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POLYCYSTIC OVARY SYNDROME

Endocrine and clinical effects of myo-inositol administration in polycystic ovary syndrome. A randomized study*

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Abstract

Objective: To evaluate the effects the administration of myo-inositol (MYO) on hormonal parameters in a group of polycystic ovary syndrome (PCOS) patients.
Design: Controlled clinical study.
Setting: PCOS patients in a clinical research environment.
Patients: 50 overweight PCOS patients were enrolled after informed consent.
Interventions: All patients underwent hormonal evaluations and an oral glucose tolerance test (OGTT) before and after 12 weeks of therapy (Group A (n¼10): MYO 2 g plus folic acid 200 mg every day; Group B (n¼10): folic acid 200 mg every day). Ultrasound examinations and Ferriman–Gallwey score were also performed.
Main outcome measures: Plasma LH, FSH, PRL, E2, 17OHP, A, T, glucose, insulin, C peptide concentrations, BMI, HOMA index and glucose-to-insulin ratio.
Results: After 12 weeks of MYO administration plasma LH, PRL, T, insulin levels and LH/FSH resulted significantly reduced. Insulin sensitivity, expressed as glucose-to-insulin ratio and HOMA index resulted significantly improved after 12 weeks of treatment. Menstrual cyclicity was restored in all amenorrheic and oligomenorrheic subjects. No changes occurred in the patients treated with folic acid.
Conclusions: MYO administration improves reproductive axis functioning in PCOS patients reducing the hyperinsulinemic state that affects LH secretion.

Keywords

Hyperinsulinemia, inositolphosphoglycan, myo-inositol, policystic ovary syndrome

History

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Introduction

Polycystic ovary syndrome (PCOS) is a common disorder of chronically abnormal ovarian function and hyperandrogenism, affecting 5–10% of female population in reproductive age. Typically PCOS is characterized by hyperandrogenism (extremely variable in its occurrence), chronic anovulation, polycystic ovaries at ultrasound evaluation and dermatological problems such as acne, hirsutism and seborrhoea [1]. PCOS is indeed the most common cause of female infertility [2].

In the last years, a great body of evidence has demonstrated the important role of altered insulin sensitivity in many, though not all, PCOS patients [3]. In addition to the abnormal hormonal parameters, patients affected by PCOS have been demonstrated to present insulin resistance, in the absence of diabetes [4], probably due to (especially in lean/normal-weight PCOS subjects) a genetic/familiar predisposition [5]. Many investigators have focused both on impaired glucose tolerance, which affects 30–40% of patients with PCOS [6], and on insulin resistance, which is present in a significant proportion of women with PCOS. Hyperinsulinaemia, a consequence of insulin resistance, may alter the FSH (Follicle-stimulating hormone)-to-LH (Luteinizing hormone) shift, preventing the selection of a dominant follicle. Moreover, insulin seems to increase granulose cells sensitivity to LH and increase the production of androgens from the ovary by stimulating cytochrome P450c17α. Some studies suggest that ovarian theca cells in PCOS-affected women are more capable to convert androgenic precursors to testosterone than in normal women [7]. Finally, and most importantly, hyperinsulinemia impedes ovulation. Several studies suggest that some abnormal action of insulin might be dependent from inositolphosphoglycan (IPG) mediators of insulin action and suggest that a deficiency in a specific D-chiro-inositol (DCI)-containing IPG may underlie insulin resistance, similarly to type 2 diabetes. DCI administration has been demonstrated to reduce insulin resistance both in lean and obese PCOS patients improving ovarian function and decreasing hyperandrogenism [8,9]. Another inositol, myo-inositol (MYO), has been reported to be greatly correlated to ovarian function and oocyte quality in patients undergoing *in vitro* fertilization (IVF) procedures, independently from circulating plasma levels [9,10].

The aim of our study was to evaluate the effects of MYO administration on hormonal and clinical parameters in a group of PCOS patients undergoing IVF.

*Capsule: Myo-inositol administration in PCOS patients modifies reproductive axis function, reducing the hyperinsulinemic state that affects LH secretion. It could also improve oocytes quality and pregnancy rates.

