The Antiseptic

Estd.1904

Indexed in IndMED

A MONTHLY JOURNAL OF MEDICINE AND SURGERY

Email: admin@theantiseptic.in www.theantiseptic.in

Vol. 115 • No. 11 NOVEMBER 2018 ISSN 0003-5998 • ₹ 100

Palliative Care in Patient with Kidney Disease and Cancer

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THE ANTISEPTIC - A MONTHLY JOURNAL OF MEDICINE & SURGERY

Vol 115 No 11 NOVEMBER 2018

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Myo-inositol: A natural Insulin sensitizer for PCOS

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Introduction:

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age. It is characterized by chronic anovulation, hyperandrogenism, and insulin resistance. It is the main cause of infertility due to the menstrual dysfunction and metabolic disorders. Women with PCOS are also at an increased risk of developing cardiovascular disorders because of dyslipidemia and insulin resistance.

The pathogenesis of PCOS is still largely unknown and various etiological factors are suspected to be involved. Compelling evidence accumulated over last two decades suggests the central role of insulin resistance and/or compensatory hyperinsulinemia in the pathogenesis of PCOS[1]. Hyperinsulinaemia, secondary to insulin resistance is found in approximately 80% of women with PCOS and central obesity, as well as in 30%-40% of lean women diagnosed with PCOS[2]. Insulin resistance and subsequent hyperinsulinemia contribute both directly and indirectly to hyperandrogenism seen in PCOS[3]. Insulin directly stimulates the ovarian theca cells to produce greater amount of androgens, and it also inhibits hepatic synthesis of sex hormone-binding globulin (SHBG), thus indirectly increasing the levels of circulating free androgens.

Myo-inositol:

Inositol is a physiological compound belonging to the sugar family. The two inositol Stereoisomer's, myo-inositol (MI) and D-chiro-inositol (DCI) are the two main Stereoisomers present in human body. Myo-inositol is synthesized from glucose-6-phosphate in two steps. First, glucose-6-phosphate is isomerised to myo-inositol-1-phosphate, which is then dephosphorylated by an inositol monophosphatase enzyme giving free myo-inositol. D-chiro-inositol is synthesized by an insulin dependent epimerase that converts myo-inositol into D-chiro-inositol. Myo-inositol is incorporated into cell membranes as phosphatidyl-myo-inositol, the precursor of inositol triphosphate. Inositol triphosphate acts as a second messenger, regulating the activities of several hormones such as FSH, TSH and insulin.[4]

In physiological conditions, the intracellular pool of inositol(s) in human ovaries and testis contains 99% of myo-inositol, whereas the remaining part is D-chiro-inositol. It means that myo-inositol is essential qualitatively and quantitatively for the functioning of the reproductive system[5]. Normally, MI/DCI ratio in blood is about 40:1[6], whereas in follicular fluid it is up to 100:1[7]. In general, the different distribution reflects the distinct roles that these two stereoisomers play within the different tissues and organs, according to the specific tissue needs.

The activation of glucose transporters and glucose utilization take place under the regulation of myo-inositol, while glycogen synthesis is mainly controlled by D-chiroinositol. In the ovary, myo-inositol regulates glucose uptake and FSH signalling[8].The relevance of MI concentrations in follicular fluid has been well documented. Chiu et al found a positive correlation between increased MI concentrations and better developmental potential of the oocytes. According to findings of their study, higher levels of MI in follicular fluid may be related to the wellbeing of follicle and improved quality of oocytes and embryos[9].

Myo-inositol: Efficacy in PCOS

Several studies in women with PCOS have shown that MI supplementation can improve menstrual irregularity and insulin resistance, while reducing hyperandrogenism[10, 11].

In a study by Minozzi and colleagues, 46 hirsute women were given 2 g MI therapy for 6 months. At the end of the study, it was observed that hirsutism was decreased and levels of total androgens, FSH and LH were also reduced, while estradiol levels increased. Insulin resistance, measured by the homeostatic model assessment (HOMA), was also significantly reduced[12].

A systemic review of six randomized controlled trials that assessed the effectiveness of MI supplementation in PCOS, reported that the higher dose of 4 gm/day for 12 and 16 weeksseems

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Specially Contributed to "The Antiseptic"
Vol. 115 No. 11 & P : 17 - 20

to achieve better results than lower doses.However, MI doses used in most published studies range from 2 to 4 gm/day .In general, no side effects havebeen reported and overall results provide level IA evidence of MI effectiveness, mainly assessed as improved insulin sensitivity[13].

