CIUŁA, Aleksandra, BORAWSKI, Michal, JAKUBIAK, Anna, MIŚKIEWICZ, Joanna, KUŹNIECÓW, Tadeusz, KARABAN, Łukasz, ZNAMIROWSKA, Patrycja, MULARCZYK, Klaudia, KUPIS, Magdalena and PASZKOWSKA, Monika. Effect of myoinositol and d-chiro-inositol on improving hormonal, metabolic and reproductive parameters in women with polycystic ovary syndrome: A review of studies. Quality in Sport. 2025;41:60350. eISSN 2450-3118.

https://doi.org/10.12775/QS.2025.41.60350 https://apcz.umk.pl/QS/article/view/60350

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).

Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). © The Authors 2025.

This article is published with open access under the License Open Journal Systems of Nicolaus Copernicus University in Torun, Poland. Open Access: This article is distributed under the terms of the Creative Commons Attribution Noncommercial License, which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non-commercial Share Alike License (http://creativecommons.org/licenses/by-nc-sa/4.0/), which permits unrestricted, non-commercial use, distribution, and reproduction in any medium, provided the work is properly cited.

The authors declare that there is no conflict of interest regarding the publication of this paper. Received: 15.04.2025. Revised: 30.04.2025. Accepted: 12.05.2025. Published: 12.05.2025.

EFFECT OF MYO-INOSITOL AND D-CHIRO-INOSITOL ON IMPROVING HORMONAL, METABOLIC AND REPRODUCTIVE PARAMETERS IN WOMEN WITH POLYCYSTIC OVARY SYNDROME: A REVIEW OF STUDIES

Authors:

1. Aleksandra Ciuła [AC]

Brothers Hospitallers of Saint John of God Hospital in Cracow

Trynitarska 11, 31-061 Cracow, Poland

https://orcid.org/0009-0000-0425-863X

ciula.aleksandra@gmail.com

2. Michał Borawski [MB]

Brothers Hospitallers of Saint John of God Hospital in Cracow

Trynitarska 11, 31-061 Cracow, Poland

https://orcid.org/0009-0008-4864-7336

michal.borawski1@gmail.com

3. Anna Jakubiak [AJ]

National Medical Institute of the Ministry of the Interior and Administration Wołoska 137, 02-507 Warsaw, Poland

https://orcid.org/0009-0004-0973-7591

jakubiak.anna98@gmail.com

4. Joanna Miśkiewicz [JM]

Provincial Hospital in Kielce Grunwaldzka 45, 25-736 Kielce, Poland https://orcid.org/0009-0002-3300-940X miskiewiczj10@gmail.com

5. Tadeusz Kuźnieców [TK]

Międzylesie Specialist Hospital in Warsaw Bursztynowa 2, 04-749 Warsaw, Poland https://orcid.org/0009-0000-2120-9549 tadeusz.kuzniecow@gmail.com

6. Łukasz Karaban [ŁK]

Międzylesie Specialist Hospital in Warsaw Bursztynowa 2, 04-749 Warsaw, Poland https://orcid.org/0009-0001-9285-469X ukaszkaraban@o2.pl

7. Patrycja Znamirowska [PZ]

Specialist Hospital Dr. Tytus Chałubiński in Radom Lekarska 4, 26-610 Radom, Poland https://orcid.org/0009-0002-7538-5315 znamirowskap@gmail.com

8. Monika Paszkowska [MP]

Międzylesie Specialist Hospital in Warsaw Bursztynowa 2, 04-749 Warsaw, Poland https://orcid.org/0009-0009-2006-0098 md.mpaszkowska@gmail.com

9. Klaudia Mularczyk [KM]

Międzylesie Specialist Hospital in Warsaw Bursztynowa 2, 04-749 Warsaw, Poland https://orcid.org/0009-0008-3250-7806 klaudia.mularczyk@gmail.com

10. Magdalena Kupis [MK]

Casimir Pulaski University of Radom, Faculty of Medical Sciences and Health Sciences Chrobrego 27, 26-600 Radom, Poland https://orcid.org/0009-0009-4454-5866

magdalenakupis13@gmail.com

Affiliations:

- Brothers Hospitallers of Saint John of God Hospital in Cracow, Trynitarska 11, 31-061
 Cracow, Poland
- 2. National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warsaw, Poland
- 3. Provincial Hospital in Kielce, Grunwaldzka 45, 25-736 Kielce, Poland
- 4. Międzylesie Specialist Hospital in Warsaw, Bursztynowa 2, 04-749 Warsaw, Poland
- 5. Specialist Hospital Dr. Tytus Chałubiński in Radom, Lekarska 4, 26-610 Radom, Poland
- 6. Casimir Pulaski University of Radom, Faculty of Medical Sciences and Health Sciences, Chrobrego 27, 26-600 Radom, Poland

