Effectiveness of Inositol on clinical features, endocrine and metabolic profiles in infertile patients with polycystic ovary syndrome

Le Viet Nguyen Sa[1], Le Minh Tam[2*], Tran Thi Nhu Quynh[2], Cao Ngoc Thanh[2]
[1]Hue Central Hospital
[2]Hue University of Medicine and Pharmacy, Hue University

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Corresponding author: Le Minh Tam. Email: leminhtam@hueuni.edu.vn.
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Abstract

Objectives: *This study aimed to assess the impact of Inositol on the clinical characteristics, endocrine and metabolic profiles of infertile PCOS patients from Vietnam.*

Methods: *From June 2018 to June 2022, a clinical trial was undertaken at the Center for Reproductive Endocrinology and Infertility on infertile women aged 18 to 40 with PCOS. The clinical, endocrine, and metabolic features of these individuals were assessed before and after 3 months of treatment with 2g of Inositol per day. Natural pregnancy rates, adverse effects, and tolerance of Inositol have also been recorded.*

Results: *After three months of Inositol treatment, 18.2% of patients with oligomenorrhea experienced regular menstruation. Inositol therapy dramatically lowered hips circumference and Testosterone levels, but had no effect on other clinical characteristics, endocrine profiles, or metabolic profiles. In the overweight and obese group, weight, BMI, waist and hip circumferences decreased dramatically while regular menstrual cycles were improving in non overweight/ obse group. 9.4% of patients reported experiencing side effects; despite this, 100% of women tolerated Inositol and maintained treatment. 18.9% of them attained pregnancy, which resulted in 17% live births.*

Conclusion: *Inositol appears to increase menstrual cycle regularity and decrease Testosterone levels; resulting in a clinical pregnancy rate of 18.9% and a live birth rate of 17.0%. Inositol appears to be more beneficial in improving weight, BMI, waist and híp circumference in the obese and overweight population.*

Keywords: *PCOS, Inosiol, endocrine, metabolic, menstrual cycle, pregnancy.*

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine condition among reproductive-aged women. Depending on diagnostic criteria and research group, the prevalence of PCOS can range from 4 to 21% [1], [2]. Women with PCOS are more likely to experience infertility, metabolic, physical, and psychological issues. Numerous studies have linked PCOS to an increased risk of early miscarriage [3]. Lim et al. reported in their comprehensive review and meta-analysis that the incidence of metabolic syndrome in women with PCOS was raised by 3.5-fold compared to women without the syndrome (OR = 3.35; 95% CI = 2.44 - 4.59) [4]. Moran et al. also showed that women with PCOS had a 2.5- and 4-fold greater risk of developing glucose intolerance and type 2 diabetes, respectively, compared to group of controls had the same body mass index [5].

Due to the association between the etiology of insulin resistance and polycystic ovarian syndrome, insulin sensitizers have been utilized in women to alleviate clinical symptoms and metabolic indicators in women with PCOS. Myo-inositol (MI) is engaged in cellular glucose absorption, induces GLUT4 translocation to the cell membrane, inhibits adenylate cyclase, and lowers the release of free fatty acids from adipose tissue, whereas D-chiro-inositol (DCI) is involved in glycogen production [6]. In addition, TSH and FSH utilise IPG as a supplementary transmitter signal [7].

Available evidence suggests that Inositol is beneficial for women with PCOS. Morley et al. observed in their meta-analysis that Inositol may increase ovulation rate (OR 3.57; 95% CI 1.72 - 7.4) [8]. Inositol was associated with enhanced ovulation (RR 2.3; 95% CI 1.1 - 4.7), menstrual cycle regulation (RR 6.8; 95% CI 2.8 - 6.6), and a greater clinical pregnancy rate than placebo (RR 3.3; 95% CI 0.4 - 27.4), according to a meta-analysis by Pundir et al. (2017). This meta-analysis also revealed a substantial decrease in serum androgen, total testosterone, free testosterone, and DHEA. However, the studies in the aforementioned meta-analyses have small sample sizes, varied individuals, and short follow-up periods. So far, no research have been undertaken on the population of infertile women in Vietnam. Therefore, the present clinical trial aimed to examine the effect of Inositol on clinical, endocrine, and metabolic parameters in infertile women with PCOS.

