European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2003; 7: 151-159

Effects of inositol on ovarian function and metabolic factors in women with PCOS: a randomized double blind placebo-controlled trial

S. GERLI, M. MIGNOSA, G.C. DI RENZO

Department of Obstetrics and Gynecology, Monteluce Hospital, University of Perugia (Italy)

Abstract. – ***Background:*** **Women with oligomenorrhea and polycystic ovaries show a high incidence of ovulation failure perhaps linked to insulin resistance and related metabolic features. A small number of reports shows that inositol improves ovarian function. Futhermore, in these trials the quality of evidence supporting ovulation is suboptimal, and few studies have been placebo-controlled. The aim of this study was to use a double-blind, placebo-controlled approach with detailed assessment of ovarian activity (two blood samples per week) to assess the validity of this therapeutic approach in this group of women.**

Methods: **Of the 283 patients randomized, 2 withdrew before treatment commenced, 147 received placebo, and 136 received inositol (100 mg, twice a day). The women which discontined the study prematurely were more numerous in the treatment group (n = 45) than the placebo group (n = 15; *P* < 0.05).**

Results: **The ovulation frequency estimated by the ratio of luteal phase weeks to observation weeks was significantly (*P* < 0.01) higher in the treated group (23%) compared with the placebo (13%). The time in which the first ovulation occurred was significantly (*P* < 0.05) shorter [23.6 d; 95% confidence interval (CI), 17, 30; compared with 41.8 d; 95% CI, 28, 56]. The number of patients failing to ovulate during the placebo-treatment period was higher (*P* < 0.05) in the placebo group, and in most cases ovulations were characterized by normal progesterone concentrations in both groups. The effect of inositol on follicular maturation was rapid, because the circulating concentration of E2 increased only in the inositol group during the first week of treatment. Significant (*P* < 0.01) weight loss (and leptin reduction) was recorded in the inositol group, whereas in the placebo group was recorded an increase of the weight (*P* < 0.05). A significant increase in circulating high-density lipoprotein was observed only in the inositol-treated group. Metabolic risk factor benefits of inositol treatment were not observed in the morbidly obese subgroup of patients (body mass index > 37). No change in fasting glucose concentrations, fasting insulin, or insulin responses to glucose challenge test was recorded after 14-wk of inositol and placebo therapy. There was an inverse relationship between body mass of the patients and the efficacy of the treatment.**

Conclusions: **These data support a beneficial effect of inositol in improving ovarian function in women with oligomenorrhea and polycystic ovaries.**

Key Words:

PCOS, Inositol, Ovarian function, Insulin resistance.

Introduction

Polycystic ovary syndrome (PCOS) is a very common disorder of premenopausal women characterized by hyperandrogenism and chronic anovulation[1,2]. Its etiology is unknown. Although specific population-based studies have not been performed yet, a 5-10% prevalence of this disorder in women of reproductive age is probably a reasonable conservative estimate. This estimate is based on the upper limit derived from studies on the prevalence of polycystic ovaries, which found that 20% of self-selected normal women had polycystic ovary morphology at ovarian ultrasound examination[3]. Many of these women had subtle endocrine abnormalities[3]. The lower estimate is based on the reported 3% prevalence rate of secondary amenorrhea for 3 or more months[4] and the consideration that up to 75% of women with secondary amenorrhea will fulfill diagnostic criteria for PCOS[5]. PCOS women

can also have less profound disturbances in menstrual function[1,3,6]. Since the report by Burghen et al[7] in 1980 where PCOS was associated with hyperinsulinemia, it has become clear that this syndrome has major metabolic as well as reproductive morbidities. The recognition of this association has also instigated extensive investigation on the relationship between insulin and gonadal function[1,8]. In turn, this association has led to the treatment of women with PCOS with insulin sensitizing agents such as troglitazone[7], inositol[8] and metformin[9-11]. A number of small randomized and non-randomized cohort studies have shown that women with PCOS respond to this therapy increasing ovarian activity and menstrual frequency. However, the relationships among treatment outcome, anthropometric changes, glycemic, metabolic and lipid profile adjustments, are less comprehensively studied and remain disputed. Some of the differences among the results already published may derive from difference in patient selection, because patient profiles can differ between infertility and endocrinology clinics and perhaps also in racial and socioeconomic makeup. Furthermore, only a minority of the studies where inositol was used are double blind and placebo-controlled trials, with the majority being small cohort studies (up to 50 patients). In particular, direct assessment of follicular development, ovulation and progesterone blood rise has been far from comprehensive. The latter point is relevant because in women with PCOS many ovulations are accompanied by subnormal progesterone concentrations[12], which may state a suboptimal follicular maturation and ovulation.

