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Myo-Inositol: The New Challenge in Treatment of Polycystic Ovary 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 associated with chronic anovulation. Myo-inisitol is insulin-sensitizing agent ingested with food and actively synthetized in liver and brain. Aim of the work: To study the effect of Myo-inositol and Metformin in treatment of PCOS with infertility in Tobruk-Libya. Methods: The study group included 800 selected cases of PCOS with infertility and insulin resistance, diagnosed and treated in Gynecology and Obstetrics department of Tobruk Medical Center, Libya, from January 2018 to January 2022. Patients then were randomly distributed into two groups; Group 1 (n = 400) in which Myo-inositol 2000 mg daily by taking two tablets (2x500 mg) after breakfast and another tow tablets after dinner and take Metformin 850 mg during lunch. Group 2 (n = 400) in which they take Metformin 850 mg during lunch only. All patients were followed up by ultrasound to see the progress of ovulation. Results: The mean age of the patients at group 1 is 29 years (range, 18–40 years) and at 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 are highly significant relationship between treatment with Myo-inisitol and Metformin (Group-1) with serum glucose level, serum insulin level, acne, hirsutism, body weight, menstrual cycle regularity, follicles diameter and pregnancy. Conclusion: Our results shows that use of Myo-inositol and Metformin is a useful treatment of polycystic ovary with infertility with improvement of laboratory, clinical and ovulation with subsequent pregnancy.

Keywords: PCOS; Infertility; Myo-inisitol

Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive condition associated with chronic anovulation. It commonly shows oligomenorrhea, irregular menstrual cycle, and increase 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 theca cells [3]. Therefore, treatment with insulin-sensitizing agent like inositol, troglitazone, or metformin in women with PCOS may lead to continuation of spontaneous ovulation [4-8]. Inositols are chemically identified as hexahydroxycyclohexanes and include a family of nine stereoisomers [9]. Myo-inositol (MI) is the most widely distributed in nature, including animals and mammals [10]. MI is ingested with food mostly from fruits, beans, grains, and nuts. 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-myo-inositol-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 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, increases binding of insulin to its receptor, increases peripheral utilization of glucose, and decreases hepatic glucose production. It 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 Polycystic ovary syndrome patients with follow up information. In this project we utilized this patient collection for treatment of PCOS and anovulation by using myo-inositol and metformin.

Methods

It 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 between the age of 18-42 years - who have Polycystic ovary syndrome (PCOS) - were included in the study. Patients gave written informed consent before sharing in the study. After we took the consent, we started our research. All patients are investigated for insulin and glucose levels to confirm the insulin resistance by increasing both insulin and glucose levels. So, we take the patients with insulin resistance in our study. All patients informed about the possible result in our study and half of them refuse using myo-inositol for financial causes. Patients then were randomly distributed into two groups; Group 1 (n = 400) in which Myo-inositol 2000 mg daily by taking two tablets (2x500 mg) after breakfast and another tow tablets after dinner and take Metformin 850 mg during lunch. Group 2 (n = 400) in which they take Metformin 850 mg during lunch only. 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 details of 800 patients selected for analyses are as follows. The mean age of the patients at group 1 is 29 years (range, 18–40 years) and at 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. (Table 1).

Variables	Group 1 (Mean)	Group 2 (Mean)
Age (years)	29	32
Pre-study glucose mg/dl	193	208
Pre- study insulin mIU/L	284	295

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

Relation of Myo-inositol and Metformin effects with respect to laboratory, clinical and radiological findings and pregnancy in group 1 and group 2 is shown in Table 2.

Variables	Group 1 (n:400) Use of Myo-inositol 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*
No (122 cases)	29	93	
Follicles diameter (Folliculometry)			
Improved (532 cases)	321	211	*P*=0.00001*
No (268 cases)	79	189	
Pregnancy			
Yes (561 cases)	347	214	*P*=0.00001*
No (239 cases)	53	186	

*p-value <0.05 was considered to be statistically significant.

Table 2: Relation of Myo-inositol and Metformin effects with respect to laboratory, clinical and radiological findings and pregnancy.

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]. Thus PCOS negatively affects not only reproduction, but also general health, sexual health, and quality of life [18].

In our study, combination of Myo-inositol and Metformin shows significant improvement of serum insulin and glucose levels with decrease body weight. That is in agree with Nestler et al., [4] the first to report the efficacy of inositol in the treatment of obese PCOS women, demonstrating increased insulin action, improved ovulatory function, and decreased serum androgen concentrations, blood pressure, and plasma triglyceride concentrations. Few years later the same effects were demonstrated in lean PCOS women [23].Donà et al. studies show 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] evaluated the efficacy of treatments 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 triglyceride, and 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 of metformin [28].

In our study, combination of Myo-inositol and Metformin shows significant improvement of acne and hirsutism. That is in agree with Minozzi et al. that shows patients with mild and moderate hirsutism with administration of 2g Myo-inositol twice daily for 6 months led to significant decrease in the severity of hirsutism and the levels of total androgens, FSH, LH, and LDL cholesterol [29].

