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The effect of a combination therapy with myo-inositol and a combined oral contraceptive pill *versus* a combined oral contraceptive pill alone on metabolic, endocrine, and clinical parameters in polycystic ovary syndrome

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Abstract

Aim. Compare the effects of a combined contraceptive pill (OCP) in combination with myo-inositol (MI) on endocrine, metabolic, and clinical parameters in patients with polycystic ovary syndrome (PCOS).

Methods. One hundred fifty-five patients with PCOS were enrolled in this prospective, open-label clinical study. Patients were assigned to receive oral treatment with OCP alone (estradiol (EE) 30 μg/gestodene 75 μg) or in combination with myo-inositol 4 g/die, for 12 months.

Results. OCP plus MI therapy resulted in a higher reduction of FG score compared with OCP alone therapy. The combined therapy (OCP plus MI) significantly decreased hyperinsulinaemia, by positively affecting the fasting insulin and glucose levels and homeostasis model assessment-insulin resistance parameters, while no significant changes were observed in the OCP group. Androgens serum levels decreased in both groups, but significantly more in the combined therapy group. The lipid profile was improved in the combined therapy group, by reducing low-density lipoprotein cholesterol levels and enhancing high-density lipoprotein cholesterol levels.

Conclusions. Our data show that a combination of combined contraceptive pill and MI may be more effective in controlling endocrine, metabolic, and clinical profile in patients with PCOS than OCP alone, and may reduce insulin levels and insulin resistance. Hence, combined treatment may become a more effective long-term therapeutic choice for controlling PCOS symptoms.

Keywords: *Polycystic ovary syndrome, insulin resistance, myo-inositol, combined oral contraceptive pill*

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous syndrome with a variety of metabolic and endocrine abnormalities and clinical symptoms. It is characterized by chronic anovulation and hyperandrogenism and affects about 5–10% of women in reproductive age [1–3]. The primary defect in PCOS appears to be an exaggerated androgen synthesis and secretion [4], particularly by ovarian theca cells [5]; insulin resistance and obesity may act as triggers of this primary defect [6], explaining the frequent association of PCOS with obesity [6,7] and insulin resistance [8]. Hyperinsulinaemia, the consequence of insulin resistance, stimulates both ovarian and adrenal androgen secretion and suppresses sex hormone-binding globulin synthesis from the liver, resulting in an increase in free, biologically active androgens. This excess in local ovarian androgen production causes a premature follicular atresia and anovulation along with other clinical manifestations of hyperandrogenism such as hirsutism, acne, seborrhea, and alopecia [9].

Furthermore, it has recently become clear that PCOS is also linked to a variety of metabolic alterations, including type 2 diabetes, metabolic syndrome, and possibly cardiovascular disease [10–12]. In particular, it has been demonstrated that androgen excess, typical of PCOS syndrome, affects the metabolism of lipids [13]. Thus, women with PCOS often show alterations in lipid pattern: decrease in high-density lipoprotein (HDL) cholesterol and total cholesterol levels and increase in triglycerides and low-density lipoprotein (LDL) cholesterol concentrations [14].

Due to chronic anovulation, women with PCOS are also thought to be at increased risk for endometrial cancer as consequence of unopposed estrogen exposure of the endometrium by the lack of progesterone secretion [15].

Oral contraceptive pills (OCPs) have been the traditional therapy for long-term treatment of PCOS in order to provide endometrial protection, regularize menses, and improve dermatological abnormalities (hirsutism, acne) by reducing ovarian androgen production.

Their main mechanisms of action include suppression of follicle-stimulating hormone, decrease of ovarian androgen secretion and free androgen levels, and therefore protection of the endometrium from the risk of developing endometrial cancer [16,17].

More recently, insulin-sensitizing drugs have been proposed as another long-term treatment for PCOS. Given the importance of hyperinsulinaemia in the development of hyperandrogenism and anovulation, it seems possible that insulin-sensitizing drugs may be useful to restore normal endocrinological and clinical parameters of PCOS by lowering insulin secretion [18]. Among these drugs the most used and studied is metformin, whose

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mechanism of action involves suppression of glucogenesis, enhancement of peripheral insulin action, and reduction of glucose absorption from the digestive tract [19]. Nevertheless, both OCPs and insulin-sensitizing drugs have several side effects.

