MYOINOSITOL: A REVIEW OF ITS USE IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT
Polycystic ovarian syndrome (PCOS) or stein - leventhal syndrome is one of the most common endocrine disorders affecting women of reproductive age. The diagnostic criteria of PCOS are Oligo ovulation and/or anovulation, excess androgen activity, polycystic ovaries on ultra sonogram. The estimated prevalence is 36% of women in India are suffering from PCOS and the Global prevalence is 2.2% to 26%. Recently, Myoinositol (MI) - a novel insulin sensitizer has been marketed for PCOS with infertility. Treatment with MI improves the ovarian function, oocyte quality, metabolic and hormonal parameters in PCOS. MI promotes weight loss in PCOS. It has been shown to reduce the systolic and diastolic blood pressure. MI is safe and effective drug and as such there are no side effects and drug interaction at clinically used doses.

KEYWORDS: Polycystic ovarian syndrome, Myoinositol, Ovulation and Oocyte quality, Metabolic dysfunction.

INTRODUCTION
Polycystic ovarian syndrome (PCOS) or stein - leventhal syndrome is one of the most common endocrine disorders, affecting up to 20% of women of reproductive age.\textsuperscript{[1]} The exact prevalence of PCOS is not known as the syndrome is not defined precisely. The estimated prevalence in women of reproductive age is 5-10%. According to the new criteria of Rotterdam, the prevalence among the general female population will raise up to 10\%.\textsuperscript{[2]}
Global prevalence -2.2% to 26% roughly 1 in 15 women Worldwide, 36% of women in India are suffering from PCOS.\textsuperscript{[3]}

**ETIOLOGY AND PATHOPHYSIOLOGY**

The increased ovarian androgen production seen in PCOS is a result of a series of complex biochemical processes which begins with disordered activity in the enzyme cytochrome P450c 17\alpha, which catalyses 17-hydroxylase and 17/20 lyase activities.\textsuperscript{[4]} the rate limiting step in androgen biosynthesis.\textsuperscript{[5]} PCOS develops due to excessive luteinizing hormones (LH) by the anterior pituitary gland with increase in LH/FSH ratio and through high levels of insulin in blood and insulin resistance. Persistently high levels of LH will produce excessive amounts of androstenedione by causing increased cytochrome P450 activity. Insulin like Growth Factor-1(IGF-1) potentiates the expression of LH receptors and stimulates LH induced androgen production and the accumulation of androgens in the ovary.\textsuperscript{[6]} IGF-1 also acts as an amplifier of the action of FSH.\textsuperscript{[7]} There is a strong implication of gene sequences in the etiology of PCOS.\textsuperscript{[8]} It is possible that a gene (CYP11A1,CYP17A1) may render the ovary susceptible to insulin stimulation of androgen secretion while blocking follicular maturation.\textsuperscript{[9]} In male genetic predisposition is expressed as premature balding.

**SYMPTOMS AND DIAGNOSTIC CRITERIA**

PCOS is one of the leading causes of female infertility. The most common immediate symptoms are anovulation-oligomenorrhea, amenorrhea and ultrasound polycystic ovaries, excess androgenic hormones (Hirsutism, Acne, Alopecia and Seborrhea) and insulin resistance. Mood disorders including depression, anxiety, bipolar disorder and binge eating disorder also occur more frequently in women with PCOS.\textsuperscript{[10]} Diagnostic criteria for PCOS have been offered by three groups.

A. The National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD) 199218; based on exclusion of other androgen excess or related disorders include all the following

1. Clinical and/or biochemical hyperandrogenism, 2. Menstrual dysfunction, B. The European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ ASRM)200419; based on exclusion of other androgen excess or related disorders includes two of the following 1. Clinical and/or biochemical hyperandrogenism, 2. Oligo-ovulation or anovulation, 3. Polycystic ovaries and C. The Androgen Excess and PCOS Society 200620: based on exclusion of other androgen excess or
related disorders includes all the following 1.Clinical and/or biochemical hyper-androgenism, 2. Ovarian dysfunction and/or polycystic ovaries.[11] The diagnostic criteria of PCOS is based on the 2003 Rotterdam Criteria, a. Oligo ovulation and/or anovulation, b.Excess androgen activity, c. Polycystic ovaries on ultrasonogram, after excluding other causes like congenital adrenal hyperplasia, cushings syndrome, hyperprolactinemia, thyroid disease, acromegaly and androgen secreting tumours of the ovary.[12]