Abstract

Polycystic ovary syndrome (PCOS) is a leading cause of anovulatory infertility, affecting 6-12% of women of reproductive age. It is characterized by hormonal and metabolic disturbances, including insulin resistance, hyperandrogenism, and dyslipidemia, which significantly impair reproductive function and overall health. Effective management of PCOS requires a multifactorial approach combining pharmacotherapy, dietary intervention, and physical activity. This literature review aims to evaluate the therapeutic potential of inositol, particularly myo-inositol (MI), in the treatment of PCOS, with a focus on its impact on metabolic, hormonal, and reproductive parameters. Scientific articles published within the last 10 years were selected from PubMed and Google Scholar using specific keywords related to inositol supplementation in PCOS. The analysis demonstrates that MI supplementation improves insulin sensitivity, lowers androgen levels, enhances follicular development, and improves oocyte quality. Furthermore, combination therapy with MI and metformin yields superior outcomes compared to monotherapy, including improved menstrual regularity, reduced hyperandrogenic symptoms, and increased conception rates. Evidence also suggests enhanced outcomes in assisted reproductive technologies, such as in vitro fertilization (IVF), following MI use. The combined application of MI, D-chiro-inositol, metformin, and lifestyle modifications appears to exert a synergistic effect, optimizing hormonal balance and fertility, while also mitigating long-term metabolic and cardiovascular risks in women with PCOS.

Purpose:

The aim of the study was to evaluate the therapeutic potential of inositol in the treatment of polycystic ovary syndrome (PCOS), with particular emphasis on its effects on metabolic, hormonal and reproductive parameters.

Materials and methods:

The study used scientific articles downloaded from PubMed and Google Scholar databases, using keywords such as: "inositol supplementation in PCOS", "the effect of inositol on metabolism" and "comparison of the effectiveness of inositol and metformin". Articles in English and older than 10 years were excluded.

Main results:

A review of available studies found that myo-inositol (MI) supplementation in women with PCOS improves insulin sensitivity, reduces androgen levels, promotes follicle maturation, and improves oocyte quality. Myo-inositol therapy, especially in combination with metformin, effectively regulates menstrual cycles, reduces symptoms of hyperandrogenism, and increases the chances of conception. In addition, combination therapy (MI + metformin) proves to be more effective than monotherapy. The results of the review also show improvements in the outcomes of assisted reproductive procedures such as in vitro fertilisation (IVF).

Applications:

Based on the literature review, it can be concluded that supplementation with myo-inositol and D-chiro-inositol, especially in combination with metformin, is a promising treatment for women with PCOS, having a beneficial effect on improving hormonal, metabolic and reproductive parameters. This therapy can increase the effectiveness of infertility treatment and improve the overall health of patients, including reducing the risk of developing metabolic and cardiovascular complications. Additionally, lifestyle changes, including diet and regular physical activity, may support a synergistic therapeutic effect, leading to better health and reproductive outcomes in women with PCOS.

Keywords: inositol, myo-inositol, d-chiro-inositol, polycystic ovary syndrome, insulin resistance

1. Admission

1.1 Characteristics of polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS), also known as Stein-Leventhal syndrome, is one of the most commonly diagnosed endocrine disorders in women. [1] Its pathogenesis is multifactorial, and the development of this syndrome is influenced by genetic, hormonal and environmental factors. [2] The key characteristics of PCOS are hyperandrogenism, ovulation disorders and dysfunction of the hypothalamic-pituitary axis. [3] Insulin resistance and hyperinsulinemia are also a common problem.

Insulin stimulates theca cells in the ovaries to produce testosterone while lowering the synthesis of sex hormone-binding globulin (SHBG). [3] During puberty, growth hormone exerts an additional influence, increasing insulin resistance. For this reason, PCOS is a significant health problem in adolescent girls. [2] Excess androgens lead to an increase in luteinizing hormone (LH) levels and a decrease in follicle-stimulating hormone (FSH) levels in the blood, which in turn interferes with the growth and maturation of ovarian follicles. [3]

Estimating the prevalence of PCOS in the population is difficult due to the large discrepancy in the diagnostic criteria used. Currently, the diagnosis of PCOS is made on the basis of meeting two of the three criteria of the Rotterdam 2003 study: ultrasound examination should reveal the presence of at least 12 follicles with a diameter of 2-9 mm and/or increased ovarian volume >10 cm3, clinical or biochemical symptoms of hyperandrogenization and ovulation abnormalities. [1,4] It is estimated that 6-12% of women struggle with this syndrome. [4]

1.2 Therapeutic methods in PCOS

The basis for therapeutic management in polycystic ovary syndrome (PCOS) is non-pharmacological treatment, including lifestyle modification – in particular healthy eating and regular physical activity. These activities allow you to maintain a healthy body weight, which is important in the context of reducing insulin resistance and normalizing menstrual cycles. Even a small weight loss (at the level of 5–10% of baseline) can lead to a significant improvement in metabolic and reproductive parameters. [5]

Insulin resistance and hyperinsulinemia occur in about 80% of obese and 30–40% of lean women with PCOS. This compound justifies the use of blood glucose-lowering drugs in the treatment of this syndrome. [5] Although hormone therapy remains an effective tool for regulating menstrual cycles and reducing the symptoms of hyperandrogenism, it is mainly recommended in the case of ineffectiveness of non-pharmacological treatment. In obese and overweight patients, a combination of hormone therapy with antidiabetic drugs m.in metrofmin seems promising.

