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Original Research Article

Evaluating a synergistic nutritional strategy in women with polycystic ovary syndrome: a multicentric retrospective analysis

Sujoy Dasgupta[1], Priti Kumar[2], Pranab Kumar Biswas[3], Jayanti Kamat[4], Prajakta Ahire[5], Kaniz Fatima[6], Aparna Hadawale[7], Suchitra Nadkarni[8], Poonam Narvekar[9], Varun Gaitonde[10], Milind Gaitonde[10], Preet R. Motiramani[11], Meenaz Dongre[12], Nisat Afrin[13], Shital Thube[14], Shashikant Singh[15], Sandesh Kamdi[16]*

[1]Genome Fertility Centre, Paddapukur, Bhowanipore, Kolkata, WB, India
[2]Department of Obstetrics and Gynecology, Naraina Medical College and Research Centre, Kanpur, Uttar Pradesh, India
[3]Department of Obstetrics and Gynecology, Calcutta National Medical College, Kolkata, West Bengal, India
[4]Department of Obstetrics and Gynecology, Kamat Hospital, Jogeshwari East, Mumbai, Maharashtra, India
[5]Department of Obstetrics and Gynecology, Panandikar Hospital, Thane West, Thane, Maharashtra, India
[6]Department of Obstetrics and Gynecology, Zainab Clinic, Mumbra, Thane, Maharashtra, India
[7]Department of Obstetrics and Gynecology, Hadwale Clinic, Dombivli East, Thane, Maharashtra, India
[8]Department of Obstetrics and Gynecology, Nadkarni Clinic, Kurla East Mumbai, Maharashtra, India
[9]Department of Obstetrics and Gynecology, Narvekar Hospital, Thane, Maharashtra, India
[10]Department of Obstetrics and Gynecology, Abhiman Hospital, Thane West, Thane, Maharashtra, India
[11]Department of Obstetrics and Gynecology, Smt. Papibhai Hospital, Ulhasnagar, Mumbai, Maharashtra, India
[12]Department of Obstetrics and Gynecology, Dongre Clinic, Kausa, Mumbra, Thane, Maharashtra, India
[13]Department of Obstetrics and Gynecology, Medford Hospital, Mumbra, Thane, Maharashtra, India
[14]Department of Obstetrics and Gynecology, Rainbow Hospital, Bhiwandi, Thane, Maharashtra, India
[15]Medical Services, Wayonext Pharmaceuticals Pvt. Ltd., Mumbai, India
[16]Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland, Baltimore, United States of America

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***Correspondence:**
Dr. Sandesh Kamdi,
E-mail: skamdi@som.umaryland.edu

ABSTRACT

Background: The objective of this study was to review clinical outcomes in women with polycystic ovary syndrome (PCOS) following 3-6 months of treatment with the marketed formulations containing insulin sensitizers, minerals, herbal extracts, amino acids, antioxidants, and vitamins.
Methods: An observational study was conducted to retrospectively review clinical records of women diagnosed with PCOS (age 15-42 years; n=211) at 14 fertility clinics in India between April 2024 and February 2025. From the day of PCOS diagnosis, patients received marketed formulations containing (1) insulin-sensitizing agents, antioxidants, and vitamins and (2) fertility blend containing herbal extracts, amino acids and minerals administered as two tablets daily for 3 to 6 months. The primary outcomes assessed were improvements in PCOS symptoms such as (menstrual cyclicity, acne, and hirsutism), body mass index (BMI), waist-to-hip ratio, ovarian cyst count, hormonal profile, and clinical pregnancy rates.
Results: Combination therapy significantly improved menstrual cyclicity in both obese (40% at 3 months; 80.56% at six months) and lean (42.30% at three months; 69.23% at 6 months) PCOS women. Significant reductions in acne, hirsutism, and ovarian cysts were observed across both the groups. Additionally, metabolic parameters and hormonal profiles improved significantly. The clinical pregnancy rate increased to 36.78% at three months and 65.16% at six months in obese women, while lean women showed rates of 38.46% and 53.84% respectively.
Conclusions: The combination of inositols, antioxidants, herbal extracts, amino acids, minerals, and vitamins offer a promising and clinically relevant treatment option for PCOS management, demonstrating significant benefits in metabolic, hormonal, and reproductive health.

