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ORIGINAL ARTICLE

Ovulation induction with myo-inositol alone and in combination with clomiphene citrate in polycystic ovarian syndrome patients with insulin resistance

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Abstract

Background: Insulin resistance plays a key role in the pathogenesis of polycystic ovarian syndrome (PCOS). One of the methods for correcting insulin resistance is using myo-inositol.
Aim: The aim of the present study is to evaluate the effectiveness of myo-inositol alone or in combination with clomiphene citrate for (1) induction of ovulation and (2) pregnancy rate in anovulatory women with PCOS and proven insulin resistance.
Patients and methods: This study included 50 anovulatory PCOS patients with insulin resistance. All of them received myo-inositolduring three spontaneous cycles. If patients remained anovulatory and/or no pregnancy was achieved, combination of myo-inositol and clomiphene citrate was used in the next three cycles. Ovulation and pregnancy rate, changes in body mass index (BMI) and homeostatic model assessment (HOMA) index and the rate of adverse events were assessed.
Results: After myo-inositol treatment, ovulation was present in 29 women (61.7%) and 18 (38.3%) were resistant. Of the ovulatory women, 11 became pregnant (37.9%). Of the 18 myo-inositol resistant patients after clomiphene treatment, 13 (72.2%) ovulated. Of the 13 ovulatory women, 6 (42.6%) became pregnant. During follow-up, a reduction of body mass index and HOMA index was also observed.
Conclusion: Myo-inositol treatment ameliorates insulin resistance and body weight, and improves ovarian activity in PCOS patients.

Keywords

Anovulation, clomiphene citrate, insulin resistance, myo-inositol, PCOS

History

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Introduction

Polycystic ovarian syndrome (PCOS) is a prevalent disorder that affects approximately 6–10% of women of reproductive age [1,2] and is a major cause of menstrual disturbances, hirsutism and female anovulatory infertility. Current evidence suggests that insulin resistance and compensatory hyperinsulinemia are central features of PCOS [3]. Hyperinsulinemia plays an important pathogenic role in the hyperandrogenism and anovulation of both obese and lean women with PCOS [4,5]. According to some studies, PCOS patients have an increased risk for diabetes mellitus [3,6] and often show an adverse cardiovascular risk profile – increased rate of arterial hypertension [7,8], dislipidemia [9–12] and subclinical inflammation and atherosclerosis [13–15] – that also can be linked to insulin resistance.

Two different inositol phosphoglycans (IPGs) containing myo-inositol (MI) or D-chiro-inositol (DCI) are known to have a role in activation of several enzymes, involved in glucose metabolism. Indeed, both IPGs act as second messenger of the insulin signaling. In particular, it has been demonstrated that MI-PG is responsible for the glucose uptake while DCI-PG is responsible for the glycogen synthesis [16]. The differences highlighted in the molecule functions reflect the tissue function. Indeed, the ratio between the two stereoisomeres (i.e. MI and DCI) range from 70:30 in glycogen storage tissue (i.e. liver, muscle and fat) to 99:1 in glucose-utilizing tissue such as brain and heart [16].

Some studies demonstrate the defects in tissue availability or altered metabolism of IPGs in PCOS patients [17,18]. It is likely that they are involved in the insulin resistance and metabolic abnormalities in these women [18].

The aim of the present study is to evaluate the effectiveness of myo-inositol alone or in combination with clomiphene citrate for (1) induction of ovulation and (2) pregnancy rate in anovulatory women with PCOS and proven insulin resistance.

Patients and methods

The present study is an open and prospective study, including 50 anovulatory PCOS patients with diagnosed insulin resistance. Three women left the study at early stage because of reasons not related to the drug – moved to another city and/or country. The duration of this study was up to six spontaneous or progestin induced cycles. Patients were included in the study after spontaneous or dydrogesterone (Duphaston, Solvay Pharma, Abbott, Brussels, Belgium) 10 days 2×10 mg induced menstrual cycle.

