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ORIGINAL ARTICLE

Myo-inositol administration positively effects ovulation induction and intrauterine insemination in patients with polycystic ovary syndrome: a prospective, controlled, randomized trial

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Abstract

Objective: The aim of the study is to investigate the effect of myo-inositol (MYO) on pregnancy rates of patients diagnosed with polycystic ovary syndrome (PCOS) who undergone controlled ovulation induction and intrauterine insemination (IUI).
Methods: A total of 196 infertile patients diagnosed with PCOS and admitted to Dokuz Eylul University Faculty of Medicine were included in the study between March 2013 and May 2016. The patients in group 1 ($n = 98$) were given 4 g MYO and 400 μg folic acid before and during ovulation induction. The patients undergone controlled ovarian hyperstimulation (COH) with recombinant FSH and IUI. The patients in group 2 ($n = 98$), were given recombinant FSH directly and 400 μg folic acid. The primary outcome measure of this study was the clinical pregnancy rate.
Results: In group 1, 9 patients conceived spontaneous pregnancy. During COH + IUI treatment three cycles were canceled in group 1 and 8 cycles in group 2. Total rFSH dose and cycle duration were significantly lower and clinical pregnancy rates were higher in group 1. The pregnancy rate for group 1 was %18.6 and for group 2 was %12.2.
Conclusıons: This study shows that MYO should be considered in the treatment of infertile PCOS patients. MYO administration increases clinical pregnancy rates, lowers total rFSH dose and the duration of the ovulation induction.

Keywords

Infertility, insulin resistance, insulin sensitizer, ovulation induction, polycystic ovary syndrome

History

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Introduction

Polycystic ovary syndrome (PCOS) is recognized as a common, heterogeneous endocrine disorder, affecting women of reproductive age [1]. The prevalence of PCOS varies depending on the criteria used to make the diagnosis. According to European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM), the prevalence is as high as %15–22 [2,3]. Women with PCOS often endure from menstrual irregularities, clinical manifestations of hyperandrogenism and infertility. PCOS is frequently associated with insulin resistance (IR) and obesity [4,5]. Evidence suggests that IR and its compensatory hyperinsulinemia play an important role in the pathogenesis. Insulin is associated with hyperandrogenism; it acts synergistically with luteinizing hormone (LH) to increase the androgen production of theca cells [6]. Therefore, administration of insulin sensitizers improves hyperandrogenemia and ovulatory functions [7].

Inositol (hexahydroxycyclohexane) belongs to the vitamin B complex group; it is a 6-carbon ring compound, having a hydroxyl group linked to each carbon of the ring, with nine possible stereoisomeric forms depending on the epimerization of the six-hydroxyl groups. Among them, myo-inositol (MYO) is the mostly represented isoform with very relevant biological functions [8]. Increasing evidence has demonstrated that MYO plays a key role in cell morphogenesis and cytogenesis, lipid synthesis, structure of cell membranes and cell growth [9]. MYO administration improves hormonal profile, oocyte maturation, insulin resistance; furthermore, it promotes the meiotic progression of germinal vesicle oocytes [10,11]. Recent studies on PCOS patients showed a decrease of androgen levels and improvement in ovulation after treatment of MYO [12].

In this study, we focused our attention on the activity of MYO. Our primary outcome was to investigate the effect of MYO on pregnancy rates of patients diagnosed with PCOS who undergone controlled ovulation induction and intrauterine insemination (IUI).

Materials/methods

This is a randomized prospective trial carried out at the Department of Obstetrics and Gynecology (Dokuz Eylul University, Izmir, Turkey) between March 2013 and May 2016. This study started after the approval by the Clinical Research Ethics Committee of the Faculty of Medicine, Dokuz Eylul University and the Turkish Health Ministry Drug and Medical Device Foundation. Informed written consent was obtained from all subjects. A total of 196 infertile, aged between 18 and 35 years, anovulatory patients diagnosed with PCOS who failed to conceive

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for >12 months, and admitted to Dokuz Eylul University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility Outpatient Clinic, were included in the study. Randomization was done according to the protocol numbers of the patients. The patients who had a protocol number ending with an odd number were allocated to group 1 ($n = 98$), whereas the even ones to group 2 ($n = 98$). The patients in group 1 were given 4 g MYO plus 400 µg folic acid (INOFOLIC; Lo.Li. Pharma, Rome, Italy). The drug usage was started at the initial examination and used twice a day continuously for 12 weeks and continued during COH + IUI. The assessment of hormonal parameters was done when the patients had their first menstrual cycle after 12 weeks. The patients undergone controlled ovarian hyperstimulation (COH) with recombinant FSH on the third day of the menstrual cycle. When the dominant follicle was formed IUI was planned. MYO treatment was stopped 10 d after IUI when the patients admitted for pregnancy test. The patients in group 2, were given recombinant FSH directly on the third day of the menstruation without MYO administration. Group 2 also received 400 µg folic acid, but not MYO. In oligo/amenorrhoeic patients, COH + IUI was started after withdrawal bleeding induced by oral progestin (5 mg medroxyprogesterone acetate twice a day. TARLUSAL; Deva Holding A.Ş. Istanbul, Turkey).