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Materials and methods

Among the 240 patients attending the Department of Reproductive Medicine and Child Development Division of Obstetric and Gynaecology – University of Pisa, Italy, candidates for ART (Assisted Reproduction Technology), fifty PCOS patients have been randomized for this study that was performed for 12 months (April 2008–April 2009). An informed consent has been obtained before entering the study and the study was approved by the local Ethics Committee. These patients were selected according to the following criteria: (a) presence of micropolycystic ovaries at ultrasound, (b) mild to severe hirsutism and/or acne, (c) oligomenorrhea (menstrual cycle>35 days) or amenorrhea, (d) absence of enzymatic adrenal deficiency and/or other endocrine disease, (e) normal PRL (Prolactin) levels (range 5–25 ng/ml), (f) no hormonal treatment for at least six months before the study. Instead the others 190 patients were excluded because they do not met the inclusion criteria. (Figure 1)

On the therapeutic program day, these 50 women were randomized into two groups (treatment and control group) according to a computer-generated randomization list prepared by one of the authors (PG.A.). Sealed and numbered envelopes, containing the allocation information, were given to ART center nurse coordinator, who assigned patients to study arms following the recruitment by the physician on the morning of therapeutic program. Twenty-five of the fifty patients were randomly assigned to the Group A or Study Group and treated with MYO 2 g+ folic acid 200 µg daily (INOFERT; Italfarmaco, Milano, Italy) dissolved in a glass of water and assumed in the morning, plus folic acid 200 µg daily, for 12 weeks. The other twenty-five patients (Group B) received only folic acid 400 µg daily for 12 weeks and were considered as the Control Group. Even if also Group B received a treatment, it was considered as ''Control'' because it is ethically correct to administer folic acid in women trying to get a pregnancy. No changes of life style or diet was required. Treatment was started the first day of spontaneous menstrual cycle or, in women with amenorrhea, after excluding pregnancy by a proper test. Clinical measurement included: LH, FSH, PRL, estradiol (17β-E2), androstenedione (A), 17-hydroxy-progesterone (17OHP) and insulin. Oral glucose tolerance test (OGTT) was performed at the baseline and 30, 60, 90, 120 and 240 minutes after the oral assumption of 75 g of glucose. All the parameters were performed at the baseline and after 12 weeks of treatment. During this period the therapy was not interrupted. After twelve weeks of treatment, an IVF cycle was performed for each patient. All patients underwent a pituitary desensitization with SC administration of 0.2 ml die of a GnRH agonist (Enantone Die; TAKEDA Italia Farmaceutici Spa, Roma, Italy) from mid-luteal phase until the day of the start and then this GnRH agonist was reduce to the value of 0.1 ml/die until the intramuscular (IM) administration of 6500 IU hCG (Ovitrelle; Merck-Serono, Geneva, Switzerland). Controlled ovarian hyper-stimulation was performed in all patients by administration of recombinant FSH (Gonal-F; Merck-Serono, Geneva, Switzerland)

