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Triple Medical Therapy Might Spare Laparoscopic Ovarian Drilling for Management of PCOS Women

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) presents with several clinical aspects, but anovulation, inflammation, and infertility are its cornerstone characteristics. **Objectives:** The current study aimed to compare the gynecological and metabolic outcomes of triple medical therapy (TMT) using metformin, myoinositol, and α-lipoic acid (Met/MI/ALA) to laparoscopic ovarian drilling (LOD) for PCOS women.

Patients and Methods: 157 PCOS women were divided into the LOD group and the TMT group, who received Met 500 mg three times, MI 2000 mg tab twice daily, and ALA 600 mg tab once daily for a 6-month (m) duration. The US evaluation of ovarian volume, body mass index (BMI), the homeostasis model assessment for insulin resistance (HOMA-IR) score, and serum levels of total testosterone (TT), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels with the calculation of the LH/FSH ratio was evaluated at 6-m and compared to baseline values. **Results:** Ovarian volume was significantly reduced in all patients, with a significantly lower volume in patients in the LOD group. Both LOD and TMT significantly decreased levels of testosterone and LH/FSH ratio, the hirsutism score, and acne grade compared to before therapies, with insignificant differences between both groups. At 6-m follow-up, 93 women (59.2%) resumed regular menstrual patterns, and 37 of the 95 married women (38.9%), got pregnant with a significant difference in favor of LOD. **Conclusion:** LOD is highly beneficial for PCOS women, especially infertile women. The triple therapy using Met/MI/ALA is appropriate for the management of PCOS women, especially those with fulminant metabolic and endocrinal manifestations.

Keywords: PCOS, Insulin resistance, Hyperandrogenemia, Laparoscopic ovarian drilling, Metformin, Myoinositol, α-Lipoic acid.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is becoming the most prevalent female endocrine reproductive disorder that affects up to 24% of women of childbearing age [(1)]. PCOS presents with several clinical aspects, but characteristically anovulation, inflammation and infertility are its cornerstone characteristics [(2)].

Despite the high prevalence of infertility among PCOS women, its underlying mechanism has not been fully established with the subsequent haziness of the therapeutic lines [(1)]. Hyperandrogenemia (HA) drives oxidative stress and inflammasome activation in ovarian granulosa cells, and these disturbances induce follicular developmental disorders, leading to infertility in PCOS women. Insulin resistance (IR) plays a pivotal role in the pathogenesis of PCOS with its related metabolic and reproductive concerns, and this recently directed attention to the use of insulin sensitizers as a part of medical therapy for PCOS women [(3)].

Metformin (Met) is recommended by evidence-based guidelines as an insulin sensitizer for medical treatment of PCOS-associated metabolic disturbances, but the burden of Met-induced side effects obligates many patients to stop therapy [(4)]. Systemic reviews documented the comparable effect of MET and myoinositol (MI) on the clinical, hormonal, and biochemical profiles of PCOS; however, MI is characterized by a better safety profile and tolerance because of its minimal side effects [(5)].

Alpha-lipoic acid (ALA) is a natural compound that has positive effects on nerve conduction and alleviation of symptoms of diabetic polyneuropathy, and it is characterized by its antioxidant and pro-oxidant properties [(6)]. ALA has very strong anti-inflammatory and antioxidant effects and a noteworthy role in the adjustment of insulin metabolic pathway [(4)]. Moreover, ALA can work synergistically with other insulin sensitizers to improve IR, and subsequently, it might ameliorate PCOS-associated reproductive problems [(7)].

Recent literature recommends the personalized pharmacological approach for PCOS medical management. This approach entails the use of combinations of various compounds with different mechanisms of action to get better overall reproductive outcomes [(1,8,9)].

PATIENTS AND METHODS

Study design:

The current prospective interventional comparative study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Benha University throughout the period from January 2022 to January 2024 with follow-up period for at least 6 months.

The study included 157 women fulfilling the Rotterdam criteria [(10)] for diagnosis of PCOS and was free of exclusion criteria

The preliminary evaluation process included all women presenting to the gynecology outpatient clinic with clinical manifestations of PCOS to assess the diagnostic criteria for PCOS and the presence of inclusion and exclusion criteria. PCOS was diagnosed according to the Rotterdam criteria [(10)] and the patient

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was diagnosed as having PCOS if there were ≥2 of these criteria.