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The routine biochemical tests described later were performed on the 3–5 days from the bleeding. After that all the patients were given myo-inositol (Inofolic, Lo.Li. Pharma, Italy, Roma, Italy), containing 2 g myo-inositol and 0.2 mg folic acid in dose of two sachets per day before meals for ovulation induction. Ovulation was assessed using ultrasound examination on days 12, 14 and 20 of the cycle.

In patients who had ovulation during follow-up, myo-inositol was given for six cycles. If pregnancy was present, all the anthropometric and biochemical tests were performed, the participation in the study was ended and the woman was directed to routine pregnancy follow-up. If no pregnancy was detected for three cycles on the fifth day of the next menstrual cycle clomiphene citrate (Clostilbegyt, EGIS Pharmaceuticals Ltd., Hungary), 50 mg daily for five days was added to myo-inositol. If no pregnancy occurred, the dose was elevated with 50 mg every following progestin-induced cycle until 150 mg daily and after that the follow-up was ceased.

In patients who were anovulatory and/or did not achieve pregnancy during the first three months of the follow-up, menstrual bleeding was induced using dydrogesterone and clomiphene was added to myo-inositol according to the above-mentioned scheme for three more cycles.

Inclusion criteria

- Age 20–35 years.
- PCOS according to Rotterdam ESHRE–ASRM Sponsored PCOS consensus workshop group. Hum Reprod, 2004.
- Anovulation and infertility $\geq$1 year.
- Willing to conceive (informed consent for the study).
- Insulin resistance, diagnosed using homeostatic model assessment (HOMA-IR) – Venous plasma glucose (mmol/l) * plasma insulin (mcU/ml)/22.5. Insulin resistance proven if HOMA $\geq$2.5.

Exclusion criteria

- Other conditions associated with hyperandrogenism and anovulation (adrenal, pituitary, ovarian, etc.).
- Other causes for the infertility (male factor, tubal factor etc.).
- Intake of hormonal or other drugs that can potentially influence the ovulation, IR and body weight.

This study has been approved by the local ethics committee.

At baseline, after the third and the sixth cycle or at cessation of follow-up because of pregnancy, the following measurements were performed: height (only at baseline), weight and standard oral glucose tolerance test (OGTT) using 75 g glucose with measurement of immunoreactive insulin (IRI) (electrochemiluminiscence method (ECLIA, Elecsys 2010, measuring range – 0.2–1000 mcU/ml) and plasma glucose (glucoso-oxidase peroxydase method (GOD-PAP); Roche Cobas Mira) at 0, 60 and 120 min. The presence of dominant follicle, ovulation and adverse events were assessed every month. The measurements are described in Table 1.

Table 1. Measurements during follow-up.

Indicator	Period of registration (cycles)
Induction of ovulation	1-2-3-4-5-6
Pregnancy	1-2-3-4-5-6
BMI	1-3-6
HOMA	1-3-6
Adverse events	1-2-3-4-5-6

Statistics

Interpretation was made only for the results of women who finished the study and/or reached the endpoint ''pregnancy''. Data were processed using the statistical package SPSS 16.0 (Chicago, IL). The following statistical methods were applied: descriptive analysis, variation analysis, Kolmogorov–Smirnov's one sample non-parametric test, Student's *t*-test for two independent samples, Mann–Whitney's non-parametric test for two independent samples and Wilcoxon signed rank test. Data are presented as mean $\pm$ SD and *N* (%).

Because of the new pregnancies, there were an increasing number of women who dropped out from the follow-up and the number of the participants decreased gradually. If pregnancy was established during the first three cycles of myo-inositol monotherapy, the woman was included for statistical workup (paired *t*-test) after the third cycle. All the patients who became pregnant during combined treatment myo-inositol + clomiphene citrate were analyzed (unpaired *t*-test) at the end of the observation.