The aim of this study was to investigate the effects of inositol on detailed ovarian function in women with oligomenorrhea and polycystic ovaries (PCOS) treated using a randomized, double blind, placebo-controlled trial of 16-wk treatment duration. Changes in anthropometric parameters, glycemic indices, leptin and lipid profile were also examined in relation to the evolution of the ovarian function.

Patients and Methods

Patients

Polycistic ovary syndrome (PCOS) is defined by the presence of characteristic morphological features of the ovary at ultrasound examination associated with menstrual disturbances, hyperandrogenism and elevated androgen activity. Women with oligomenorrhea (cycle length 41d; 8 cycles per year) or amenorrhea and PCOS, aged less than 35 yr, were recruited from gynecology, endocrine, and infertility outpatient clinics. Patients with significant hyperprolactinemia, abnormal thyroid function tests, and congenital adrenal hyperplasia were excluded. Transvaginal ultrasound examinations by a single observer (Z.E.H.) were performed to assess ovarian appearance, and ovaries were diagnosed as polycystic (PCOS) according to the criteria of Adams et al[13]. None of the patients was taking medications likely to influence hormonal profiles. This diagnosis was used on the understanding that the overhelming majority of the patients defined on this basis would demonstrate elevated androgen activity, symptoms of hyperandrogenism, or both[14].

Protocol

Ovarian activity was investigated before and throughout the study, using two blood samples per week to assess reproductive hormone concentrations. Before randomization, all patients underwent a 4-wk period of investigation to confirm abnormal ovarian function. The same assessment schedule was maintained through a subsequent 16-wk treatment period after randomization to inositol (Gestosan, Lo.Li. Pharma, Rome, Italy) or matching placebo. Anthropometric, endocrine, and ovarian ultrasound assessments were effected before and after 14-wk treatment (effectively between 12-16 wk). The latter temporal window was used in order to allow that the measurements could be taken outside the luteal phase. The tests were performed only after confirmation that the circulating progesterone concentration was less than 6 nmol/liter. Inositol was administered at a dosage of 100 mg twice daily.

Randomization and Study Power

Randomization was performed in a double-blind way; patients received either inositol or placebo according to the code provided by a computer-generated table of randomization. The study power was based upon predicted changes in the ovulation rate and circulating lipoprotein concentrations, using da-

ta derived from the literature[15] and our own pilot study. The calculation was adapted to account for the fact that 70-80% of the cases would have classical PCOS, a significant drop out rate (15%), and a failure to attain normal menstrual frequency in another 15% of the cases. It was estimated that 38 patients in each arm would detect changes in high-density lipoprotein (HDL) cholesterol with more than 90% power with a type 1 error (a) 0.05. It was predicted that the study required 55 cases in each arm to achieve the stated aim. Before randomization and during the ovarian function assessment, all patients were evaluated for endocrine factors while outside the luteal phase (progesterone concentration, 6 nmol/liter) when they attend the hospital after an overnight fast. Blood samples were taken to assay E2, T, androstenedione, LH, FSH, triglycerides, cholesterol, low-density lipoprotein (LDL) cholesterol, and HDL cholesterol. Then, a standardized 75-g oral glucose tolerance test (GTT) was performed with blood samples collected at 0, 60 and 120 min for determination of serum glucose and insulin concentrations. This process was repeated at the 14-wk assessment point.

Ovarian Activity Ovulation and the Luteal Ratio

Ovarian activity was monitored using serum E2 rapid (same day) measurements; where follicular activity was diagnosed (E2 > 300 pmol/ liter), progesterone and LH concentrations were determined to diagnose ovulation and the luteal phase. Ovulation frequency was calculated using the ratio of luteal phase weeks to observation weeks (the luteal ratio), so that a patient with normal menstrual rhythm would show two luteal weeks in four observation weeks, yielding to a ratio of 0.5, expressed as a luteal ratio of 50%. One patient conceived during the last week of the treatment, and her data were included in the completed trial analyses, because all samples and tests scheduled had been undertaken in the period of treatment.