PCOS among adolescents is an emerging problem that needs careful assessment, timely intervention, and appropriate treatment.[13,14] The first urban community-based study diagnosing PCOS and phenotypes among adolescent and young girls in India, showed the prevalence of PCOS among them was 22.5% by Rotterdam and 10.7% by Androgen Excess Society criteria. Non-obese were comprised 71.8% of PCOS diagnosed by Rotterdam criteria. Hyperinsulinemia was present among 19.2% of diagnosed PCOS cases. Obese girls with PCOS were more hirsute, hypertensive, and had significantly higher mean insulin and 2 hr post 75g glucose levels compared with non-obese PCOS. Moreover this prevalence is relatively higher than that reported by most studies, mainly due to use of different diagnostic criteria, study settings, age groups of the sample studied and hence cannot be compared.[13]

ASSOCIATION OF PCOS WITH OTHER CO-MORBIDITIES
Risk factors for PCOS in adults includes type 1 diabetes, type 2 diabetes and gestational diabetes. Insulin resistance affects 50%–70% of women with PCOS leading to a number of co-morbidities including metabolic syndrome, hypertension, dyslipidemia, glucose intolerance, and diabetes.[11,15,16,17] Impaired Glucose Tolerance (IGT) has been found to increase the risk of cardio vascular diseases(CVD), mortality and progression to diabetes mellitus in general population. Recent population based data noted a mortality rate of 5.5% over 5 years for those with IGT versus 1.9% with normal glucose tolerance. Furthermore, lifestyle intervention, drugs like metformin and glitazones can prevent IGT progression to diabetes mellitus, strengthening the argument for early treatment of PCOS women with insulin sensitizers. Gestational diabetes have been associated with an increased prevalence of PCOS.[11]

MANAGEMENT
Treatment for PCOD includes diet control, weight loss, oral contraceptives, topical eflornithine hydrochloride for hirsutism, anti androgens, insulin sensitizing agents – Metformin, Rosiglitazone and pioglitazone and surgical drilling of ovarian cyst. Women with
PCOS could respond favourably to insulin sensitizing drugs. Previous studies have shown that the use of metformin, Pioglitazone or myoinositol reduces serum androgens, serum total and free testosterone concentrations and improves ovulation in women with PCOS.\[18\] Efficacy of metformin is still debated, either alone or in association with clomiphene citrate. Furthermore metformin treatment is associated with a higher incidence of side effects, such as nausea or vomiting and other gastrointestinal disturbance.\[19\] while the use of thiazolidinediones has been related to weight gain and more recently to cardiovascular events, fragility fractures and bladder cancer.\[20\]

Recently, Myoinositol (MI) - a novel insulin sensitizer has been marketed for PCOS with infertility cases. MI could be proposed as an alternative to metformin treatment because the former can affect insulin target tissues and cells and potentiate insulin effects without the side effects of metformin. Several studies have demonstrated treatment with MI is effective in reducing hormonal, metabolic and oxidative abnormalities in PCOS patients by improving Insulin Resistance.\[21\]

**MYO-INOSITOL**

**Chemistry and source**

MI in 1850 Johannes Joseph Scherer (1814-1869) isolated from the muscle a hexahydroxycyclo- hexane that he named Inositol [from Ancient Greek stem ofίς (is, in-, “sinew, fiber“), -ose (in- dicting a carbohydrate), -ite (“ester“), -ol (“an alcohol“)], as it formally belongs to the sugar family.\[22\] Inositol was found the main component of phytates, i.e. salts of the inositol hexaphosphoric acid. The discovery of phytate dates from 1855 to 1856 when Hartig first reported small round particles in various plant seeds similar in size to potato starch grains.\[23\] Those particles were rich in phosphorous, calcium and magnesium but without proteins or lipids. Inositol or cyclohexane-1,2,3,4,5,6-hexol is a chemical compound with formula $C_6H_{12}O_6$, a sixfold alcohol (polyol) of cyclohexane. MI is one of nine stereoisometric of a C6 sugar alcohol that belongs to vitamin B-Complex group.\[24,25\] Inositol is a carbohydrate, assayed at half the sweetness of table sugar (sucrose).\[26\] MI is the precursor of inositol triphosphate, a second messenger regulating many hormones such as
Thyroid Stimulating Hormone, Follicle Stimulating Hormone (FSH) and insulin.\cite{27}