2. METHODS

From June 2018 to June 2022, women aged 18 to 40 years with PCOS who visited the Center for Endocrinology and Reproduction at Hue University of Medicine and Pharmacy (HueCREI), were included in this clinical trial.

PCOS is diagnosed when at least two of the following three criteria are present according to the Rotterdam criteria: (1) amenorrhea and oligomenorrhea; (2) the clinical or subclinical presence of hyperandrogenism; (3) ultrasound evidence of polycystic ovaries (with 12 small follicles 2 - 9 mm in at least one ovary and/or ovarian volume ≥ 10 cm^3. PCOS is diagnosed after ruling out all other hyperandrogenic disorders (9).

Exclusion criteria included congenital adrenal hyperplasia and androgen production-producing tumors, Cushing's disease, patients with a history of ovarian surgery, ovarian tumours, ovarian endometriosis, or ovarian failure, obstruction of both fallopian tubes, severe oligoasthenoteratozoospermia.

All participants were assessed as the following study procedure:

- Evaluation of clinical characteristics, including height, weight, BMI, waist circumference, and evaluation of hirsutism, acne, baldness, and acanthosis nigricans symptoms.

- On days 1-2 of the menstrual cycle, the patient will undergo an ultrasound utilizing an Aloka SSD3500SX ultrasound with a 7MHz frequency vaginal probe, and endocrine and metabolic assays were conducted. Ovary volume were measured in all three planes, and the antral follicle number in each ovary was counted. The volume of the ovary was computed using the formula length x width x height x 0.523.

- On the same day, serum blood tests quantified AMH, FSH, E2, LH, Testosterone, Prolactin, blood lipid balance, fasting blood glucose levels, blood glucose levels 2 hours after the glucose tolerance test, and HbA1C. By radioimmunoassay, the levels of FSH, LH, Estradiol, Progesterone, Prolactin, and Testosterone were determined. ECLIA electrochemiluminescence immunoassay was used to quantify serum AMH on an Elecsys Roche System equipment. Blood lipids were measured using a Roche/Hitachi Cobas C system.

The patient will be treated with Inositol 500 mg x 4 tablets per day (Inositol tablets containing 500 mg of the active component Inositol - Baxco Pharmaceutical, Inc. Irwindale, CA 91010, USA) within three months. After three months of treatment, the patient's clinical features, endocrine levels, and metabolism will be reevaluated. Additionally, the patient experienced adverse effects and tolerance to Inositol; spontaneous pregnancy rate was also evaluated.

Study variables included:

Amenorrhea or oligomenorrhea was characterized as a menstrual cycle lasting longer than 35 days or having less than eight cycles per year [9].

Clinical hyperandrogenism was defined as the presence of acne, male pattern baldness, acanthosis nigrican, or hirsutism (enhanced Ferriman and Gallwey scores 3 for Asian women).

- BMI was computed using the formula square of weight/height. Patients were classified as obese if their BMI was equal or greater than to 25 kg/m^2 and as overweight if their BMI was greater than or equal to 23 kg/m^2.

- Hyperandrogenemia was described when the total concentration of Testosterone was greater than 0.70 ng/mL [11],[12],[13].

The SPSS 20.0 statistical program was used for data entry and processing (SPSS Inc, Chicago III). Categorical variables are expressed as the number of cases and percentages, while continuously distributed variables are expressed as the mean standard deviation. Before and after therapy, differences in metabolic endocrine parameters were assessed using the paired t-test if the data were normally distributed and the Wilcoxon test if the data were not normally distributed. Using mc Nemar's test, the difference in rates before and after treatment was determined. With $p < 0.05$, the algorithms are statistically significant.