Exclusion criteria encompassed maintenance on any other therapies for PCOS, the presence of manifest diabetes mellitus, morbid obesity with a body mass index of >35 kg/m^2, and the presence of other causes for infertility for women seeking pregnancy.

Evaluation tools

1. History taking for age, marital, and fertility statuses and menstrual patterns such as infrequent menstrual periods with an interval between menstrual periods of ≥35 days or amenorrhea, which is defined as the absence of vaginal bleeding for three consecutive cycles.
2. Determination of BMI as weight divided by height in square meters and grading as overweight if Body Mass Index (BMI) was <30 kg/m^2, obese if BMI was ≥30 kg/m^2, and morbid obese if BMI was ≥35 kg/m^2.
3. Evaluation for manifestations of clinical hyperandrogenemia (HA) using the modified Ferriman-Gallwey (FG) map [(11)] for assessment of hirsutism and acne scoring on a 4-grade scoring system [(12)]**.** An FG score of ≥8 indicates HA; the higher the FG scores and acne grade, the higher HA status.
4. Evaluation for the presence of insulin resistance (IR) using the homeostasis model assessment of insulin resistance (HOMA-IR) that interprets the relation between fasting blood glucose (FBG) and serum insulin levels [(13)]**.** And a HOMA-IR index of ≥2 indicates the presence of IR [(14)]**.**
5. Fasting blood samples were obtained for estimation of FBG and serum levels of insulin, total testosterone (TT), dehydroepiandrosterone (DHEA), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), and LH/FSH ratio was calculated.

Randomization was performed using a software program, with 1:1 sequence and even number dropping to get the sequence for each group, which was numerically transformed and printed on special cards. Cards were enveloped, and the enrolled patients were asked to choose an envelope. According to the randomization sequence, patients were divided into TMT and LOD groups.

Treatment protocol

A) TMT Group

Patients received cidophage 500 mg tab (Metformin hydrochloride, Chemical Industrial Development, Cairo, Egypt) in a daily dose of one tab three times; viocyst tab (Viomix Pharmaceutical Industries, Egypt) that contains a combination of myoinositol (MI), D-chiro-inositol (DCI) in a 40:1 ratio and was received as one tab twice daily, and thiotacid compound 600 mg tab (α-lipoic acid 600, Eva Pharma, Egypt) in a single daily dose.

B) LOD Group

The procedure of LOD was performed under light intravenous anesthesia, using a 3-port procedure; a primary subumbilical port and two lateral posts. The laparoscope was inserted through the primary port), and ovarian cauterization was used to create 4-punctures bilaterally, for a depth of 4 mm by applying 40 W mixed current in the monopolar electrosurgical needle for 4-sec to deliver 640 J [(15)]**.** After completion of cauterization, the laparoscope was removed, the wound was closed using absorbable suture material, and the patient was transferred to the post-anesthesia care unit. LOD was performed as an outpatient procedure, and patients were discharged when they could move unaided and took oral fluids.

Follow-up

Patients were asked to attend the outpatient clinic after 6-m of treatment to re-evaluate the clinical parameters and lab investigations.

Study outcomes

The primary outcome was the frequency of women who got regular menstruation and/or pregnancy on natural intercourse and without ovarian stimulation in both groups.

The secondary outcome was the improvement of both clinical and biochemical HA and IR.

Ethical considerations

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Benha University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical analysis

Quantitative data were presented as mean and standard deviation (SD) and were compared by independent t-test for intergroup variance and paired t-test for intragroup variance. Qualitative data were presented as frequency and percentage**,** Mann-Whitney test was used to compare between the 2 groups, and use Wilcoxon signed-rank test was used to compare before and after in the same group. Analyses were conducted using the software program; IBM SPSS statistics data analyzer (IBM, USA, Ver. 22), with a p-value cutoff at 0.05 to qualify the significance of the comparisons.

RESULTS

The preliminary clinical evaluation excluded 21 women for the detection of exclusion criteria, and 164 women were randomly allocated into the two study groups, but during the 6-m follow-up period, seven women of the TMT group were missed and excluded from the statistical analyses (Fig. 1).

