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MYOINOSITOL AN EFFECTIVE TREATMENT FOR POLYCYSTIC OVARIAN SYNDROME PATIENTS OF EAST INDIA

Gynaecology

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ABSTRACT

Polycystic Ovarian syndrome is a well studied metabolic and hormonal disorder in women, characterised by chronic oligo or anovulation, hyperandrogenism and impaired glucose intolerance causing menstrual problems, infertility and obesity. This study is regarding the use of myo inositol along with folic acid as a promising tool in the management of infertility and other symptoms in patients with polycystic Ovarian syndrome. In this study 75 patients with infertility used myoinositol 2 gm along with folic acid 200 ugm ,twice a day for 3 to 4 months.

In these patients, hormonal levels of free testosterone and progesterone were analysed before and after the treatment and also the follicles formation pattern seen before and after the treatment. During this period around 70 % of the women restored ovulation. Pregnancy rate was around 40% of all myoinositol plus folic acid users. Testosterone levels were decreased to 50% after 3 to 4 months of treatment. There were no obvious side effects among the users.

Thus we concluded that myo-inositol is an effective and safe mode of treatment for infertile PCOS patients of East India.

KEYWORDS

PCOS, myoinositol, infertility, Insulin resistance

INTRODUCTION

In North East India Polycystic ovary syndrome (PCOS) is the most common cause of infertility, ovarian dysfunction and menstrual irregularity, affecting 5% –10% of women in reproductive age [1]. Although this incidence is low compared to the whole population, which is about 10 – 15% . The European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine sponsored a Consensus Meeting in Rotterdam (2003) [2,3], in order to reach a general agreement of the scientific community on diagnostic criteria for this syndrome. Although nowadays the criteria established in Rotterdam are widely accepted, they leave out a crucial condition related to PCOS: insulin resistance.

Several studies have reported that insulin resistance is common in PCOS women, regardless of the body mass index (BMI). Hyperinsulinemia due to insulin resistance occurs in approximately 80% of women with PCOS and central obesity, as well as in 30%–40% of lean women diagnosed with PCOS [4,5].

Insulin resistance is significantly exacerbated by obesity, and it is a key factor in the pathogenesis of anovulation and hyperandrogenism [5,8]. The importance of insulin resistance in PCOS is also suggested by the fact that insulin-sensitizing compounds, such as metformin, pioglitazone have been proposed as treatment to solve the hyperinsulinemia-induced dysfunction of ovarian response to endogenous gonadotropins. Rescuing the ovarian response to endogenous gonadotropins reduces hyperandrogenemia, re-establishes menstrual cyclicity and ovulation, increasing the chance of a spontaneous pregnancy [9–11]. In particular, metformin induces reduction of total and free testosterone concentrations [12]. However, metformin, can induce, gastrointestinal side effects [13] and may result in reduced patients' compliance.

Further studies have suggested that impairment in the insulin pathway could be due to a defect in the inositolphosphoglycans (IPGs) second messenger [14,15]. IPGs are known to have a role in activating enzymes that control glucose metabolism [16,17]. In PCOS women, a defect in tissue availability or altered metabolism of inositol or IPGs mediators may contribute to insulin resistance [18]. Inositol belongs to the vitamin B complex group. Epimerization of the six hydroxyl groups of inositol leads to the formation of up to nine stereoisomers, including myo-inositol (MYO) and D-chiro-inositol (DCI); both stereoisomers were used, as insulin sensitizer drugs, in the treatment of PCOS treatments [19–23]. Human adults consume approximately 1 g of inositol (mainly MYO) per day in different biochemical forms [18]. Circulating free MYO is taken up by most tissues by a membrane-associated sodium-dependent inositol co-transporter; inositol uptake is inhibited by glucose [24]. In particular, it was shown that MYO had 10 times more affinity for the transporter compared to DCI (25).

Furthermore, elevated concentrations of MYO in human follicular fluid play a role in follicular maturity and provide a marker of good-quality oocytes [32,33].

