Myo-Inositol versus Metformin in Women with Polycystic Ovarian Syndrome Undergoing Induction of Ovulation: A Randomized Controlled Trial

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a reproductive endocrine disorder that affects a significant number of young women worldwide.

Objective: to assess the effectiveness of induction of ovulation with Aromatase Inhibitors (letrozole) in women with PCOS via myoinositol versus metformin.

Materials & Methods: In this randomized clinical trial, 66 women who were undergoing ovulation induction and were separated into two groups, each consisting of 33 infertile women who met the criteria of Rotterdam for PCOS. The study was carried out at Menoufia university Hospital and outpatient clinic from May 2023 to july 2024.

Results: Demographic characteristics, cumulative pregnancy, and ovulation rate did not exhibit any significant variances among the two groups. Fasting insulin during the follow-up was considerably lower in comparison with the baseline level in each group. The myoinositol group exhibited a significant decrease in comparison to the metformin group.

Conclusion: we advise some PCOS patients that there is no significant difference between metformin and myoinositol regarding ovulation and pregnancy rates. It should also highlight that myoinositol is not inferior to metformin.

Keywords: Metformin, Letrozole, Myoinositol, Polycystic ovary syndrome.

INTRODUCTION

Anovulatory infertility is most commonly caused by polycystic ovarian syndrome (PCOS), which affects 15-20% of infertile women. Approximately 75% of women who suffer from PCOS experience infertility due to anovulation. [1]

PCOS diagnosis necessitates two of the following: clinical and/or biochemical evidence of hyperandrogenism, oligo/anovulation, and atypical ovaries on USG results.

In order to ascertain the presence of PCOS, the Rotterdam criteria are implemented. various PCOS features presence or absence has resulted in the definition of various phenotypes. [2]

Hyperinsulinemia, caused by insulin resistance, affects almost 80% of women with PCOS and central obesity. Additionally, 30–40% of slender women who have been diagnosed with PCOS have hyperinsulinemia. [3]

Approximately 80% of women with central adiposity and PCOS are diagnosed with hyperinsulinemia as a result of resistant insulin. Additionally, 30–40% of slender women who have been diagnosed with PCOS have hyperinsulinemia. [4]

Metformin has been the subject of the most extensive research among insulin sensitizers, and It may have positive effects on metabolism and reproduction, according to the available researchs. [5]

Despite the fact that metformin has been in use for decades and there is evidence that it increases the clinical pregnancy rate when taken in conjunction with clomiphene (CC) rather than independently, it has not been able to improve the live birth rates of infertile PCOS women. [6]

Additionally, the primary issue with metformin is its gastrointestinal adverse effects, which may have an impact on its compliance [7].

The inositols, which are a recent addition to insulin sensitizers, have been the subject of the most extensive research. In the case of myo-inositol, it functions as a post-receptor mediator (second messenger) of the insulin signal through a membrane-associated sodium-dependent inositol co-transporter, thereby reducing hyperinsulinemia. GLUT4 is a protein. The inositols, which are a recent addition to insulin sensitizers, have been the subject of the most extensive research. Myo-inositol is the case.[8]

Glucose entry into the cell is facilitated by myo-inositol. The benefits of myoinositol include improving ovarian function, raising SHBG, decreasing serum androgens, decreasing serum total and free testosterone, and decreasing the LH/FSH ratio. [9]

The treatment of Myoinositol resulted in a reduction in hyperandrogenemia, an increase in ovulation, and the restoration of fertility in a study on PCOS. It improves the integrity of oocytes and embryos, as well as the maturation of follicles and oocytes. Although metformin has been regarded as the gold standard for PCOS therapy for an extended period, recent research has concentrated on myoinositol as an alternative.[10, 11]