The Ethics Committee in Biomedical Research, University of Medicine and Pharmacy, Hue University, approved the study (approval number: H2018/432). Before enrolling in the trial, the patients were provided with a thorough explanation and written confirmation.

3. RESULTS

Our study involved 58 patients who matched the inclusion criteria and consented to participate; after 3 months of treatment, 5 patients did not return, and 9 patients became pregnant during Inositol treatment. Table 1 displayed the change in clinical features following three months of Inositol administration.

Table 1. Changes in clinical characteristics after three months of Inositol treatment in the group of patients with PCOS and the overweight/obese and non-overweight/obese subgroups

Characteristics	Total (n = 44)			Overweight/Obese (n = 11)			No Overweight/Obese (n = 33)		
	Pre-treat	Post-treat	P	Pre-treat	Post-treat	p	Pre-treat	Post-treat	p
Regular mense	6 (13.6%)	14 (31.8%)	0.008**	1 (9.1%)	3 (27.3%)	0.500**	5 (15.2%)	11 (33.3%)	0.031**
Systolic BP (mmHg)	104.55 ± 12.24	105.80 ± 11.05	0.119*	107.73± 17.80	107.73 ± 16.03	1.000	103.49 ± 9.88	105.15 ± 9.06	0.119*
Diastolic BP (mmHg)	66.59 ± 8.05	67.27 ± 7.88	0.366*	65.46 ± 10.36	65.45 ± 10.36	1.000	66.97 ± 7.28	67.88 ± 6.96	0.366*
Weight (kg)	51.27 ± 7.65	50.77 ± 6.70	0.089	60.00 ±7.09	57.91 ± 6.80	<0.001	48.36 ± 5.30	48.39 ± 4.74	0.761*
BMI (kg/m^2)	20.91 ± 2.66	20.71 ± 2.22	0.102*	24.54 ± 1.74	23.68 ± 1.69	<0.001	19.70 ± 1.59	19.72 ± 1.30	0.885
Waist (cm)	75.82 ± 7.80	75.61 ± 6.74	0.367*	85.55 ±6.55	83.73 ± 5.80	0.002	72.58 ± 5.01	72.91 ± 4.51	0.580*
Hips (cm)	91.00 ± 5.84	90.18 ± 4.85	0.016	96.55 ± 6.50	94.73 ± 5.27	0.045	89.15 ± 4.31	88.67 ± 3.66	0.340
mFG	2.70 ± 3.94	2.66 ± 3.93	0.157*	2.09 ± 4.57	2.09 ± 4.57	1.000*	2.91 ± 3.76	2.85 ± 3.75	0.157*
Hirsutism	19 (43.2%)	19 (43.2%)	1.000**	3 (27.3%)	3 (27.3%)	1.000**	16 (48.5%)	16 (48.5%)	1.000**
Acne	8 (18.2%)	8(18.2%)	1.000**	2 (18.2%)	3 (27.3%)	1.000**	6 (18.2%)	5 (15.1%)	1.000**
Male pattern baldness	3 (6.9%)	2 (4.6%)	1.000**	0 (0%)	0 (0%)	NA**	3 (9.0%)	2 (6.0%)	1.000**
Acanthosis nigricans	0 (0%)	1 (2.3%)	1.000**	0(0%)	0 (0%)	NA**	0 (0%)	1 (3.0%)	1.000**

