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Mini Review

Myo-inositol and D-chiro-inositol as a Therapeutic Consideration for Polycystic Ovarian Syndrome

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Abstract

The polycystic ovarian syndrome (PCOS) is the most common endocrine disorder among the women of reproductive age. PCOS is also the leading cause of anovulatory infertility in 90 - 95% of the cases. Furthermore, the driving mechanism of insulin resistance puts the PCOS women at four-fold risk of type II diabetes in the long-run. Traditional treatments for the PCOS include insulin sensitizers and oral contraceptives which may present the challenge of tolerability. Given the challenges surrounding the PCOS therapy, the option of myo-inositol (MI) and D-chiro-inositol (DCI) needs to be explored further as they have shown some promise. By using MI and DCI, the changes in metabolic and endocrine parameters were noted in as little as 12 weeks and in most this was comparable to the metformin therapy. The risk of side effects appears to be minimal when using the inositol therapy. The smaller randomized clinical trials suggest a possible alternative or a synergistic option to the conventional PCOS therapy.

Keywords: *Polycystic Ovarian Syndrome; Insulin Resistance; Inositol; Myo-Inositol; D-Chiro-Inositol; Hyperandrogenism*

Background

The prevalence of polycystic ovarian syndrome (PCOS), as per the criteria set by Embryology/American Society for Reproductive Medicine and European Society for Human Reproduction is estimated to be as high as 20% [1]. The PCOS is the most common cause of anovulatory infertility (90-95%) and the infertility affects about 40% of the PCOS women [1-3]. The polycystic ovarian syndrome (PCOS) can be characterized by hyperandrogenism, irregular menses, and polycystic ovaries. The clinical presentation of the PCOS may include acne, hirsutism, acanthosis nigricans, weight gain, centripetal obesity, and irregular menses.

The insulin resistance driving the PCOS can lead to type II diabetes in the long run. A recent Danish registry study with 18,477 PCOS women who were age-matched with three groups of 54,680 controls found that the risk of type II diabetes was four times higher in the PCOS women and occurred at a median age of 31 years which was four years younger than the controls [4]. Given the prevalence of PCOS and its long-term implications along with the treatment challenge posed by poor tolerability of metformin at higher doses, the efficacy and safety of adjunct or alternate treatments needs to be explored. Myo-inositol and D-chiro-inositol have shown some therapeutic promise for the PCOS patients.

Myo-inositol (MI) and D-chiro-inositol (DCI) play a role in glucose uptake and oogenesis. In the glucose uptake process, MI and DCI are incorporated into inositol phosphoglycans which are secondary messengers of insulin [5]. Deficiency of the inositol can reduce the phosphatidylinositol-3 (PI3) kinase activity which leads to poor uptake of blood glucose [5]. In the ovaries, Myo-inositol regulates calcium metabolism which is involved in activation and completion of meiosis, release of cortical granules, and inhibition of polyspermy [6]. MI is converted to DCI by epimerase which is dependent on the metabolic balance [6]. In the insulin-resistant patients, the epimerase activity is reduced and as a result, MI to DCI ratio is increased [6]. However, within the ovaries of the PCOS patients, MI to DCI ratio is decreased

as the epimerase activity increases [7,8]. Given the above mechanisms, it's plausible that the insulin resistant patients may benefit from using MI and DCI. Over the years, many clinical studies have been conducted to explore the efficacy and safety of myo-inositol and D-chiro-inositol use in patients with PCOS.

Inositol alone or in combination with other PCOS therapy

Some studies have compared the use of myo-inositol and/or D-chiro-inositol with the standard PCOS therapy. A systematic review and meta-analysis of the randomized clinical trials from 1994 to 2017 compared metformin to the MI use in PCOS patients [9]. There was no significant difference found between the metformin and MI users on fasting insulin, homeostatic model of assessment-insulin resistance (HOMA-IR), testosterone, sex hormone binding globulin (SHBG), and BMI [9]. Consequently, the adverse events risk was significantly higher in women on metformin than those on MI [9]. In a randomized controlled clinical trial, PCOS women were given metformin or MI for 12 weeks. The MI, when compared with metformin, significantly reduced fasting plasma glucose, serum insulin, HOMA-IR, triglycerides, VLDL cholesterol, and significantly increased the quantitative insulin sensitivity check index [10]. There was also upregulation of PPAR-gamma when compared to the metformin [10].

In a meta-analysis of randomized controlled trials inclusive of PCOS women on myo-inositol alone or in combination with D-chiro-inositol, a significant decrease in fasting insulin, HOMA-IR, and testosterone were noted after MI supplementation [11]. Furthermore, a significant increase in SHBG was noted in patients who took MI for at-least 24 weeks [11]. In a randomized controlled trial involving PCOS women, one group received myo-inositol and another group received metformin for 12 weeks [12]. After 12-weeks of intervention, when compared to the metformin, it was found that MI significantly decreased total testosterone, showed improvement of Ferriman-Gallwey scores and hs-CRP levels, and down-regulated expression of interleukin-1 (IL-1) [12].