Metformin reduces androgen production in the adrenal glands and ovaries and increases SHBG production. [6] It has many benefits both metabolic and related to the reproductive system. However, its numerous side effects must be taken into account.

1.3 Role of inositols in metabolism

In recent years, special attention has been paid to inositols as natural, well-tolerated compounds with an adjunct to the treatment of PCOS. [6] Inositol is a cyclic carbohydrate that occurs naturally in nature. There are 9 stereo-isomers of inositol, of which myo-inositol (MI) and d-chiro-inositol (DCI) are the two main ones in the human body. [9] In humans, it occurs in endogenous and exogenous forms. It is produced mainly by the kidneys, about 2 g of myo-inositol per day, and the average dietary intake is 0.5-1.0 g/day. DCI is formed by the conversion of myo-inositol through an insulin-dependent mechanism. The need for myo-inositol increases as a result of high sugar intake, antibiotic use, sodium deficiency, as well as insulin resistance and diabetes.

MI and DCI play a significant role in glucose metabolism. Myo-inositol induces the translocation of the GLUT4 receptor to cell membranes, which increases glucose uptake while reducing the release of free fatty acids from adipose tissue. [7] While DCI participates in glycogen synthesis. Both compounds reduce blood glucose concentrations, with DCI shifting metabolism towards glycogen synthesis and MI towards catabolism.

In a properly functioning ovary, the MI/DCI ratio is about 100:1 in the follicular fluid. Physiologically, myo-niositol (MI) stimulates FSH secretion, while d-chiro-inositol (DCI) acts as an aromatase inhibitor. In the ovaries of women with PCOS, there is a greater conversion of myo-inosivok to DCI. [8]. The DCI/MI ratio increases, which stimulates the production of androgens in the granulosa layer by reduced aromatase activity.

Excess glucose reduces the absorption and biosynthesis of myo-inositol and increases its degradation and excretion in the urine, which leads to its deficiency.

The aim of this study is to analyze the potential of inositol as an adjunctive agent in the treatment of polycystic ovary syndrome, with particular emphasis on its effects on metabolic, hormonal and reproductive mechanisms.

2. Metabolic benefits of inositol supplementation

Women with polycystic ovary syndrome (PCOS) often struggle with metabolic disorders such as dyslipidemia, type 2 diabetes or hypertension. It is estimated that as many as 70% of

patients have an abnormal lipid profile, which significantly increases the risk of developing cardiovascular disease – one of the main causes of death in the general population. [10]

The results of the study indicate that the use of a supplement containing myo-inositol and D-chiro-inositol (MI-DCI) may have important metabolic benefits, such as improving the lipid profile and reducing insulin resistance. Regular intake of MI-DCI may thus contribute to the reduction of cardiovascular risk in women with PCOS.

Evidence for the effectiveness of such therapy is provided by a multicenter, retrospective study conducted in 29 medical facilities in India, including women aged 12–45 years diagnosed with PCOS. The participants took a preparation containing 550 mg of myo-inositol and 150 mg of D-chiro-inositol in tablet form, twice a day for a period of three months. The aim of the study was to assess the effect of therapy on the symptoms of polycystic ovary syndrome. [11] The results showed that the use of MI-DCI was associated with an improvement in lipid parameters – a statistically significant reduction in LDL cholesterol (by an average of 9.81 mg/dL), total cholesterol (by 19.89 mg/dL) and triglycerides (by 15.15 mg/dL) was observed, without significant changes in HDL cholesterol levels. [11] These data suggest that preparations based on inositol isomers may be a valuable complement to the treatment of the metabolic aspects of PCOS.

Due to the promising results of studies on the use of inositol in the treatment of polycystic ovary syndrome (PCOS), analyses have been initiated to assess the potential synergistic effect resulting from the concomitant use of metformin – considered the basic insulin sensitizing drug – and inositol. The aim of these studies was to verify whether the combination of these two substances can lead to a more significant improvement in endocrine, metabolic and reproductive parameters compared to monotherapy [12].

One study conducted at the Department of Gynecology and Obstetrics of the University Clinical Center of Serbia compared the effects of myo-inositol (MI) and metformin (MET) on metabolic parameters in patients with PCOS and insulin resistance, but with a normal body mass index (BMI) value. After the end of therapy, a statistically significant reduction in the area under the curve (AUC) for insulin was observed during the oral glucose tolerance test (OGTT) in both groups. The conclusions of the study indicate that both MET and MET show comparable therapeutic efficacy in improving insulin resistance, reducing hyperandrogenemia and regulating the menstrual cycle in patients with normal body weight [17].

