The use of inositol(s) isomers in the management of polycystic ovary syndrome: a comprehensive review

Antoaneta Gateva, Vittorio Unfer & Zdravko Kamenov

To cite this article: Antoaneta Gateva, Vittorio Unfer & Zdravko Kamenov (2018): The use of inositol(s) isomers in the management of polycystic ovary syndrome: a comprehensive review, Gynecological Endocrinology, DOI: 10.1080/09513590.2017.1421632

To link to this article: https://doi.org/10.1080/09513590.2017.1421632

Published online: 08 Jan 2018.

Submit your article to this journal

View related articles

View Crossmark data
The use of inositol(s) isomers in the management of polycystic ovary syndrome: a comprehensive review

Antoaneta Gateva, Vittorio Unfer and Zdravko Kamenov

Clinic of Endocrinology, Alexandrovska University Hospital, Medical University, Sofia, Bulgaria; Health Department, UniPolisi – Institut des Etudes Universitaires, Disentis, Switzerland

ABSTRACT

The aim of this review is to present the current data about the role of inositols in the management of polycystic ovary syndrome (PCOS) women and in the prevention and treatment of gestational diabetes mellitus (GDM). We analyzed the available literature with key words PCOS, Myo-inositol, D-chiro-inositol, assisted reproductive technologies and GDM. The most recent literature would suggest that Myo-inositol, D-chiro-inositol and their combination in physiological ratio 40:1 could represent an important therapeutic strategy for the improvement of metabolic, hormonal and reproductive aspects of PCOS. In assisted reproductive technologies, however, myo-inositol and the combined treatment, despite D-chiro-inositol monotherapy, are able to improve clinical outcomes. Myo-inositol monotherapy results more effective in preventing and treating GDM even if a larger cohort of studies is needed to better clarify these results.

INTRODUCTION

Polycystic ovary syndrome (PCOS) affects approximately 6–10% of fertile women [1,2] and it is a major cause of menstrual disturbances, hirsutism and female infertility. PCOS diagnosis is based on the presence of two out of three criteria – (1) oligo- or anovulation; (2) clinical and/or biochemical signs of hyperandrogenism; (3) polycystic ovaries and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing’s syndrome) [3].

Role of inositols in PCOS

Different studies highlighted the involvement of Inositol in PCOS onset and development. Inositols are present in nature in nine stereoisomer derived from epimerization of the six hydroxyl groups. Among them, Myo-inositol (MI) is the most abundant one, with several important biological functions, whereas D-Chiro-Inositol (DCI), the second most abundant, plays integrative roles [4]. Specifically, MI regulates glucose intake and use, whereas DCI controls glycogen synthesis [5]. In the ovary, MI is involved in glucose uptake and FSH signaling; DCI is involved in the insulin-induced androgens synthesis. In particular, at ovarian level, DCI is involved in the insulin-mediated testosterone overproduction [6,7]. Of note, liver, fat and muscle display a significant variability in MI and DCI content in agreement with the distinct functions exerted by the two isomers. Furthermore, MI/DCI ratio is determined by tissue requirement and it derives from MI into DCI enzymatic conversion, controlled by a NAD–NADH-dependent epimerase.

Some studies demonstrated defects in tissue availability or altered metabolism of inositol phosphoglycans (IPG) in PCOS [8,9]. DCI was found to be involved in postreceptor insulin signaling [10,11] including androgen synthesis [7]. Due to MI involvement in FSH signaling, its impairment in PCOS might be caused by MI deficiency [7,12]. A systematic review [13] showed that less (DCI)-containing inositol phosphoglycan (DCI-IPG) was released in PCOS women compared to controls and this seems positively correlated with IR and hyperinsulinemia. DCI administration had beneficial effects on ovulation, anthropometric and metabolic markers in PCOS by enhancing insulin sensitivity. It has also been shown that American PCOS patients have decreased glucose-stimulated release of DCI-IPG and increased urinary clearance of DCI (uClDCI) associated with hyperinsulinemia [8]. Greek women, with or without PCOS, display increased uClDCI and decreased AUGCDCI-IPG in association with higher insulin levels but adiposity independent. Increased clearance of inositols could reduce tissue availability of DCI and decrease the release of DCI-IPG mediator, which could contribute to IR and compensatory hyperinsulinemia [14]. It has been demonstrated that in PCOS, the increased release of glucose-stimulated DCI-IPG via DCI supplementation is significantly correlated with improved insulin sensitivity. The significant relationship between DCI-IPG release and insulin sensitivity prompted some scientists to suggest that the DCI-IPG mediator may be a target for therapeutic interventions in PCOS [15]. However, this approach needs particular caution reminding the different roles played by MI and DCI [16–19]. Both MI and DCI are necessary to assure the correct glucose metabolism in cooperation with insulin. In physiological conditions, the intracellular pool of inositol in human ovaries is about 99% of MI whereas DCI is the remaining part [20]. Insulin controls the epimerase-converting MI into DCI. It is important to highlight that the ovary maintains normal insulin sensitivity also in the presence of systemic IR [21–23]. This can explain why increased insulin release stimulates ovarian epimerase activity leading to intracellular DCI increase and MI decrease.
In agreement with this, in hyperinsulinemic PCOS women unexpectedly high levels of DCI can be found in the ovary, with concomitant MI depletion. This finding was called ‘The ovarian paradox’ [16] and might be considered the main cause of FSH-signaling impairment in PCOS [20]. In these conditions, glucose uptake and metabolism could negatively affect oocyte quality depending on MI [18].