PATIENTS AND METHODS

In this randomized clinical trial, 66 women who were undergoing ovulation induction and were separated into 2 groups. Each group included 33 infertile women who satisfied the criteria of Rotterdam for PCOS, which includes criteria such as oligo-anovulation, hyperandrogenism (biochemical or clinical symptoms), and the presence of polycystic ovaries as confirmed by ultrasonography. The initial group was composed of 33 cases who were administered myoinositol in the form of viocyst tablet (Viomix Pharmaceutical industries) twice a day for a period of three months. Each tablet Contains:

in addition to aromatase inhibitors (Letrozole 2.5 mg) (Techno Pharma) starting on each cycle second day for five days. The second group also consisted of 33 cases who received a daily dose of 1500 milligrams of metformin in the form of Cidophage (CID Pharma) 500 mg 3 times a day along with the same dosage of Aromatase inhibitors (Letrozole) & cycle schedule as that of the first group. The investigation was carried out at the University Hospital of Menoufia from May 2023 to July 2024.

Inclusion Criteria:

- Under the age of 40 and over the age of 18.
- PCOS was diagnosed in patients accord-

ing to the Rotterdam criteria. The following conditions are included in the list: oligo-anovulation, hyperandrogenism, and polycystic ovaries. Polycystic ovaries are characterized by the existence of twelve or more follicles that are two to nine millimeters in diameterand/or in at least one ovary, a volume greater than ten milliliters.

- Hysterosalpingography/laparoscopy reveals bilateral patent tubes.

Exclusion criteria:

- Male factor infertility.
- Uncontrolled hypo/hyperthyroidism couples.
- Bilateral tubal block, renal or liver disease.
- Having a fasting glucose level of 126 mg/dl or above is diabetes mellitus (DM).
- Hyperprolactinemia.
- Drug allergy to myo-inositol.
- Before entering the study, MET and oral contraceptive tablets were required to be paused for a minimum of one and 3 months, respectively.

Interventions: Women who visited the outpatient clinic underwent a history-taking process that included questions on cycle regularity, age, hirsutism, infertility, weight gain or obesity, high blood pressure, acne, diabetes mellitus, and a PCOS family history.

Clinical examination: We conducted a clinical evaluation that included general assessment (body mass index, appearance, and hyperandrogenism symptoms, such as acne, and hirsutism), examination of the pelvis, and examination of the abdomen.

Laboratory investigations: Regular laboratory tests such as fasting and postprandial blood glucose, CBC, HbA1c, TSH, LH, and FSH levels were measured throughout the menstrual cycle third day. Serum prolactin, free testosterone, semen analysis, & levels of mid luteal progesterone (day 21).

A Versana Balance ultrasound machine from GE healthcare with Microconvex Array Probe (4.2 - 10.0 MHz) was used in transvaginal sonography. The screening day was either the second or third cycle day.

The following outcomes were used to compare the two groups before and after the treatment.

Myo-inositol Powder	550 mg
D-chiro-inositol	13.8 mg
Folic acid	0.2 mg

Outcomes:

Primary outcome:

- Occurrence of ovulation.

Secondary outcomes:

- Occurrence of pregnancy.
- Assessment of change in weight and BMI after 3 months in case of not achieving pregnancy.
- The effect on insulin sensitivity after 3 months in case of not achieving pregnancy
- Assesment of improvement in hormonal and biochemical parameters.

Adverse effects: Clinical adverse effects of myoinositol containing medications include headaches, and loss of appetite. Metformin can cause symptoms like vomiting, diarrhea, nausea, loss of appetite, altered taste, and urticaria. Aromatase inhibitors (Letrozole) manifests symptoms such as amenorrhea,headaches, breast pain, and vasomotor flushes.

Ethical Consideration: The medication utilized in the investigation is confirmed by the Egyptian Ministry of Health. The Ethics Committee of the GOTHI Research Centre approved the research protocol (Ethical approval ID: HD00175). Prior to enrollment, written informed consents were gathered from individuals or their legal representatives. The aim of this research was to perform research on humans in compliance with Helsinki Declaration, the code of World Medical Association ethics.