Previous studies have demonstrated that MYO is capable of restoring spontaneous ovarian activity, and consequently fertility, in most patients with PCOS [21]. Here, we aim to provide an overview on the clinical outcomes of MYO as a treatment to improve ovarian function and hormonal parameters in women with PCOS in East India.

MATERIALS AND METHODS

A total of 75 women, 20 to 40 age years of age, with PCOS defined by oligo- or amenorrhea (menstrual cycle of more than 35 days), hyperandrogenism (hirsutism, acne or alopecia) or hyperandogenemia (elevated levels of total or free testosterone) and typical ovarian features on ultra-sound scan, were enrolled in the study.

All patients attended our infertility unit that had lasted for 12 to 14 months. Other medical conditions causing ovulatory dysfunction, such as hyperprolactinemia or hypothyroidism, or androgen excess, such as adrenal hyperplasia or Cushing's syndrome, were excluded by hormonal tests. All women underwent assessment of tubal patency and all male partners were evaluated with semen sample analyses, without finding any defect. Thus, it was determined that the most likely cause of the couple's subfertility was ovulation dysfunction only.

PCOS women were treated orally with MYO 2 g plus folic acid 200 ugm, twice daily, continuously, for 3 to 4 months and patients were instructed to register their menstrual bleeding pattern throughout the follow-up period of 6 months. Furthermore, in order to evaluate the restoration of spontaneous ovarian activity, weekly determination of serum progesterone and testosterone levels, as well as transvaginal ultrasound scan documenting the presence of follicular growth or luteal cyst, were performed after the first menstrual cycle. Pre- and post-treatment hormone concentrations were statistically compared.

Moreover, eventual pregnancies were confirmed by a positive test for urinary b-human chorionic gonadotropin and ascertainment of a foetal heart beat on ultrasound scan.

RESULTS

Baseline clinical and biochemical features of the PCOS patients are reported in Table I. The outcome of treatment is shown in Tables I and II.

After MI 2 gm plus folic acid 200 ugm, twice daily administration for 3 to 4 months, 66 out of the 75 women (88%) had a menstrual cycle. Fifty four of these 66 patients presented monthly menstruations during the follow up period. All of them maintained spontaneous ovulation activity, documented by follicular growth and increased serum progesterone concentrations in the luteal phase (mean 10.5 +1.6 ng/ml). Furthermore, after treatment with MI, these women showed significantly decreased concentrations of serum total testosterone

(95.6 + 8.3 vs. 35.2 + 6.5 ng/dl; p ¼ 0.003) and free testosterone (1.0 + 0.6 vs. 0.38 + 0.12 ng/dl; p ¼ 0.005). The length of successive cycles was improved to 31 + 2 days.

Six out of the 66 women showed only a follicular development on ultrasound without progesterone elevation , while six women did not have any further ovarian activity after the first cycle.

During the observational period of 6 months a total of thirty biochemical pregnancies occurred. Twenty seven out of the thirty were singleton pregnancies documented at ultrasound scan, while three of them were biochemical abortions. Three out of the twenty seven pregnancies evolved in a spontaneous abortion at 7 to 8 weeks of gestation. No multiple pregnancy was noted.

DISCUSSION

In the study of Genazzani et al. [34], 20 PCOS patients were recruited, five patients were amenorrheic and 15 oligomenorrheic. Ten of the 20 patients (Group A) were randomly assigned to be treated with MYO 2 g plus folic acid 200 µg every day (Inofolic®, LO.LI. Pharma, Rome, Italy). The other patients (Group B, control group) were administered only folic acid at the daily dosage of 200 µg. No changes of life style or diet were required from the patients.