Anthropometric and Lifestyle Parameters

Anthropometric data were recorded (height, weight, waist, and hip measurements) before and at the 14th week of the trial by a single trained observer (Z.E.H.) using standardized techniques[16]. The body mass index (BMI) was calculated using the standard formula (kilograms per square meter). Each volunteer completed a questionnaire concerning medical and social history (desiring pregnancy, smoking habits), from which subjective information about menstrual patterns, skin oiliness, acne, and hirsutism were obtained. Ovarian ultrasound assessments were also performed before starting the treatment and at 14 wk by the same observer.

Assay Methods

The reproductive hormones, E2 and progesterone, were assayed routinely using the semiautomated Immulite technology (Diagnostic Products, Los Angeles, CA). The analytes T, LH, FSH, and human chorionic gonadotrophin were assayed retrospectively in batches using the same system. Inhibin-B was measured using the specific two-site immuno-assay (Serotec Ltd., Oxford, UK). Plasma glucose was measured using the glucose oxidase method (Glucose Reagent Kit, Bayer, Newbury, UK), whereas insulin was measured using a competitive RIA (Coat-A-Count I, Diagnostic Products). Plasma total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol measurements were obtained by a modification of the standard Lipid Research Clinics protocol[17]. Plasma leptin concentrations were measured by a validated in-house RIA[18].

The intra- and interassay coefficients of variation were less than 7 and 10%, respectively, over the sample concentration range. The detection limit of the assay was 0.5 ng/ml.

Data Analyses and Statistics

Data were analyzed on the basis of the intention to treat and also on completed treatment parameters where relevant. Fasting and post-glucose insulin [area under curve (AUC)], SHBG, waist to hip ratio (WHR), triglyceride, and the ovulatory function were compared between treatment and placebo groups after log transformation if the distributions were not normal. Hormone and comparative data were presented with confidence limits at 95%. Statistical information was prepared using the SPSS for Windows software (SPSS, Inc., Chicago, IL). Hormone data were compared using t test after log transformation if distributions were normalized.

Ethical Approval

The study was approved by the local Ethical Committee, and all patients signed a written consent.

Results

Recruitment, Randomization, and Pretreatment Assessments

A total of 323 women were interviewed for inclusion in the study. Of these, two women were diagnosed with late onset congenital adrenal hyperplasia. Another 38 women did not have true oligomenorrhea on further assessment or declined to proceed for personal reasons. Thus, a total of 283 patients were randomized in two groups, receiving either inositol or placebo. The motivations that lead the patients to perform the first visit were different, and infertility was a complaint in only about half of the patients in each group. There was no difference in the proportions of infertile women within the groups (Table I). Although patient selection was based on the more wide-ranging definition often used in Europe (i.e., ultrasound-diagnosed PCOs and oligomenorrhea), 90% had biochemical or clinical evidence of hyperandrogenism. Table I also shows that the inositol and placebo groups were matched for menstrual frequency in the preceding year, age, BMI, T, SHBG, fasting glucose, hemoglobin A1c, and circulating lipid fractions before treatment. The number of patients who were willing to undergo fertility treatment were also similar in each group. All women showed a classical picture of PCOs at vaginal ultrasound scan.

Treatment Compliance

The difference in the drop out rates (excluding pregnancies) between the placebo (n = 5) and treatment (n = 15) groups was significant ($P > 0.05$) In the placebo group, the drop outs occurred after 1, 1, 5, 6, and 7 wk. In the inositol-treated patients, the discontinuations also occurred early, with seven cases in the first 3 wk and the remaining between 6-10 wk. Two patients in this latter group discontinued for reasons unrelated to the study.

Conception During Treatment

There were eight conceptions in eight patients during the study, and one miscarriage in the first trimester. However, only 42 patients declared before the study that they wished to conceive. Of these, the distribution of pregnancies between the groups was: placebo, 1 of 19 patients; inositol 4 of 23 patients.

These figures are not significantly different ($P = 0.23$).

Ovarian Function: Ovulation

An intention to treat analysis revealed that 8 of the total 136 inositol-treated patients

Table I. Characteristics of the patients randomized to receive inositol or placebo treatment.