Statistical analysis: The collected data was reviewed & manually coded. Utilizing the Statistic Package for Social Science Version 22 (SPSS 22) for Windows, the numerical codes that were entered into the computer were subjected to statistical analysis. For parametric variables, range, standard deviation, and mean were required. Range, median, and interquartile range were needed for non-parametric variables, whereas range, number, and percentage were needed for categorical variables. The subsequent assessments were implemented: The test of Chi square (X2) was used for qualitative data comparison, along with independent and paired t-tests, confidence intervals (CI), interquartile range, and Fisher's exact test. The coefficient interval was set at ninety-five percent. The following probability

The significance level was determined by utilizing (P) values. We defined statistical significance as a P-value less than 0.05.

RESULTS

Neither group differed significantly from the other with regard to the demographic variables (age, parity, and duration) compared to baseline level at the third month (Table 1).

Table (1): Comparison between the two studied groups regarding age and duration of infertility.

	Group I "n=33"	Group II "n=33"	P
Age (years) Range Mean S.D.	 21-33 26.11 4.02	 20-35 29.26 4.38	0.107
Duration of infertility (years) Range Mean S.D.	 2.0-7.0 4.01 1.69	 1.5-6.0 3.81 1.46	0.207

Table (1) demonstrates a comparison among the 2 groups in relation to the infertility duration and Age. The two groups didn't differ statistically in relation to the infertility duration (P > 0.05).

Table (2): Comparison between the two studied groups regarding type of infertility.

	Group I (n = 33)		Group II (n = 33)		P
	No.	%	No.	%	
Type of infertility Primary Secondary	 28 5	 84.8 15.2	 27 6	 81.8 18.2	0.608

Table (2) presents a comparison of the 2 groups. When it comes to the type of infertility, statistical analysis revealed no significant difference among the 2 groups (P > 0.05).

Table (3): Comparison between the two studied groups regarding menstrual irregularity, hyperandrogenism and PCO appearance by conventional ultrasound

	Group I (n = 33)		Group II (n = 33)		P
	No.	%	No.	%	
Menstrual irregularity Yes	33	100	28	84.8	0.934
Hyperandrogenism Yes	28	84.8	26	78.7	0.205
PCO appearance by US Yes	33	100.0	33	100.0	1

Neither group demonstrated a statistically significant difference with the other with respect to hyperandrogenism (hirsutism-acne-elevated total or free testerone) or PCO appearance by ultrasound (P > 0.05).

Table (4): Overall Ovulation and pregnancy in the 2 groups of study.

	Group I (n = 33)		Group II (n = 33)		P
	No.	%	No.	%	
Ovulating	24	72.7	21	63.6	0.105
Pregnancy	11	33.3	8	24.2	0.078

Table (4) displays the overall rates of ovulation and pregnancy after 3 months of treatment. There was no statistically significant difference among the 2 groups (P > 0.05).

Table (5): Body mass index in the two studied groups before and after treatment and difference.

BMI	Group I "n=33"	Group II "n=33"	P
Before Range Mean S.D.	 17.2-34.0 24.58 3.37	 18.1-32.1 26.28 2.15	0.0927
BMI	Group I "n=22"	Group II "n=25"	P
After Range Mean S.D.	 16.01-32.11 22.50 3.19	 16.47-30.84 24.20 2.48	0.102
Decrease Range Mean S.D.	 1.1-3.13 2.56 0.74	 1.17-4.09 2.08 0.56	0.498

Table (5) illustrates the body mass index of the two groups prior to and following treatment, as well as the discrepancy. Using BMI as a measure, there was no statistically significant difference among the 2 groups (P > 0.05).

Table (6): HOMA- IR in the two studied groups before and after treatment and difference.

Homa IR	Group I "n=33"	Group II "n=33"	P
Before Range Mean S.D.	 1.310-6.58 4.42 0.80	 2.220-5.397 3.17 0.66	0.3483
Homa IR	Group I "n=22"	Group II "n=25"	P
After Range Mean S.D.	 1.094-4.731 2.98 0.78	 1.12-4.11 3.03 0.56	0.3502
Decrease Range Mean S.D.	 0.513-2.739 0.94 0.53	 1.179-1.811 0.74 0.28	0.4777

Table (6) demonstrates the disparity in HOMA-IR between the groups of study before and after treatment. In terms of the decrease in HOMA-IR, when comparing the two groups, the results did not show any statistically significant diuretic ($P > 0.05$).