Endocrine profile was evaluated after treatment, on day 7 of the first menstrual cycle occurring after the 10–12th week of treatment. Consistent and significant changes were observed in Group A. Indeed, plasma luteinizing hormone (LH), prolactin (PRL), LH/ follicle-stimulating hormone (FSH) ratio and insulin levels significantly decreased; furthermore, the homeostatic model assessment (HOMA) index that measures insulin resistance was also reduced. Furthermore, after oral glucose load, both insulin response and the area under the curve (AUC) were significantly lower ($p < 0.01$ and $p < 0.05$, respectively).

Ferriman-Gallway score decreased after 12 weeks of MYO administration although the reduction was not statistically significant (22.7 + 1.4 to 18 + 0.8). Ovarian volumes were significantly reduced (12.2 + 0.6 to 8.7 + 0.8 ml, $p < 0.05$). No changes were observed in Group B.

Furthermore, as long as the patients were treated with MYO, the normal menstrual cycles was restored, while patients assigned to the Group B remained oligomenorrheic throughout the study.

Costantino et al. [35] recruited 42 patients; after randomization, 23 received 2 g of MYO plus 200 µg of folic acid (Inofolic®, LO.LI. Pharma) twice a day and 19 received 400 µg folic acid alone as placebo. Among the 42 women, seven had impaired glucose tolerance and were assigned as follows: four of them received MYO and three received placebo.

The study started when patients were in the follicular phase of the menstrual cycle; no changes in usual habits for food, sport and lifestyle were required.

During the present study, patient treated with MYO showed a reduction in both systolic and diastolic pressure values (131 ± 2 to 127 ± 2 mmHg and 88 ± 1 to 82 ± 3 mmHg, respectively), while these values increased in the placebo group (128 ± 1 to 130 ± 1 mmHg; p = 0.002 and 86 ± 7 to 90 ± 1 mmHg; p = 0.001, respectively).

Furthermore, in the MYO treatment group, plasma triglycerides decreased from 195 ± 20 to 95 ± 17 mg/dl and total cholesterol significantly decreased from 210 ± 10 to 171 ± 11 mg/dl. Although there was no change in the fasting plasma insulin and glucose concentration in either group, AUC, for both insulin and glucose, decreased during the oral glucose tolerance test (8.54 ± 1.149 to 5.535 ± 1.792 µU/ml/min; p = 0.03 and 12.409 ± 686 to 10.452 ± 414 mg/dl/min; p = 0.04, respectively) for MYO-treated patients. No changes were observed in the placebo group.

Consequently, the composite whole body insulin sensitivity index (ISI) significantly increased from 2.80 ± 0.35 to 5.05 ± 0.59 mg/dl in the MYO group, while it did not change in the placebo group. Ovulation was restored in 16 (69.5%) women belonging to the MYO group and four(21%) belonging to the placebo group (p = 0.001). After treatment, the progesterone (P) peak was higher in the MYO group (15.1 ± 2.2 ng/ml) compared to placebo. Furthermore, a significant reduction in total serum T (99.5 ± 7 to 34.8 ± 4.3 ng/dl, p = 0.003) and in free T (0.85 ± 0.11 to 0.24 ± 0.03 ng/dl, p = 0.01) was observed.

Testosterone reduction was accompanied by an increase in serum sex hormone binding globulin. Furthermore, there was reduction of more than 50% in the serum dehydroepiandrosterone sulphate in the MYO group (366 ± 47 to 188 ± 24 µg/dl; p = 0.003), while it was not significant in the placebo group.

Papaleo et al. [20] broaden the clinical use of MYO by evaluating its effect on oocyte quality and the ovarian stimulation protocol for PCOS women. Sixty women were enrolled in the study; after randomization, 30 were assigned to receive 2 g MYO and 200 µg folic acid (Inofolic®, LO.LI. Pharma) twice a day (Group A); 30 received 400 µg folic acid only (Group B).