Results

The characteristics of the study participants are shown in Table 2. After myo-inositol treatment, ovulation occurred in 29 women (61.7%) while 18 (38.3%) resulted anovulatory. Of the ovulatory women, 11 became pregnant (37.9% of the ovulatory and 23.4% of all the patients) and 18 (62.1% and 38.3%, respectively) were not pregnant. In non-pregnant women clomiphene citrate was started, and six patients (33.3% from the non-pregnant or 12.8% from all women) became pregnant and 12 (66.7% or 25.5%) did not.

Of the 18 myo-inositol-resistant patients, after clomiphene treatment 13 (72.2% or 27.7%) ovulated and five (27.8% or 10.6%) did not achieve ovulation. Six out of the 13 ovulatory women (42.6% or 12.8%) became pregnant and seven (53.8% or 14.9%) did not. The total number of pregnancies achieved in the study was 23 (48.9%). The distribution of the women is shown in Figure 1.

Table 3 shows the distribution according to body mass index (BMI) of the patients that ovulated with myo-inositol treatment, became pregnant with myo-inositol tretatment, did not become pregnant with myo-inositol tretatment or were resistant to myo-inositol. Ovulating patients had lower baseline BMI than non-ovulating. Most of the women who ovulated or became pregnant with myo-inositol were normal weight or overweight, while most of the patients resistant to myo-inositol were obese. From the normal weight women, 73% became ovulating and 40% became pregnant. From the overweight women, 83% and 25% became pregnant and from the obese women 40% and 10%. From the non-obese women (normal + overweight), 78% became ovulating and 33% became pregnant. Analyzing these ratios it appears that compared to a normal weight woman, the obese one has nearly the half probability to ovulate and a quarter the chance to became pregnant with this protocol. Compared to non-obese women, the obese have half and one-third of the chance to become ovulating and pregnant, respectively.

Table 2. Baseline characteristics of the group ($n = 47$).

Age (years)	28 $\pm$ 4
Height (cm)	164.2 $\pm$ 5.6
Weight (kg)	80.0 $\pm$ 19.5
BMI (kg/m^2)	29.1 $\pm$ 7.9
HOMA	3.6 (2.7–5.2)

Data presented as mean $\pm$ SD and for HOMA as median (25–75 percentiles).

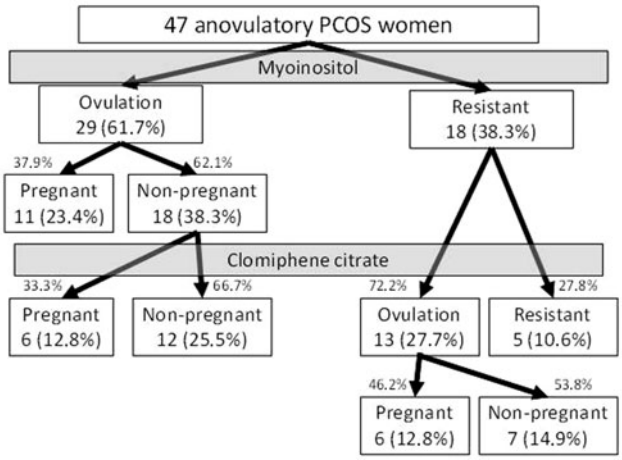

Figure 1. Study design. The numbers given in the rectangles represent *N* (%) from the total number of women. The numbers out of the rectangles represent the *N* (%) distribution in the previous group of patients.

Table 3. Distribution of women according to the BMI.

	Normal	Overweight	Obese
All 47 women	15 (32%)	12 (26%)	20 (44%)
Ovulating with MYO	11	10	8
Pregnant with MYO	6	3	2
Non-pregnant with MYO	9	9	8
Resistant	1	0	4

During follow-up, BMI was reduced from $29.7 \pm 7.3\,kg/m^2$ at baseline to $29.1 \pm 7.1\,kg/m^2$ ($p < 0.001$) after the third cycle in the whole group of patients; from 30.6 ± 7.6 at baseline to 30.2 ± 7.2 at third cycle; and $29.9 \pm 6.9\,kg/m^2$ ($p < 0.001$) at sixth cycle in the patients who did not become pregnant during the first three cycles (Figure 2).

