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Use of Myo-inositol for Ovulation Induction in Patients with Polycystic Ovary Syndrome

Authors
Dr Tabassum Ahmed[1], Dr Renu Rohtagi[2], Dr Punit Hans[3]
[1]Assistant Professor, Dept. (Obst&Gynae), NMCH, Patna, Bihar
[2]Associate Professor, Dept. (Obst&Gynae), NMCH, Patna, Bihar
[3]Junior Resident, Dept. (Obst&Gynae), NMCH, Patna, Bihar

Abstract
Objectives: *Administration of isoform of inositol (myo-inositol) belonging to Vitamin B complex would improve insulin receptor activity, in restoring normal ovulatory function.*
Method:*25 PCOS patients of child bearing age were enrolled in the study. Only ovulatory disorders due to PCOS were included in the study. All other factors of infertility were excluded.*
Myo-inositol combined with folic acid 2 gram twice daily was administered continuously for a period of six months Ovulation was assessed by ultrasound scan and hormonal profile and number of spontaneous menstrual cycle eventual pregnancies were assessed
Result: *20 out of 25 (80%) patients restored at least one spontaneous menstrual cycle. During treatment of whom 16 (64%)had normal ovulatory activity during follow up period.A total of 12 singleton pregnancy (48%) occurred. 2 pregnancies terminated in spontaneous abortion.*
Conclusion: *Myo-inositolis a simple and safe treatment for ovulation induction and subsequent pregnancy. The therapy did not cause multiple pregnancy.*
Keywords: *PCOS, Ovulation induction, Myo-inositol*

Introduction

PCOS is a condition that manifests as irregular menstrual cycles, chronic anovulation most often manifested as oligomenorrhoea hyperandrogenism (Clinical or Bio Chemical) with polycystic ovaries. Hyperandrogenism and anovulation that accompanies PCOS may be caused by abnormalities in 4 endocrinologically active compartments: (a) Ovaries, (b) Adrenal Glands (c) Periphery (fats), (d) hypothalamus pituitary compartment. In PCOS patients the ovarian compartments is the most consistent contributor of androgen. It is the most common cause of ovulatory disorder and female infertility and affects 6 to 10 % of women in child bearing age. PCOS is associated with approximately 80 – 90% of women who suffer from infertility due to anovulation.

Recently, many investigators have focused on the impaired glucose tolerance that affects 30-40% of patients with PCOS. 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. An inositol phosphoglycan molecule is known to have a role in activating enzymes that control

glucose metabolism. Indeed, a defect in tissue availability or altered metabolism of DCI or inositol phosphoglycan contribute to their insulin resistance.

Isoforms of inositol belong to the vitamin B complex. Elevated concentration of MI in human follicular fluid appears to play a role in follicular maturity and provides a marker of good-quality oocytes. 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.

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

Materials and Methods

A total of 25 women, 25 to 35 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 testosterone) and typical ovarian features on ultra

sound scan, were enrolled in the study. The study period was from March 2015 to March 2016. Other medical conditions causing ovulatory dysfunction, such as hyperprolactinemia or hypothyroidism, or androgen excess, 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 mg 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.

Moreover, eventual pregnancies were confirmed by a positive test for plasma b-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 40.5 + 6.5 days of MI administration, 20 out of the 25 women (80%) had a first menstrual cycle. Sixteen of these 20 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 10.6 + 1.5 ng/ml). Furthermore, after treatment with MI, these women showed significantly decreased concentrations of serum total testosterone (90.6 ± 8.5 vs. 44.2 ± 6.5 ng/dl; p = 0.003). The length of successive cycles was improved to 30.5 + 3.2 days.

Two out of the 20 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 12 biochemical pregnancies occurred. All were singleton pregnancies. Two out of the twelve pregnancies evolved in a spontaneous abortion at 7 weeks of gestation.

Table I. Clinical and biochemical features of the patients

	Baseline	After myo-inositol
Age (years)	30 ± 4	
Body mass index (kg/m^2)	26.5 ± 2.5	
Follicle-stimulating hormone (mUI/ml)	6.5 ± 2.5	
Luteinizing hormone TSH (mUI/ml)	8.3 ±3.2	
Prolactin (ng/ml)	20.1 ± 2.5	
Thyroid-stimulating hormone	1.70 ± 0.80	
Serum progesterone (ng/ml)	1.8 ± 0.5	10.1 ± 1.5
Serum total testosterone (ng/dl)	90.6 ± 8.5	44.2 ± 6.5*

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)	20 (80)
No. of patients with restored monthly ovulation(% of patients)	16 (64)
No. of pregnancies	12
No. of abortions (% of pregnancies)	2 (20)
Multiple pregnancy	0

Discussion

Insulin-sensitizing agents have been recently suggested as the therapy of choice for polycystic ovary syndrome (PCOS), since insulin resistance and associated hyperinsulinemia are recognized as important pathogenetic factors of the syndrome. In fact, almost all obese PCOS women and more than half of those of normal weight are insulin resistant, and therefore present some degree of hyperinsulinemia. For this reason, the use of insulin sensitizers had been suggested in most patients with PCOS, as a treatment useful in the reduction of serum androgen levels and gonadotropins, and subsequent ovulation. These therapies have also been associated with a decrease in hirsutism and acne, and with a regulation of menses and an improvement of ovulation and fertility.

A defect in the insulin signal pathway (inositol-containing phosphoglycan mediators) had been discovered to be implicated in the pathogenesis of insulin resistance. As consequence, the administration of different isoforms of inositol as D-Chiro-inositol (DCI) or myo-inositol (MYO) is demonstrated improving the physiological insulin-receptor activity, restoring spontaneous ovulatory function in most of PCOS women.

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]. Metformin treatment is associated with a higher incidence of side-effects such as nausea, vomiting and other gastrointestinal disturbances [17].

MI administration increases the action of insulin in patients with PCOS, thereby improving ovulatory function and decreasing serum testosterone concentration [6,18,19]. 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]. Our study demonstrated that MI oral supplementation restores spontaneous ovulation and menstrual cycles, and increases progesterone secretion in theluteal 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. All pregnancies obtained in the follow-up period were singleton.

Conclusion

To conclude MI is a simple and safe treatment that is able to restore spontaneous fertility in most patients with PCOS with singleton pregnancy.

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