Keywords: Antioxidants, Infertility, Inositols, PCOS, Pregnancy

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder that primarily affects women of reproductive age, with significant implications for their long-term metabolic and reproductive health.[1] The condition is characterized by a constellation of clinical manifestations, including irregular menstrual cycles, hyperandrogenism (hirsutism, acne, and alopecia), polycystic ovarian morphology (PCOM), and infertility.[2,3] According to the Indian Fertility Society, PCOS affects 3.7-22.5% of adult women and approximately 12% of adolescent girls in India.[4] Despite decades of research, the precise etiopathogenesis of PCOS remains elusive, though it is widely recognized as a multifactorial condition driven by genetic, environmental, and lifestyle factors.[1]

One of the primary pathophysiological mechanisms underlying PCOS is insulin resistance (IR), which is observed in approximately 65-95% of affected women.[2] Obesity is a major contributor to IR, with 65-80% of women with PCOS being overweight or obese.[5] Furthermore, oxidative stress plays a crucial role in disrupting insulin signalling and metabolic homeostasis in PCOS.[6] Vitamin D deficiency, which affects 67-85% of women with PCOS, further exacerbates IR and reproductive dysfunction.[7]

The hyperinsulinemia associated with IR exacerbates ovarian dysfunction by amplifying luteinizing hormone (LH) activity, leading to excessive androgen production by the theca cells of the ovarian follicles and contributing to hyperandrogenism.[8] Additionally, hyperinsulinemia disrupts the balance of key reproductive hormones, including progesterone, follicle-stimulating hormone (FSH), and anti-Müllerian hormone (AMH), all of which are strongly implicated in PCOS pathophysiology.[9] Insulin also alters ovarian function by disrupting the physiological ratio of myo-inositol (MI) to D-chiro-inositol (DCI), which are essential for proper ovarian signaling.[10] Additionally, hyperinsulinemia contributes to elevated homocysteine levels, which are significantly higher in women with PCOS and have been associated with an increased risk of early miscarriage, spontaneous abortion, and neural tube defects (NTDs).[11]

Given these underlying mechanisms, effective therapeutic strategies for PCOS must target IR, oxidative stress, and hormonal imbalance to restore ovarian function and improve reproductive health. Emerging evidence suggests that a combination of inositols (MI and DCI), vitamin D, and antioxidants such as N-acetylcysteine (NAC) can enhance insulin sensitivity and improve PCOS-related symptoms.[12,13] Chromium picolinate has also been shown to improve glucose metabolism, particularly in obese and diabetic individuals.[14] Furthermore, folic acid supplementation plays a crucial role in reducing the risk of hyperhomocysteinemia-related complications in pregnant women with PCOS.[12]

A previous study by our group investigated the effects of combined treatment of insulin sensitizers, antioxidant, and vitamins in women with PCOS over a 3-month period. The treatment led to significant improvements in menstrual cyclicity, acne, and hirsutism; however, key aspects such as hormonal regulation and ovarian morphology were not fully assessed.[12] Therefore, the present study aimed to evaluate the long-term (6-month) effects of a combination therapy containing inositols, antioxidants, herbal extracts, minerals, and vitamins on metabolic parameters (fasting glucose, fasting insulin, and IR), hormonal balance (LH:FSH ratio, AMH, free testosterone, and progesterone), and ovarian morphology (number and size of ovarian cysts) in both obese and lean women with PCOS.

METHODS

Study design and population

A retrospective study was conducted on women of reproductive age (15-42 years) with a confirmed diagnosis of PCOS attending fertility clinics across various states in India between April 2024 and February 2025.

Ethics and trial registration

As this was a retrospective observational study involving anonymized patient data, clinical trial registration was not required. This study was approved by the institutional ethics committee (no: 2024-02) prior to data collection, and informed consent was waived in accordance with ethical guidelines. All patients' clinical data were anonymized and coded before submitting to the data analyst to ensure patient confidentiality.

Data collection

The clinical records of 387 reproductive age females having sign and symptoms of PCOS were randomly collected and retrospectively analysed to evaluate the efficacy of marketed formulations containing insulin sensitizers, antioxidants, amino acids, vitamins, and minerals in the study. These patients were screened for the presence of signs and symptoms of PCOS as per the Rotterdam criteria.[12-13]

Screening of subjects

Each patient was screened by the gynecologist for the signs and symptoms of PCOS. Acne and hirsutism were evaluated using the global acne score and modified Ferriman-Gallwey scoring system respectively.[12] The inclusion/exclusion criteria to review the clinical record is described in Table 1.

Table 1: Inclusion and exclusion criteria.