In 1988, Larner et al came to the conclusion that the two inositol stereoisomers.\cite{28,20} MI and D-chiro-inositol (DCI), are chemical mediators of insulin, acting through different mechanisms. MI produces second messengers for FSH and glucose uptake, while D-chiroinositol provides second messengers for promoting glucose uptake and glycogen synthesis.\cite{20,24} Both D-chiro-inositol and MI have similar structures, differing in the stereochemistry of only one hydroxyl group.\cite{29} MI is synthesized from glucose-6-phosphate (G-6-P) in two steps. First, G-6-P is isomerised by an inositol-3-phosphate synthase enzyme to myoinositol 1-phosphate, which is then dephosphorylated by an inositol monophosphatase enzyme (called IMPase 1) to give free MI.\cite{24} MI is a component of cell membrane and is an essential nutrient required by the human cells for the growth and survival in the culture.\cite{27} In healthy adults, the serum concentration of MI remains within a range of 20-70 μmol/L. However, in new-born infants and fetuses, serum concentrations of MI are several times higher than in adults.\cite{30} In humans most inositol is synthesized in the kidneys, in typical amounts of a few grams per day.\cite{31,32} Certain studies were reported that testes, the prostate, the epididymis and seminal vesicles contain a large amount of MI.\cite{30} The seminal fluid is one of the richest sources of inositol. In females MI is rich in ovarian fluid. MI is naturally present in a variety of plant foods. It is present in high concentration in fruits, beans, grains, and nuts.\cite{20,24,33}

**MECHANISM OF ACTION**

MI is a precursor of D-chiro inositol. D-chiroinositol is synthetized by an insulin dependent epimerase that converts MI into D-chiro-inositol.
Insulin binds to its receptor forms a complex called Insulin Receptor Substrate (IRS). IRS Stimulates messenger called PI3 kinase. Activated PI3 kinase activates GLUT 4. Glucose is then taken up by GLUT4 through glucose channel for utilizing energy. Then IRS Complex breaks down releasing the receptor to go back to its original site. MI helps in both production and activation of PI3.\textsuperscript{[34]}

**USES**

Inositol has been found to be an effective in treatment of PCOS, including insulin resistance, hyperandrogenism, and oligo-amenorrhea.\textsuperscript{[35,36]} It has been implicated in insulin signal transduction.\textsuperscript{[37,38]} Additionally MI supplementation improves features of dysmetabolic syndrome in post-menopausal women, including triglycerides, HDL cholesterol and diastolic blood pressure.\textsuperscript{[39]} Other uses in panic disorder, Obsessive Compulsive Disorder (OCD), unipolar and bipolar depression, acute respiratory distress syndrome in premature infants and lithium induced psoriasis.\textsuperscript{[40,41]} It is possibly safe for most adults sometimes it may cause nausea, tiredness, head ache, dizziness. Inositol can boost the effects of selective Serotonin Reuptake Inhibitors.\textsuperscript{[42]}

**DOSE, ADMINISTRATION AND DURATION**

Dose is 200- 4000 mg once a day before breakfast for PCOS. MI is available in two types of dosage form one in powder form and another newer pharmaceutical preparation -soft gelatin capsule. A study of administration of MI powder and MI soft gelatin capsules resulted in a different bioavailability. Soft gelatin capsule form of MI showed similar pharmacokinetic parameters compared with three times higher doses of MI in powder form.\textsuperscript{[43]} Many clinical trials underline the association between insulin tissue sensitivity increment and DCI or MI oral administration for at least 3 months.\textsuperscript{[44]}
CLINICAL OUTCOMES OF THE MI ON PCOS

MI and Infertility/Ovulation and Oozyte quality

Several studies showed MI improves oocyte and embryo quality in PCOS. The prevalence of infertility caused mainly by anovulation in PCOS women varies between 35-94%. Treatment with MI on PCOS with oligo, high testosterone, hirsutism cases showed, improves ovarian function and metabolic and hormonal parameters. Another study showed in women with PCOS, 69.5% ovulated in MI group compared to 21% ovulated in placebo. Calcium signalling in oocytes has been extensively studied in various species because of inositols putative role in oocyte maturation and the early stages of fertilization and quality of the oocytes. The presence of high levels of MI can indicate the well being of the follicle. The comparative study between MI and DCI showed, MI improved the oocyte and embryo quality than DCI in PCOS. Another study showed though Myo and/or D-chiroinositol administration improves insulin sensitivity only MI is a quality marker for oocytes evaluation. A study showed MI improved oocyte quality in patients undergoing Intra Cytoplasmic Sperm Insemination (ICSI), or with prior failed attempts at ICSI or diagnosed with PCOS or as poor responders. Another study on patients undergoing ovulation induction for ICSI showed that, insulin lowering medications, particularly different isoforms of inositol, represent novel therapies for restoring spontaneous ovulation, with a potential positive effect also on human oocyte meiotic maturation. The effects of MI in women with PCOS are well studied in a systematic review of randomized controlled trials study showed an overview on the clinical outcomes of the MI use as a treatment to improve ovarian function and metabolic and hormonal parameters in women with PCOS.