	Placebo		Inositol	
	Mean	CIs	Mean	CIs
Age (yr)	29.2	27.5-30.7	28.6	26.9-30.3
Menses per year	4.0	3.1-4.9	4.6	3.5-5.6
BMI (kg/m 2)	35.0	32.6-37.3	34.2	31.7-36.7
WHR	0.88	0.86-0.90	0.88	0.86-0.90
LH (IU/liter)	10.1	8.3-11.9	8.3	6.9-9.7
T (nmol/liter)	3.8	3.3-4.2	3.0	2.6-3.5
SHBG (nmol/liter)	28.1	22.6-33.6	29.2	24.3-34.1
Free androgen index	13.7	10.7-16.8	10.3	8.6-12.1
Fasting insulin (mIU/liter)	18.4	14.5-22.3	16.7	13.0-20.4
Insulin AUC (GTT)	228	177-280	191	155-227
Fasting glucose (nmol/liter)	4.93	4.81-5.05	5.05	4.87-5.23
Leptin (ng/ml)	40.7	33.8-47.7	40.0	32.1-48.0
Inhibin-B (pg/ml)	82	67-97	101	88-115

No. of patients: placebo-treated, 147 (infertile, 19; hirsutism, 22); inositol-treated, 136 (infertile, 23; hirsutism, 13). P values are NS. CIs, Confidence intervals (95%).

Table II. Details of ovulations during placebo and inositol treatment.

	Placebo	Inositol	P
Observation weeks	503	345	
Luteal weeks [luteal ratio (%)]	66 (13)	78 (23)	< 0.001
Luteal phases with P_{max} 7 ng/ml (%)	5 (13)	2 (8)	NS
Days to first ovulation, mean	41.8	23.6	0.02
(CIs, 95%)	(28, 56)	(17, 30)	

P_{max}, Maximum progesterone concentration.

failed to ovulate during treatment, compared with 17 of 147 placebo-treated. This difference was statistically significant (Fisher's exact test; $P = 0.04$; odds ratio, 0.38).

Table II shows the data from all cases in which ovulation data (over any length of time) were available. The inositol-treated group had a significantly increased frequency of ovulation compared with the placebo group, defined by the luteal ratio. The distributions show that the placebo group was dominant at low ovulation rate (zero and one ovulations), whereas the inositol group was dominant in the high ovulation rate (two to four ovulations). Contingency table analysis (Fisher's Exact test) showed these distributions to be marginally different as follows: zero and one ovulation, $P = 0.059$; two to four ovulations, $P = 0.059$. Table II also shows the frequency of ovulations with deficient luteal phases assessed by the maximum progesterone concentration less than 7 ng/ml. There was no significant difference between the incidences of this phenomenon in either group. In fact, the concentrations of progesterone recorded during the monitoring of ovarian function indicated that most of the ovulations showed normal endocrine profiles during both inositol and placebo treatment. All patients started treatment outside the luteal phase, and the delay to the first ovulation after starting the program (Table II) was significantly shorter in the inositol-treated group.

Initial Responses to Treatment: Follicular Development

Inhibin-B is a marker of early follicular granulosa cell activity, and circulating E2 represents follicular maturation. Table III shows the E2, inhibin-B, and T concentrations on the first and eighth days of treatment, showing that the inositol-treated group had a significant ($P = 0.03$, paired data) increase in mean E2, whereas the control group showed no change. There was no change in the circulating inhibin-B or T concentrations. These profiles suggest that although improved follicular maturation was detected, no change occurred in the other markers of ovarian metabolism (total immature granulosa cell activity and stromal androgen biosynthesis).

Table III. The reproductive hormone changes over the first week of inositol treatment.

	Day 1		Day 8		P
	Mean	CIs	Mean	CIs	
Placebo					
E2 (pmol/liter)	164	110-217	183	127-240	NS
Inhibin-B (pg/ml)	82	67-97	88	71-105	NS
T (nmol/liter)	3.8	3.4-4.5	4.2	3.5-4.9	NS
Inositol					
E2 (pmol/liter)	142	123-161	226	150-302	< 0.03
Inhibin-B (pg/ml)	101	88-114	96	83-108	NS
T (nmol/liter)	3.1	2.4-3.8	3.5	2.8-4.2	NS

Metabolic and anthropometric assessments

Table IV shows that after 14-wk treatment, the BMI decreased significantly in the inositol group, whereas it increased in the placebo group. There was no change seen in the WHR in either group. The circulating leptin concentration declined in the inositol-treated group, in contrast to the control group, but there were no change recorded in the fasting glucose, fasting insulin, or insulin AUC in response to the glucose challenge in either group. Circulating very LDL (VLDL) showed little change during the treatment period, but the LDL showed a trend toward reduction. HDL increased significantly in the inositol-group. It is possible that the reduction in HDL was related to the weight loss achieved in the inositol-treated patients, although the ANOVA ($r > 0.34$; $P > 0.07$) did not reach conventional levels of significance.