During the treatment period, a reduction of HOMA index was also observed – from median 3.6 (2.7–5.2) at baseline to 2.8 (2.1–3.6) ($p < 0.001$) after the third cycle in the whole group of patients and from 3.4 (2.8–5.3) at baseline to 2.9 (2.5–3.9) ($p < 0.001$) at third cycle and 2.8 (2.2–3.5) (NS, but $p < 0.001$ compared to baseline) at sixth cycle in the patients who did not become pregnant during the first three cycles (Figure 2).

Table 4 shows the differences in ovulating and myo-inositol non-responding women. Generally, myo-inositol resistant women were of the same age as ovulating patients but were more obese with higher HOMA index on the third cycle during the treatment.

On the other hand, patients who became pregnant during myo-inositol monotherpay ($n = 11$) had lower BMI at baseline (26.8 ± 5.8 versus $30.6 \pm 7.6\,kg/m^2$, NS) and at third cycle (25.4 ± 5.7 versus $30.2 \pm 7.2\,kg/m^2$, $p < 0.01$) and lower HOMA index at baseline (4.0 ± 1.7 versus 4.5 ± 2.6, NS) and at third cycle (2.3 ± 0.8 versus 3.6 ± 2.1, $p < 0.05$) than those who did not achieve pregnancy.

Safety assessment of myo-inositol administration showed that only two women (4.3%) had adverse events (gastro-intestinal complaints) that did not lead to treatment discontinuation.

Discussion

Polycystic ovarian syndrome is one of the most common endocrinopathies in women of reproductive age. The established link between PCOS and insulin resistance makes place for insulin sensitizing agents as most successful therapeutic strategies. Many studies [30,31] demonstrate a beneficial effect of metformin and thiazolidindiones on the metabolic and reproductive disturbances of these patients. Recently, DCI was found to be involved in postreceptor insulin signaling [32,33]. Now we have some data that MI treatment in PCOS patients has a positive effect on ovulatory function, oocyte quality, hyperinsulinemia, metabolic parameters and hyperandrogenism, and it become a novel method to improve spontaneous ovulation [34] or ovulation induction [20,21,35].

It has been shown that follicles containing good quality oocytes have higher concentration of myo-inositol in follicular fluid [19]. Some studies have demonstrated that myo-inositol treatment in patients with PCOS improved ovarian function and fertility [20–22], decreased the severity of acne and hirsutism [23], reduced BMI [24], improved insulin sensitivity, reduced serum testosterone levels, plasma tryglicerides, systolic and diastolic blood pressure [25] and increased high-density lipoprotein (HDL)-cholesterol [26]. However, some of these effects were not observed in morbidly obese patients ($BMI > 37\,kg/m^2$) and inverse relationship between BMI and treatment efficacy was described [26], while others demonstrate that myo-inositol administration is more effective in obese patients with high fasting insulin plasma levels [27]. Combined treatment with myo-inositol and combined contraceptive pill turned out to be more effective in controlling endocrine, metabolic and clinical profile in patients with PCOS than oral contraceptive alone [28]. Myo-inositol also showed a possible role for primary prevention of gestational diabetes in PCOS patients [29].