In women with PCOS many ovulations are accompanied by elevated E2 and subnormal P concentrations, which may indicate a suboptimal follicular maturation and ovulation with a collection of high numbers of germinal vesicles and degenerated oocytes at ovum pick-up. Its increased frequency of ovulation defined by luteal ratio, increase in ovulation rate evidenced by increase in E2 concentrations over the first week of treatment and shorter mean time to first ovulation. Another study also confirmed that the association between concentration of MI with follicular volume, E2 and better developmental of the oocytes suggests that higher level of MI in ovarian follicular fluid may be related to the wellbeing of the follicle and the quality of oocyte. Study on PCOS with chronic anovulation and infertility undergoing assisted reproduction techniques showed number of follicles with a
diameter of more than 15 mm visible at ultra sound scan during stimulation and the number of oocytes retrieved at the pickup resulted significantly higher in MI group.[39]

Additionally, another study on PCOS women who underwent in vitro Fertilization (IVF) cycles, the efficacy of a treatment with MI + folic acid + melatonin compared with MI + folic acid alone on oocyte quality showed the beneficial efficacy of MI + folic acid in improving fertility and suggested that the concomitant supplementation of melatonin can ameliorate oocyte quality and pregnancy outcomes in women with poor oocyte quality history.[24] Furthermore, recently it was proposed as a preventing agent for folate resistant neural tube defects (NTDs).[31]

Melatonin is present in both male and female reproductive system. Increased level of melatonin in the ovarian follicular fluid and seminal fluid maintains the reproductive function. It plays role as an antioxidant and free radical scavanger which protects follicles from oxidative stress, rescuing them from atresia, leading to complete follicular maturation and ovulation and also in human seminal fluid contains melatonin, and spermatozoa express melatonin receptors; melatonin is able to stimulate flagellar motility of spermatozoa. Furthermore, it has been demonstrated that there is a direct correlation between melatonin concentrations in follicular fluid and oocyte quality.[57,58]

The dosage of MI and D-chiroinositol in the follicular fluid of PCOS patients verses healthy subjects, follicular fluid from spontaneous cycles of healthy patients contains high concentrations of MI and low concentrations of D-chiroinositol while in PCOS patients, the ratio of the two molecules is completely opposite. Therefore, such findings supported the “DCI paradox”, accordingly to which “ovaries in PCOS patients likely present an enhanced MI to D-chiroinositol epimerization that leads to a MI tissue depletion that could eventually be responsible for the poor oocyte quality characteristic of these patients. Indeed, increasing DCI dosage progressively worsens oocyte quality and ovarian response.[59,60] Further support is provided by the data collected by Isabella and Raffone, who showed that increasing doses of D-chiroinositol produce “ovary toxicity”, characterized by a negative impact on oocyte quality, and a progressive reduction in the ovary response to FSH and negatively impacting oocyte quality.[24]

Patients have abnormal menstruation patterns attributed to chronic anovulation. Some women have oligomenorrhea or secondary amenorrhea. Oligomenorrhea has been observed in 85-
90% of women with PCOS and as many as 30-40% of amenorrheic patients have PCOS. Dysfunctional uterine bleeding and infertility are the other consequences of anovulatory menstrual cycles. The menstrual irregularities in PCOS usually manifest around the time of menarche.\textsuperscript{[61]} Several studies have reported MI capable of restoring spontaneous ovarian activity and consequent fertility\textsuperscript{[53]} and improves ovulatory function.\textsuperscript{[35,62,53]} A Study on PCOS less than 35 years showed both metformin and MI can be considered as first line treatment for restoring normal menstrual cycles.\textsuperscript{[63]}

**MI and Pregnancy**

Generally PCOS patients are subfertile as a consequence of 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. But treatment with MI therapy did not cause multiple pregnancy.\textsuperscript{[62]}

A 2-year, prospective, randomized, open-label, placebo-controlled study was carried out in pregnant women with a family history of type 2 diabetes who were treated with 2 g MI plus 200 µg folic acid twice a day may reduce the incidence of Gestational Diabetes Mellitus and the delivery of macrosomia fetuses.\textsuperscript{[64]}