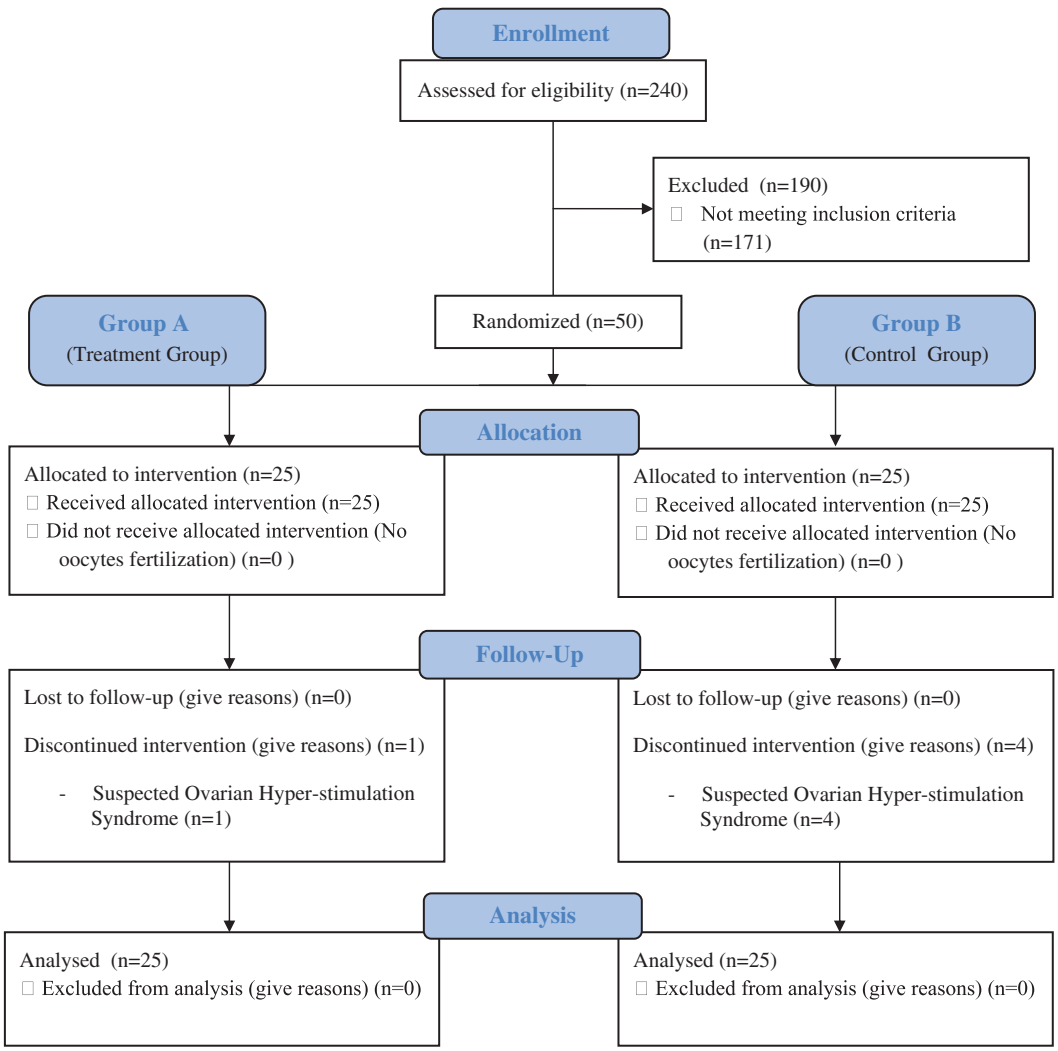

Figure 1. CONSORT Flowchart of the study.

with a starting dose of 150 IU/die. Patients were monitored by measuring 17β-E2 and Progesterone plasma concentration and the size of follicles on day 5-7-9 and 10 of the stimulation. The gonadotropin dose was adjusted according to the individual response. Intramuscular hCG was injected when serum 17β-E2 concentration exceeded 200 pg per follicle and at least three follicles with a minimum diameter of 18 mm were identified. 36 hours after hCG injection, all patients have been submitted to the oocyte pick-up, with transvaginal guidance. For all patients enrolled in our study, according to Italian IVF law (in force from March 2004 to May 2009), a maximum of three oocyte per patient were inseminated. Oocyte and sperm preparation for conventional IVF (fertilization in vitro embryo-transfer)/ICSI (intracytoplasmic sperm injection) procedure have been thoroughly described by Artini et al., and Papaleo et al., respectively [11,12]. Laboratory determinations of insulin, glucose and DCI-IPG insulin mediator bioactivity assay have been performed according to previously described [13].

Only one embryologist evaluated oocytes and embryos quality, and chose the technique used for each patient. Intramuscular progesterone in- oil administration, 341 mg every three days, and intravaginal progesterone gel administration, 90 mg daily, was started on the day of embryo transfer, and treatment was continued until either a serum pregnancy test was negative or an embryonic heart beat was sonographically confirmed.

Statistical analysis

We tested data for significant differences between groups, after analysis of variance (one-way ANOVA), using Student's *t*-test for paired (within the same group) and unpaired data (between the two groups), as appropriate. The area under the curve of OGTT (AUC, subtracted from the baseline value) was computed using the trapezoid formula so that to evaluate the insulin response to oral glucose load. Insulin sensitivity was computed as glucose-to insulin ratio since this ratio has been shown to be a good index of insulin sensitivity in women with PCOS [14,15]. HOMA index, computed as [basal glucose]6[basal insulin]/22.5, was also evaluated since it indicates the insulin resistance [16].

A p value <0.05 was considered statistically significant.

Results

All the 50 studied patients among the two Groups underwent ovarian stimulation. 45 patients arrived until the day of oocytes pick-up; five patients were cancelled because of a suspected Ovarian Hyper-Stimulation Syndrome: 1 patient belonged to the Group A and 4 women to the Group B. (Figure 1)

We observed the presence of eventual modifications in both metabolism/hormones and reproduction in the two Groups. (Group A: INOFERT plus folic acid 200 mg daily; Group B: only folic acid at the daily dosage of 400 mg).

