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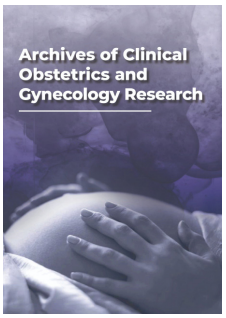

Myoinositol: The New Challenge in Treatment of Polycystic Ovary (PCOS) with Infertility

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Abstract

Introduction: *Polycystic ovarian syndrome (PCOS) is the most prevalent endocrine disorder in women of reproductive age, affecting approximately 6–15% of them and associated with chronic anovulation. Myoinositol is an insulin-sensitizing agent ingested with food and actively synthetized in the liver and brain.*

Aim of the work: *To study the effect of Myoinositol and Metformin in the treatment of PCOS with infertility in the area of Tobruk - Libya.*

Methods: *The study group included 800 selected cases of PCOS with infertility and insulin resistance, diagnosed and treated in the Gynecology and Obstetrics department of Tobruk Medical Center, Libya, from January 2018 to January 2022. Patients were randomly distributed into two groups: Group 1 (n = 400) in which Myoinositol 2000 mg was given daily by taking two tablets of Celine® (Laboratoires Surveal) after breakfast and another two tablets after dinner and Metformin 850 mg taken only during lunch. Group 2 (n = 400) in which only Metformin 850 mg was taken during lunch. The individual treatment period was 8 months. All patients were followed up by ultrasound to see the progress of ovulation.*

Results: *The mean age of the patients in group 1 is 29 years (range, 18–40 years) and that in group 2 is 32 years (range, 22–42 years). Mean pre-study serum glucose level is 193 mg/dl in group 1 and 208 mg/dl in group 2. Mean pre-study Insulin level is 284 mIU/L in group 1 and 295 mIU/L in group 2. There was a highly significant improvement in serum glucose level, serum insulin level, acne, hirsutism, body weight, menstrual cycle regularity, follicles diameter and pregnancy in the group treated with a combination of Myoinositol and Metformin.*

Conclusion: *Our results show that the use of Myoinositol and Metformin is a useful combination treatment of polycystic ovary patients with infertility showing improvement of laboratory, clinical and ovulation with subsequent pregnancy.*

Background

Polycystic ovary syndrome (PCOS) is a common reproductive condition associated with chronic anovulation. It commonly presents with oligomenorrhea, irregular menstrual cycle, and increased androgen level, with typical ovarian ultrasound features [1]. It is the most prevalent cause of disorder of ovulation and subfertility in females and affects approximately 6-10% of childbearing women in population [2]. Although its pathogenesis is poorly understood, the role of insulin in the pathogenesis of hyperandrogenemia in PCOS is central. Insulin resistance in association with luteinizing hormone (LH) increases the production of androgen in ovarian theca cells [3]. Therefore, treatment with insulin-sensitizing agent like myoinositol, rosiglitazone, or metformin in women with PCOS may lead to continuation of spontaneous ovulation [4-8]. Inositols are chemically identified as hexahydroxy-cyclohexanes and include a family of nine stereoisomers [9]. Myoinositol (MI) is the most widely distributed in nature, including humans and mammals [10]. MI is ingested with food mostly from fruits, beans, grains, and nuts. However, daily intake of MI from phytate-rich food does not exceed 500–700 mg/day.

MI can also be actively synthetized (up to 4 g/day) in human body (especially the liver and brain) [11]. The cellular precursor of MI is glucose-6-phosphate, which is isomerized to inositol-3-phosphate (IP3) by D-3-myoinositol-phosphate synthase. IP3 is then dephosphorylated to free MI by inositol monophosphatase-1. Free inositol may also be obtained by recycling inositol-1,4,5-trisphosphate and inositol1,4-bisphosphate. MI biosynthesis varies among tissues depending

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on changing functional requirements [9]. There is a complex relationship between glucose and MI metabolism. On the one hand MI inhibits duodenal glucose absorption and reduces blood glucose rise, suggesting the existence of a competitive affinity for the same transporter system [9,12]. On the other hand, glucose significantly counteracts cellular uptake of inositol and may induce MI depletion by the activation of the glucose-sorbitol pathway. Inhibiting aldose reductase in cultured cells restores MI levels counteracting the depleting effect of sorbitol [13].

Metformin is an insulin sensitizer that lowers fasting levels of plasma insulin, C-peptide, and proinsulin-like molecules. It also increases binding of insulin to its receptor, increases peripheral utilization of glucose, and decreases hepatic glucose production. Metformin also lowers theca cell androgen synthesis in vitro [14]. Metformin has a positive effect on metabolic disturbances and bleeding disorders in women with PCOS [15]. Due to increased incidence of polycystic ovary syndrome (PCOS) in Tobruk, Libya, we were able to collect a cohort of 800 PCOS patients with follow up information in the period extending from January 2018 to January 2022. In this project we utilized this PCOS and anovulation patient cohort for management and treatment using myoinositol in combination with metformin or metformin alone.