*Wilcoxon Signed Ranks Test/ paird samples t test

**McNemar test

BP: blood pressure; BMI: body mass index; mFG: modified Ferriman Gallway

After using Inositol, the rate of normal menstrual periods increased by 18.2% in women with oligomenorrhea ($p < 0.05$). Weight and BMI dropped insignificantly (51.27 ± 7.65 to 50.77 ± 6.70 kg, $p = 0.089$ and 20.91 ± 2.66 to 20.71 ± 2.22 kg/m^2, $p = 0.102$) while hips circumference decreased signigicantly (91.00 ± 5.84 to 90.18 ± 4.85 cm, $p = 0.016$) in the total treated patients. The characteristics of hyperandrogenism did not alter or changed minimally without statistical significance ($p > 0.05$). Subgroup analysis showed a significant decrease in weight, BMI, waist and hips circumference ($p < 0.05$) in overweight/obese group while there was an significant increase in regular menstrual cycles in non overweight-obese group ($p < 0.05$).

Table 2. Changes in endocrine and metabolic features following 3 months of Inositol treatment in the group of patients with PCOS, the overweight/obese subgroups, and the non-overweight/obese subgroups.

Characteristics	Total (n = 44)			Overweight/Obese (n = 11)			No Overweight/Obese (n = 33)		
	Pre-treat	Post-treat	p	Pre-treat	Post-treat	p	Pre-treat	Post-treat	p
Basic FSH (IU/L)	6.2 ± 1.14	6.02 ± 1.19	0.148	5.70 ± 1.00	5.83 ± 1.22	0.626	6.35 ± 1.13	6.04 ± 1.15	0.005
Basic LH (IU/L)	10.72 ± 6.24	9.88 ± 5.07	0.104*	8.87 ± 5.05	9.07 ± 4.40	0.604	11.49 ± 6.49	10.11 ± 5.17	0.047*
Basic Estradiol (pg/ml)	40.94 ±18.04	40.08 ± 12.26	0.852*	44.91 ±25.53	46.58 ± 13.83	0.091*	40.14 ±13.28	38.62 ± 11.95	0.492
Testosterone (ng/mL)	0.277 ± 0.136	0.245 ± 0.111	0.033	0.281 ± 0.157	0.268 ± 0.116	0.618	0.275 ± 0.122	0.237 ± 0.104	0.033

Prolactin (IU/L)	419.92 ± 208.82	400.52 ± 160.73	0.455	534.81 ± 263.27	395.63 ± 139.37	0.101	380.06 ± 168.91	404.81 ± 167.16	0.094
Cholesterol (mmol/L)	4.53 ± 0.72	4.58 ± 0.90	0.735	4.44 ± 0.87	4.87 ± 1.13	0.286*	4.55 ± 0.66	4.48 ± 0.78	0.534
Triglycerides (mmol/L)	1.22 ± 0.87	1.26 ± 0.82	0.674*	1.33 ± 0.62	1.37 ± 0.73	0.764	1.15 ± 0.93	1.18 ± 0.83	0.681*
LDL-Cholesterol (mmol/L)	3.12 ± 0.69	3.14 ± 0.97	0.918	3.12 ± 0.82	3.42 ± 1.15	0.437	3.10 ± 0.64	3.02 ± 0.85	0.516
HDL- Cholesterol (mmol/L)	1.32 ± 0.32	1.31 ± 0.26	0.647	1.23 ± 0.33	1.24 ± 0.31	0.713	1.38 ± 0.31	1.34 ± 0.25	0.420
G0 (mmol/L)	5.13 ± 0.46	5.06 ± 0.34	0.194	5.13 ± 0.64	4.98 ± 0.46	0.095	5.07 ± 0.41	5.04 ± 0.32	0.633
G2 (mmol/L)	6.60 ± 1.55	6.32 ± 1.16	0.171	7.01 ± 1.94	6.78 ± 1.31	0.560	6.32 ± 1.34	6.04 ± 1.08	0.221
HbA1c (%)	4.99 ± 0.33	5.03 ± 0.37	0.579	4.95 ± 0.46	5.03 ± 0.38	0.667	4.97 ± 0.30	5.00 ± 0.37	0.726

*Wilcoxon Signed Ranks Test

FSH: Follicle Stimulating hormone; LH: Luteinizing hormone; LDL: low density lipoprotein; HDL: high density lipoprotein; G0: fasting glucose; G2: glucose concentration after 2 hours.