As shown in Table 1, both groups were comparable for age (34.9 ± 2.1 versus 36.2 ± 2.3), infertility duration (40 ± 18 versus 42 ± 10.1) and BMI (26.5 ± 6.1 versus 26.3 ± 7).

Significant changes were observed in the Study Group since several hormonal parameters modified during the treatment. Indeed LH, PRL, A and insulin concentration significantly decreased, as well as LH/FSH ratio, insulin sensitivity glucose/insulin ratio and the HOMA index. Insulin response was significantly reduced in the mio-inosytol treated group as well as the AUC of insulin with respect to baseline conditions. Contrary no changes were observed in the Control Group. (Table 2; Figures 2 and 3).

After 12 weeks of treatment significant changes were observed between Group A and B when data were compared after the treatment.

Table 1. Caracteristics and outcome of patients.

Variable	Group A ($n=25$)	Group B ($n=25$)	p Value
Age (years)	34.9 ± 2.1	36.2 ± 2.3	NS
Duration of infertility (months)	40 ± 18	42 ± 10.1	NS
Body mass index (kg/m^2)	26.5 ± 6.1	26.3 ± 6.8	NS
Duration of stimulation (days)	11.5 ± 0.8	12.6 ± 1.1	0.002
No. of 75-UI ampules or vials of FSH	27 ± 6.5	31.8 ± 9	0.002
17β-E2 level on day of hCG administration (pg/ml)	1839 ± 520	2315 ± 601	0.005
N° of cancelled cycles	1	4	0.005
N° of follicles <12 mm	1.2 ± 2	4.6 ± 3.6	0.002
N° follicles ≥12 < 16 mm	3.5 ± 2.9	7.2 ± 3.6	0.003
N° follicles ≥16 mm	7.4 ± 3.2	5.3 ± 3.5	0.05

NS: no statistically significant.
Data are reported as means ± SD.

First of all, in the MYO treated group, the duration of stimulation was lower then in control group (11.5 ± 0.8 versus 12.6 ± 1.1; $p = 0.002$) and also r-FSH units used were fewer in the MYO treated group. Moreover in the Group A there was only one, while four cancelled cycles were in the Group B. In both groups, the cause of the cancellation was a high risk of ovarian hyperstimulation syndrome (OHSS) development.

17β-E2 levels (1839 ± 520 versus 2315 ± 601; $p < 0.002$), evaluated the day of hCG administration, were lower in the MYO-treated group. Analyzing the follicular pattern at the oocyte pick-up (PU) day, it's important to notice that small dimension follicles (diameter <12 mm) in the study group are considerably fewer than in the control group (1.2 ± 2 versus 4.6 ± 3.6; $p = 0.002$), and also that intermediate follicles amount (diameter 12–16 mm) are lower in the Group B than in Group A (3.5 ± 2.9 versus 7.2 ± 3.6; $p = 0.003$). On the other hand, there are more large dimension follicles (>16 mm) in the Group A (7.4 ± 3.2 versus 5.3 ± 3.5; $p = 0.05$). (Table 1)

At the oocyte pick-up surgeons recovered a lower number of oocytes in the MYO-treated group rather than in the control group (6.5 ± 3.1 versus 10.8 ± 8.8; $p = 0.04$). However a higher number of Group A oocytes were of top-quality than the control group (82% versus 65%; $p = 0.05$). In compliance with Italian IVF law, no more than three oocytes per patient were injected. Evaluating each condition, in Group A 9 FIVET and 15 ICSI have been performed, while in the Group B the number of FIVET was similar to the number of ICSI performed (11 versus 10). Among the transferred embryos, top quality ones were fewer in the treated group as compared to the control group (54% versus 64%; NS).

Finally, pregnancy rate (βHCG positive) was considerably higher in the treated group (60% versus 32%; $p < 0.05$). 10 clinical pregnancies developed in Group A (40%) and 4 in Group B (16%), while the delivery rate was 8 versus 3 (32% versys 12%; $p < 0.05$), respectively (Table 3).

Discussion

Recently, the recognition that a metabolic dysfunction, peripheral insulin resistance, might be one of the main trigger point of PCOS, has induced clinicians to use compounds to improve insulin sensitivity such as metformin [17] and troglitazone [18]. Since hyperinsulinemia stimulates ovarian androgens production in PCOS patients [19] attention has been given to IPG mediators as post-receptor mediators or second messenger of insulin signalling [20].