Table (7): Side effects of myo-inositol and metformin in the 2 groups of study.

Variable	Group I (n=33)		Group II (n=33)		$\chi 2$	P
	No.	%	No.	%		
Abdominal discomfort	2	6.1	9	27.3	5.35	**0.021***
Nausea	3	9.1	10	30.3	4.69	**0.030***
Vomiting	0	0	4	12.1	4.26	**0.039***
Diarrhea	1	3	7	21.2	5.12	**0.024***
Indigestions	1	3	6	18.2	4.00	**0.046***
Loss of appetite	8	24.2	2	6.1	4.24	**0.039***
Headache	7	21.2	1	3	5.12	**0.024***

Table (7) demonstrates the adverse effects of metformin and myo-inositol in the two groups that were examined. Myoinositol group had more complaints about loss of appetite and headache while Metformin group had more GIT manifestation.

DISCUSSION

The most frequently diagnosed endocrine disorder in women of reproductive age is polycystic ovary syndrome (PCOS). This syndrome is a condition that is heterogeneous in nature and has an uncertain etiology. Therefore, there is strong evidence indicating that the development of this condition is influenced by the intricate interactions between genetic, environmental, and behavioral factors.[12] In Pasquali's explanation, the reasoning behind using metformin, a well-established insulin sensitizer, is well explained. [13] " The accompanying article, "Pros," by Pasquali, provides a concise overview of the treatment of metformin potential insulin sensitizing mechanisms. It elucidates the rationale behind the anticipated advantages of metformin in PCOS and delineates these mechanisms, a compound known as myo-inositol (myo-ins) has been

found to be advantageous in the context of fertility and pregnancy. It is a harmless substance. Since myo-ins are involved in several signaling processes, including the insulin and gonadotropin, it is believed to have a positive influence on fertility. In particular, it has been shown in many clinical trials to help infertile women conceive.[14] The age range of the two groups who participated in our study was 20–35 years. The two groups were not significantly different from one another. Implementation of this measure was undertaken to mitigate the influence of age on the results, in agreement with our study Ibrahim M, chose for his comparative study two groups matched in age, the mean age in the two groups was 28.8±3.13 and 29.7±3.65 years. [15] Regarding the duration of infertility, the two studied groups show insignificant difference ($p > 0.05$), and this give advantage to eliminate all the other contributing risk factors which may effect on the outcomes. The secondary infertility rate in group I was 15.2%, while it was 18.2% in group II. There was no statistically significant difference ($P > 0.05$) in the type of infertility between the two groups according to our investigation. This study's results matched those of Richard et al, who reported secondary infertility in 20.0% and 12.5% of the two groups, respectively, without any significant difference. [16] All the patients involved in our study had at least one of symptoms and signs of PCOs, in group I, all patients experienced menstrual irregularity, whereas in group II, 84.8% of patients experienced menstrual irregularity. Although the two groups did not differ significantly in terms of symptoms, hyperandrogenism was found in 84.8% of group I patients and 78.7% of group II patients, in all comparative treatment study of PCOs, the two groups must be matched regarding demographic and basic clinical data to predict only the effect of different treatment on outcomes. [14, 17] In our study, ovulation was 24(72.7%) and 21(63.6%) at both groups respectively and pregnancy was 11(33.3%) and 8(24.2%) respectively after 3 months of treatment .. The two studied groups didn't show any significant difference regarding overall ovulation and pregnancy ($P > 0.05$), it was found that both rate of ovulation and pregnancy was higher with myoinositol group than metformin group. Studying ovulation rates, researchers found that in comparison to the placebo group, While just four out of nineteen women in the placebo group ovulated, sixteen out of twenty-three women in the myoinositol group ovulated. [18] The effectiveness of metformin treatment in women with PCOS was assessed in a meta-analysis and systematic review by Cochrane. The clinical pregnancy and ovulation rates were elevated by metformin throughout this investigation, despite the fact that it did not affect the percentage of live births. The study conducted by Tang confirmed the substantial adverse effects of metformin on the gastrointestinal system.[19]. In their systematic review and meta-analysis, Pundir et al. [20] showed that myo-inositol appeared to enhance the ovulation rate in comparison to the placebo. Before and after therapy, BMI of the two groups did not differ significantly ($P > 0.05$). There was no statistically significant difference among the 2 groups in terms of the drop in BMI, even though both groups showed a positive decrease of more than 2 kg/m2.The findings of this study were consistent with those of Fruzzetti et al. [21] he demonstrated that a notable decrease in BMI from 28.4 ± 5.2 to 26.8 ± 5.8, was observed in the metformin group during the sixth month of therapy when the prescribed regimen of 1500 mg/day (500 mg orally thrice daily).In contrast to our research, another study determined that the effects of myo-inositol in humans are also contingent upon BMI. For instance, obese women in PCOS encountered a decrease in their BMI as a result of myo-inositol supplementation, whereas non-obese women did not.[22] There was no statistically significant change ($P > 0.05$) between the two groups' pre- and post-FBS . There was a reasonable reduction in fasting blood sugar levels in the two groups. By reducing both