Ovarian function improvement, as well as hormonal and metabolic parameters, was demonstrated after MI treatment in PCOS [12]. Moreover, MI shows results comparable or slightly better than metformin in ovulation induction but without any side effects [24]. On the contrary, high doses of DCI alone, administered to PCOS subjects, were found significantly detrimental for oocytes and therefore for fertility [25]. While MI is a well-established safe molecule [26], the data are lacking on DCI.

Myo-inositol and D-chiro-inositol supplementation effect on reproductive and metabolic abnormalities in PCOS

A recent International Consensus Conference on MI and DCI in Obstetrics and Gynecology indicates that both MI and DCI are involved in several biological pathways and in PCOS pathogenesis. Furthermore, sufficient clinical data on MI plus DCI assumption demonstrates the improvement of metabolic and reproductive aspects of PCOS [19]. MI and DCI have a plasmatic ratio of 40:1 respectively in physiological condition. This ratio could represent the best choice to restore ovarian cells function increasing MI content and at the same time exploiting the DCI advantages. Indeed, the 40:1 ratio, rather than MI or DCI separately, shows better result for counteracting both hyperinsulinemia and hyperandrogenism in PCOS. Although it seems a very promising therapeutic option, further clinical evidence are needed [4].

Inositol and metabolic abnormalities in PCOS

Nestler et al. [27] were the first reporting DCI efficacy in the treatment of obese PCOS, demonstrating increased insulin action, improved ovulatory function and decreased blood pressure, serum androgen and triglyceride concentrations. Treatment with MI is effective in reducing hormonal, metabolic and oxidative abnormalities in PCOS patients by improving insulin resistance [28]. Zacchè et al. [29] showed a reduction of HOMA index from 2.9 ± 0.8 to 1.4 ± 0.5 (p < .01) in PCOS patients after three months of MI treatments. Genazzani et al. [30] demonstrated the same effect in overweight PCOS women - HOMA reduction from 2.8 ± 0.6 to 1.4 ± 0.3 (p < .01). On the other hand, Minozzi et al. [31] reported a reduction from 2.9 ± 0.9 to 1.8 ± 1.0 (p < .05) after 12 months of treatment with a combination of MI and combined oral contraceptive, that was significantly more than oral contraceptive alone. The beneficial effect of MI on insulin sensitivity was confirmed in other studies [32,33], where plasma insulin levels, glucose-to-insulin ratio and HOMA index, plasma LH, prolactin, testosterone levels and LH/FSH ratio significantly improved after 12 weeks of treatment. A very recent study reported MI to be more effective in the reduction of testosterone, mFG score and serum hs-CRP levels compared to metformin in PCOS with normoinsulinemia and hyperinsulinemia [34].

Inositol and weight in PCOS

While some studies found significantly decreased BMI following MI treatment [35–37], AD Genazzani et al. [30] showed a nonsignificant change of BMI, although plasma LH, prolactin, testosterone, insulin levels and LH/FSH were significantly reduced and insulin sensitivity was significantly improved after 12 weeks of treatment. The Ferriman–Gallway score decreased although the reduction was not statistically significant (22.7 ± 1.4 to 18.0 ± 0.8) whereas the reduction of the ovarian volumes was significant (12.2 ± 0.6 ml to 8.7 ± 0.8 ml, p < .05). In another study, fasting glucose, LDL, DHEAS, total cholesterol and prolactin levels decreased significantly in MI + folic acid-treated patients [38].