The present study analyzes the effect of a combined therapy with myo-inositol + clomiphene in anovulatory PCOS patients. It provides a useful information that in non-ovulating or non-pregnant patients after myo-inositol treatment an association with clomiphene citrate could be useful to achieve the goal of ovulation/pregnancy. This study supports the hypothesis that MI is effective not only for ovulation induction but also on metabolic disturbances in PCOS patients and it has good safety profile. One of the main characteristics of this study is that it included only women with proven insulin resistance that, in general, are a difficult therapeutic target in long-term aspect. Our results – restoration of ovulation in 29 women (61.7%) and pregnancy in 11 (23.4%) after myo-inositol treatment are lower, but still fit with those shown by Papaleo et al. [20] who demonstrate ovulation in 72% and pregnancy in 40%. Raffone et al. [22], in a comparative study for ovulation induction between myo-inositol and metformin, showed that myo-inositol induced ovulation in 65% and resulted in pregnancy in 30% of the patients.

In our study population a moderate but statistically significant decrease in BMI was demonstrated after six months of treatment ($p < 0.001$), as previously reported [27]. It should be noted that in most studies that are focused on myo-inositol treatment in PCOS patients, no significant BMI reduction was observed when hyperinsulinemic response to glucose load was not a selection criterion. Indeed, Genazzani et al. [34] showed a non-significant change of BMI – from 29 ± 1.6 to 28.3 ± 1.3 after three months of myo-inositol monotherapy and Minozzi et al. [28] also failed to demonstrate a significant difference in BMI – from 26.7 ± 2.7 to 27 ± 2.4 after 12 months of treatment with a combination of myo-inositol and combined oral contraceptive. On such basis, our data clearly support the relevance of testing insulin sensitivity using a glucose load. Indeed, the presence of hyperinsulinemic response to OGTT seems to be relevant for the response to the integrative treatment with myo-inositol. Because of the open design of our study, we cannot exclude the possibility that weight reduction could be a result of the lifestyle change routinely advised in overweight and obese patients. A more pronounced decrease of IR