Subgroup Analyses

Characteristics of the Group That Responded to Inositol With Normal Ovulation Frequency

A total of 11 patients who responded to inositol by establishing normal ovulation frequency (n = 6) and/or pregnancy (n = 5) were compared with those patients who did not respond with establishment of normal ovarian function (less than three ovulations in 16 wk; n = 19). The two groups showed similar BMI, WHR, and circulating E2 and inhibin-B concentrations. However, re-sponders to inositol treatment showed significantly lower T (2.5 nmol/liter vs. 3.5 nmol/liter; 95% CI = 0.07 and 2.1, respectively; $P < 0.04$), higher SHBG (36.5 nmol/liter vs. 26.3 nmol/liter; 95% CI, 20.6 and 0.13; $P < 0.05$), and thus lower free androgen index (7.2 vs. 11.9; 95% CI, 1.2 and 8.1; $P = 0.01$). Fasting insulin, glucose concentrations and responses to the GTT were not significantly different.

Metabolic Responses and Obesity

It was observed that morbidly obese women (BMI = 37; n = 11) showed a similar number of ovulations (mean, 1.6) during 16-wk inositol treatment to the leaner women (mean, 2.1), but they showed no indication of changes in either BMI (pretreatment, 42.5 kg/m 2; week 14, 42.3 kg/m 2) or HDL cholesterol (pretreatment, 0.95 mmol/liter; week 14, 0.95 mmol/liter). The leaner women (BMI = 37 kg/m 2) showed distinct changes during treatment as follows: BMI, pretreatment, 29.4 kg/m 2; week 14, 28.5 kg/m 2 (P = 0.01); or HDL cholesterol, pretreatment, 1.21 mmol/liter; week 14, 1.32 mmol/liter (P = 0.02).

Discussion

This study is the first which present a comprehensive, detailed endocrinological assessment of ovarian function in the context of a large randomized placebo-controlled trials of inositol in women with abnormal ovarian

Table IV. Changes in metabolic parameters during placebo or inositol treatment.

	Placebo (n =39 pairs)			Inositol (n =26 pairs)		
	Pretreatment	14 wk	P	Pretreatment	14 wk	P
BMI (SD)	35.3	35.6	0.04	35.2	34.6	0.03
WHR	0.88	0.88	NS	0.88	0.88	NS
Leptin (ng/ml) (SD)	40.6	38.5	NS	41.1	37.3	0.05
Fasting insulin (mIU/liter)	18.4	17.5	NS	16.8	16.4	NS
GTT insulin AUC	221	221	NS	188	204	NS
Fasting glucose (mmol/liter)	4.9	5.0	NS	5.0	5.0	NS
Total cholesterol (mmol/liter)	4.93	4.90	NS	4.61	4.50	NS
Triglycerides (mmol/liter)	1.40	1.44	NS	1.62	1.63	NS
VLDL cholesterol (mmol/liter)	0.42	0.54	NS	0.52	0.54	NS
LDL cholesterol (mmol/liter)	3.41	3.27	NS	3.01	2.81	0.09
HDL cholesterol (mmol/liter)	1.13	1.13	NS	1.08	1.14	0.03

Statistical probability by t test for paired data.

function. Our data show clear beneficial effect of inositol treatment upon ovarian function, anthropometric measures, and lipid profiles in women with oligomenorrhea and PCOS. We observed that more than 30% of the patients established normal ovarian rhythm (three or more ovulations) through the 16-wk treatment period. This contrasted with 18% for the placebo group. The ovulations showed normal progesterone concentration profiles in a high frequency of the cycles indicating that these were fertile cycles. The mean time until the first ovulation was significantly shorter in the inositol-treated group (24 d) than in the placebo-treated group (42 d).

This suggests a relatively rapid effect of treatment upon ovarian function, which is further supported by the significant increase in E2 concentrations during the first week of treatment.