The present study supports the hypothesis that MYO supplementation, similarly to DCI administration, induces the

Table 2. Hormonal pattern of PCOS patients under study.

	Group A ($n=25$)		Group B ($n=25$)	
	Baseline	Under treatment	Baseline	Under treatment
LH mIU/ml	13.5 ± 2.2	8.6 ± 1.6***	14.1 ± 2.1	12.1 ± 3.2***
FSH mIU/ml	5.5 ± 0.5	3 ± 0.3	3.9 ± 0.4	4.4 ± 0.5
PRL ng/ml	16 ± 4	11.2 ± 2.2*	17.1 ± 2.3	15.7 ± 1.9*
E2 pg/ml	84.6 ± 17	89.1 ± 16.4	87.5 ± 14.7	77.4 ± 17
T ng/100ml	52.4 ± 5.6	53.8 ± 6.2	60.3 ± 7.2	54.2 ± 9.1
17OHP ng/ml	1.3 ± 0.2	1.4 ± 0.3	1.3 ± 0.3	1.2 ± 0.4
A ng/100ml	168 ± 19.6	167.5 ± 29	180.3 ± 23.1	189 ± 24
Insulin μU/ml	11.4 ± 2.2	5.5 ± 1.1***	11.4 ± 1.3	10.1 ± 1.1***
LH/FSH	2.5 ± 0.4	2.1 ± 0.4***	2.8 ± 0.5	2.5 ± 0.6**
BMI	28 ± 1.6	27.3 ± 1.3	26.6 ± 2.1	27.5 ± 1.7
Glucose/insulin	8.9 ± 1.8	16.5 ± 2.9**	8.2 ± 3.2	8.4 ± 2.6**
HOMA INDEX	2.5 ± 0.6	1.1 ± 0.3**	2.5 ± 0.4	2.4 ± 0.7**
	*<0.05; **<0.01; ***<0.005 versus baseline		* <0.05; **<0.01; ***<0.005 versus Group A	

Data are reported as means ± SD.

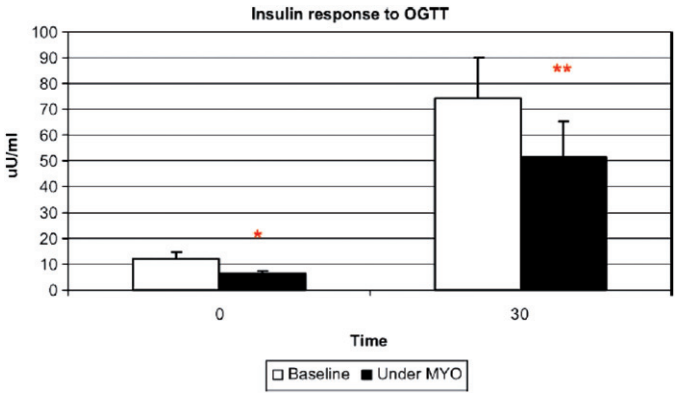

Figure 2. Patients under MYO administration presented a reduction of both insulin plasma levels before and 30 minutes after oral glucose load. (mean + SEM) *$p<0.05$, **$p<0.01$.

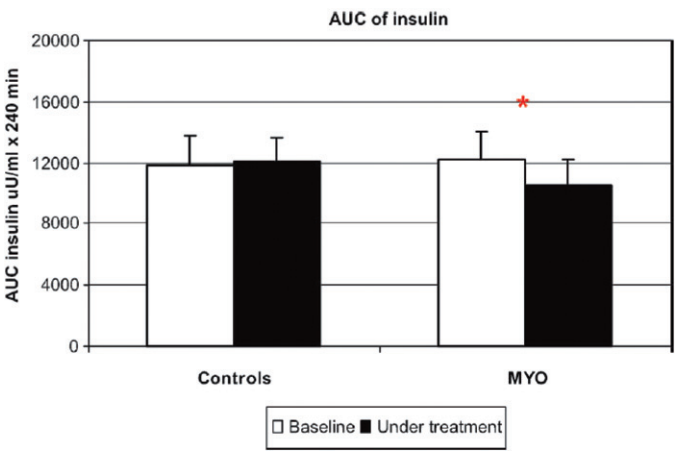

Figure 3. AUC of insulin after oral glucose load (OGTT). MYO administration significantly reduced the AUC of insulin after 12 weeks of treatment (Group A). Control subjects (Group B) did not show changes. (mean + SEM) *$p<0.05$.

reduction of insulin levels. It could probably act on the high availability of such precursors of IPG and, thus, ameliorate performances of this second messenger of the insulin signal [10].