In another study, 196 women with PCOS were given a combination therapy containing 500 mg of metformin and 600 mg of myo-inositol (Met-Myo) or metformin alone (500 mg) twice

a day for 24 weeks. The main objective was to assess the effect of the therapy on insulin resistance and menstrual cycle regulation after 12 and 24 weeks of treatment. The results showed that after 24 weeks, HOMA-IR was significantly reduced in the Met-Myo group, while in the Met group the improvement was smaller and did not reach the level of statistical significance. The mean reduction in HOMA-IR was 32% in the Met-Myo group and 11% in the Met group, respectively. Based on these results, it was concluded that the combination therapy with metformin and myo-inositol is more effective than metformin monotherapy in improving insulin resistance and regulating the menstrual cycle in women with PCOS, which indicates the potential therapeutic advantage of this strategy [12].

In addition, other studies comparing the effects of metformin and myo-inositol on metabolic parameters have shown that myo-inositol supplementation led to significant reductions in blood glucose and insulin levels, HOMA-IR values, triglycerides and VLDL cholesterol. At the same time, an increase in the value of the QUICKI index, indicating an improvement in insulin sensitivity, was observed. Myo-inositol, on the other hand, did not significantly affect other lipid parameters, however, supplementation resulted in increased expression of the PPAR-γ gene, which suggests a beneficial effect on glucose and lipid metabolism [16].

Subsequent studies confirmed that 12 weeks of myo-inositol supplementation in women with PCOS led to improvements in fasting glucose, insulin, HOMA-IR and QUICKI levels. In addition, it increased the expression of the PPAR-γ gene without affecting the expression of the GLUT-1 gene. Improvements in triglycerides and VLDL cholesterol were also noted, while other lipid fractions and LDLR gene expression remained significantly unchanged. Importantly, the combination of myo-inositol with D-chiro-inositol resulted in an improved lipid profile in obese women with PCOS, and the combination therapy of myo-inositol with monacolin K for 6 months led to a reduction in triglycerides, total cholesterol and LDL levels [16].

In a comparative study [19], in which patients were given metformin (1500 mg/day) or myo-inositol (4 g/day), an improvement in insulin resistance indices (HOMA-IR, AUC-insulin, Matsuda index) was shown in both groups, with a greater effect noted in the MET group. In 53% of patients taking metformin and in 44% of patients taking myo-inositol, menstrual cycles normalized. However, it is worth noting that metformin caused gastrointestinal adverse reactions (nausea, lack of appetite, diarrhoea) in about 10% of the participants, and three patients discontinued the study due to drug intolerance. Myo-inositol was better tolerated, however, its higher cost may be an important factor in the therapeutic decision. Both

substances have shown comparable efficacy in improving BMI, insulin sensitivity, and regulation of the menstrual cycle [19].

3. Hormonal benefits of inositol supplementation

In recent years, there has been a dynamic increase in the number of scientific studies evaluating the effectiveness of myo-inositol (MI) and D-chiro-inositol (DCI) therapy in women with polycystic ovary syndrome (PCOS), especially in the context of hormonal parameters. Inositol, as a natural compound, has a promising effect regulating the hypothalamic-pituitary-ovarian axis, improving the regularity of menstrual cycles and reducing the symptoms of hyperandrogenism, such as hirsutism. This paper analyzes a number of available scientific studies focusing on the potential hormonal benefits of inositol supplementation in patients with PCOS.

The study, conducted at the Department of Obstetrics and Gynecology at Sree Balaji Medical College and Hospital in Chennai, included 90 women diagnosed with PCOS according to the Rotterdam criteria. For a period of six months, the participants took inositol supplementation at a dose of 1 mg per day. The results showed that as many as 68% of patients regained the regularity of menstrual cycles. In addition, there was a statistically significant decrease in luteinizing hormone (LH) levels, a decrease in the LH/FSH ratio, as well as a decrease in fasting insulin levels and HOMA-IR values. The obtained data suggest that myo-inositol supplementation significantly improves both hormonal and metabolic profiles in women with PCOS. [10]

Bahadur et al. et al. conducted another study involving 72 women aged 18–45 years, comparing the effectiveness of metformin monotherapy (MET) and combination therapy, combining metformin with myo-inositol and D-chiro-inositol. After six months of treatment, 61.1% of patients in the combination group had regular menstrual cycles compared to 36.1% in the control group. In addition, a significant reduction in LH levels and a decrease in the LH:FSH ratio were observed in the MI and DCI groups, indicating a beneficial effect of the combination therapy on the endocrine disrupted system typical of PCOS. [14]