We showed a significance improvement of menstrual cycle regularity and ovulation by measurement of follicles diameter with subsequent pregnancy. The same results were obtained in some studies that have demonstrated that Myo-inositol 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 thus 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 of Myo-inositol treatment. Similar results were shown in another study that demonstrated significantly higher ovulation frequency in the MI-treated group (25%) with shorter time to first ovulation compared with the placebo (15%) [39].

Raffone reported that 65% of Myo-inositol treated patients restored spontaneous ovulation activity, compared to 50% of metformin treated patients [40]. 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].

Conclusion

Our results shown that use of Myo-inositol and Metformin is a useful treatment of polycystic ovary with infertility with improvement of laboratory, clinical and ovulation with subsequent pregnancy. We are attentive that further, larger researches are compulsory as meta-analysis in Libya.

References

1. Ehrmann DA: Polycystic ovary syndrome. N Engl J Med. 2005, 352:1223-1236.
2. Franks S: Polycystic ovary syndrome. N Engl J Med. 1995, 333:853-861.
3. Baillargeon JP, Nestler JE: Polycystic ovary syndrome: a syndrome of ovarian hypersensitivity to insulin?. J Clin Endocrinol Metab. 2006, 91:22-24.
4. Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G: Ovulatory and metabolic effects of Dchiro-inositol in the polycystic ovary syndrome. N Engl J Med. 1999, 340:1314-1320.
5. Gerli S, Papaleo E, Ferrari A, Di Renzo GC: Randomized double blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS. Eur Rev Med Pharmacol Sci. 2007, 11:347-354.
6. Gerli S, Mignosa M, Di Renzo GC: Effects of inositol on ovarian function and metabolic factors in women with PCOS: a randomized double blind placebo-controlled trial. Eur Rev Med Pharmacol Sci. 2003, 7:151-159.
7. Ng EH, Wat NM, Ho PC: Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomiphene-resistant polycystic ovaries: a randomized, double blinded placebo-controlled trial. Hum Reprod. 2001, 16:1625-1631.
8. Legro RS, Barnhart HX, Schlaff WD, et al.: Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007, 356:551-566.
9. Bevilacqua, A.; Bizzarri, M. Inositols in Insulin Signaling and Glucose Metabolism. Int. J. Endocrinol. 2018, 2018, 1–8.
10. Halsted, C.H. Handbook of Vitamins: Nutritional, Biochemical, and Clinical Aspects. J. Nutr. 1987, 117, 397.
11. Beemster, P.; Groenen, P.; Steegers-Theunissen, R. Involvement of Inositol in Reproduction. Nutr. Rev. 2002, 60, 80–87.
12. Chukwuma, C.I.; Ibrahim, M.A.; Islam, S. Myo-inositol inhibits intestinal glucose absorption and promotes muscle glucose uptake: A dual approach study. J. Physiol. Biochem. 2016, 72, 791–801.
13. Cammarata, P.R.; Chen, H.Q.; Yang, J.; Yorio, T. Modulation of myo-[3H] inositol uptake by glucose and sorbitol in cultured bovine lens epithelial cells. II. Characterization of high- and low-affinity myo-inositol transport sites. Investig. Ophthalmol. Vis. Sci. 1992, 33, 3572–3580.
14. Sivalingam VN, Myers J, Nicholas S, Balen AH, Crosbie EJ. Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications. Hum Reprod Update. 2014;20:853-868.

15. Palomba S, Falbo A, Zullo F, Orio F Jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. Endocr Rev. 2009;30:1-50.
16. Azziz, R.; Carmina, E.; Dewailly, D.; Diamanti-Kardarakis, E.; Escobar-Morreale, H.F.; Futterweit, W.; Janssen, O.E.; Legro, R.S.; Norman, R.J.; Taylor, A.E.; et al. Positions statement: Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: An Androgen Excess Society guideline. J. Clin. Endocrinol. Metab. 2006, 91, 4237–4245.
17. Teede, H.J.; Deeks, A.; Moran, L.J. Polycystic ovary syndrome: A complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010, 8, 41.
18. Aversa, A.; La Vignera, S.; Rago, R.; Gambineri, A.; Nappi, R.E.; Calogero, A.E.; Ferlin, A. Fundamental Concepts and Novel Aspects of Polycystic Ovarian Syndrome: Expert Consensus Resolutions. Front. Endocrinol. 2020, 11, 516.
19. Usadi, R.S.; Legro, R.S. Reproductive impact of polycystic ovary syndrome. Curr. Opin. Endocrinol. Diabetes Obes. 2012, 19, 505–511.
20. Moran, L.; Gibson-Helm, M.; Teede, H.; Deeks, A. Polycystic ovary syndrome: A biopsychosocial understanding in young women to improveknowledge and treatment options. J. Psychosom. Obstet. Gynecol. 2010, 31, 24–31.
21. Deeks, A.; Gibson-Helm, M.; Teede, H. Is having polycystic ovary syndrome (PCOS) a predictor of poor psychological function including depression and anxiety. Hum. Reprod. 2011, 26, 1399–1407.
22. Teede, H.J.; Misso, M.L.; Costello, M.F.; Dokras, A.; Laven, J.; Moran, L.; Piltonen, T.; Norman, R.J. International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil. Steril. 2018, 110, 364–379.
23. Iuorno, M.J.; Nestler, J.E. Insulin-lowering drugs in polycystic ovary syndrome. Obstet. Gynecol. Clin. North. Am. 2001, 28, 153–164.
24. Donà, G.; Sabbadin, C.; Fiore, C.; Bragadin, M.; Giorgino, F.L.; Ragazzi, E.; Clari, G.; Bordin, L.; Armanini, D. Inositol administration reduces oxidative stress in erythrocytes of patients with polycystic ovary syndrome. Eur. J. Endocrinol. 2012, 166, 703–710.
25. Genazzani, A.D.; Lanzoni, C.; Ricchieri, F.; Jasonni, V.M. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweith patients with polycystic ovary syndrome. Gynecol. Endocrinol. 2008, 24, 139–144.
26. Unfer, V.; Facchinetti, F.; Orrù, B.; Giordani, B.; Nestler, J. Myo-inositol effects in women with PCOS: A meta-analysis of randomized controlled trials. Endocr. Connect. 2017, 6, 647–658.
27. Shokrpour, M.; Foroozanfard, F.; Ebrahimi, F.A.; Vahedpoor, Z.; Aghadavod, E.; Ghaderi, A.; Asemi, Z. 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, 406–411.
28. 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, 511–514.
29. Minozzi, M.; D'Andrea, G.; Unfer, V. Treatment of hirsutism with myo-inositol: A prospective clinical study. Reprod. Biomed. 2008, 17, 579–582.