Table 2 showed the changes in endocrine and metabolic parameters. The concentration of total Testosterone dropped significantly (0.277 ± 0.136 to 0.245 ± 0.111ng/mL; p= 0.033). Other indices of lipid balance and related factors of sugar metabolism did not alter significantly (p > 0.05). In the subgroup analysis of women who were neither overweight nor obese, baseline FSH, LH and total Testosterone levels reduced significantly (p < 0.05).

Table 3. Inositol adverse effects, tolerance, and spontaneous pregnancy rate

Characteristics	N	Percentage (%)
Adverse effects	5	9.4
Digestive disorders	1	1.9
Fatigue	3	5.6
Others	1	1.9
Tolerance	53	100
Getting pregnancy	10	18.9
Clinical pregnancy	9	17.0
Live birth	9	14.0

Table 3 demonstrates that 9.4% of women who took Inositol experienced adverse effects, primarily fatigue. Inositol was well tolerated by 100% of women, who all continued medication. 18.9% of these women were pregnant, resulting in 17% of live births.

4. DISCUSSION

Changes in clinical characteristics following Inositol therapy

We observed a statistically significant improvement in the menstrual cycle (+18.2%, p = 0.005) after three months of Inositol administration. Weight and BMI decreased insignificantly insignificantly (51.27 ± 7.65 to 50.77 ± 6.70 kg, p = 0.089 and 20.91 ± 2.66 to 20.71 ± 2.22 kg/m^2, p = 0.102)) while hips circumference decreased signigicantly (91.00 ± 5.84 to 90.18 ± 4.85 cm, p = 0.016) in the total treated patients. Waist circumference and mFG score tended to decrease, although not statistically significantly.

Genazzani A. et al. (2012) found that after 8 weeks of treatment with Myo-Inositol and an unrestricted diet, patients dropped a statistically significant amount of BMI [14]. Most recently, Zareadeh M et al (2021) conducted a meta-analysis of the effects of Inositol on BMI across a total of 15 clinical studies and discovered that supplementation with Inositol significantly lowered body mass index (BMI) (WMD = -0.41 kg/m2; 95% CI: -0.78, -0.04; p = 0.028). The greatest pronounced effect was noticed in women with PCOS who were also overweight or obese. In addition, Myo-Inositol exhibited a stronger BMI-reducing impact than Inositol [15].

In patients with mild to moderate hirsutism, supplementation with 2g MI per day was associated with a significant reduction in hirsutism severity, total androgen levels, FSH, LH, and LDL-C [16]. The aforementioned study by Genazzani A. et al. (2008) similarly revealed a reduction in mFG scores, although not statistically significant (22.7 1.4 to 18.0 0.8), as well as a reduction in Testosterone levels following 12 weeks of therapy with MI [17].

Multiple studies have demonstrated that treatment with MI improves ovarian and reproductive function, decreases hyperandrogenism, acne, and hirsutism, and has positive effects on metabolic and regulatory parameters in individuals with PCOS. Numerous endocrine variables influence reproductive and ovulatory processes. Therefore, Inositol becomes a method for enhancing natural ovulation or stimulating ovulation [6]. During six months of treatment with MI, Papaleo et al. observed that menstrual cycle therapy was restored and sustained [18]. Similar investigations also revealed that the MI group ovulated more frequently than the placebo group [19][20].

Changes in metabolic endocrine parameters following Inositol treatment

After 3 months of treatment with Inositol, total Testosterone levels decreased statiscally significantly (0.277 ± 0.136 to 0.245 ± 0.111ng/mL; p= 0.033). Other endocrine and lipid balance measures were not statistically significant. Blood glucose tended to drop, although this trend did not achieve statistical significance.