In the Group A (Inofolic®), the stimulation protocol was milder and shorter. Indeed, both the total recombinant FSH (r-FSH units) (1958 ± 695 vs. 2383 ± 578; p = 0.01) and number of stimulation days (11.4 ± 0.9 vs. 12.4 ± 1.4; $p < 0.01$) were significantly reduced. Furthermore, oestradiol (E2) levels (2232 ± 510 vs. 2713 ± 595 pg/ml; $p < 0.02$) after human chorionic gonadotropin administration were significantly lower in the Group A. These resulted in significant lower number of cancelled cycles because of hyperstimulation risk (E2 > 4000 pg/ml). The number of oocytes retrieved did not differ between the two groups, whereas in the group treated with MYO the number of immature oocytes and degenerated oocytes was significantly reduced (1.0 ± 0.9 vs. 1.6 ± 1.0; p= 0.01), with a trend for increased percentage of metaphase II stage oocytes (0.82 ± 0.11% vs. 0.75 ± 0.15%).

No differences were reported in fertilization and cleavage rates, the number of transferred embryos, and the number of topquality transferred embryos and pregnancy rate.

Gerli et al. [22] enrolled 92 patients to evaluate MYO effects on ovarian and metabolic factors; 45 received 2 g MYO combined with 200 µg folic acid twice a day (Inofolic®, LO.LI. Pharma), 47 received 400 µg folic acid as placebo.

There were eight conceptions and one miscarried in the first trimester. However, only 42 of the patients declared before the study that they wished to conceive. Among these, the distribution of pregnancy was: placebo one out of 19 patients, while in the MYO group it was four out of 23 patients.

An intention to treat analysis revealed that eight of 45 MYO patients failed to ovulate during treatment, compared with 17 out of 47 placebo-treated patients (p = 0.04); the MYO-treated group had a significantly increased frequency of ovulation compared with the placebo group. According to these data, the concentrations of P recorded during monitoring of ovarian function indicated that most of the ovulations showed normal endocrine profiles during both MYO and placebo treatment. All patients started treatment outside the luteal phase, and the delay to the first ovulation after starting the program was significantly shorter in the MYO-treated group (24.5 vs. 40.5, p = 0.02).

The analysis of E2, inhibin-B, and T concentrations on the first and eighth day of treatment showed that the MYO-treated group had a significant (p = 0.03) increase in E2 levels, whereas the control group showed no change. There was no change in circulating levels of inhibin-B or T concentrations.

The BMI decreased significantly in the MYO group (p = 0.04). No change was observed in the waist-to-hip ratio in either group. Circulating leptin concentration declined in the MYO group, in contrast to the control group, but there was no change recorded in the fasting glucose, fasting insulin or insulin AUC in response to the glucose challenge in either group.

The very-low-density lipoprotein showed little change during the treatment period, but the low-density lipoprotein (LDL) showed a trend toward reduction, and the high-density lipoprotein (HDL) increased significantly in the MYO group.

Raffone et al. [36] performed a study aiming to compare the effects of metformin and MYO on PCOS patients: 120 women were recruited; 60 patients were treated with metformin 1500 mg/ day (Glucophage®,

Merck Pharma, Rome, Italy), while 60 received 4 g MYO plus 400 µg folic acid (Inofolic®).

Among the patients treated with metformin, 50% restored spontaneous ovulation activity; in these patients, ovulation occurred after 16.7 (+2.5) days from the day 1 of the menstrual cycle. Pregnancy occurred spontaneously in 11 of these patients; seven women dropped out. The remaining 42 patients were treated with 1500 mg of metformin plus r-FSH for a maximum of three cycles. Pregnancy occurred in 11 women, nine of these pregnancies occurred in the metformin-resistant patients (n = 23), two in the group which had ovulation restored with metformin alone. The total pregnancy rate was 36.6%, five of the 22 pregnancies (22.7%) evolved in spontaneous abortion at 9 weeks of gestation.

Seven subjects in the metformin group dropped out because of the development of side effects and loss of follow-up.