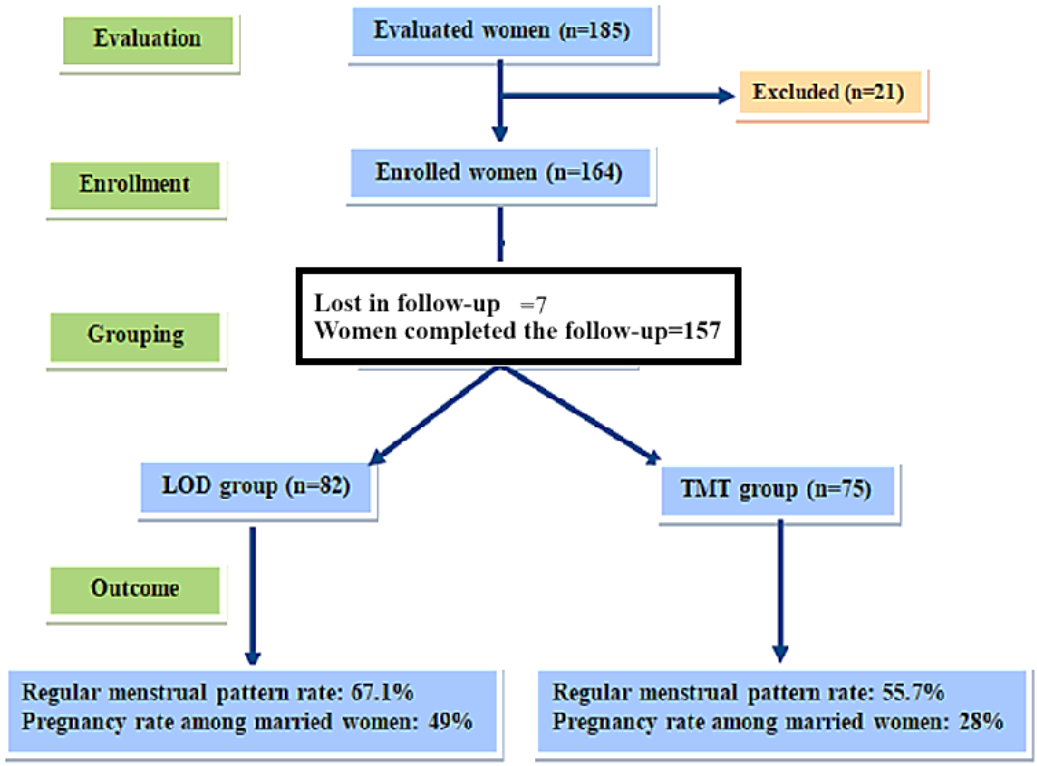

Figure 1: Study Flow Chart

The enrolment data of these 157 women showed insignificant differences as shown in Table 1.

Table 1: Patients' Sociodemographic data

Parameter	Group	LOD (n=82)	TMT (n=75)	P
Age (years)	Mean (SD)	29.2 (3.8)	30 (4.2)	0.219
BMI (kg/m^2)	Average	2 (2.4%)	6 (8%)	0.286
	Overweight	23 (28.1%)	20 (26.7%)	
	Obese-I	57 (69.5%)	49 (65.3%)	
	Mean (SD)	31 (2.16)	30.6 (3.14)	0.351
Marital status	Single	33 (40.2%)	29 (38.7%)	0.840
	Married	49 (59.8)	46 (56.1)	
Fertile status	Fertile	18 (36.7%)	15 (32.6%)	0.794
	Primary infertility	10 (20.4%)	12 (26.1%)	
	Secondary infertility	21 (42.9%)	19 (41.3%)	
Menstrual pattern	Oligomenorrhea	55 (67.1%)	51 (68%)	0.901
	Amenorrhea	27 (32.9%)	24 (32%)	

Ovarian volume was determined before the treatment, and as represented by the estimated greatest ovarian diameter, it showed an insignificant difference between both groups. At the 6-m follow-up, the estimated greatest ovarian diameter was significantly reduced in all patients in comparison to that estimated before treatment, but was significantly lower in patients in the LOD group, with a significantly higher percentage of change in the estimated greatest ovarian diameter than with TMT (Fig. 2).