At week 14 assessment, the inositol patients showed significant reductions in weight, in contrast to patients in the placebo group who actually increased their BMI. Significant reductions in circulating leptin and increased HDL cholesterol concentrations in the inositol-treated group were associated with the weight loss were. LDL cholesterol showed a trend toward reduction, and overall the LDL cholesterol to HDL cholesterol ratio improved significantly in the inositol group (data not shown). Despite the increase in ovulation frequency, there were no changes in circulating androgen concentrations, glycemic indices, basal or provoked insulin levels, or circulating VLDL cholesterol concentrations. Our data on HDL cholesterol are important, because no previous study has addressed this important issue.

Subgroup analyses comparing those patients who showed a high ovulation rate during inositol treatment with those who were resistant to it indicated that the least androgenic patients were more likely to respond with establishment of normal menstrual rhythm. Furthermore, the morbidly obese patients (BMI > 37) showed no cardiovascular risk factor (BMI and HDL cholesterol) benefit. Taken together, these data suggest that either higher doses of inositol may prove to be more beneficial in the morbidly obese patient or such patients may be resistant to this form of therapy. These statements remain to be tested in future studies. A number of reports have indicated that insulin sensitizing agents improve ovulation rates in women with PCOS, and they have shown conflicting results with respect to changes in ovulation rate and also changes in endocrinology during inositol treatment. Our results are consistent with two studies[12,13] that also show that inositol treatment failed to determine any changes in hyperandrogenism or hyperinsulinemia.

On the other hand, several studies have shown decreases in hyperandrogenism and markers of insulin resistance with inositol in PCOS[9-14]. A recent comprehensive multicenter, multidose study using the peroxisome proliferator-activated receptor agonist troglitazone[7] showed improvements in hyperandrogenism, mediated through circulating free androgens rather than total androgen concentrations, and also in glycemic indices. These changes were dose-related, as were improvements in ovulation rates. It is possible that patient selection criteria may have an impact on the potential for beneficial effects of inositol on surrogate markers of insulin resistance and hyperandrogenism.

The principal inclusion criteria in our study was disturbances of ovarian function, whereas in other studies the emphasis may have been on more profound metabolic derangements, including clinical manifestations of hyperandrogenism. It is noteworthy that the higher doses of troglitazone treatment (300 and 600 mg) were associated with weight increase in women who were generally overweight at the time of starting[7]. Weight loss achieved in the inositol-treated patients would be considered a beneficial side effect of the treatment, and indeed in our study women in the active arm lost significant weight during treatment, whereas those on placebo gained weight over the 4-month period. The increase in ovulation rate seen in the inositol-treated patients appeared to take place rapidly, as evidenced by significant increases in circulating E2 concentrations, representing follicular maturation, within the first 8 days of treatment and also the shorter mean time to first ovulation. This effect is likely to have taken place before significant weight loss or changes in the lipid profiles, and also in the absence of changes in glycemic indices. This leads to the possibility

of direct gonadal effects of inositol as has been demonstrated for the peroxisome proliferator-activated receptor agonist troglitazone[29]. Our randomized study provides some support for this proposal, although it should be noted that ovulation was only modestly improved in the inositol group. Indeed, only a third of the treated cases established normal ovulation frequency with immediate effect. Thus, before the treatment with inositol might become an established practice in this clinical circumstance, larger and longer controlled studies should be undertaken. These should be dose-determining and aimed to define patient characteristics that best predict beneficial response to inositol treatment. Furthermore, we also suggest that the problems of maternal obesity be carefully considered with such treatment, and that weight loss may be the better approach[31] in many circumstances.

Finally, the high dropout rate in the inositol arm (more than 30%) is notable. Clinically, this observation is important and indicates that significant side effects on the dosage regime we used are common. Most of the discontinuation cases occurred at the early part of treatment, suggesting that women prescribed inositol should be adequately counseled and perhaps actively supported through this stage.

In conclusion, using a comprehensive, detailed endocrinological assessment of ovarian function, we have shown that inositol treatment increases ovulation rates by a significant but modest degree in women with oligomenorrhea and PCOS. Continued treatment also resulted in significant weight loss (and leptin reduction) and an associated change in HDL cholesterol. These beneficial effects of inositol support a future therapeutic role in women with PCOS.

Further large randomized studies are needed to determine appropriate dosages and duration of the treatment.

References

1) *Dunaif A, Givens JR, Haseltine F, Merriam GR (eds).* The Polycystic Ovary Syndrome. Blackwell Scientific, Cambridge, MA, 1992.