Minozzi et al. [31] also failed to demonstrate a significant difference in BMI after 12 months of treatment with MI plus combined oral contraceptive. Serum androgen levels decreased in both groups, but significantly more in the combined therapy group. The lipid profile was improved in the combined therapy group, by reducing low-density lipoprotein (LDL) levels and enhancing high-density lipoprotein (HDL) levels. Combined treatment with MI and combined contraceptive pill turned out to be more effective in controlling endocrine, metabolic and clinical profile in patients with PCOS than oral contraceptive alone. In a very recent study [39], an improved insulin resistance and ovulatory function was observed after MI and DCI treatment in PCOS patients. In other studies, MI improved insulin sensitivity and induced a reduction in serum testosterone and DHEAS levels, plasma triglycerides, systolic and diastolic blood pressure [40] and increased HDL-cholesterol [37,41]. Some of these effects, however, were not observed in morbidly obese patients (BMI > 37) and inverse relationship between BMI and treatment efficacy was described [36,41]. Others however demonstrated that MI administration was more effective in obese patients with high fasting insulin plasma levels [42].

The beneficial metabolic effect of MI was demonstrated also in adolescent PCOS patients (aged 13–19 years), showing a significant reduction in weight, BMI, glucose, C-peptide, insulin and HOMA-IR. During oral contraceptive use weight and BMI slightly increased, but metabolic parameters did not change. Combination of MI + oral contraceptive did not change weight and BMI, while C-peptide, insulin and HOMA-IR were reduced [43].

Inositol and gestational diabetes mellitus in PCOS

MI also showed a possible role for primary prevention of gestational diabetes mellitus (GDM) in PCOS patients, due to its insulin-sensitizing activity. D’Anna et al. investigated the role of MI supplementation throughout the whole pregnancy; women treated with metformin, who stopped the treatment during pregnancy were considered as control group. Prevalence of GDM in the MI group was 17.4% versus 54% in the control group, with a highly significant difference. Consequently, in the control group the risk of GDM occurrence was more than doubled compared to MI group, with an odds ratio 2.4 (confidence interval 95%, 1.3–4.4) [44]. In patients with GDM previously diagnosed, an improvement in glucose homeostasis measurements was detected (fasting glucose and insulin and consequently HOMA index) after MI treatment [45]. More recent findings on the supplementation of MI, administered since early pregnancy, have shown the reduction of GDM incidence both in non-obese [46] and obese women [47]. A pilot study endorsed MI as a safe first-line medical treatment for uncontrolled GDM [48]. Besides these randomized controlled trials, a systematic review and a meta-analysis [49], highlighted the key role of MI in reducing insulin resistance.
and preventing GDM. Furthermore, the Cochrane systematic review linked the effect of MI with the reduction of fasting and 1-h postprandial blood glucose concentration at the end of treatment [50]. A number of studies demonstrated that the combination of MI and DCI in their physiological plasma ratio 40:1 reduced LDL-cholesterol, triglycerides and HOMA-index [51] and it was more effective than MI alone [52]. A recent pilot study, assessed the efficacy and safety of MI combined with DCI in 40:1 ratio in type-2 diabetic patients bringing new promising data into the clinical research [53]. Analyzing the results, this combination could be considered as a valuable therapy for reducing blood glucose levels and might be taken for the prevention of GDM. Contrarily, Farren et al. have concluded that MI plus DCI (40:1) is not effective in the prevention of GDM; however, they have not taken into consideration many pivotal aspects in which these molecules rely heavily on [54]. First of all, insulin resistance is a hallmark of prediabetes and type-2 diabetes but not type 1. In this study, women with either a family history of type 1 or 2 diabetes were examined and these two groups were heterogeneous populations with different pathogenic mechanisms underlying their insulin resistance or deficit in insulin secretion. Furthermore, lifestyle changes have not been considered. Uncontrolled diet might have worsened the blood sugar range. Another critical point could be the hefty power analysis of the study, estimating a 50% reduction in GDM, which could be reputed inconsiderably auspicious and ambitious. Therefore, further research is necessary in order to examine the real role of these two molecules combined on the prevention of GDM; preferably with a more concise study design and a more homogeneous population in order to identify more plausible and conclusive findings.

**Inositols, ovulatory function and fertility in PCOS**

Some studies have demonstrated that MI treatment in patients with PCOS improved ovarian function and fertility [24,55,56], decreased the severity of hyperandrogenism, acne and hirsutism [29,32,57] and positively affected metabolic and hormonal parameters deeply involved in the reproductive axis function and ovulation [33]. For these reasons, it became a novel method to improve spontaneous ovulation [30,41,55] or ovulation induction [36,58,59].