Other insulin-sensitizing drugs came recently in the market and their effects on women with PCOS are currently under investigation. Among these is myo-inositol, a substance belonging to vitamin B complex. Inositol phosphoglycan molecule is known to have a role in activating enzymes that control glucose metabolism [20,21]. A defect in tissue availability or altered metabolism of inositol or inositol phosphoglycan mediators, as in women with PCOS, may contribute to insulin resistance [22,23]. Previous studies have shown that the use of insulin-sensitizing drugs reduces serum androgens, and improves ovulation in women with PCOS [24,25].

A deficiency of myo-inositol has been found in women with PCOS affected by insulin resistance [26], and the administration of myo-inositol reduces serum insulin, decreases serum testosterone, and enhances ovulation [26–28].

Due to the different beneficial actions, aim of the present study is to evaluate the effect of treatment with OCP, alone or in combination with myo-inositol, on insulin sensitivity, lipid and endocrine profiles, and clinical outcome (hirsutism) in women with PCOS.

Materials and methods

Patients

The patients were recruited among those that fulfilled two out of three diagnostic criteria for PCOS, according to the 2003 Rotterdam Consensus conference [29].

Women who presented a secondary endocrine disorder, those wishing to conceive during the next 12 months and those with contradictions to oral contraceptive use have been excluded.

None of the patients included in the study had a personal history of hypertension, diabetes mellitus or cardiovascular events, or received treatment with oral contraceptives, or other drugs for the previous 6 months before entering the study.

Before entering the trial a written informed consent was obtained from the patients, and the study was approved by the local ethics committee.

Study design and protocol

In this prospective, open-label study, 155 patients included were assigned to one of the following treatment groups: group OC, 75 patients, receiving a monophasic low-dose combined oral contraceptive pill (EE 30 μg/gestodene 75 μg, Minulet®, Wyeth Lederle S.p.A., Latina, Italy) assumed in the evening in a cyclic regimen (21 days of assumption followed by 7 days of suspension) for 12 months. Group OCMYO, 80 patients, receiving the same OCP (EE 30 μg/gestodene 75 μg) assumed in the evening in a cyclic regimen (21 days of assumption followed by 7 days of suspension), in combination with myo-inositol plus folic acid (4 g myo-inositol plus 400 μg folic acid, Inofolic®, LO.LI.Pharma S.r.l., Rome, Italy) assumed daily for 12 months.

Treatment was started the first day of a spontaneous menstrual cycle or, in women with amenorrhea, after excluding pregnancy.

Main outcome measurements

Clinical and anthropometric measurement included: age, body mass index (BMI), serum levels of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, apolipoprotein B (apoB), lipoprotein(a) [Lp(a)], fasting glucose level, fasting insulin level, insulin resistance, measured by homeostasis model assessment (HOMA-IR), testosterone (T), sex hormone-binding globulin (SHBG), Δ4-androstenedione (A), dehydroepiandrosterone (DHEAS), leutenizing hormone (LH), and hirsutism score, evaluated by using a modification of the Ferriman–Gallwey (FG) score (42), that quantitated terminal hairs in nine body areas. For the present study, hirsutism scores and serum and plasma samples were obtained in the early follicular phase, i.e. within the first 6 days of the menstrual cycle or after excluding a pregnancy in amenorrheic patients. All the parameters were measured at the baseline and after 12 months of treatment.

Statistical analysis

Data are given as mean $\pm$ SD. The baseline characteristics of the patients assigned to OC or OCMYO group were compared using unpaired *t*-test. Change in parameters between the groups over 12 months of treatment was assessed using the Mann–Whitney test for nonparametric data and the unpaired *t*-test for normally distributed data. Logarithmic transformation was used to ensure a normal distribution as needed. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics of the patients

All 155 patients, who were eligible after screening, concluded the 12-month trial. Baseline clinical, anthropometric, hormonal, and metabolic parameters of the patients, belonging to the group OC and OCMYO are listed in Table I (second and forth column). Groups were well matched at baseline except for total and LDL cholesterol levels ($p=0.002$, $p<0.001$, respectively) and triglycerides level ($p=0.01$ in the OC and OCMYO group).

Effects of the treatments on clinical parameters and sex hormones profile

There were no differences regarding baseline age and BMI values between the treatment groups (Table I), and the FG score was statistically similar between the groups at the baseline. BMI remained stable in both groups during the treatment.