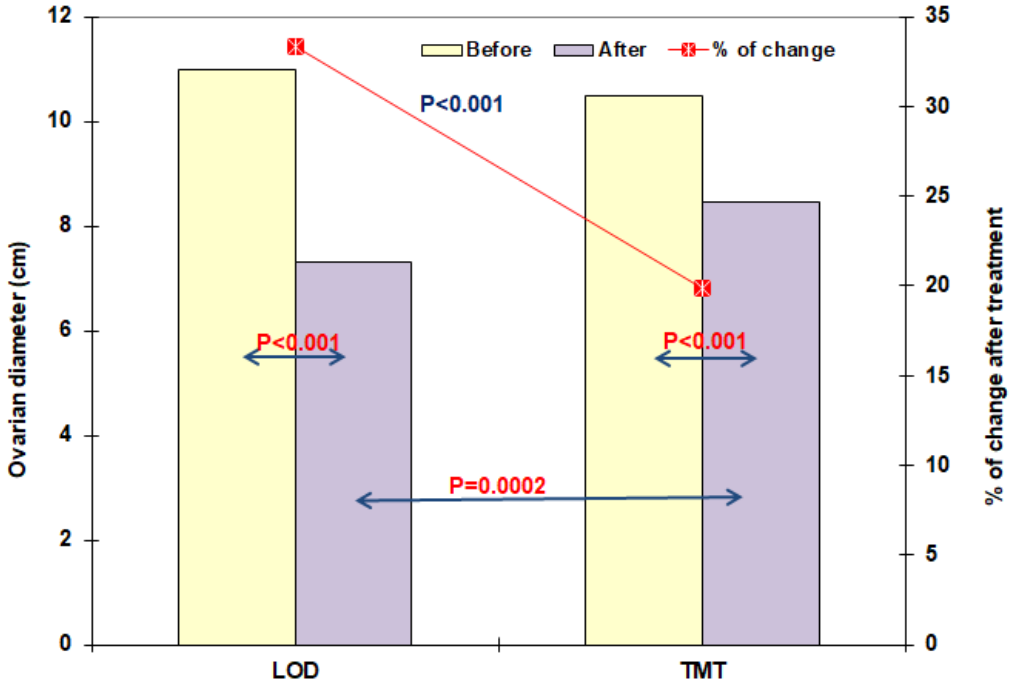

Fig. (2): Ovarian diameter estimated before and after treatment received by patients of both groups

Despite the insignificant reduction of the frequency of hirsute women in comparison to the frequency reported before treatment in both groups, the hirsutism score was significantly lower after LOD and TMT in comparison to the score determined before treatment. Regarding acne, both therapeutic lines significantly reduced the frequency of patients who had acne in comparison to the frequencies detected before treatment. Among patients who had acne, the frequency of low grade was significantly higher after treatment than before treatment, but the difference was non-significant between both groups (Table 2).

Table 2: The effect of the received treatment on clinical HA of women of both groups

Group and Time / Manifestation			Before treatment		After treatment	
			LOD (n=82)	TMT (n=75)	LOD (n=82)	TMT (n=75)
Hirsutism	Frequency of presence of hirsutism	FG>8	24 (29.3%)	28 (37.3%)	17 (20.7%)	20 (26.7%)
		FG<8	58 (70.7%)	47 (62.7%)	65 (79.3%)	55 (73.3%)
		P	0.283		0.381	
		P1			0.207	0.161
	FG hirsutism score	Mean	7 (1.63)	7.64 (2.94)	5.55 (1.93)	6.13 (2.61)
		P	0.089		0.110	
		P1			<0.001	0.0011
Acne	Frequency of acne presence	No	45 (54.9%)	36 (48%)	58 (70.7%)	50 (66.7%)
		Yes	37 (45.1%)	39 (52%)	24 (29.3%)	25 (33.3%)
		P	0.389		0.583	
		P1			0.036	0.021
	Grade among cases had acne	1	16 (43.3%)	14 (35.9%)	20 (83.3%)	19 (76%)
		2	11 (29.7%)	13 (33.3%)	3 (12.5%)	5 (20%)
		3	6 (16.2%)	9 (23.1%)	1 (4.2%)	1 (4%)
		4	4 (10.8%)	3 (7.7%)	0	0
		P	0.803		0.777	
		P1			0.016	0.011

P indicates the value for significance between LOD and TMT groups; P1 indicates the value of significance between before and after treatment.