Another study, involving overweight or obese women from Italy and Mexico diagnosed with PCOS, aimed to evaluate the effects of inositol on hormonal parameters. The participants took 2 g of myo-inositol in combination with 200 µg of folic acid and 50 mg of alpha-lactalbumin twice a day, which was designed to improve the bioavailability of the active substance. Already after three months of therapy, a significant increase in the concentration of

progesterone, treated as a marker of ovulation, was observed. This effect also persisted after six months of treatment. In addition, a significant decrease in the level of total testosterone, free testosterone and androstenedione was noted. Importantly, androstenedione levels also showed a decreasing trend in the later period of therapy, which may be important in the context of long-term control of hyperandrogenism symptoms. [15]

In the study by Januszewski et al. the effect of myo-inositol and D-chiro-inositol therapy in a 10:1 ratio on selected hormonal and metabolic parameters in patients with PCOS was evaluated. Already after three and six months of therapy, a significant reduction in body weight, a decrease in the level of free testosterone (fT), FSH, LH and insulin, as well as an increase in the concentration of sex hormone-binding globulin (SHBG) were observed. In addition to the beneficial hormonal effects, an improvement in the condition of the skin has also been noticed, which may translate into an improvement in the quality of life of patients and a reduction in the negative psychological effects associated with PCOS symptoms. [18] Another study compared the effectiveness of metformin monotherapy with a combination therapy combining metformin with myo-inositol. Although improvements in menstrual cycle regularity were noted in both groups, this effect was clearly more pronounced in the combined therapy group (P< 0.001). The pregnancy rate was similar in the two groups, but only patients in the myo-inositol group showed significant improvements in quality of life as assessed by the PCOSQ score (p < 0.001). These results suggest that the inclusion of myo-inositol in standard metformin therapy may have additional clinical benefits, especially in the context of menstrual cycle regulation and subjective well-being of patients. [20]

4. Reproductive benefits of inositol supplementation

Polycystic ovary syndrome (PCOS) is one of the most common causes of infertility in women of childbearing age, affecting between 9% and 18% of this population. It is responsible for about 70–80% of cases of anovulatory infertility [2], making it a major factor in interfering with ovulation. An important indicator of fertility disorders in the group of patients with this syndrome is also increased levels of anti-Müllerian hormone (AMH), which negatively affects the maturation of ovarian follicles and reduces the chances of getting pregnant. [5,10]

The hormonal and metabolic disorders observed in PCOS affect not only reproductive capacity, but also the overall health of women. Effective treatment of infertility in patients with this syndrome requires a comprehensive therapeutic approach, taking into account both endocrine and metabolic aspects [3]. Improving tissue sensitivity to insulin plays a key role in restoring normal ovulatory function, reducing the recruitment of immature oocytes and

lowering androgen levels – both in plasma and in ovarian follicles – which directly translates into increased chances of fertilization [6, 7].

Despite this, metformin, despite a long history of use in the treatment of PCOS, does not show a clear effect on the live birth rate. However, it may increase the rate of clinical pregnancies, especially when used in combination with other pharmacological preparations [6, 17].

Clinical studies emphasize the special role of inositoles – especially myo-inositol – as an effective support for infertility therapy in women with PCOS. Myo-inositol, which is a natural isomer of vitamin B8, has a beneficial effect on insulin metabolism by improving cell sensitivity to insulin, reduces androgen levels, supports ovarian follicle maturation and improves oocyte quality [6,7,11]. Importantly, higher concentrations of myo-inositol in the follicular fluid correlate with better oocyte quality and greater developmental potential.

Myo-inositol supplementation – often combined with d-chiro-inositol or folic acid – is considered to be a safe, well-tolerated and effective method supporting the treatment of PCOS, especially in women preparing for assisted reproductive procedures, such as in vitro fertilization (IVF) [7, 13].

One study evaluated the effectiveness of metformin (500 mg) and myo-inositol (600 mg) compared to metformin (500 mg) monotherapy in women with polycystic ovary syndrome (PCOS) infertility who underwent ovulation induction. After three months of treatment, patients who did not become pregnant underwent three additional cycles of ovulation stimulation with intrauterine insemination (IUI). In the group receiving combination therapy, a marked improvement in the regularity of menstrual cycles, shortening their length and reducing the intensity of bleeding was noted. Although the incidence of spontaneous pregnancies during the first three months of treatment was higher in the combination group (23.3%) than in the control group (13.3%), the difference did not reach the level of statistical significance. However, significant differences appeared after three cycles of IUI – the percentage of clinical pregnancies was 63.3% in the group with combined therapy and 33.3% in the control group (p = 0.001), while the live birth rate was 55% and 26.7%, respectively (p = 0.002) [24].