Both treatments shown a decrease in FG score ($p<0.001$ in OC group and $p<0.001$ in OCMYO group, between baseline and the end of treatment; Table I). At the end of the treatment, FG score was significantly lower in OCMYO group compared with OC group $p<0.001$).

Endocrine profile was statistically ameliorated in both groups.

Comparing the treatment groups a significant improvement in testosterone, androstenedione and DHEAS levels occurred in the OCMYO group (testosterone: $p<0.001$; androstenedione: $p<0.001$; DHEAS: $p<0.01$, at the end of the treatment). Free androgen index decreased in both

Table I. Clinical, endocrine, and metabolic parameters of the patients assigned to group OC or to group OCMY at the baseline and at the end of the treatment.

Parameter	Group OC ($n = 75$)		Group OCMYO ($n = 80$)	
	Baseline	After 12 months	Baseline	After 12 months
Anthropometric parameters				
Age, years	29.4 ± 4.1		28.8 ± 3.8	
BMI, kg/m^2	26.2 ± 2.6	26.5 ± 2.5	26.7 ± 2.7	26.7 ± 2.4
Symptoms/hormonal parameters				
Hirsutism score (modified Ferriman–Gallwey score)	10.2 ± 3.4	8.1 ± 2.3*	9.7 ± 3.6	6.7 ± 1.9*,†
Testosterone level, nmol/l	2.34 ± 0.26	1.65 ± 0.19*	2.29 ± 0.33	1.29 ± 0.25*,†
A level, nmol/l	14.20 ± 1.98	10.78 ± 1.74*	13.95 ± 1.02	8.74 ± 1.33*,†
Free androgen index	13.37 ± 2.30	2.24 ± 1.98*	12.65 ± 2.81	2.15 ± 1.76*
DHEAS level, ng/ml	3167 ± 543	2756 ± 478*	3210 ± 487	2538 ± 506*,†
SHBG level, nmol/l	17.5 ± 2.3	87.4 ± 14.6*	18.1 ± 1.9	91.5 ± 13.8*
LH level, IU/l	6.8 ± 1.2	3.7 ± 0.7*	7.1 ± 0.9	3.5 ± 1.1*
Insulin resistance				
Fasting Insulin, mU/l	12.3 ± 3.1	12.1 ± 3.5	12.9 ± 3.3	8.7 ± 2.7*,†
Fasting Glucose, mmol/l	4.9 ± 0.9	4.7 ± 0.8	5.0 ± 0.7	4.5 ± 1.0*
Insulin resistance (HOMA-IR)	2.7 ± 0.8	2.5 ± 0.9	2.9 ± 0.9	1.8 ± 1.0*,†
Lipid profile				
Total cholesterol level, mmol/l	4.88 ± 0.56	5.15 ± 1.23	4.67 ± 0.23†	4.84 ± 0.89
HDL cholesterol level, mmol/l	1.21 ± 0.15	1.19 ± 0.22	1.28 ± 0.43	1.45 ± 0.71†
LDL cholesterol level, mmol/l	2.92 ± 0.44	3.05 ± 0.67	2.57 ± 0.72†	2.28 ± 0.81*,†
Triglycerides level, mmol/l	1.55 ± 0.56	1.75 ± 0.74	1.81 ± 0.67†	1.95 ± 0.78
ApoB level, mg/dl	85 ± 21	91 ± 23	81 ± 27	89 ± 32
Lp(a) level, mg/dl	29 ± 12	32 ± 18	26 ± 21	30 ± 23

A: Δ4-androstenedione, DHEAS: dehydroepiandrosterone sulfate, SHBG: sex-hormone binding-globulin, LH: leuteinizing hormone, HDL: high-density lipoprotein, LDL: low-density lipoprotein, ApoB: apolipoprotein B, Lp(a): lipoprotein(a).
Data are reported as means ± DS.
*$p < 0.05$, compared with the level at the baseline.
†$p < 0.05$, between OC and OCMYO groups.

groups but the difference between the groups at the end of the treatment was not statistically significant. LH levels significantly decreased in both groups during the treatment ($p < 0.001$ in OC group and $p < 0.001$ in OCMYO group between baseline and the end of treatment).

Effects of the treatments on insulin resistance and glucose metabolism

Both PCOS groups had normal levels of glucose throughout the study, but only in OCMYO group the decrease during the treatment was statistically significant ($p < 0.001$ in OCMYO group). The difference between the groups at the end of the treatments was not statistically different.