Our data support what recently reported by Papaleo et al. [21] who demonstrated the efficacy of MYO in ameliorating the response to ovulation induction by a group of PCOS patients, and also they demonstrated that several hormonal changes took place after MYO administration. So, also our data suggest that a deficiency in the IPG precursors such as MYO and/ or DCI might be an additional cofactor contributing to the pathophysiology of the insulin resistance in PCOS patients. Indeed, recent data demonstrated that PCOS patients have lower DCI-levels of plasma and higher DCI urinary levels then healthy eumenorrheic women [22]. Our study demonstrated that MYO administration, besides DCI, has a modulatory role on insulin sensitivity, gonadotropin and androgen secretion, though no significant differences for plasma or urinary MYO concentrations have been previously reported in PCOS patients. However, it cannot be excluded that a minimal part of such positive effects observed during MYO administration might be related also to a minimal MYO-DCI conversion.

Table 3. Pregnancy outcome, oocyte and embryo quality in patients A-group and B-group.

Characteristic	Group A	Group B	*p* Value
N of retrieved oocytes	6.5 ± 3.1	10.8 ± 8.8	<0.05
Top-quality oocytes (%)	82	36	<0.05
Fertilization rate (%)	66	60	NS
N embryos transferred	2.5 ± 0.8	2.1 ± 0.5	NS
Top-quality embrios (%)	54	64	NS
N of βhCG positive (%)	15 (60)	8 (32)	<0.05
N of clinical pregnancies (%)	10 (40)	4 (16)	<0.05
Delivery rate (%)	32	12	<0.05

NS: no statistically significant.
Data are reported as means ± SD.

In the present study, we evaluated mostly the effects caused by MYO administration in patients treated with FIVET/ICSI protocol, and we noticed a positive effect both for gonadotropins response and pregnancy rate concordantly with previous studies. [12]. Another interesting aspect is about the follicular pattern present in PCOS patients after 12-weeks MYO treatment. Even if the number of follicles evaluated with transvaginal echography at the PU day were fewer then the control group, follicles dimensions were quite similar to the normal non-PCOS size. In the study group was discovered a higher amount of large-size follicles (diameter >16 mm) and a lower amount of intermediate size follicles, mostly seen in PCOS patients and also in the control group (Table 1). Moreover a 17β-E2-peak level at the PU day was

less relevant in MYO treated patients compared to control ones, with a lower risk of OHSS.

The lower amount of intermediate size follicles led to a lower amount of oocytes retrieval at the PU day, but the large diameter of recovered follicles determined top-quality oocytes that were in significantly higher quantity compared to control group. This means that MYO treatment is relevant for oocytes development.

MYO is an important constituent of follicular microenvironment, playing a determinant role in both nuclear and cytoplasmatic oocyte development [23]. Therefore higher MYO level in the follicular fluid can be well indicative of oocytes quality [24].

In Group A, top quality embryos were fewer than in the Group B, but in the MYO treated group, we performed a higher number of ICSI (62.5% versus 47.6%). Since we could inseminate a maximum number of three embryos, there could have been a higher chance to use spermatozoons with DNA alterations [25].

Pregnancy rate was evaluated by dosing β-HCG 15 days after PU and then by performing ultrasound echography in order to individuate for the ovular chamber and heart beat (6–7 weeks). Values obtained in treated group are significantly relevant compared to controls.

In conclusion though the number of patients is too small, our data support the hypothesis that a defect of insulin signal transduction has to be considered as part of the physiopathological factors that participate to the triggering of the PCO ''syndrome''. In fact MYO supplementation is efficient in changing many of the hormonal disturbances of PCOS, improving insulin sensitivity of target tissues and positively affecting the hormonal functions. It is possible through the reduction of insulin levels. It is then possible that it could modify the reproductive axis, improving oocytes quality and pregnancy rates.

Declaration of interest

The authors declare to have no Conflict of Interest.

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Notice of Correction

This paper published online on 22 January 2013 contained an error in the title. The word ''polycystic'' was misspelled as ''policystyc''. The error has been corrected for this version.