basal and postprandial plasma glucose levels, metformin improves glucose tolerance in type 2 diabetics; it is an antihyperglycemic drug. Unlike other oral antihyperglycemic drugs, its pharmacologic methods of action are unique. The groups did not differ significantly with respect to levels of fasting insulin.[23] The therapy led to a reduction in the level of HOMA-IR. Both groups were compared using HOMA-IR before and after therapy, The results did not show any statistically significant association, nevertheless ($P > 0.05$). Our research indicates that both groups experienced an improvement in their hormone status, which encompassed luteinizing hormone, follicle stimulating hormone, and prolactin. Both groups showed some improvement, but the percentage was not significantly different. A significant amount of research supports these results.[24] In terms of testosterone levels, both groups experienced a reduction in both total and unbound testosterone. As a result, the two groups didn't show any statistically significant association in terms of testosterone levels prior to and following the study ($P > 0.05$). The serum testosterone level is positively impacted by metformin administration, an insulin sensitizing agent, as it increases the tissues insulin sensitivity in PCOS and exerts its action over serum insulin.[25] our study results were in line with a double-blind trial in which forty-two women with PCOS were administered either folic acid alone as a placebo or myo-inositol in combination with folic acid. A reduction of 99.5 +/- 7 to 34.8 +/- 4.3 ng/dl ($P = 0.003$) was seen in the blood total testosterone level of the group that received Myo-inositol. Also, there was a decline in the serum free testosterone level, which decreased from 0.85 +/- 0.1 to 0.24 +/- 0.33 ng/dl ($P = 0.01$) and from 0.89 +/- 0.12 to 0.85 +/- 0.13 ng/dl ($P = 0.01$). The adverse effects of metformin and myoinositol in the two groups under investigation exhibit a substantial increase in the group of metformin in comparison to the group of myoinositol. Abdominal discomfort was higher at group II with 9(27.3%) followed by nausea at the same group with 10 (30.3%). Loss of appetite was higher at group I with 8(24.2%) followed by headache with 7(21.2%). A statistically significant difference was observed among side effects of myoinositol and metformin in the two studied groups ($P < 0.05$). The main side effects associated with metformin treatment are the gastrointestinal symptoms of nausea, diarrhea, flatulence, bloating, anorexia, metallic taste and abdominal pain. These symptoms occur with variable degrees in patients and in most cases resolve spontaneously. In conclusion, the Ovulation and pregnancy rate were higher with myoinositol group than metformin group . Myoinositol decreased FBS, insulin levels and thus, increased insulin sensitivity in PCOS women. Overall, myoinositol was better tolerated than metformin.

CONCLUSION

According to the results above, we advise some PCOS patients that there is no significant difference between metformin and myoinositol regarding ovulation and pregnancy rates. It should also highlight that myoinositol is not inferior to metformin.

DECLARATIONS

- Consent for publication: Authors granted permission for the work to be submitted.
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- Conflicts of interest: No conflicts of interest.

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