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Myo-inositol in patients with polycystic ovary syndrome: A novel method for ovulation induction

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Abstract

Background. Polycystic ovary syndrome (PCOS) is often characterized by chronic oligo- or anovulation (usually manifested as oligo- or amenorrhea), and hyperandrogenism. In addition, 30–40% of PCOS women have impaired glucose tolerance, and a defect in the insulin signaling pathway (inositol-containing phosphoglycan mediators) seems to be implicated in the pathogenesis of insulin resistance. PCOS patients are subfertile as a consequence of such ovulatory disorders and often need drugs, such as clomiphene citrate or follicle-stimulating hormone, for ovulation induction, which increases the risk of multiple pregnancy and ovarian hyperstimulation syndrome. We hypothesized that the administration of an isoform of inositol (myo-inositol), belonging to the vitamin B complex, would improve the insulin-receptor activity, restoring normal ovulatory function.

Materials and methods. Twenty-five PCOS women of childbearing age with oligo- or amenorrhea were enrolled in the study. Ovulatory disorder due to PCOS was apparently the only cause of infertility; no tubal defect or deficiency of male semen parameters was found. Myo-inositol combined with folic acid (Inofolic®) 2 g twice a day was administered continuously. During an observation period of 6 months, ovulatory activity was monitored with ultrasound scan and hormonal profile, and the numbers of spontaneous menstrual cycles and eventually pregnancies were assessed.

Results. Twenty-two out of the 25 (88%) patients restored at least one spontaneous menstrual cycle during treatment, of whom 18 (72%) maintained normal ovulatory activity during the follow-up period. A total of 10 singleton pregnancies (40% of patients) were obtained. Nine clinical pregnancies were assessed with fetal heart beat at ultrasound scan. Two pregnancies evolved in spontaneous abortion.

Conclusion. Myo-inositol is a simple and safe treatment that is capable of restoring spontaneous ovarian activity and consequently fertility in most patients with PCOS. This therapy did not cause multiple pregnancy.

Keywords: *Myo-inositol, polycystic ovary syndrome, ovulation induction*

Introduction

Polycystic ovary syndrome (PCOS) is a medical condition that causes irregular menstrual cycles, chronic anovulation most often manifested as oligo- or amenorrhea, and androgen excess, with the typical ovarian ultrasound features [1]. It is the most common cause of ovulatory disorders and female infertility, and affects approximately 6–10% of women in childbearing age [2]. However, its pathogenesis is still poorly understood.

Recently, many investigators have focused on the impaired glucose tolerance that affects 30–40% of patients with PCOS [3]. Insulin plays a direct role in the pathogenesis of hyperandrogenemia in PCOS, acting synergistically with luteinizing hormone to enhance the androgen production of theca cells [4]. An inositol phosphoglycan molecule containing D-chiro-inositol (DCI) is known to have a role in activating enzymes that control glucose metabolism [5]. Indeed, a defect in tissue availability or altered metabolism of DCI or inositol phosphoglycan

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mediators has been found in PCOS women and may contribute to their insulin resistance [6,7].

Isoforms of inositol belong to the vitamin B complex. Epimerization of the six hydroxyl groups of inositol results in the formation of up to nine stereoisomers, including myo-inositol (MI) and DCI. MI is widely distributed in nature whereas DCI, the product of epimerization of the C1 hydroxyl group of MI, is relatively rare [8].

Elevated concentration of MI in human follicular fluid appears to play a role in follicular maturity and provides a marker of good-quality oocytes [9]. Furthermore, experiments on mouse oocytes showed that supplementation of MI in the culture medium increased meiotic progression of germinal vesicles by enhancing the intracellular $Ca2^{+}$ oscillation [10].

Thus we hypothesized that the administration of MI, a precursor of DCI, would improve insulin activity and restore ovulatory function and fertility in amenorrheic women with PCOS.

Materials and methods

A total of 25 women, 28 to 38 age years of age, with PCOS defined by oligo- or amenorrhea (six or fewer menstrual cycles during a period of 1 year), hyperandrogenism (hirsutism, acne or alopecia) or hyperandogenemia (elevated levels of total or free testosterone) and typical ovarian features on ultrasound scan, were enrolled in the study.

All patients attended our IVF Unit for infertility that had lasted for more than 14–16 months. Other medical conditions causing ovulatory dysfunction, such as hyperprolactinemia or hypothyroidism, or androgen excess, such as adrenal hyperplasia or Cushing's syndrome, were excluded by hormonal tests. All women underwent assessment of tubal patency and all male partners were evaluated with two different semen sample analyses, without finding any defect. Anovulation was ascertained by weekly plasma progesterone concentration <2.5 ng/ml. Thus, at the end of diagnostic procedures, it was determined that the most likely cause of the couple's subfertility was ovulation dysfunction only.

PCOS women were treated orally with MI 2 g plus folic acid 200 μg (Inofolic®; Loli Pharma, Rome, Italy) as soluble powder, twice daily, continuously, until the end of the study or a positive pregnancy test. Patients were instructed to register their menstrual bleeding throughout the follow-up period of 6 months. Furthermore, in order to evaluate the restoration of spontaneous ovarian activity, weekly determination of serum progesterone and testosterone levels, as well as transvaginal ultrasound scan documenting the presence of follicular growth or luteal cyst, were performed after the first menstrual cycle. Pre- and post-treatment hormone concentrations were statistically compared using the two-tailed t test.