The fasting insulin levels and the HOMA-IR values decreased during the treatments in both groups, but significantly only in OCMYO group (fasting insulin: $p < 0.001$ in OCMYO group, HOMA-IR: $p < 0.001$ in OCMYO group) and the decreases were significantly higher in the OCMYO group compared with OC group (fasting insulin: $p < 0.001$ and HOMA-IR: $2p < 0.001$).

Effects of the treatments on serum lipid profile

At baseline there was a difference in total cholesterol, LDP cholesterol and triglycerides serum levels between the treatment groups.

During the treatment total cholesterol levels increased in both groups, but not significantly. LDL cholesterol levels increased not significantly in OC group, while a significant decrease in OCMYO group occurred ($p < 0.05$). The difference in LDL cholesterol levels between the groups at the end of the treatment was statistically significant ($p < 0.001$). HDL cholesterol increased during the treatment only in OCMYO group, but not significantly. At the end of the treatment the mean value of HDL levels was significantly higher in OCMYO group ($p < 0.01$).

Finally, ApoB and Lp(a) levels remained similar in both groups during the treatment, and no differences between the groups at the end of the treatments have been detected.

Discussion

OCPs are the traditional therapy for the chronic treatment of PCOS symptoms in women who do not seek for pregnancy. In fact, they can exert a number of beneficial effects as regularization of menstrual cycles, amelioration of clinical aspects of PCOS (hirsutism, acne, etc.), and protection of endometrium from developing cancer [30].

The newer oral contraceptive preparations are generally safer than those previously commercialized, although their administration in patients with PCOS and their long-term actions are coming under control. Literature data show that OCPs were generally associated with reduced glucose tolerance, hyperinsulinaemia and insulin resistance [30–32]. Regarding lipid metabolism, OCPs could be responsible of LDL, total cholesterol and triglycerides increase in women with PCOS [30,33–35]. Consequently, OCPs could enhance the long-term risk for type 2 diabetes and cardiovascular diseases. This opened a speculation about insulin-sensitizing drugs as a safer treatment alternative for patients with PCOS. Among them, we considered myo-inositol, that has been demonstrated in previous

studies to be effective in controlling clinical symptoms [25,36], restoring ovulation and controlling hyperinsulinaemia and metabolic disorders in patients with PCOS [24,27,28].

The results of this prospective, open-label trial showed that the combination of OCP and myo-inositol is a more effective treatment for the clinical symptoms of PCOS (hirsutism) and for the control of the endocrine disorders, typical of hyperandrogenism, than OCP alone. A general amelioration of hormonal profile in both treatment groups has been detected and, in particular, a significant higher decrease of serum androgen concentrations (testosterone, androstenedione, DHEAS) occurred in the combined treatment (OCP plus myo-inositol). Thus, the combined treatment with OCP and myo-inositol is a more effective way of treating hyperandrogenism and its clinical evidences.

Furthermore, in our study the combination of OCP and myo-inositol has been effective on glucose and insulin profile, unlike OCP alone, endorsing the fact, previously demonstrated that OCPs therapy could negatively affect insulin resistance and glucose tolerance. The addition of an insulin-sensitizing drug, as myo-inositol, could therefore counterbalance the negative effects of OCPs therapy on hyperinsulinaemia and insulin resistance.

The effects of OCP and OCP plus myo-inositol on lipid profile and cardiovascular risk factors are similar. A better control of LDL and a higher enhancement of HDL cholesterol serum levels occurred in the combined treatment group. This finding is especially important considering that decreased HDL cholesterol levels are among the most common lipid abnormalities associated with PCOS [37,38] and are a recognized cardiovascular risk factor [39].

However, our study is not free of limitations, especially the relatively short duration of treatment, considering that PCOS is a chronic condition that requires long-term interventions; therefore, we are not able to evaluate the possible long-term side effects of OCPs.

Further investigations, such as a double blind prospective randomized trial on long-term PCOS-treated patients, is required to confirm the beneficial combination of OCPs treatment with insulin-sensitizing agents, as myo-inositol.

In summary, both groups OCPs and OCPs plus myo-inositol are effective for the treatment of the symptoms and the hormonal and metabolic abnormalities of PCOS. However, the combination of OCPs and myo-inositol seems to be superior in terms of clinical and biochemical hyperandrogenism and hyperinsulinaemia control, and in the reduction of cardiovascular risk factors (bad lipid profile).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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