Methods

This was a randomized controlled trial conducted at Gynecology and Obstetrics department of Tobruk Medical Center, Libya, from January 2018 to January 2022. A total of 800 female patients aged 18-42 years - with PCOS - were included in the study. Patients gave written informed consent before participating in the study. After obtaining the patients 'consent, the research was started following the approval of the Tobruk Medical Center ethics committee. All patients were investigated for fasting insulin and glucose levels to confirm the insulin resistance by calculation. Patients with insulin resistance were recruited in our study. Patients were thereafter randomly distributed into two groups; Group 1 (n = 400) in which Myoinositol 2000 mg was given daily by taking two tablets of Celine® (Laboratoires Surveal) orally after breakfast and another two tablets after dinner and Metformin 850 mg taken during lunch. Group 2 (n = 400) in which Metformin 850 mg was taken orally during lunch only. The duration of the treatment was 8 months. All patients were followed up by ultrasound to see the progress of ovulation.

Statistical analysis

The collected data were coded then entered and analyzed using the SPSS version 22 (Statistical package for social science). Descriptive statistics was done for categorical variables by frequency and percentage, and for numerical variables in the form of mean and standard deviation (mean ± SD). Suitable statistical tests of significance were used, Chi-Square ($\chi 2$) test for categorical data, p-values equal to or less than 0.05 were considered statistically significant.

Results

The baseline characteristics of the 800 patients selected for analyses are as follows: The mean age of the patients in group 1 is 28.54 years (range, 18–40 years) and in group 2 is 32 years (range, 22–42 years). Mean pre-study serum glucose level is 152.80 mg/dl in group 1 and 172.31 mg/dl in group 2. Mean pre-study Insulin level is 31.62 mIU/L in group 1 and 37.11 mIU/L in group 2 (p>0.05). (Table 1).

Table 1. *Mean age and pre-study serum glucose and insulin levels in group 1 and group 2.*

Variables	Group 1 (Mean)	Group 2 (Mean)
Age (years)	28.54 ± 6.37	31.93 ± 5.86
Pre-study glucose mg/dl	152.80 ± 4.61	172.31 ± 4.36
Pre- study insulin mIU/L	31.62 ± 2.33	37.11 ± 1.95

Table 2. *Pre- and Post-Treatment Glucose and Insulin Levels in PCOS Patients Treated with Myoinositol + Metformin (Celine) or Metformin Alone*

Variable	Group 1: Myoinositol + Metformin (mean ± sd)	Group 2: Metformin Only (mean ± sd)
Pre-study glucose (mg/dL)	152.80 ± 4.61	172.31 ± 4.36
Post-study glucose (mg/dL)	123.77 ± 7.72	148.36 ± 15.84
Pre-study insulin (mIU/L)	31.62 ± 2.33	37.11 ± 1.95
Post-study insulin (mIU/L)	22.69 ± 2.89	28.14 ± 4.72

Table (2) summarizes the results of glucose and insulin levels in two groups of PCOS patients treated with either Myoinositol + Metformin (Group 1) or Metformin alone (Group 2). Group 1 demonstrated a greatly lower post-study glucose mean (123.77 ± 7.72 mg/dL) compared to Group 2 (148.36 ± 15.84 mg/dL). A similar trend was observed in post-study insulin levels, where Group 1 exhibited a mean of 22.69 ± 2.89 mIU/L compared to 28.14 ± 4.72 mIU/L in Group 2. This shows a more evident improvement in metabolic parameters with the combination therapy. The smaller standard deviation (SD) values in Group 1 for insulin suggest a more consistent therapeutic effect among participants.

The combination of Myoinositol and Metformin resulted in greater mean percentage reductions in both glucose (19.02%) and insulin levels (28.26%) compared to Metformin alone (13.91% for glucose and 24.18% for insulin). These differences were statistically significant (p-value<0.05), indicating that the combination of Myoinositol and Metformin has a a significant effect on reducing both glucose and insulin levels compared to Metformin alone.

Table 3. *Mean Percentage Differences in Glucose and Insulin Levels Between Treatment Groups*

Variable	Group 1: Myoinositol + Metformin	Group 2: Metformin Only	p-value
Glucose mean % difference	19.02%	13.91%	0.000*
Insulin mean % difference	28.26%	24.18%	0.000*

Table 4. *Relation of Myoinositol and Metformin effects with respect to laboratory, clinical and radiological findings and pregnancy.*

Variables	Group 1 (n:400) Use of Myoinositol and Metformin	Group 2 (n:400) Use of Metformin only	Chi-square test
Serum glucose level			
Improved (642 cases)	372	270	P=0.00001*
Not (158 cases)	28	130	
Serum insulin level			
Improved (702 cases)	368	334	P=0.000246*
Not (98 cases)	32	66	
Acne			
Improved (503 cases)	302	201	P=0.00001*
Not (297 cases)	98	199	
Hirsutism			
Improved (582 cases)	343	239	P=0.00001*
Not (218 cases)	57	161	
Body weight			
Decreased (312 cases)	193	119	P=0.00001*
Not (488 cases)	207	281	
Menstrual cycle regularity			
Improved (678 cases)	371	307	P=0.00001*
Not (122 cases)	29	93	
Follicles diameter (Folliculometry)			
Improved (532 cases)	321	211	P=0.00001*
Not (268 cases)	79	189	
Pregnancy			
Yes (561 cases)	347	214	P=0.00001*
No (239 cases)	53	186	

The relation of Myoinositol and Metformin effects and frequency of responders with improvement of parameters with respect to laboratory, clinical and radiological findings as well as pregnancy in group 1 and group 2 is shown in Table (4).