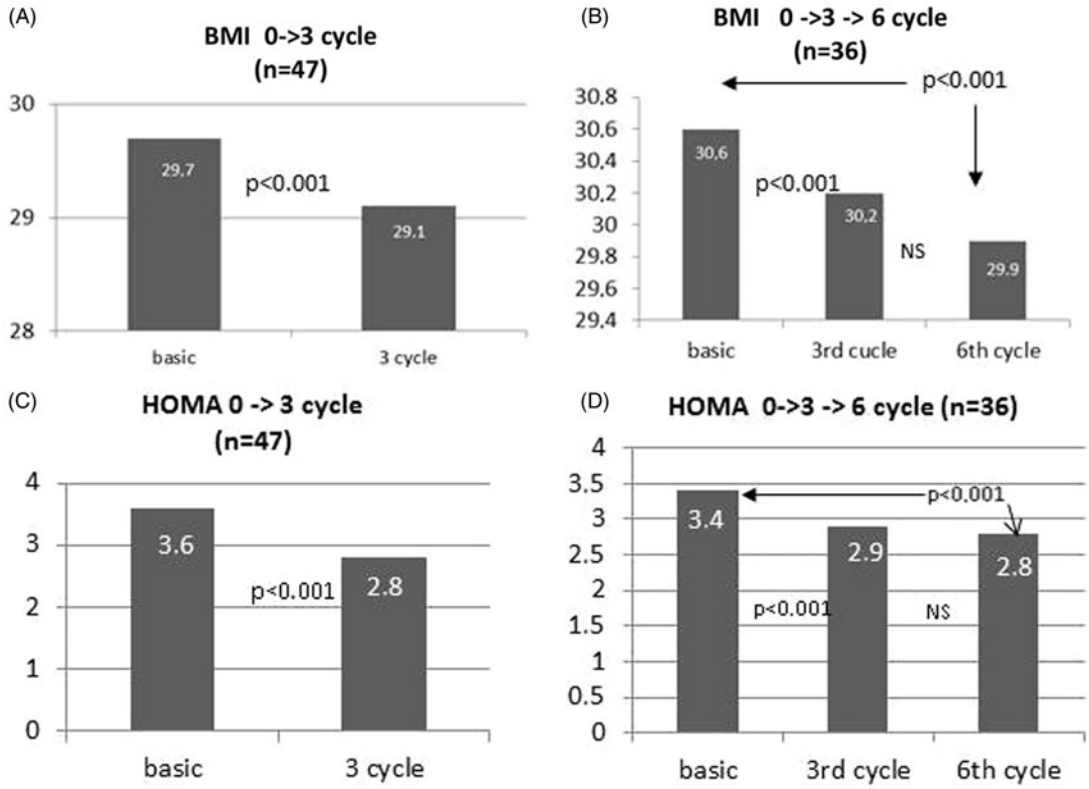

Figure 2. A and B. BMI change during treatment with myo-inositol alone or combination of myo-inositol and clomiphene. C and D. Median HOMA index change during treatment with (A) myo-inositol alone in the whole group of women comparing baseline to the third cycle ($n = 47$) and (B) with the combination of myo-inositol + clomiphene in the non-pregnant women after the monotherapy comparing baseline to third and sixth cycle ($n = 36$).

Table 4. Differences between ovulating and non-ovulating women.

	Non-ovulating n=18	Ovulating n=29	p Between ovulating and non-ovulating women
Age	28.2 ± 4.2	27.9 ± 4.0	NS
Height	163.9 ± 7.3	164.4 ± 4.5	NS
HOMA 0	4.0(2.8–7.0)	3.2(2.7–4.8)	NS
HOMA 3	3.5(2.7–5.2)*	2.7(2.0–3.0)**	<0.05
BMI 0	33.2 ± 9.08	27.5 ± 5.09	<0.05
BMI 3	32.6 ± 8.51	26.8 ± 5.03*	<0.05

Data are presented as mean ± SD, except for HOMA as median (25–75). *$p < 0.05$; **$p < 0.001$ baseline versus three months.

and weight loss are prognostic markers for higher conception probability.

The reduction of HOMA index after three and after six months is in line with that demonstrated by other beneficial effects of myo-inositol on insulin resistance. Zacche et al. [23] showed a reduction of HOMA index from 2.9 ± 0.8 to 1.4 ± 0.5 ($p < 0.01$) in PCOS patients after three months of myo-inositol treatments and Genazzani et al. [34] demonstrated the same effect in overweight PCOS women – HOMA reduction from 2.8 ± 0.6 to 1.4 ± 0.3 ($p < 0.01$), while Minozzi et al. [28] showed a reduction from 2.9 ± 0.9 to 1.8 ± 1.0 ($p < 0.05$) after 12 months treatment with a combination of myo-inositol and combined oral contraceptive. All these data as well as our reports support a broader spectrum and effectiveness of other mechanisms, different from the insulin sensitizing effect of myo-inositol in induction of ovulation.

In line with this, recent data from Artini et al. [36] demonstrated the relevant effect of Myo-inositol administration in improving and making better not only the ovulation induction but also the quality of oocytes. In fact, myo-inositol administration reduces the amount of gonadotropins used for the ovulation induction and doubled the ''optimal'' oocytes, improving the delivery rate.

In addition, our data further support the evidence by Nordio et al., showing that a therapy based on MI is indeed effective in overweight women, although the lead-time in order to obtain significant clinical results is higher compared to a treatment based on both stereoisomers, MI and DCI, in the physiological plasma ratio of 40:1 [37].

Conclusions

(1) Myo-inositol therapy is an effective and well-tolerated option for ovulation induction and pregnancy in women with PCOS with insulin resistance.
(2) The ovulation induction and pregnancy results from the treatment are poorer in women with higher degree of IR.
(3) More pronounced decrease of IR and weight loss are prognostic markers for higher conception probability.
(4) The combination with clomiphene citrate additionally increases the ovulation and pregnancy rate.

Declaration of interest

None of the authors have conflict of interest except for Gianfranco Carlomagno who is a Lo. Li. Pharma employee.

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