In a study by Papaleo [55], 88% of patients restored at least one spontaneous menstrual cycle during 6 months of MI treatment, of whom 72% maintained normal ovulatory activity during the follow-up period. In another study, the ovulation frequency was significantly higher in the MI-treated group (25%) compared to placebo (15%), and the ovulation time was significantly shorter [24.5 d; 95% confidence interval (CI), 18, 31; compared with 40.5 d; 95% CI, 27, 54] [41]. Raffone et al. showed that 65% of MI-treated patients restored spontaneous ovulation activity (30% of these obtained pregnancy), compared to 50% of metformin-treated patients (18.3% of these obtained pregnancy) after a mean of 14.8 (±1.8) days and 16.7 (±2.5) days from the day 1 of the menstrual cycle, respectively [24]. Gerli et al. [37] showed that ovulation frequency was significantly higher (p < .01) in MI-treated group (23%) compared to placebo (13%). E2 concentration increased only in MI group during the first week of treatment inducing follicular maturation. In another study ovulation was restored in 69.5% of women in MI group and in 21% in placebo group (p = .001). After treatment, the peak level of progesterone was higher in MI patients (15.1 ± 2.2 ng/ml) compared to placebo (6.6 ± 1.3 ng/ml) [40]. In another study, progesterone and AMH levels, ovarian volume, ovarian antral follicle, and total antral follicle counts decreased significantly both in MI and in combined contraceptive treated patients with PCOS [38]. In an observational study performed on 3602 infertile women with PCOS, a treatment with MI and folic acid restored ovulation in 70% of women and in 545 pregnancies (15.1% of all MI-treated patients) for mean 10.2 weeks [60].

MI turned out to be more effective in combination with metformin than metformin alone in restoring menstrual cycle regularity, although body weight, BMI, waist and hip circumferences decreased significantly in all groups (diet only; diet + metformin; diet + metformin + MI) [61]. Compared to clomiphene citrate MI showed a nonsignificant trend to lower drug resistance rate (30.6% vs. 36.8%, p = .62), lower ovulation rate (69.4% vs. 79.3% (p = 0.31) and higher pregnancy rate 33.3% vs. 28.2% (p = .13). Among pregnancies, the rate of multiple pregnancy was 18.1% in clomiphene group and 0% in the MI group [58]. In a study by Kamenov et al. [36], MI monotherapy resulted in 61.7% ovulation rate (of those 37.9% became pregnant) during three spontaneous menstrual cycles. In MI-resistant patients, a combination of MI and clomiphene citrate was used in the next three cycles and on this combination 72.2% ovulated (42.6% of those became pregnant). MI supplementation also produced very good clinical results with a significant reduction in cancelation rate (0% vs. 40%) and the consequent improvement in clinical pregnancy rate (PR) (33.3% vs. 13.3%) in insulin-resistant patients with PCOS, undergoing gonadotropin ovulation induction using the low-dose step-down regime [59].

Finally, very recently [18] the role of MI and DCI, combined or alone, as a treatment of PCOS was analyzed in a systematic review. The randomized controlled trials included in the review support the hypothesis of a primary role of IPGs as second messengers of insulin signaling and demonstrate that MI supplementation improved the hormonal profile and reduced insulin levels in PCOS patients.

**Myo-inositol and D-chiro-inositol in assisted reproduction technology**

MI was shown to be essential for proper oocyte maturation [62] and direct correlation between MI concentration in the follicular fluid and high oocyte quality has been found [63]. Additionally, using MI in assisted reproduction technologies has drawn the interest of scientific community [64]. The clinical trials performed so far showed that MI treatment resulted in significant improvements in hormonal responses. Furthermore, MI increased the total number of retrieved oocytes and improved oocyte quality, thus increasing the embryo quality produced after fertilization. In patients with PCOS undergoing IVF, MI treatment increased the number of follicles with a diameter >15 mm, visible at ultrasound, during stimulation and the number of oocytes retrieved after pick-up. In addition, MI reduced the average number of immature oocytes (deregenerated oocytes 0.93% vs 14.37%, p < .02; germinal vesicles 1.4% vs. 9.37%, p < .02) and the mean number of transferred embryos was significantly higher [65]. Compared to the administration of folic acid alone, the treatment of MI + folic acid, for 3 months before intracytoplasmic sperm injection (ICSI) in PCOS patients, led to shorter embryo/blastocyst development period between microinjection and 5-cell stage. In combined treatment group 34.62% of pregnancies were obtained, compared to 20% in folic acid only group, but the difference was not significant [66].
MI administration reduces the amount of gonadotropins used for ovulation induction and it double the ‘optimal’ oocytes, improving the delivery rate. In a study by Papaleo et al., the number of retrieved oocytes did not differ between the two groups, whereas in the group treated with MI the number of immature and degenerated oocytes was significantly reduced (1.0 ± 0.9 vs. 1.6 ± 1.0; p = 0.01), with a higher trend of metaphase-II stage oocytes. The total r-FSH units (1,958 ± 695 vs. 2,383 ± 578) and number of days of stimulation (11.4 ± 0.9 vs. 12.4 ± 1.4) were significantly reduced in the MI plus folic acid-treated group compared to controls, receiving folic acid alone. Furthermore, estradiol levels during the peak (2,232 ± 510 vs. 2,713 ± 595 pg/mL) after hCG administration were significantly lower in patients receiving MI [56]. This effect was confirmed by Lisi et al. in a study where the total amount of gonadotropins used to reach follicular maturation was found significantly lower and the number of retrieved oocytes was significantly reduced in the group pretreated with MI [67].