Papaleo et al [14] reported that 2 gm MI plus 200 mcg of folic acid, twice a day for 6 months restored spontaneous ovarian activity and fertility in patients with PCOS. In these patients, MI induced normal ovulatory activity in 72% of cases, with a pregnancy rate of 40% during the 6-month observation period.

In a double blind trial conducted by Ciotta et al.[15] patients received 2 gm of MI plus 200 mcg folic acid or 200 mcg folic acid only, twice a day, for 3 months. At the end of treatment, in the MI group there was a higher number of follicles with diameter > 15 mm, visible at ultrasound during stimulation and more oocytes were collected.

In another randomised controlled trial, 20 overweight PCOS women received 2 gm of MI plus 200 mcg folic acid or 200 mcg folic acid alone for 12 weeks. Patients taking MI experienced an improvement of reproductive axis and IR state after 12 weeks of supplementation, while no change occurred in patients treated only with folic acid

After 12 weeks of MI administration plasma LH, PRL,T, insulin levels and LH/FSH ratio were significantly reduced and insulin sensitivity, expressed as glucose-to-insulin ratio and HOMA index, significantly improved. Menstrual cycle was restored in all subjects with amenorrhea or oligomenorrhea[16].

Positive effects of MI on ovarian function have been confirmed by one more study in50 overweight PCOS patients. In this study, group A was given 2 gm MI plus 200 mcg folic acid daily for 12 weeks and group B was administered only 200 mcg folic acid daily. The Authors found significant improvement in hormonal parameters and restoration of menstrual cycle in all patients with amenorrhea and oligomenorrhea belonging to group A, while no changes were noted in group B patients. Moreover, reduced plasma LH, prolactin, LH/FSH ratio, and insulin resistance measured by HOMA index were observed in the MI group.[17]

In a recent study, 50 anovulatory PCOS patients with insulin resistance were given 2 gm MI and 200 mcg folic acid twice a day, for three cycles. Ovulation and pregnancy were achieved in 61.7 and 37.9% of women, respectively.[18]

Myo-inositol Vs Metformin

According to current guidelines, insulin-sensitizers are the first line therapy in women with PCOS. Besides metformin, MI is now considered as an appropriate insulin-sensitizing agent who could benefit women with PCOS[19].

In a comparative study, fifty PCOS women with insulin resistance and/or hyperinsulinemia were randomized to treatment with metformin (1500 mg/day) or myo-inositol (4 g/day) for six months. Insulin Resistance was defined as HOMA-IR >2.5. The insulin sensitivity improved in both treatment groups. The BMI was also significantly decreased and the menstrual cycles were normalized in about 50% of the women[20].

In another comparative study[21], one hundred twenty patients with polycystic ovarian syndrome and 14–16 months of infertility were enrolled in a randomized, controlled clinical trial. Patients were randomly assigned to receive either 1,500 mg/day metformin or 4 grams of myo-inositol plus 400 mcg folic acid daily. The primary endpoint was restoration of spontaneous ovulation (measured by monitoring serum progesterone levels weekly and transvaginal ultrasound to confirm). Secondary endpoints included resistance to treatment (percentage of patients who did not restore spontaneous ovulation), pregnancy rate, and abortion rate. Fifty percent of the patients who received metformin restored spontaneous ovulation, and 18.3% of these achieved pregnancy. While sixty-five percent of patients treated with myo-inositol restored spontaneous ovulation, and 30% of these achieved pregnancy.

In the remaining patients who did not respond to monotherapy, r-FSH was added. In each of the 2 groups (metformin plus r-FSH group or myo-inositol and folic acid plus r-FSH group), 11 pregnancies occurred. The total pregnancy rates were 36.6% for patients receiving metformin and 48.4% for patients receiving myo-inositol. The study demonstrated a statistically significant difference in restoration of spontaneous ovulation in patients taking myo-inositol over metformin. There was an overall higher rate of pregnancy in the myo-inositol group. In addition, patients on myo-inositol reported no side effects during the course of treatment. This study concluded that Myo-inositol should be considered as a first-line treatment in patients with PCOS experiencing chronic anovulation or infertility secondary to anovulation.

Myo-inositol Vs D-Chiro-inositol

In the ovary of PCOS women, there is an imbalance between

MI and DCI concentrations, with a putative MI deficiency, which might impair the FSH signalling[22]. Due to ovarian MI deficiency, glucose uptake and metabolism of both oocytes and follicular cells are negatively affected, compromising oocyte quality which depends on MI levels.[23].