The diagnosis of PCOS was made according to the Rotterdam criteria; as prescribed, two out of three features were detected in the patients: oligomenorrhea (fewer than six menstrual periods in the preceding year) and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; presence of ≥ 12 follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume (>10 mL) [3]. Smoking, hyperprolactinemia, hypogonadotropic hypogonadism, pregnancy, thyroid disease, congenital adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome were ruled out during the screening phase. None among the enrolled patients had taken, at least in the previous six months, oral contraceptives, antiandrogens or any drug that could influence hormonal metabolism. Male factor infertility was an exclusion criterion.

Initial physical examination included weight, height, waist and hip circumferences, to calculate waist/hip ratio (WHR), and body mass index (BMI). BMI calculated as kg/m^2, was used as a measure of overall obesity. The patients BMI was between 18.5 and 29.9 kg/m^2. The WHR was used to assess the abdominal obesity. The waist circumference was measured at the midpoint of lowest margin of 12th rib, and the lateral iliac crest during the normal expiration. The hip circumference was measured at the maximum distance between major trochanters. All anthropometric measurements were made by the same operator.

Serum levels of fasting plasma glucose and insulin, follicle stimulating hormone (FSH), LH, estradiol (E2), prolactin (PRL), thyroid stimulating hormone (TSH), total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), sex hormone binding globulin (SHBG) and progesterone were measured. Normal insulin sensitivity was defined by fasting serum glucose and insulin levels with homeostatic model of insulin resistance (HOMA-IR). HOMA-IR was calculated by the formula: HOMA-IR = fasting blood glucose (mg/dL) × fasting insulin (µIU/mL)/405. HOMA-IR ≥ 2.5 was accepted as insulin resistance. All blood tests were performed between the days 2 or 3 of the menstrual cycle except progesterone. Blood samples for progesterone were studied on day 21st of the menstrual cycle. Fasting venous blood samples were taken between 08:00 and 10:00 am after a 12-h overnight fast.

All COH + IUI cycles were performed only with recombinant FSH (rFSH, follitropin alpha) (Gonal F, Serono, Istanbul, Turkey). COH was initiated with 37.5–150 IU rFSH on day third of the menstrual cycle. On days 10–12 of the menstrual cycle, we assessed follicular development and endometrial thickness by transvaginal ultrasonography. Once a leading follicle of ≥18 mm was identified, ovulation triggering was performed using 250 µg/0.5 mL choriogonadotropin alpha (Ovitrelle, Merck, Istanbul, Turkey) and a single IUI was planned 36 h later. If more than five follicules ≥18 mm in size developed and/or the endometrial thickness was <7 mm, the cycle was canceled.

The primary outcome measure of this study was the clinical pregnancy rate, which was defined as observable cardiac activity by a transvaginal ultrasonography above six weeks of gestation.

Data were analyzed by using Statistical Program for Social Sciences (SPSS) version 16 (SPSS Inc., Chicago, IL). The level of significance was accepted when $p < 0.05$.

Results

A total of 196 patients were analyzed, among them 98 patients received MYO for 12 weeks before COH + IUI who formed group 1. Group 2 was constituted from 98 patients who directly undergone COH + IUI. Baseline demographic and clinical characteristics of the groups are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients.

Parameter (mean ± SD)	Group 1 ($n = 98$)	Group 2 ($n = 98$)	*p
Age (years)	28.65 ± 3.13	28.81 ± 4.21	0.31
BMI (kg/m^2)	24.16 ± 3.11	25.19 ± 2.41	0.22
WHR	0.80 ± 0.12	0.82 ± 0.16	0.56
Duration of infertility (years)	2.1 ± 0.8	1.9 ± 1.1	0.97
Third day FSH (mIU/mL)	4.18 ± 1.78	4.88 ± 1.21	0.43
Third day LH (mIU/mL)	7.83 ± 3.01	8.29 ± 2.46	0.25
Third day E2 (pg/mL)	68.38 ± 18.36	57.85 ± 19.12	0.11
21st d progesterone (ng/mL)	1.45 ± 0.21	1.81 ± 0.76	0.56
TSH (µU/mL)	1.64 ± 0.75	1.78 ± 0.79	0.78
PRL (ng/mL)	18.18 ± 6.23	21.48 ± 9.56	0.39
Fasting glucose (mg/dL)	86.32 ± 7.56	83.89 ± 8.11	0.15
Fasting insulin (µIU/dL)	10.98 ± 8.61	11.21 ± 8.54	0.32
HOMA-IR	2.43 ± 1.78	2.47 ± 1.93	0.44
IR + patients (n, %)	47 (%47.9)	45 (%45.9)	0.56

*$p < 0.05$ is statistically significant.
Independent samples t test.
Abbreviations: BMI; body mass index, WHR: waist/hip ratio, FSH; follicle stimulating hormone, LH; luteinizing hormone, E2: estradiol, TSH; thyroid stimulating hormone, PRL: prolactin, HOMA-IR: homeostasis model assessment-insulin resistance, IR+; IR positive.