30. Regidor, P.-A.; Schindler, A.E.; Lesoine, B.; Druckman, R. Management of women with PCOS using myo-inositol and folic acid. New clinical data and review of the literature. Horm. Mol. Biol. Clin. Investig. 2018, 34.
31. Papaleo, E.; Unfer, V.; Baillargeon, J.-P.; Fusi, F.; Occhi, F.; De Santis, L. Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. Fertil. Steril. 2009, 91, 1750–1754.
32. Zacchè, M.M.; Caputo, L.; Filippis, S.; Zacchè, G.; Dindelli, M.; Ferrari, A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. Gynecol. Endocrinol. 2009, 25, 508–513.
33. Ciotta, L.; Iozza, I.; Rubbino, G.; Iemmola, A.; Lizzio, I.; Teodoro, M.C.; Palumbo, M. Treatment of hyperandrogenism by myo-inositol. In Proceedings of the 14th World Congress of Gynecological Endocrinology, Firenze, Italy, 4–7 March 2010.
34. Unfer,V.; DiNicola, S.; Laganà, A.S.; Bizzarri, M. Altered Ovarian Inositol Ratios MayAccount for Pathological Steroidogenesis in PCOS. Int. J. Mol. Sci. 2020, 21, 7157.
35. Di Berardino, O.M.; Monteleone, P.; Valentino,V.; Ruggiero, M.; Papini, F.; Cela,V.; Artini, P.G.; Genazzani, A.R. Myo-inositol administration in PCOS patients after IVF. In Proceedings of the 14th World Congress of Gynecological Endocrinology, Firenze, Italy, 4–7 March 2010.
36. Kamenov, Z.; Kolarov, G.; Gateva, A.; Carlomagno, G.; Genazzani, A.D. Ovulation induction with myo-inositol alone and in combination with clomiphene citrate in polycystic ovarian syndrome patients with insulin resistance. Gynecol. Endocrinol. 2015, 31, 131–135.
37. Morgante, G.; Orvieto, R.; Di Sabatino, A.; Musacchio, M.C.; De Leo, V. The role of inositol supplementation in patients with polycystic ovary syndrome, with insulin resistance, undergoing the low-dose gonadotropin ovulation induction regimen. Fertil. Steril. 2011, 95, 2642–2644.
38. Papaleo, E.; Unfer, V.; Baillargeon, J.-P.; De Santis, L.; Fusi, F.; Brigante, C.; Marelli, G.; Cino, I.; Redaelli, A.; Ferrari, A. Myo-inositol in patients with polycystic ovary syndrome: A novel method for ovulation induction. Gynecol. Endocrinol. 2007, 23, 700–703.
39. Le Donne, M.; Metro, D.; Alibrandi, A.; Papa, M.; Benvenga, S. Effects of three treatment modalities (diet, myoinositol or myoinositol associated with D-chiro-inositol) on clinical and body composition outcomes in women with polycystic ovary syndrome. Eur. Rev. Med. Pharmacol. Sci. 2019, 23, 2293–2301.
40. Raffone, E.; Rizzo, P.; Benedetto, V. Insulin sensitizer agents alone and in co-treatment with rFSH for ovulation induction in PCOS women. Gynecol. Endocrinol. 2010, 26, 275–280.
41. Le Donne, M.; Alibrandi, A.; Giarrusso, R.; Monaco, I.L.; Muraca, U. Diet, metformin and inositol in overweight and obese women with polycystic ovary syndrome: Effects on body composition. Minerva Ginecol. 2012, 64, 23.