The above-mentioned study by Costantino D et al. (2009) reported that the MI group decreased the total Testosterone concentration by 65% (99.5 ± 7 to 34.8 ± 4.3 ng/dL vs 116.8 ± 15 to 109 ± 7.5 ng/dL in the placebo group, p = 0.003); a decrease in free Testosterone (0.85 ± 0.1 to 0.24 ± 0.33 ng/dL vs 0.89 ± 0.12 to 0.85 ± 0.13 ng/dL; p = 0.01). Serum TG levels decreased considerably in the Inositol group, from 195 ± 20 to 95 ± 17 mg/dL, compared to 155 ± 21 to 148 ± 19 mg/dL in the placebo group (p=0.001). In addition, MI decreased insulin levels following oral glucose delivery. In addition, 16/23 (69.5%) of the women in the MI group ovulated, compared to 4/19 (21%) of the women in the placebo group (p=0.001). The authors concluded that MI treatment decreased testosterone and insulin levels and enhanced a number of metabolic variables and ovulation rate [21].

The most current systematic review and meta-analysis was conducted by Hayamizu K. et al. (2022) on 9 clinical trials with 577 patients. Compared to the control group, this meta-analysis revealed that Inositol improved fasting insulin levels, glucose tolerance test area under the curve, free Testosterone levels, SHBG levels, and ovulation rate (RR 1.42, 95% CI – 1.00 - 2.02, p = 0.05). Regarding the gonadotropins, only two of the studies included in this meta-analysis that investigated changes in female hormone levels demonstrated an increase in estradiol levels and a substantial decrease in LH and FSH levels [22].

Regarding lipid profile improvement, Tabrizi et al. (2018) conducted a meta-analysis and comprehensive review of 14 RCTs in patients with metabolic syndrome, demonstrating that Inositol supplementation improved TG and LDL-C levels, but had no discernible effect on HDL-C levels. Notably, the authors also reported a favorable effect of Inositol supplementation on HDL-C levels in PCOS women [23].

Subgroup analysis of PCOS patients with or without overweight/obese

In the group of overweight and obese women with PCOS, subgroup analysis revealed that weight, BMI, waist circumference, and hips circumference dropped significantly. Metabolic endocrine indicators did not show any significant alterations. Inositol was helpful at regulating menstruation in the group of non-obese women, without significantly improving weight and BMI, but FSH, LH and Testosterone levels decreased statistically.

Nesler et al. are the first to describe the efficacy of DCI in the treatment of obese women with PCOS, as seen by higher insulin activity, improved ovulatory function, and decreased serum testosterone levels and blood pressure [24]. Then, Genazzani A. et al. demonstrated that MI is effective for regulating the metabolism and endocrine system by reducing insulin resistance According to the findings of the study, the HOMA index reduced from 2.8 ± 0.6 to 1.4 ± 0.3 ($p < 0.01$) [17].

Pregnancy rate, tolerance, and adverse effects

In our study, 9.4% of women who took Inositol experienced adverse effects, although all patients tolerated the drug and continued treatment. 18.9% of these women got pregnant, resulting in 17% live births. Although there were few research analyzing the pregnancy rate of Inositol in women with SRB, Regidor et al. (2016) found that 70% of infertile women recovered after taking 4g of Myoinositol for 12 weeks. Recovery of ovulation and the achievement of 545 pregnancies resulted in a pregnancy rate of 15.1% [26]. Our investigation is one of the first to track a live birth after its occurrence.

5. CONCLUSIONS

Inositol treatment for 3 months significantly improved menstrual cycle, hips circumference and testosterone levels. Blood glucose measures tended to decrease; lipid profile parameters did not improve. The rate of spontaneous conception is 18.9%. Inositol was well tolerated, and only 9.4% of women reported

adverse effects. Inositol appears to be more effective for obese and overweight women in improving weight, BMI, waist and hips circumference.

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