Fruzzetti., *et al.* randomized PCOS women to the metformin (1500 mg/day) or myo-inositol (4 g/day) group. There was similarity in results across both the groups which included improved insulin sensitivity, significant BMI decrease, and normalization of menstrual cycle in 50% of women [13]. Januszeweski., *et al.* placed PCOS women on a combined therapy of 550 mg of MI and DCI (10:1 ratio), two tablets daily for six months. There was a significant reduction and decrease in free testosterone, follicle stimulation hormone (FSH), luteinizing hormone (LH) and insulin levels, and a significant increase in SHBG [14]. After 6 months, serum glucose levels during 75g oral glucose tolerance test (OGTT) also decreased [14].

Few studies have explored using myo-inositol as an adjunct therapy to the standard PCOS therapy. Agrawal., *et al*. looked at the synergy between metformin and MI. PCOS women were placed in group I who received metformin 500 mg and MI 600 mg thrice a day and group II received daily dose of Metformin 1500 mg [15]. If a spontaneous conception was not achieved in 3 months, then three cycles of ovulation induction and intrauterine insemination were given [15]. There was a significant improvement in the length of menses and bleeding days, HOMA-IR, and live birth rates (55% vs. ~27%) in group I compared to group II [15].

In an adolescent study in girls (13-19 years) with PCOS, three groups were created: group 1 received drospirenone 3 mg/ethinyl estradiol 30 mcg, group 2 received 4 g myo-inositol and 400 mg folic acid, and group 3 received both. In group 2, significant reduction in weight, BMI, glucose, C-peptide, insulin, HOMA-IR, free testosterone, and LH was detected [16]. The weight and BMI slightly increased in group 1 [16]. However, in group 3, weight and BMI didn't change, but there was reduction in C-peptide, insulin, HOMA-IR, total testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEA-S), LH and anti-mullerian hormone levels, and SHBG increased [16]. This study illustrates that the combination of OCP and MI combination reduces the androgen levels, improves metabolic profile, and the negative impact of OCPs on weight gain is neutralized [16]. A randomized study in PCOS patients receiving MI plus DCI (40:1 ratio) or placebo (folic acid) for six months found significant reductions of LH, free testosterone, fasting insulin and HOMA index, and an increase in 17-beta-Estradiol in the group receiving MI and DCI [17].

Ovarian stimulation/IVF in conjunction with MI and DCI

Some studies have explored pregnancy outcomes in PCOS women on myo-inositol and/or D-chiro-inositol undergoing targeted pregnancy induction treatments such as ovarian stimulation, *in-vitro* fertilization (IVF), intrauterine insemination (IUI), etc. Mendoza., *et al*. took 60 PCOS women who were undergoing intracytoplasmic sperm injection (ICSI) and divided them into study group who took 550 mg MI + 150 mg DCI twice daily or control group who took 550 mg MI + 13.8 mg DCI twice daily. The pregnancy and live birth rates were significantly higher in the study group compared to the control group, 65.5% vs 25.9% and 55.2% vs. 14.8%, respectively [18]. In addition to this, the risk of ovarian hyperstimulation syndrome was much higher in the control group (18.5%) versus the study group (3.44%) [18]. In another study, intake of MI during IVF reduced the number of gonadotropins in both the PCOS and non-PCOS women and the length of controlled ovarian hyperstimulation in the PCOS women [19].

A population of 196 infertile patients diagnosed with PCOS were divided into group 1 which received 4g MI and 400 mcg folic acid before and during ovulation induction and into group 2 which directly received recombinant FSH (rFSH) and 400 mcg folic acid [20]. If group 1 didn't achieve spontaneous pregnancy, they were given rFSH and 400 mcg folic acid. Nine patients in group 1 conceived spontaneous pregnancy [20]. In group 1, the total rFSH dose and cycle duration were significantly lower and clinical pregnancy rates were higher [20]. A small cohort of PCOS patients treated with MI, clomiphene, and folic acid were compared to those who solely received clomiphene. It was found that the ovulation rate was significantly higher with MI and clomiphene group compared to the clomiphene alone group, 65.5% vs. 42% [21]. Furthermore, MI and clomiphene cumulative pregnancy rate was 53.8% vs. 42.2% for the clomiphene group [21]. The above studies illustrate improved outcomes for women with PCOS on MI who are undergoing ovarian stimulation or pregnancy induction procedures.

Conclusion

Multiple studies have shown positive results in PCOS women on myo-inositol and D-chiro-inositol. Using MI and DCI, the changes in metabolic and endocrine parameters were noted in as little as 12 weeks and in most cases these cases were comparable to the metformin therapy. As illustrated by the studies, the risk of side effects appears to be minimal when using inositol therapy. Although large randomized clinical trials would be helpful to assess the long-term safety and efficacy of the inositol in the PCOS patients, the smaller randomized clinical trials suggest a possible alternative or synergistic option to the conventional PCOS therapy.

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