**MI and Insulin resistance**

Several studies have reported that insulin resistance is common in PCOS women, regardless of the body mass index.\textsuperscript{[65]} The prevalence of insulin resistance in PCOS ranges from 50%–70% and occurs Independent of obesity. The effect of obesity on insulin resistance is additive to that of PCOS.\textsuperscript{[66,67]} MI increases whole body insulin sensitivity index\textsuperscript{[46]} and a 12 weeks study on PCOS showed improved glucose to insulin ratio and Homeostatic Model Assessment (HOMA) index\textsuperscript{[68]} decreased serum free testosterone concentration, Dehydroepiandrosterone-Sulfate (DHEA-S) and increased Sex hormone-binding globulin (SHBG).\textsuperscript{[35,46,68]} and reduced LH/FSH ratio.\textsuperscript{[68]} Some leading researchers conclude, “Myoinositol administration is a simple and safe treatment that ameliorates the metabolic profile of patients with PCOS, reducing hirsutism and acne”\textsuperscript{[69]} through its actions of decreased testosterone and insulin levels, the participants who supplemented with MI experienced a reduction in hirsutism, and improvements in skin appearance. A 12 weeks study with 2 grams of MI + 200 mcg folic acid showed improved insulin sensitivity, androgen levels\textsuperscript{[70]} and loss of weight.\textsuperscript{[55]} A study on insulin resistant women with the PCOS showed oral administration of D-chiroinositol would improve insulin sensitivity.\textsuperscript{[35]}
Recently a scientific literature mentioned a new molecule: the N-acetyl- cysteine (NAC) - a mucolytic drug acting as insulin sensitizer, represents an effective and safe strategy in the treatment of PCOS patients. This molecule appears to exert its beneficial effect both by increasing the insulin secretion by the beta cells of the pancreas and by inducing an increased sensitivity to the organism itself. A study conducted to evaluate the efficacy of NAC + Inositol + folic acid on ovulation rate and menstrual regularity in PCOS patients with and without insulin resistance suggested inositol and NAC may have additional noninsulin-related mechanisms of action that allow achieving benefits also in those patients with negative HOMA-index.\[^{71}\]

Another study showed administration of MI on PCOS with micro polycystic ovaries at USG showed LH, prolactin, insulin levels and LH/FSH were reduced, insulin sensitivity results improved and menstrual cyclicity restored.\[^{70}\]

**MI on Obesity**

Obesity is common in women who have PCOS. Obesity is present in nearly half of all women with PCOS, ranging from 30% to 60\%.\[^{72}\] Presence of obesity is a risk factor to amplify the consequences of PCOS and metabolic dysfunction like insulin resistance.\[^{2}\] An increased early clinical and subclinical markers of atherosclerosis like endothelial dysfunction, impaired pulse wave velocity, increased carotid intima media wall thickness, presence of carotid plaque and increased coronary artery calcification observed in PCOS women are further exacerbated by obesity.\[^{73}\] Previous studies showed that MI reduces plasma triglycerides, total cholesterol,\[^{46,35}\] LDL cholesterol and increased HDL cholesterol.\[^{55}\] Women ischemia Evaluation Study(WISE) highlighted that PCOS women undergo through an increased number of cardiovascular events. The combined therapy MI plus D-chiro-inositol improves the metabolic profile of PCOS women by significantly reducing total cholesterol, LDL, triglycerides, fasting insulin, fasting glucose and HOMA index and significantly increased HDL level, therefore reducing the cardiovascular risk.\[^{73}\] and weight loss in MI group by reducing circulating leptin level.\[^{55}\] But in another randomized controlled trial combined therapy with MI and D-chiro-inositol was more effective to reduce the risk of metabolic disease in PCOS in overweight patients compared to MI supplementation alone, after three months of treatment.\[^{74}\] Treating women with MI has been shown to reduce systolic and diastolic blood pressure.\[^{46,35}\]
Reactive oxygen species (ROS) has been considered to play a critical role in the success of different artificial reproduction techniques. ROS are produced within the follicle, especially during the ovulatory process, and it is believed that oxidative stress may be a cause of poor oocyte quality. High levels of oxidants, such as $\text{H}_2\text{O}_2$, have been found in fragmented embryos.\textsuperscript{[75]} Oxidative stress is involved in the pathogenesis and future complications of PCOS. This condition occurs when reactive oxygen species (ROS), which are intermediaries of a normal oxygen metabolism, are produced faster than the endogenous antioxidant defense systems can neutralize. Oxidation can lead to inter- and/or intramolecular cross-linking, thus inducing protein degradation, clustering and enzyme inactivation. A study on MI administration reduces oxidative stress in erythrocytes of patients with polycystic ovary syndrome. Previous studies have demonstrated that hyperglycemia increases ROS generation from peripheral blood leukocytes. The resulting oxidative stress may contribute to a pro-inflammatory state that induces IR and hyperandrogenism in women with this disorder and also increases the risk of cardiovascular disease.\textsuperscript{[21]}