However, a higher risk of ovarian hyperstimulation syndrome (OHSS) in the group receiving combination therapy was noted. Five cases of OHSS were reported – two associated with gonadotropin administration and three associated with multiple pregnancies. No case of OHSS was reported in the control group. All three multiple pregnancies (twin pregnancies)

occurred in the combination therapy group, which may indicate both a higher ovulation potential of this method and an increased risk of complications [24].

Another study focused on evaluating the efficacy of myo-inositol (Myo) compared to metformin (Met) in reducing the risk of ovarian hyperstimulation syndrome (OHSS) and improving the outcomes of assisted reproductive procedures (ART) in women with polycystic ovary syndrome (PCOS). A double-blind, randomized control study was conducted at the ART Clinic, AIIMS, New Delhi. Patients were randomly assigned to two groups: Myo (2 g twice a day) and Met (850 mg twice a day), for a period of three months before the planned IVF cycle. The results showed that although the incidence of OHSS was lower in the Myo group (10%) than in the Met group (20%), the difference was not statistically significant. On the other hand, the cumulative pregnancy rate in the Myo group (43.2%) was significantly higher compared to the Met group (22.7%), as was the percentage of spontaneous pregnancies (26% vs. 12%). In this study, myo-inositol was found to be as effective as metformin in reducing the risk of OHSS, and in addition, it contributed to better ART outcomes in women with PCOS undergoing antagonistic IVF cycles.

Combined with the results of the previous cited study, these results highlight the need to carefully balance the effectiveness of ovulation induction with patient safety in the context of individualized PCOS treatment. [22]

D-chiro-inositol (DCI), the second stereoisomer of inositol, also has beneficial effects, especially when administered in the right proportion to MYO. The most commonly used and physiologically justified ratio of MI:DCI is 40:1. Studies have shown that the combination of MYO and DCI in this proportion produces better clinical outcomes than using each compound alone. Despite this, some authors point out that the absolute dose of DCI may be more important than the ratio itself. The doses used in previous studies (13.8–27.6 mg/day) may have been too low to produce the expected therapeutic effect.

Therefore, one study used a higher dose of DCI (300 mg), based on previous reports suggesting its positive effect on oocyte quality. In this study, the pregnancy rate in the study group (SG) was significantly higher than in the control group (CG) — 65.5% vs. 25.9%, respectively. In addition, the pregnancies after embryo transfer were also higher in the SG group (68% vs. 31.6%; p = 0.017). These results indicate that the use of high-dose DCI in combination with MYO may significantly increase the effectiveness of fertility treatment in women with PCOS undergoing ICSI. [23]

Mendoza et al. in their randomized clinical trial, they showed that a higher than standard recommended dose of D-chiro-inositol (DCI) significantly improves the quality of oocytes (OQ), especially their cytoplasm, in women with polycystic ovary syndrome (PCOS) undergoing the ICSI procedure. This was the first clinical trial to investigate the effects of different doses of DCI on egg quality. Previous reports suggested that higher pregnancy rates with a disturbed myo-inositol/DCI ratio do not necessarily correlate with improved oocyte maturation, which may be due to the effect of DCI on the embryo implantation process or other, more difficult to measure oocyte quality parameters. [21]

The results of the study showed that a higher dose of DCI (300 mg) significantly improved the quality of the cytoplasm of oocytes – assessed as one of the main indicators of oocyte quality – achieving a 1.6-fold improvement compared to the lower dose group. Beneficial changes were also noted in other parameters, such as the elasticity of the cell membrane and the ability of the egg to accept sperm, but not all of these differences were statistically significant, indicating the need for further studies with a larger group of patients.

Attention was also drawn to the role of DCI in lowering testosterone levels and improving insulin sensitivity – regardless of the dose used – which may have an additional, indirect effect on the quality of the oocyte cell membrane and potentially increase the chances of implantation success. These results suggest that the use of higher doses of DCI may represent a promising therapeutic strategy in PCOS patients undergoing sperm injection into the cytoplasm of the egg (ICSI). [21]

The study by Özay et al. evaluating the effect of myo-inositol (MYO) therapy on ovarian stromal blood flow in women with PCOS. The patients were divided into six groups. Three of these included patients with polycystic ovary syndrome (PCOS): the first group was treated with oral contraceptives (OCPs) containing 30 μ g of ethinyl estradiol and 3 mg of drospirenone, the second group received 4 g of myo-inositol with 400 μ g of folic acid per day, and the third received no treatment. The other three groups were healthy women who received OCP, MYO or no intervention at all. Women with PCOS had lower baseline values of resistance indices (RI) and pulsacity indices (PI) than healthy women, which indicates ovarian blood supply disorders. After three months of OCP and MYO therapy, a significant increase in RI and PI was observed in groups 1 and 2 (p < 0.001), suggesting improved blood flow and a reduction in excessive vascularization of the ovarian stroma. In the untreated groups (groups 3

and 6), no changes in these parameters were observed. It is likely that it was the decrease in LH levels, which stimulates the follicular sheath cells to overproduce androgens, that contributed to the improvement of Doppler indices and better blood supply to the ovaries. This is another study that suggests the beneficial effects of MYO as an alternative to hormonal therapy in regulating blood flow and hormonal balance in women with PCOS. [25]