The estimated levels of the studied hormones showed insignificant differences between samples of women of both groups, either before or after treatment. However, the applied treatment policies induced significantly decreased levels of testosterone, DHEA, and LH/FSH ratio in samples obtained after the end of treatment in comparison to the levels estimated in samples obtained before treatment (Table 3).

Table 3: The effect of the received treatment on patients' hormonal profiles

Group and Time / Hormone		Before treatment		After treatment	
		LOD (n=82)	TMT (n=75)	LOD (n=82)	TMT (n=75)
Serum total testosterone (ng/dl)	Mean	75.4 (26.9)	80 (25.7)	66.9 (23.9)	69.3 (21.2)
	P	0.272		0.505	
	P1			0.033	0.0061
Serum dehydro-epiandrosterone (µg/dl)	Mean	304.5 (61.3)	323 (73.6)	282.5 (59.4)	300 (67.2)
	P	0.088		0.085	
	P1			0.021	0.047
LH (IU/L)	Mean	12.9 (4.7)	13.1 (3.8)	12.1 (4.3)	12.4 (3.5)
	P	0.722		0.681	
	P1			0.257	0.196
FSH (IU/L)	Mean	5.5 (1.88)	5.48 (1.72)	5.97 (1.85)	5.94 (1.71)
	P	0.945		0.921	
	P1			0.110	0.102
LH/FSH ratio	Mean	2.41 (0.6)	2.44 (0.44)	2.04 (0.51)	2.11 (0.38)
	P	0.691		0.357	
	P1			0.00005	<0.001

P indicates the value for significance between LOD and TMT groups; P1 indicates the value of significance between before and after treatment.

The provided TMT significantly improved glucose homeostasis with a significant reduction of levels of FBG and serum insulin with subsequent significant reduction of HOMA-IR score at the end of therapy in comparison to levels determined before the start of treatment. On the contrary, LOD allowed a significant reduction of FBG levels but an insignificant reduction of serum insulin and HOMA-IR score compared to measures determined before surgery. Despite the insignificant differences between patients in both groups before treatment, all measures were significantly lower after TMT than LOD at 6-m follow-up. According to the HOMA-IR score, the incidence of IR women before the start of therapy was insignificant between both groups but was significantly lower among TMT women than among LOD women. Moreover, the incidence of IR women was insignificantly decreased after LOD, while was significantly decreased after TMT. The received TMT, mostly through increasing insulin sensitivity, allowed significant weight reduction that was manifested as a significant increase in the frequency of average weight women with a decrease in the frequency of obese women in comparison to the BMI grade determined before the initiation of treatment and to women in the LOD group and a significant reduction of the calculated index (Table 4).

Table 4: The effect of the received treatment on the metabolic profile of the studied women

Group and Time / Parameter			Before treatment		After treatment	
			LOD (n=82)	TMT (n=75)	LOD (n=82)	TMT (n=75)
Fasting blood glucose (mg/dl)		Mean	99.6 (7.8)	100.6 (7.1)	97.1 (7.9)	93.9 (6.4)
		P	0.416		0.0064	
		P1			0.044	<0.001
Fasting serum insulin (IU/L)		Mean	6.46 (3.44)	5.788 (2.55)	5.58 (2.95)	4.74 (1.97)
		P	0.172		0.039	
		P1			0.071	0.0027
HOMA-IR		Mean	1.65 (0.96)	1.44 (0.72)	1.45 (0.83)	1.11 (0.54)
		P	0.128		0.003	
		P1			0.158	0.0018
Patients' distribution according to insulin sensitivity		Sensitive	48 (58.5%)	52 (69.3%)	52 (63.4%)	65 (86.7%)
		Resistant	34 (41.5%)	23 (30.7%)	30 (36.6%)	10 (13.3%)
		P	0.160		0.0008	
		P1			0.522	0.010
BMI (kg/m^2)	Grade	Average	2 (2.4%)	6 (8%)	3 (3.7%)	16 (21.3%)
		Overweight	23 (28.1%)	20 (26.7%)	27 (32.9%)	35 (46.7%)
		Obese-I	57 (69.5%)	49 (65.3%)	52 (63.4%)	24 (32%)
		P	0.286		0.00005	
		P1			0.688	0.00002
	Index	Mean	31 (2.16)	30.6 (3.14)	30.3 (2.22)	28.1 (3.13)
		P	0.351		0.00003	
		P1			0.048	<0.001