### Safety
Several previous studies suggested MI is a safe and effective drug. The safety data of the MI trials report mild side effects such as, nausea and one of flatus and mild insomnia only at 12 g/day or higher. Notably the dosage of 4 g/day of inositol commonly used in clinics is completely free of side effects.\textsuperscript{[31]} Another study on pharmacokinetics and safety of a single intravenous dose of MI in preterm infants suggest supplemental inositol is safe and beneficial for preterm infants with respiratory distress. So for there is no evidence for MI drug interaction.\textsuperscript{[76]}

A study on pharmacokinetics of inositol phosphates are synthesized from the parent molecule inositol, with daily dietary consumption of inositol estimated at one gram. Once inositol reaches the cells of the intestinal tract, it is phosphorylated to create inositol hexaphosphate, and then subsequently dephosphorylated to its lower forms (IP1-5), which play important roles in signal transduction. Independent of the route of administration, MI has been found to be absorbed almost instantaneously, transported intracellular and dephosphorylated into lower inositol phosphates. MI can reach targeted tumor tissue as early as one hour post-administration.\textsuperscript{[32]}

Agents that affect the PI3K/AKT/mTOR pathway have potential as chemotherapeutic agents. Evidence shows that metformin and derivatives of MI also inhibits PI3K/AKT/mTOR
signaling. In vitro studies have confirmed that MI specifically inhibits this pathway in lung-cancer cell lines. In addition, the activity of AKT and PI3K has been evaluated in the patients who had received MI, and regression of dysplasia correlates with decreased PI3K activity. Combining inositol with budesonide, dexamethasone, N-acetyl cystine and/indole 3 carbinol increased efficacy even further. In several studies, oral inositol inhibited lung tumorigensis in mice exposed to carcinogen.[77]

MI deficiency in the ovary would impair the FSH signaling, resulting in an increased risk of ovarian hyperstimulation syndrome in PCOS patients. It is well known the patients with elevated levels of insulin need a higher number of FSH IU when undergoing ovary stimulation protocols. The physiological ratio of these two isomers is 40:1 (MI/DCI) and seems to be an optimal approach for the treatment of PCOS disorders. In order to ensure the proper dose and clinical efficacy without compromising ovarian function, certain modern technologies enabled manufacturing the product as soft gel capsules, by reducing the dose to a third of the original powder- base drug. From the above innovative formulation scientists expected to obtain a two-fold effect: 1. An action on liver, mainly exerted by D-chiroinositol, aimed at reducing insulinemic levels; 2. A selective effect on the ovary, where MI is thought to counteract the increased D-chiroinositol levels, and hence reestablishing FSH sensitivity.[24]

Development of soft gelatin capsules is of growing interest and several studies report the ability to perform a uniform, faster and enhanced absorption compared to other oral forms.[78,79]

CONCLUSION
In conclusion, by analyzing various studies on MI supplementation and combination with other drugs in the management of PCOS and insulin resistance cases suggested, MI is a safe and effective drug. It gives positive effect on the reproductive axis, other metabolic and hormonal parameters in women with PCOS. Limited studies are available regarding prevalence of PCOS in India, on MI- a novel insulin sensitizing agent. No study had been made till now pertaining to supplementation of inositol on PCOS treatment. It is clear that the underlying pathophysiology of PCOS is not fully understood. Further, as per the statement given by our Indian authors’ PCOS is an emerging disorder during adolescence, screening and early intervention is necessary to improve the reproductive health of adolescents and prevent future morbidities. Hence, further studies are needed to explore the
prevalence, etiology, pathophysiology of PCOS, drug efficacy, safety, mechanism of action other than improving insulin sensitivity of target tissues in PCOS and risk associated PCOS cases.

With the present review, we aim to provide an overview on the clinical outcomes of the MI use as a treatment to improve ovarian function and metabolic and hormonal parameters in women with PCOS.

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