After 12 weeks of MYO administration, there was a significant increase in day 21 serum progesterone levels ($p < 0.01$) and decrease in fasting insulin ($p = 0.03$), fasting glucose ($p = 0.04$) and HOMA-IR ($p < 0.04$).

Table 2 shows the COH + IUI protocols and clinical pregnancy rates of group 1 and 2. In group 1, during the 12 weeks MYO treatment, nine patients conceived spontaneous singleton pregnancy. During COH + IUI treatment three cycles were canceled in group 1 and 8 cycles in group 2. In group 1, 2 patients were canceled due to no response to exogenous rFSH and 1 patient was canceled due to the risk of ovarian hyperstimulation syndrome (OHSS). In group 2, 5 patients were canceled due to no response to exogenous rFSH and three patients were canceled due to the risk of OHSS. Therefore, the data for groups were calculated for 86 and 90 patients, respectively. Total rFSH dose and cycle duration were significantly lower and clinical pregnancy rates were higher in group 1. In group 1, from 16 pregnant patients, two patients conceived twin pregnancy. In group 2, from 11 pregnant patients, one patient conceived twin pregnancy.

When we analyze patients according to insulin resistance, 47 patients (%47.9) in group 1 and 45 patients (%45.9) in group 2 had IR which is shown in Table 3. Group 1 patients with IR had significantly lower total dose of rFSH and the duration of the ovulation induction was significantly shorter. In addition, the clinical pregnancy rates were statistically higher in group 1 compared to group 2 (Table 3). MYO treatment also significantly decreased the cycle cancelation in patients with IR (Table 3).

Discussion

PCOS is the main cause of anovulatory infertility in patients of reproductive age. The pathogenesis of PCOS mainly focuses on the hyperinsulinemia and hyperandrogenism. Many studies demonstrated a positive effect of insulin-sensitizing agents in the treatment of PCOS. Recently, attention has been given to inositolphosphoglycan and second messengers of insulin signaling. MYO usage increases the action of insulin and as a result improves ovulatory function and decrease serum androgen concentrations. Because of IR and hyperandrogenism are related to anovulation mechanism in PCOS, insulin sensitizers, such as inositol may improve ovarian response to gonadotrophins.

In this study, the effect of MYO treatment on IUI results was evaluated in PCOS women. Our study findings show that MYO administration increases ovulation. To show the relationship between MYO and ovulation, we observed serum progesterone levels. In group 1, after 12 weeks of MYO, there was a significant increase in serum progesterone levels in 21st d of menstrual cycle. Many studies have demonstrated that the rates of ovulation and regularization of menstrual cycles were developed after MYO treatment [13–15]. Raffone showed %65 improvement in ovulation activity and increased serum progesterone levels in luteal phase [13] and this ratio was determined %82 in Gerli's study [14]. In our study after MYO usage, 72 patients became ovulatory (%73.4).

In line with literature [16–19], our research demonstrated significant changes in serum HOMA-IR, fasting glucose and fasting insulin levels. Genazzani et al. [18] presented that MYO administration is effective in lowering insulin levels and improves the hormonal disturbances which results in regulation of menstrual cycles and ovulatory functions [18]. As a consequence, MYO could be an alternative insulin sensitizer agent in PCOS women who complains from infertility.

It is shown that MYO ameliorate ovarian function and the usage of MYO before ovulation induction increases the success of treatment [10,20,21]. Likewise this study, Papaleo [22] showed

Table 2. Comparison of COH + IUI protocols and clinical pregnancy rates.

Parameter	Group 1 ($n = 86$)†	Group 2 ($n = 90$)‡	*p
Administered total rFSH dose (IU)	689.23 ± 73.54	776.56 ± 87.12	0.02
Duration of the administration of rFSH (days)	8.59 ± 2.3	12.1 ± 1.8	0.03
Trigger day endometrial thickness (mm)	10.3 ± 1.2	9.8 ± 2.3	0.13
>17 mm follicle number (n)	2.1 ± 0.7	2.0 ± 0.7	0.09
Clinical pregnancy rate, n (%)	16 (%18.6)[a]	11 (%12.2)[b]	0.02
Abortion rate, n (%)	2 (%12.5)	2 (%18.2)	0.07
Canceled cycle number, n (%)	3 (%3.37)	8 (%8.16)	0.06

†9 patients who conceived pregnancy spontaneously were excluded. Also three cycles were canceled.
‡8 cycles were canceled.
*$p < 0.05$ is statistically significant.
[a]patients had twin pregnancies.
[b]patient had twin pregnancy.
Independent samples t test.