Moreover, eventual pregnancies were confirmed by a positive test for plasma β-human chorionic gonadotropin and ascertainment of a fetal heart beat on ultrasound scan.

Results

Baseline clinical and biochemical features of the PCOS patients are reported in Table I. The outcome of treatment is shown in Tables I and II.

After a mean of 34.6 ± 5.5 days of MI administration, 22 out of the 25 women (88%) had a first menstrual cycle. Eighteen of these 22 patients presented monthly menstruations during the follow-up period. All of them maintained spontaneous ovulation activity, documented by follicular growth and increased serum progesterone concentrations in the luteal phase (mean 10.5 ± 1.8 ng/ml). Furthermore, after treatment with MI, these women showed significantly decreased concentrations of serum total testosterone (95.6 ± 8.5 vs. 45.2 ± 6.7 ng/dl; $p = 0.003$) and free testosterone (1.0 ± 0.8 vs. 0.38 ± 0.1 ng/dl; $p = 0.005$). The length of successive cycles was improved to 31.7 ± 3.2 days.

Two out of the 22 women showed only a follicular development on ultrasound without progesterone elevation during weekly blood sampling, while two women did not have any further ovarian activity after the first cycle.

During the observational period of 6 months a total of ten biochemical pregnancies occurred. Nine of the ten were singleton pregnancies documented at ultrasound scan, while one of them was a biochemical abortion. One out of the nine pregnancies

Table I. Clinical and biochemical features of the patients.

	Baseline	After myo-inositol
Age (years)	32 ± 4	
Body mass index (kg/m^2)	28.5 ± 2.4	
Follicle-stimulating hormone (mUI/ml)	4.5 ± 2.8	
Luteinizing hormone TSH (mUI/ml)	6.3 ± 3.1	
Prolactin (ng/ml)	19.1 ± 2.7	
Thyroid-stimulating hormone	1.78 ± 0.85	
Serum progesterone (ng/ml)	1.8 ± 0.7	10.5 ± 1.8
Serum total testosterone (ng/dl)	95.6 ± 8.5	45.2 ± 6.7*
Serum free testosterone (ng/dl)	1.0 ± 0.8	0.38 ± 0.1†
Serum androstenedione (ng/dl)	230 ± 35	205 ± 28

Significant difference compared with baseline: *$p = 0.003$; †$p = 0.005$.

Table II. Outcome of treatment with myo-inositol.

No. of patients treated	25
No. of patients with menstrual cycle after treatment (% of patients)	22 (88)
No. of patients with restored monthly ovulation (% of patients)	18 (72)
No. of pregnancies	10
No. of pregnancies/no. of treated patients (%)	40
No. of pregnancies/no. patients with restored monthly ovulation (%)	55
No. of abortions (% of pregnancies)	2 (20)
Multiple pregnancy	0

evolved in a spontaneous abortion at 7 weeks of gestation. No multiple pregnancy was noted.

Discussion

PCOS is one of the most common endocrine disorders affecting women. Insulin resistance and hyperinsulinemia are strictly inherent to the phenotype of a high proportion of women with PCOS. A defect in insulin action has been suspected, particularly as consequence of a deficiency of DCI, a component of inositol phosphoglycan.

Chronic anovulation is often the main cause of infertility in patients of reproductive age. It is well known that ovulation induction is a complex issue owing to the increased risk of ovarian hyperstimulation syndrome and multiple pregnancy [11,12]. Clomiphene citrate, an antiestrogen, is the common first-choice drug in women with newly diagnosed PCOS, while insulin-lowering medications represent novel therapies for restoring spontaneous ovulation [13,14]. The efficacy of metformin is still debated, both alone and in association with clomiphene citrate [15,16]. Metformin treatment is associated with a higher incidence of side-effects such as nausea, vomiting and other gastrointestinal disturbances [17].

DCI administration increases the action of insulin in patients with PCOS, thereby improving ovulatory function and decreasing serum testosterone concentration [6,18,19]. MI, a precursor of DCI, is widely distributed in nature whereas DCI is relatively rare [7]. MI is present in human follicular fluid, where elevated concentrations appear to play a positive role in follicular maturity and provide a marker of good-quality oocytes [9]. Supplementation of MI in culture medium increased meiotic progression of germinal vesicles in mouse oocytes by enhancing the intracellular Ca^{2+} oscillation [10]. However, no data exist on therapy with MI in anovulatory women of reproductive age.

Our study demonstrated that MI oral supplementation restores spontaneous ovulation and menstrual cycles, and increases progesterone secretion in the luteal phase, in most infertile patients with PCOS. The present results are in line with other studies evaluating insulin-sensitizing agents in monotherapy or in association with clomiphene citrate [7,13,14, 16–18], suggesting the positive effect that MI plays on spontaneous ovarian activity. Furthermore, we found that MI therapy is able to reduce serum testosterone, both total and free, as already demonstrated with DCI. All pregnancies obtained in the follow-up period were singleton, and there was no increased incidence of abortion.

In conclusion, MI is a simple and safe treatment that is able to restore spontaneous fertility in most patients with PCOS.

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