In a combination of MI with folic acid and melatonin, the mean number of retrieved oocytes did not differ compared to MI + folic acid group. Besides, the group co-treated with melatonin reported a significantly greater mean number of mature oocytes (6.56 ± 1.64 vs 5.76 ± 1.56; p = 0.047), lower mean number of immature oocytes (1.31 ± 0.74 vs. 1.91 ± 0.68; p = .001) and higher mean number of top-quality embryos (class 1 and 2) (1.69 ± 0.64 vs 1.24 ± 0.75; p = .01) [68]. The synergic effect of this combination was confirmed by Unfer et al., who studied the combination of MI and melatonin in women who failed to conceive in previous in vitro fertilization (IVF) cycles due to poor oocyte quality. This treatment increased the number of mature oocytes, fertilization rate and the number of both, total and top-quality transferred embryos, compared to the previous IVF cycle, while there was no difference in the number of retrieved oocytes [69].

In another study comparing the effects of MI and DCI [17], the total number of retrieved oocytes did not differ between two groups, but the number of mature oocytes was significantly increased in the MI group compared to DCI. Concurrently, the number of immature oocytes decreased in MI treated patients. Furthermore, the MI-treated group showed an increase in the mean number of top-quality embryos and in the total number of pregnancies compared to the DCI-treated group. In line with this finding, Isabella’s and Raffone’s groups [25] administered increasing amounts of DCI to PCOS women undergoing IVF treatment, starting eight weeks prior to hormonal ovarian stimulation. The authors found out that increasing DCI dosage progressively worsens oocyte quality and ovarian response. On the other hand, the combined therapy with MI and DCI, based on the physiological plasmatic ratio (40:1) unlike the monotherapy with DCI was able to improve oocyte and embryo quality, as well as pregnancy rates, in PCOS women undergoing IVF [70]. The combination of MI plus DCI gave a greater result in the ovarian stimulation protocol compared to DCI alone.

A very interesting finding is that treating fertile women with MI vaginal suppositories for three consecutive days in the peri-ovulation period improved sperm total motility in postcoital test performed on cervical mucus (sperm progressive motility was significantly increased, compared to non-progressive motility, and the number of immotile spermatozoa decreased). Moreover, it positively affected their conceiving capacity, without changes in cervical mucus structural and biochemical characteristics [71].

Finally, overall evidence from literature analyzed by the International Consensus Conference on MI and DCI in obstetrics and gynecology supports the beneficial effects of MI treatment in assisted reproduction for improving ovarian response to exogenous gonadotropins as well as oocyte and embryo quality. In this regard, administration of MI, alone or in combination with DCI (in the physiological plasmatic ratio of 40:1), could be useful to improve assisted reproduction outcomes [64].

Conclusions

The most recent literature reports that MI, DCI and in particular their combination in the physiological ratio 40:1 could represent an important therapeutic approach for the improvement of metabolic, hormonal and reproductive aspects of PCOS. In assisted reproductive technologies, however, MI and the combined treatment, unlike DCI monotherapy, are able to improve clinical outcomes. Finally, MI showed promising results as a safe approach for the prevention and treatment of GDM. Although the Farren’s group has not produced significant result on GDM prevention using MI and DCI in the physiological ratio (40:1), further RCTs are needed, including more heterogeneous group of patients characterized by IR as main alteration behind this pathology.

Disclosure statement

The authors report no conflict of interest.

References