Table 3. Comparison of COH + IUI protocols and clinical pregnancy rates for insulin resistant patients.

Parameter	Group 1 IR+ ($n = 47$, %47.9)	Group 2 IR+ ($n = 45$, %45.9)	*p
Administered total rFSH dose (IU)	656.22 ± 86.11	773.14 ± 67.19	0.02
Duration of the administration of rFSH (days)	8.43 ± 2.4	12.9 ± 2.1	0.02
Trigger day endometrial thickness (mm)	11.2 ± 0.9	10.3 ± 1.8	0.09
>17 mm follicle number (n)	2.2 ± 0.8	2.1 ± 1.1	0.12
Clinical pregnancy rate, n (%)	7 (%43.7)	4 (%36.4)	0.04
Canceled cycle number, n (%)	2 (%4.26)	5 (%11.1)	0.04

*$p < 0.05$ is statistically significant.
Independent samples t test.
Abbreviations: IR: insulin resistance

significant decrease in total rFSH dose and duration of ovulation induction. Our data suggests that, PCOS patients undergoing ovulation induction benefit from MYO. This effect may arise from its insulin lowering activity and intracellular role in oocyte maturation.

Calcium is shown to play a pivotal role in the oocyte maturation. Calcium has a role in the regulation of diverse cellular functions and previous studies showed that calcium signals may trigger meiotic resumption in mammalian oocytes. MYO effects the calcium signaling pathways and increase the oocyte maturation [23,24].

Although there are many investigations about outcomes of MYO usage on pregnancy rates with assisted reproductive techniques, such as IVF, there is no study focusing on the effect of MYO on patients undergoing IUI. This prospective controlled study is the first and largest one for IUI in the literature. Our study demonstrated that the patients using MYO before IUI have a higher clinical pregnancy rate compared to patients who directly encounter IUI (group 1 pregnancy rate %18.6, group 2 pregnancy rate %12.2; $p = 0.02$). Ciotta et al. [21] observed the effect of MYO on pregnancy outcomes of PCOS patients who undergone ovulation induction [21]. In terms of clinical pregnancy rates they found no significant change with MYO usage [21]. Although their research showed no significant change in pregnancy rates, number of mature oocytes retrieved were significantly higher [21] .Raffone et al. [13] compared the effect of MYO and metformin on ovulation and spontaneous pregnancies. Their data showed that MYO and metformin can be used for first line therapies for restoring spontaneous ovulation and menstrual cycles and to increase the rate of pregnancy [13]. Regidor evaluated 3602 patients with PCOS after at least 2–3 months MYO treatment and demonstrated %15.1 spontaneous pregnancy rate [15]. It was %9.18 in our study. These findings support that the efficacy of MYO in reduction of insulin resistance, may develop ovulatory functions and fertility.

In our study, we divided the patients to subgroups according to IR. In terms of clinical pregnancy rates, total rFSH dose and duration of stimulation, insulin resistant PCOS patients' results were similar with patients who did not have insulin resistance. In contradistinction to all PCOS patients, insulin resistant PCOS patients' cycle cancelation rate was significantly lower under MYO treatment. Like this study, Morgante [10] and Papaleo [22] found less cancelation rate in patients who were given MYO. In the light of these findings, we can speculate that MYO treatment is more effective in lowering the cycle cancelation rate of ovulation induction in IR + PCOS patients.

Conclusions

This study shows that MYO should be considered in the treatment of infertile PCOS patients. Considering previous studies in the literature, MYO lowers insulin and androgen levels, which results in the regulation of menstrual cycles and ovulatory functions. Also MYO affects calcium-signaling pathways and improves oocyte maturation. This study is the first one reporting the effect of MYO on IUI results. MYO administration increases clinical pregnancy rates, lowers total rFSH dose and the duration of the ovulation induction. In addition, especially in insulin resistant infertile PCOS patients, the cycle cancelation rate reduces after MYO usage. In summary, adding MYO supplementation during ovulation induction and IUI seems rational to produce good clinical outcomes.

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Declaration of interest

No financial relationship with the any organization. Authors have full control of all primary data. Written informed consent was obtained from the patients for publication. Copies of the written consents are available for review by the Editor-in-Chief of this journal on request. The authors report no conflicts of interest.

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