The effects of myo-inositol and D-chiro-inositol on oocyte quality in euglycemic PCOS patients were compared in a prospective, controlled, randomized trial[24] Eighty-four PCOS patients, undergoing ovulation induction for ICSI, were recruited for this study. Forty-three participants received Myo-Inositol 2 gm twice a day and forty-one patients received D-chiro inositol 0.6 gm twice a day.

The results showed that the total number of oocytes retrieved did not differ in the two treatments groups. However, the number of mature oocytes were significantly increased and the number of immature oocytes decreased in the myo-inositol group compared to the D-chiro-inositol group. Furthermore, myo-inositol treated patients showed an increase in the mean number of top quality embryos and in the total number of pregnancies compared to D-chiro inositol-treated patients.

The study concluded that myo-inositol treatment rather than D-chiro-inositol is able to improve oocyte and embryo quality during ovarian stimulation protocols.

In another study, 54 women, aged <40 years and diagnosed with PCOS were enrolled. Patients with insulin resistance and/or hyperglycaemia were excluded from the study. Patients were randomly divided into 5 groups (n=10-12): a placebo group, and 4 groups (A-D) that received 300-600-1200-2400 mg of DCI daily, respectively. All treatments were carried out for 8 weeks before follicle stimulating hormone (rFSH) administration. The results showed that total r-FSH units increased significantly in the two groups that received the higher doses of DCI. The number of immature oocytes was also significantly increased in the three groups that received the higher doses of DCI. Concurrently, the number of MII oocytes was significantly lower in the D group compared to placebo group. In addition, the number of grade I embryos was significantly reduced by DCI supplementation. The study concluded that increasing DCI dosage progressively worsens oocyte quality and ovarian response.[25]

Myo - inositol: Assisted Reproduction

A number of recent studies have evaluated the role of inositol in ART outcome in women with PCOS. The data from these studies support the notion that inositol has a beneficial effect on ovarian stimulation and ART outcomes in PCOS patients.

Papaleo et al.[26] investigated the effect of myo-inositol supplementation of 2 gm twice a day on ART outcomes in sixty patients with PCOS undergoing ovarian stimulation for intra cytoplasmic sperm injection (ICSI) cycles. They found significant reduction in the total number of days of stimulation (11.4± 0.9 versus 12.4 ± 1.4, $P = 0.01$), significantly lower peak E2 levels at hCG administration (2,232 ± 510 versus 2,713 ±595 pg/mL, $P = 0.02$), and reduction in degenerated oocytes (1.0 ± 0.9 versus 1.6 ± 1.0, $P = 0.01$) without compromising oocyte yield in the myo-inositol group.

Myo-inositol, D-Chiro-Inositol: What is the right dose?

The clinical trials conducted till date suggest that the ratio between MI and DCI may be less important than the absolute concentrations of either MI or DCI in treatment of PCOS. The usual therapeutic dose of myo-inositol appears to be 2-4 gm/day, while that of D-Chiro-inositol appears to be 300-1500 mg/day. Unfortunately available pharmaceutical preparations based on MI/DCI combination provide very lowamounts of DCI (13.8–27.6 mg), insufficient to achieve levels shown to be effective clinically[27]

Conclusion:

Polycystic ovary syndrome is a common endocrine and metabolic disorder characterized by oligo-anovulation, hyperandrogenism, and insulin resistance. Insulin resistance plays a key role inthe pathogenesis of this syndrome, both in lean and obese women.

From the currently available evidence, it can be concluded that myo-inositol is an effective and generally safe, natural treatment option for PCOS. Results of a number of randomised controlled trials have shown that myo-inositol supplementation in women with PCOS may lead to an improvement in insulin sensitivity, restoration of ovulation, improvement in oocyte quality and a reduction in hyperandrogenism , which in turn, helps to increase their fertility. These beneficial actions of myo-inositol supplementation in PCOS patients are seen after 3-6 months of administration. The therapeutic dose of Myo-inositol varies from 2 to 4 grams per day and is not associated with any serious adverse effects.[28]. As myo-inositol is better tolerated than metformin, it offers an attractive alternative to metformin, particularly in patients

who cannot tolerate metformin or in whom metformin is contra-indicated.

Besides improving insulin sensitivity, glucose metabolism, hormonal pattern and infertility in PCOS, myo-inositol supplementation has beneficial effects on metabolic syndrome characteristics (obesity, lipid profile) and it also reduces risk of type 2 diabetes mellitus and gestational diabetes.[29].While, DCI supplementation has shown dose-dependent harmful effects on oocyte quality and ovarian response in PCOS women without insulin resistance and/or hyperglycaemia undergoing in vitro fertilization procedure[25].

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