In the MYO group, 65% of patients restored spontaneous ovulation activity, ovulation occurred after a mean of 14.8 (+1.8) days from the day 1 of the menstrual cycle. Pregnancy occurred spontaneously in 18 of these patients and four women dropped out. The remaining 38 patients were treated with 4 g/day MYO, 400 µg/day folic acid and r-FSH in small doses (37.5 U/day for three cycles). Pregnancy occurred in a total of 11 women, eight of these pregnancies occurred in the MYO-resistant patients (n = 17), three in the group which had ovulation restored with MYO alone.

The total pregnancy rate was 48.4%, six of the 29 pregnancies (20.6%) evolved in spontaneous abortion. The efficacy in restoring regular ovulation was evaluated by comparing both the percentage of patients who responded to the treatment and the median length of follicular phase in metformin and in MYO group: ovulation occurred after a mean 16.7 (+2.5) days from the day 1 of the menstrual cycle in the metformin group and after a mean 14.8 (+1.8) in the MYO group. The median between metformin and MYO differed significantly ($p < 0.003$).

CONCLUSION

In Northeast India, PCOS is one of the most common ovulatory dysfunction causing female infertility. Insulin résistance and hyperinsulinemia are strictly inherent to a high proportion of women with PCOS. A defect in insulin action has been suspected, particularly as consequence of a deficiency of DCI, a component of inositol phosphoglycan.

Chronic anovulation is often the main cause of infertility in patients of reproductive age. It is well known that ovulation induction is a complex issue owing to the increased risk of ovarian hyperstimulation syndrome and multiple pregnancy [11,12].

Clomiphene citrate, an antiestrogen, is the common first-choice drug in women with newly diagnosed PCOS, while insulin-lowering medications represent novel therapies for restoring spontaneous ovulation [13,14]. The efficacy of metformin is still debated, both alone and in association with clomiphene citrate [15,16]. Metformin treatment is associated with a higher incidence of side-effects such as nausea,vomiting and other gastrointestinal disturbances [17].

DCI administration increases the action of insulin in patients with PCOS, thereby improving ovulatory function and decreasing serum testosterone concentration [6,18,19]. MI, a precursor of DCI, is widely distributed in nature whereas DCI is relatively rare [7]. MI is present in human follicular fluid, where elevated concentrations appear to play a positive role in follicular maturity and provide a marker of good quality oocytes [9].

Our study demonstrated that MI oral supplementation restores spontaneous ovulation and menstrual cycles, and increases progesterone secretion in the luteal phase, in most infertile patients with PCOS.

The present results are in line with other studies evaluating insulin-sensitizing agents in monotherapy or in association with clomiphene citrate [7,13,14,16–18], suggesting the positive effect that MI plays on spontaneous ovarian activity. Furthermore, we found that MI therapy is able to reduce serum testosterone, both total and free. All pregnancies obtained in the follow-up period were singleton, and there was no increased incidence of abortion.

In conclusion, MI is a simple and safe treatment that is able to help spontaneous ovulation and fertility in most patients with PCOS.

Table I : Clinical and biochemical features of the patients

	Before myo-inositol	After myo-inositol
Age (years)	30 +/- 10	
Body mass index (kg/m2)	28.5 +/- 2.4	
Menstrual cycle length	>35 days	31 +/- 2days
Serum progesterone (ng/ml)	1.8 +/- 0.6	10.5 +/- 1.6
Serum total testosterone (ng/dl)	95.6 +/- 8.3	35.2 +/- 6.5*
Serum free testosterone	1 +/- 0.6	0.38 +/- 0.12^

Significant difference compared with baseline: *p ¼ 0.003; ^ p ¼ 0.005.

Table II. Outcome of treatment with myo-inositol.

Number of patients treated	75
No. of patients menstruated after treatment (% of patients)	66 (88 %)
No. of patients with restored monthly ovulation (% of patients)	54 (72 %)
No. of pregnancies (% of patients)	30 (40 %)
No. of pregnancies/no. patients with restored monthly Ovulation (%)	55 %
No. of abortions (% of pregnancies)	6 (20 %)
Multiple pregnancy	0

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