5. Summary:

This paper examines the therapeutic potential of inositol in the treatment of polycystic ovary syndrome (PCOS), which requires a complex approach that takes into account both hormonal and metabolic disorders. Available data indicate that inositol has a beneficial effect on insulin sensitivity, restoration of ovulation and general well-being of patients, being a valuable supplement or alternative to standard pharmacotherapy. As a natural nutraceutical agent that improves insulin sensitivity, it has an effectiveness comparable to metformin (MET) in terms of metabolic, hormonal and glycemic parameters. An additional advantage of myo-inositol (MI) therapy is its better tolerance and lower incidence of side effects compared to metformin, making it a promising therapeutic option for the treatment of PCOS. A growing body of research also points to the potential role of synergistic action of different isomers of inositol – in particular the combination of myo-inositol and D-chiro-inositol in the right proportions – which may increase the effectiveness of therapy, especially in the context of improving oocyte quality and fertility indicators. For this reason, inositol is gaining more and more interest not only as part of symptomatic treatment, but also as a support in the treatment of PCOS-related infertility.

Disclosure

Authors do not report any disclosures.

Author's contributions

Conceptualization: AC; Methodology: MB; Software: n/a; Check:; AJ, JM; Formal analysis: ŁK, MB; Investigation: AC, MB, AJ, JM; Resources: MB, AJ; Data curation: AC, MB, JM, MP, KM, PZ, ŁK, TK, AJ, MK; Writing - rough preparation: TK, ŁK, MB; Writing - review and editing: AC, ŁK, MP; Visualization: KM, PZ, MK; Supervision: TK, ŁK, MP; Project administration: AC; Receiving funding: n/a.

All authors have read and agreed with the published version of the manuscript.

Funding statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data availability statement

Not applicable.

Acknowledgments

The authors declare that there are no acknowledgments for this study.

Conflict of Interest Statement

The authors declare no conflict of interest.

References:

- [1] Facchinetti F, Gambineri A, Aimaretti G, et al. Delphi consensus on the diagnostic criteria of polycystic ovary syndrome. *J Endocrinol Invest*. Published online January 20, 2025. doi:10.1007/s40618-025-02533-4
- [2] Yüksel Ö, Atmaca FG, Dursun F, et al. Frequency of "PCOS" and "Being at Risk for PCOS" in Obese Adolescent Girls in Light of Current Definitions. *J Clin Res Pediatr Endocrinol*. Published online January 31, 2025. doi:10.4274/jcrpe.galenos.2025.2024-7-31
- [3] Stańczak NA, Grywalska E, Dudzińska E. The latest reports and treatment methods on polycystic ovary syndrome. *Ann Med.* 2024; 56(1):2357737. doi:10.1080/07853890.2024.2357737

- [4] Skiba MA, Islam RM, Bell RJ, Davis SR. Understanding variation in prevalence estimates of polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2018; 24(6):694-709. doi:10.1093/humupd/dmy022
- [5] Lete I, Martínez A, Lasaga I, Centurión E, Vesga A. Update on the combination of myo-inositol/d-chiro-inositol for the treatment of polycystic ovary syndrome. *Gynecol Endocrinol*. 2024; 40(1):2301554. doi:10.1080/09513590.2023.2301554
- [6] Chaudhary S, Kulkarni A. Metformin: past, present, and future. *Curr Diab Rep.* 2024; 24(6):119-130. doi:10.1007/s11892-024-01539-1
- [7] Bizzarri M, Monti N, Piombarolo A, Angeloni A, Verna R. Myo-Inositol and D-Chiro-Inositol as Modulators of Ovary Steroidogenesis: A Narrative Review. *Nutrients*. 2023; 15(8):1875. Published 2023 Apr 13. doi:10.3390/nu15081875
- [8] DiNicolantonio JJ, H O'Keefe J. Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes. *Open Heart*. 2022; 9(1):e001989. DOI:10.1136/OpenHRT-2022-001989
- [9] Kiani AK, Paolacci S, Calogero AE, et al. From Myo-inositol to D-chiro-inositol molecular pathways. *Eur Rev Med Pharmacol Sci.* 2021; 25(5):2390-2402. doi:10.26355/eurrev 202103 25279
- [10] Sharon P M, P M, Manivannan A, Thangaraj P, B M L. The Effectiveness of Myoinositol in Women With Polycystic Ovary Syndrome: A Prospective Clinical Study. *Cureus*. 2024; 16(2):E53951. Published 2024 Feb 10. doi:10.7759/cureus.53951
- [11] Vyas L, Raiturker AP, Sud S, et al. Management of polycystic ovary syndrome among Indian women using myo-inositol and D-chiro-inositol. *Bioinformation*. 2022; 18(2):103-110. Published 2022 Feb 28. doi:10.6026/97320630018103
- [12] Kriplani A, Tank P, Singh P, et al. A Phase III, Double-Blind, Randomized, Multicenter, Clinical Trial to Evaluate the Efficacy and Safety of a Fixed-Dose Combination of Metformin Hydrochloride and Myo-Inositol Compared to Metformin in Patients With Polycystic Ovary Syndrome. *Cureus*. 2024; 16(12):E75616. Published 2024 Dec 12. doi:10.7759/cureus.75616 [13] Bodepudi R, Seher S, Khan SA, et al. Myoinositol Versus Metformin in the Treatment of Polycystic Ovarian Syndrome: A Systematic Review. *Cureus*. 2023; 15(7):E41748. Published 2023 Jul 11th doi:10.7759/cureus.41748
- [14] Bahadur A, Arora H, Ravi AK, et al. Comparison of Clinical, Metabolic and Hormonal Effects of Metformin Versus Combined Therapy of Metformin With Myoinositol Plus D-Chiro-Inositol in Women With Polycystic Ovary Syndrome (PCOS): A Randomized