2) *Franks S.* Polycystic ovary syndrome. N Engl J Med 1995; 333: 853-861.

3) *Polson DW, Wadsworth J, Adams J, Franks S.* Polycystic ovaries–a common finding in normal women. Lancet 1998; 1: 870-872.

4) *Pettersson F, Fries H, Nillius SJ.* Epidemiology of secondary amenorrhea. Am J Obstet Gynecol 1973; 117: 80-86.

5) *Hull MGR.* Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies.Gynecol Endocrinol 1987; 1: 235-245.

6) *Goldzieher JW, Green JA.* The polycystic ovary. I. Clinical and histologic features. J Clin Endocrinol Metab 1962; 22: 325-338.

7) *Burghen GA, Givens JR, Kitabchi AE.* Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. J Clin Endocrinol Metab 1980; 50: 113-116.

8) *Dunaif A, Hoffman AR.* Insulin resistance and hyperandrogenism: clinical syndromes and possible mechanisms. In: Pancheri P, Zichella L (eds) Biorhythms and Stress in the Physiopathology of Reproduction. Hemisphere Publishin Co, Washington, DC, 1998; pp 293-317.

9) *Pugeat M.* Genetics of the polycystic ovarian syndrome and therapeutic perspectives. Rev Med Chir Soc Med Nat Iasi 2000; 104: 11-19.

10) *Laboureau-Soares Barbosa S, Rodien P, Rohmer V.* 2002 Polycystic ovary syndrome: treatment with insulin-sensitizing agents. Ann Endocrinol (Paris) 2002; 63: 31-35.

11) *Iuorno MJ, Nestler JE.* Insulin-lowering drugs in polycystic ovary syndrome. Obstet Gynecol Clin North Am 2001; 28: 153-164.

12) *Fleming R, McQueen D, Yates RWS, Coutts JRT.* Spontaneous follicular and luteal function in infertile women with oligomenorrhoea: role of luteinizing hormone. Clin Endocrinol (Oxf) 1995; 43: 735-739.

13) *Adams J, Polson JW, Franks S.* Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. Br Med J 1986; 293: 355-359.

14) *White DM, Polson DW, Kiddy D, et al.* Induction of ovulation with low-dose gonadotropins in polycystic ovary syndrome: an analysis of 109 pregnancies in 225 women. J Clin Endocrinol Metab 1996; 81: 3821-3824.

15) *Pirwany IR, Yates RW, Cameron IT, Fleming R.* Effects of the insulin sensitizing drug metformin on ovarian function, follicular growth and ovulation rate in obese women with oligomenorrhoea. Hum Reprod 1999; 14: 2963-2968.

16) *World Health Organization 1989 Measuring obesity: classification and distribution of anthropometric data.* Copenhagen: WHO (Nutr UD, EUR/ICP/NUT 125).

17) *Lipid Research Clinics Program.* Lipid and lipoprotein analysis, manual of laboratory operations, 1. Bethesda, MD: National Institutes of Health, DHEW Publications; 1975; 75.

18) *McConway MG, Johnson D, Kelly A, Griffin D, Smith J, Wallace AM.* Differences in circulating concentrations of total, free and bound leptin relate to gender and body composition in adult humans. Ann Clin Biochem 2000; 37: 717-723.

19) *Nestler JE, Jakubowicz DJ, Iuorno MJ.* Role of inositolphosphoglycan mediators of insulin action in the polycystic ovary syndrome. J Pediatr Endocrinol Met 2000; 13 (Suppl 5): 1295-1298.

20) *Nestler JE.* Inositolphosphoglycans (IPGs) as mediators of insulin's steroidogenic actions. J Basic Clin Physiol Pharmacol 1998; 9: 197-204.

21) *Larner J, Allan G, Kessler C, Reamer P, Gunn R, Huang LC.* Phosphoinositol glycan derived mediators and insulin resistance. Prospects for diagnosis and therapy. J Basic Clin Physiol Pharmacol 1998; 9: 127-137.

22) *Gasic A, Bodenburg Y, Nagami M, Green A, Urban RJ.* Troglitazone inhibits progesterone production in porcine granulosa cells. Endocrinology 1998; 139: 4962-4966.

23) *Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ.* Weight loss in obese infertile women results in improvement in the reproductive outcome for all forms of fertility treatment. Hum Reprod 1998; 13: 1502-1505.