P indicates the value for significance between LOD and TMT groups; P1 indicates the value of significance between before and after treatment

The applied therapeutic lines improved PCOS-induced gynecological problems, as manifested after 6-m follow-up by the resumption of the regular menstrual pattern by 93 women (59.2%), with a significantly higher frequency of women resumed regular menstrual pattern after LOD than after TMT. Moreover, among women who still had irregular menstrual patterns, 57 women (89.1%) still had oligomenorrhea, and 7 women (10.9%) still had amenorrhea with insignificantly lower frequency among women in the LOD group than women in the TMT group. Furthermore, 37 of the 95 married women got pregnant for a rate of 38.9%, with a significantly higher pregnancy rate among women of LOD (49%) than women in the TMT group (28.3%), as shown in Table 5 and Figure 4.

Table 5: Patients' distribution according to the gynecological outcomes after LOD and TMT

Outcomes		Total (n=157)	LOD (n=82)	TMT (n=75)	P
Menstrual pattern	Regular	93 (59.2%)	55 (67.1%)	38 (50.7%)	0.037
	Irregular	64 (40.8%)	27 (32.9%)	37 (49.3%)	
Irregular menstrual pattern	Oligomenorrhea	57 (89.1%)	22 (81.5%)	35 (94.6%)	0.097
	Amenorrhea	7 (10.9%)	5 (18.5%)	2 (5.4%)	
Pregnancy among married women	Pregnant	37 (38.9%)	24 (49%)	13 (28.3%)	0.038
	No	58 (61.1%)	25 (51%)	33 (71.7%)	

DISCUSSION

The applied therapies for the studied PCOS women resulted in significant improvement of their gynecological and metabolic problems with varied extent of improvement that showed bi-directional fashion. LOD as predicted significantly reduced the ovarian size, and was associated with more improvement in menstrual patterns and significantly higher pregnancy rates among married women than TMT[15].

These results supported the previously reported by **Sinha *et al.*** [16] who reported resumption of regular menstruation and improved rates of ovulation and clinical pregnancy to 76% and 42% in PCOS who managed using LOD. Also, **Hatırnaz *et al.*** [17] compared LOD versus transvaginal ovarian aspiration and detected superior outcomes with LOD in the form of a significant reduction of serum anti-müllerian hormone and antral follicular count, but other variates showed insignificant differences.

In support of the efficacy of LOD, **Mahey *et al.*** [18] documented that for PCOS patients who have chronic anovulation, persistently elevated serum anti-müllerian, and luteinising hormones, and failed to have successful pregnancy outcomes despite multiple ovulation induction cycles, repeat LOD resulted in a successful outcome in terms of good oocyte yield and successful live birth with supernumerary embryos frozen for future use. **Seow *et al.*** [19] attributed LOD-induced improvements to the acute aseptic inflammatory response initiated by the thermal effects of cauterization with subsequent apoptosis of the pre-antral follicles, re-start of normal follicular recruitment, development, and maturation, and the resultant normalization of the "hypothalamus-pituitary-ovary" axis, decreased local and systemic androgen levels, and spontaneous ovulation.

On the other side, TMT significantly improved the PCOS-associated metabolic disturbances more superiorly than LOD, especially the reported significantly higher frequency of insulin-sensitive women with subsequent utilization of the accumulated insulin, resulting in decreased serum insulin. Concomitantly with increased insulin sensitization, glucose metabolism was adjusted as evidenced by the decrease in FBG and subsequent reduction of HOMA-IR score. Further, the adjusted insulin sensitivity shifted lipid metabolism towards the β-oxidation pathway leading to fuel consumption, mobilization of free fatty acid from adipose tissue, which is also insulin sensitive, to liver and muscle to be consumed for ATP synthesis as complementary fuel source to the decreased glucose levels, and this recycling process resulted in loss of body weight and decreased BMI[7] .

