our study revealed a substantial decrease in TSH levels within the MI-treated group, whereas no significant difference was observed in the placebo or metformin-treated groups. Notably, no previous studies have reported similar significance in this regard.

In our current investigation, within the MI group, 16 of 20 patients (80%) demonstrated ovulation, indicating positive outcomes. This contrasts with the metformin group, where 12 of 20 patients (60%) exhibited positive results, and the placebo group, in which only 3 of 20 patients (15%) experienced positive outcomes. These findings align with those of previous research conducted by Costantino et al., who emphasized that MI yielded the highest rate of ovulation restoration compared to placebo [8]. In a study conducted by Raffone et al., comparing the efficacy of metformin and MI in 120 PCOS patients, it was observed that out of 60 women treated with metformin, 50% experienced restored spontaneous ovulation, with 11 women achieving spontaneous pregnancy, while seven discontinued treatments due to side effects. Conversely, in the MI-treated group, 65% of the 60 women experienced restored spontaneous ovulation, with 18 women achieving spontaneous pregnancy. This study suggests that MI treatment may be more effective than metformin as a first-line treatment for reinstating normal menstrual cycles in PCOS patients [18]. Our study corroborates these findings, indicating that MI outperformed both metformin and placebo in enhancing hormonal and metabolic profiles, leading to an increased frequency of ovulation and improved pregnancy outcomes. Moreover, in our study, among the 60 PCOS women evaluated, only 4 exhibited mild hirsutism on the upper lip, as per the Ferriman-Gallwey visual scale [19], with a score below 8, which is considered normal. In our study, 3 out of 20 patients treated with metformin showed mild GIT disturbance, but there was no dropout. The MI group did not exhibit any adverse events. These results were similar to those of previous studies by Carlomagno G M et al. [20] who stated that a dosage of 4gm/day commonly used in clinics, is completely free of side effects.

Conclusion

Given that PCOS often emerges during adolescence, early intervention is imperative to enhance the reproductive health of adolescents and to mitigate future complications. Our findings suggest that myoinositol (MI), a non-hormonal drug, is effective in PCOS treatment by regulating menstrual cycles, inducing ovulation, and enhancing pregnancy success rates in cases of infertility. Notably, MI demonstrates a high degree of safety and effectiveness, with minimal to no observed side effects compared with both placebo and metformin. These observations underscore the potential inclusion of MI in PCOS treatment protocols, particularly for infertility management in the foreseeable future.

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