- Controlled Trial. *Cureus*. 2021; 13(6):E15510. Published 2021 Jun 7. doi:10.7759/cureus.15510
- [15] Hernandez Marin I, Picconi O, Laganà AS, Costabile L, Unfer V. A multicenter clinical study with myo-inositol and alpha-lactalbumin in Mexican and Italian PCOS patients. *Eur Rev Med Pharmacol Sci.* 2021; 25(8):3316-3324. doi:10.26355/eurrev 202104 25743
- [16] Shokrpour M, Foroozanfard F, Afshar Ebrahimi F, et al. Comparison of myo-inositol and metformin on glycemic control, lipid profiles, and gene expression related to insulin and lipid metabolism in women with polycystic ovary syndrome: a randomized controlled clinical trial. *Gynecol Endocrinol*. 2019; 35(5):406-411. doi:10.1080/09513590.2018.1540570
- [17] Gudović A, Bukumirić Z, Milincic M, et al. The Comparative Effects of Myo-Inositol and Metformin Therapy on the Clinical and Biochemical Parameters of Women of Normal Weight Suffering from Polycystic Ovary Syndrome. *Biomedicines*. 2024; 12(2):349. Published 2024 Feb 2. doi:10.3390/biomedicines12020349
- [18] Januszewski M, Issat T, Jakimiuk AA, Santor-Zaczyńska M, Jakimiuk AJ. Metabolic and hormonal effects of a combined Myo-inositol and d-chiro-inositol therapy on patients with polycystic ovary syndrome (PCOS). *Ginekol Pol.* 2019; 90(1):7-10. doi:10.5603/GP.2019.0002
- [19] Fruzzetti F, Perini D, Russo M, Bucci F, Gadducci A. Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS). *Gynecol Endocrinol.* 2017; 33(1):39-42. doi:10.1080/09513590.2016.1236078
- [20] Nazirudeen R, Sridhar S, Priyanka R, et al. A randomized controlled trial comparing myoinositol with metformin versus metformin monotherapy in polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2023; 99(2):198-205. doi:10.1111/cen.14931
- [21] Mendoza N, Galan MI, Molina C, et al. High dose of d-chiro-inositol improves oocyte quality in women with polycystic ovary syndrome undergoing ICSI: a randomized controlled trial. *Gynecol Endocrinol*. 2020; 36(5):398-401. doi:10.1080/09513590.2019.1681959
- [22] Rajasekaran K, Malhotra N, Mahey R, Khadgawat R, Kalaivani M. Myoinositol *versus* metformin pretreatment in GnRH-antagonist cycle for women with PCOS undergoing IVF: a double-blinded randomized controlled study. *Gynecol Endocrinol*. 2022; 38(2):140-147. doi:10.1080/09513590.2021.1981282
- [23] Mendoza N, Diaz-Ropero MP, Aragon M, et al. Comparison of the effect of two combinations of myo-inositol and D-chiro-inositol in women with polycystic ovary syndrome undergoing ICSI: a randomized controlled trial. *Gynecol Endocrinol*. 2019; 35(8):695-700. doi:10.1080/09513590.2019.1576620

[24] Agrawal A, Mahey R, Kachhawa G, Khadgawat R, Vanamail P, Kriplani A. Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial. *Gynecol Endocrinol*. 2019; 35(6):511-514. doi:10.1080/09513590.2018.1549656

[25] Özay AC, Emekçi Özay Ö, Okyay RE, Gülekli B. The effect of myoinositol on ovarian blood flows in women with polycystic ovary syndrome. *Gynecol Endocrinol*. 2019; 35(3):237-241. doi:10.1080/09513590.2018.1520827