Discussion

Polycystic ovarian syndrome (PCOS) is the most prevalent endocrine disorder in women of reproductive age, affecting approximately 6–15% of them [16–18]. It is a major cause of menstrual disturbances, hirsutism, and female anovulatory infertility [19]. However women with PCOS may also have other comorbidities including psychological (anxiety, depression, body image) [17,20,21], metabolic (obesity, insulin resistance, metabolic syndrome, prediabetes, type 2 diabetes, cardiovascular risk factors (hypertension, dyslipidemia), and increased risk for sleep apnea, endometrial carcinoma, and pregnancy-related complications (gestational diabetes, preeclampsia, pregnancy-induced hypertension, postpartum hemorrhage and infection, preterm delivery, meconium aspiration, stillbirth, operative deliveries, and shoulder dystocia) [22]. Consequently, PCOS negatively affects not only reproduction, but also general health, sexual health, and quality of life [18].

In our study, combination of Myoinositol and Metformin showed a significant improvement of serum insulin and glucose levels with a decrease in body weight. That is in alignment with Nestler et al., [4] who was the first to report the efficacy of inositol in the treatment of obese PCOS women, showing an increased insulin action, improved ovulatory function, and decreased serum androgen concentrations, blood pressure, and plasma triglycerides concentrations. Few years later the same effects were demonstrated in lean PCOS women [23]. Donà et al. study showed that treatment with MI proved its effectiveness in reducing hormonal, metabolic, and oxidative abnormalities in PCOS patients by improving insulin resistance [24]. Genazzani et al. [25] demonstrated the same effect in overweight PCOS women. A recent meta-analysis by Unfer et al. [26] evaluating the efficacy of treatment of PCOS with MI, showed significant reductions in fasting insulin. In Shokrpour et al. study, the effect of MI on fasting plasma glucose serum, insulin levels, serum triglycerides, VLDL-cholesterol levels and quantitative insulin sensitivity check index was significantly higher compared with metformin [27]. MI and metformin in combination could act in an additive or synergistic way allowing the use of reduced doses of metformin in patients intolerant to the normal therapeutic administration dose of metformin [28].

In our study, combination of Myoinositol and Metformin shows significant improvement of acne and hirsutism. That is in alignment with Minozzi et al. that showed that the

administration of 2g myoinositol twice daily for 6 months to patients with mild and moderate hirsutism, led to significant decreases in the severity of hirsutism and the levels of total androgens, FSH, LH, and LDL cholesterol [29].

We also showed a statistically significant improvement in menstrual cycle regularity and ovulation, follicles diameter with subsequent pregnancy. These same results were obtained in previous studies that demonstrated how Myoinositol treatment in patients with PCOS improved ovarian function and fertility [30,31], decreased the severity of hyperandrogenism, acne and hirsutism [32-33], and positively affected metabolic parameters and modulated various hormonal parameters deeply involved in the reproductive axis function and ovulation [34,35] and hence how it became a novel method to improve spontaneous ovulation [5] or ovulation induction [36,37].

In a study by Papaleo [38] there was a beneficial effect on restoration and maintenance of normal menstrual cycle during 6 months treatment with Myoinositol. Similar results were also obtained in another study that showed significantly higher ovulation frequency in the MI-treated group (25%) with shorter time to first ovulation as compared to placebo (15%) [39].

Raffone reported that 65% of Myoinositol treated patients restored spontaneous ovulation activity, compared to 50% of metformin treated patients [40]. Also, the combination of MI and metformin showed better effect on menstrual cycle than metformin alone despite the similar effect of both treatments on weight, body mass index (BMI), waist and hip circumferences [41]. It's also worth noting that the presence of saw palmetto in Celine®, containing a lipsterolic extract of Serenoa repens (LSESr) and β-sitosterol with 5-α reductase inhibition properties, may have played a role in enhancing the decrease in testosterone levels and improving the hyperandrogenic skin symptoms (acne and hirsutism) in those treated with the combination medications [42,43].

Conclusion

Our results have shown that the combination use of Myoinositol and Metformin is a useful treatment of polycystic ovary with infertility and showed amelioration in metabolic, hormonal, clinical and ovulation all of which improved subsequent pregnancy rates. We are attentive that further, larger clinical researches such as RCTs are necessary for more solid data.

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