Unfortunately, a review of the literature detected that no study tried a similar triple combination of metformin, myoinositol, and α-lipoic acid (ALA) for the management of PCOS women. However, the obtained results are in line with multiple recent studies that tried these drugs separately or in various combinations for such patient populations.

Combined ALA and DCI therapy for PCOS women was tried by **Fruzzetti *et al.*** [20] who detected improved menstrual cycle length, restoration of ovulation, and improved insulin sensitivity, especially in IR women. Using the same combination for overweight PCOS patients who had diabetic relatives and undergoing controlled ovarian hyperstimulation for ART, **Artini *et al.*** [21] found such a combination allowed a reduction in the consumed doses of gonadotropin, and provided shorter stimulation days, a higher number of Metaphase II (MII) oocytes, and a higher number of fertilized oocytes. So, this study recommended such combination as a strategy in overweight PCOS patients with familial diabetes underwent ART.

Cirillo *et al.* [22] detected normalization of serum levels of high-mobility-group-box-1 in PCOS women patients with improved ovarian expression levels of

cystic-fibrosis-transmembrane-conductance-regulator and concomitantly improved insulin sensitivity and subsidence of inflammation with combined therapy of ALA and MI.

Thereafter, **Genazzani *et al.*** [23] found the combined therapy of DCI plus ALA was more effective for PCOS women than women without familial DM, but both showed significantly decreased LH, androstenedione, plasma insulin, and HOMA index, with significant reduction of BMI. This study attributed the beneficial metabolic effects of such a combination to the restoration of hepatic insulin clearance. Using ALA and pioglitazone combination **Pei *et al.*** [9] reported significantly improved BMI, oxidative stress levels, lipid metabolism, and menstrual status than any of the drugs used as a single therapy.

Recently, **Nazirudeen *et al.*** [24] found that combined Met/MI therapy significantly improved menstrual cycle regularity and PCOS questionnaire scores compared to Met alone. Moreover, a recent meta-analysis detected 26 studies comparing MI versus Met or placebo for PCOS women and found that the risk of getting a regular menstrual cycle with MI was 1.79 times higher than placebo and was non-inferior to metformin. He also detected significantly lower levels of sex hormones with concomitant higher levels of sex-hormone-binding globulin, and metabolically, he found the blood levels of insulin and glucose were significantly lower with decreased BMI levels with MI than placebo [25].

In support of the efficacy of ALA, **Fruzzetti *et al.*** [26] reported improved cycle regularity in 71.2% and 85.7% of PCOS women who received ALA in combination with MI at doses of 1000 and 2000 mg daily, respectively, without further improvement of metabolic parameters and attributed the great improvement to the combined actions, not to the used dose of MI. As another piece of evidence for the efficacy of ALA, **Scarinci *et al.*** [27] using ALA as a solo therapy at a dose of 800 mg/day for PCOS women, reported an increased number of menstrual cycles during the 6 months in all patients, with a reduction of BMI in the normoinsulinemic population, and a reduction of serum insulin in hyperinsulinemic patients, and increased total antioxidant capacity in all patients.

The reported improved menstrual pattern with TMT in line with improved insulin sensitivity was attributed to the normalization of serum levels of high-mobility-group-box-1 in PCOS women patients with improved ovarian expression levels of cystic-fibrosis-transmembrane-conductance-regulator, and concomitantly, improved insulin sensitivity and subsidence of inflammation with combined therapy of ALA and MI [21]. Thereafter, **Ezeh *et al.*** [28] suggested that IR and hyperinsulinemia, but not HA, is the determinant factor for the degree of menstrual dysfunction. He also considered metabolic correction by insulin sensitizers as the appropriate line for the management of PCOS-associated menstrual dysfunction.

CONCLUSION

Laparoscopic ovarian drilling is highly beneficial for PCOS women, especially infertile women. Triple therapy using Met/MI/ALA is an appropriate medical policy for the management of PCOS women, especially those with fulminant metabolic and endocrinal manifestations. The triple medical therapy is advantageous over LOD for being non-invasive, spares hospitals and patients' resources, and is free of anesthesia and surgery-related complications with non-inferior gynecological outcomes but superior metabolic and endocrinal outcomes.

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