Inclusion criteria
Premenopausal women between 18-45 years of age
BMI less than 42
Adequate hepatic, renal and haematological functions
Patients willing to give informed consent
Exclusion criteria
Post-menopausal women
Women with hysterectomy
Patients with congenital adrenal hyperplasia
Patients diagnosed with Cushing's syndrome.
Patients diagnosed with androgen secreting tumors
Patients with thyroid dysfunction (T3, T4 level is higher than that in normal women of reproductive age)
Patients with hypo-gonadotropic and hypo-gonadism (central origin of ovarian dysfunction)
Pregnant or lactating mothers.
Cardiovascular, respiratory, or endocrinological diseases that required the prescribed medication
Current or smoking history
Patients on any other insulin sensitizer or oral contraceptives in past six months

Out of 387 medical reports, a total of 211 cases were identified with confirmed clinical and biochemical diagnosis of PCOS. The demographic and baseline characteristics such as age, anthropometric evaluation [BMI and waist circumference (WC)], and marital status, duration of infertility, previous treatment, and occupation are given in Table 2.

Treatment intervention

All adolescent and adult patients were received a marketed formulation, OVA-BD™ (intervention 1, Wayonext Pharmaceuticals Pvt., Ltd., Mumbai, India). In addition, married women diagnosed with PCOS and seeking ovulation induction for fertility treatment were also supplemented with a fertility-specific blend, Dreamfert-F™ (intervention 2, Wayonext Pharmaceuticals Pvt., Ltd., Mumbai, India). The detailed compositions of both formulations are provided in Table 3. Each formulation was administered as two tablets per day, for a minimum of three months and up to six months from the date of PCOS diagnosis.

Hormonal assessment

Blood sample analysis was conducted by the government approved laboratories to assess serum levels of FSH, LH, AMH, insulin, sex hormone binding globulin (SHBG), and free testosterone during the follicular phase of the menstrual cycle. Serum progesterone levels were measured during the luteal phase. IR was evaluated based on fasting serum glucose concentration, and the homeostatic model assessment (HOMA) index was calculated using the formula: HOMA = fasting serum concentration of insulin (mIU/ml) × fasting serum concentration of glucose (mg/dl)/405.[16]

Outcome measurement

The changes in sign and symptoms (menstrual cyclicity or ovulation restoration, acne and hirsutism), body weight, waist and hip circumference, number of ovarian cysts, hormonal parameters and the clinical pregnancy after 3 to 6 months treatment were set as a primary outcome. The secondary outcome was the evaluation of side effects reported in those patients' undergoing treatment.

Data collection

The medical records of all PCOS were thoroughly analysed. Each patient's record was assessed for the baseline (day 1 visit) and subsequent visits at 3 and 6 months to evaluate clinical parameters. As a result, each patient served as her own control.

Statistical analysis

The data are represented as mean ± standard deviation (SD), and the differences between baseline and post intervention values within the study groups were analysed by one-way analysis of variance (ANOVA) followed by post-hoc Bonferroni multiple comparisons test using GraphPad Prism software. Statistical significance was set at a p value of <0.05.

RESULTS

Baseline characteristics of patients

The baseline demographic and clinical characteristics of the study cohort are summarized in Table 2. Out of the 211 medical records screened, 162 belonged to married women with infertility, while 49 were from unmarried adults and adolescents diagnosed with PCOS. Infertile women

(n=142; 122 obese, 20 lean) were received with both the study interventions (intervention 1 and 2) with or without ovulation inducing agents (letrozole or clomiphene citrate) and unmarried adults and adolescents (n=39; 33 obese, 6 lean) were supplemented with intervention 2 with or without combined oral contraceptive pills (OCPs).

After three months, 142 patients attended the follow-up visit, while 20 infertile patients were lost to follow-up. Among the 49 unmarried adults and adolescents, 39 returned for follow-up, whereas 10 were lost to follow-up. Similarly, after six months, 76 patients attended the follow-up visit, while 57 patients discontinued treatment after resuming fertility within three months and 9 were lost to follow-up. Among the unmarried adults and adolescents, 32 returned for follow-up, while 7 were lost to follow-up. The reasons for lost follow-up in each visit were that patients saw an improvement in the symptoms or were not present in town or due to the migration of their families. Figure 1 shows the details of the patients at each stage of the study.

The data of the subjects (n=211) were divided based on their BMI, that is, obese (n=178, 84.4%) and lean (n=33, 15.6%). The average body weight and waist-hip ratio of obese women was higher by 43% and 7% than that in lean women respectively. The age ranged from 15 to 42 years, and most of them were married (77%). Moreover, 53% of the women were housewives, 37% were working and 10% were students. The systolic and diastolic blood pressure of all the subjects was found to be in the normal range. All women showed ultrasound evidence of polycystic ovaries, oligo/anovulation and signs of hyperandrogenism (hirsutism and acne). The primary and secondary infertility was observed in 71% and 29% of women respectively with an average infertility duration of 3.5 years. Among these, some women also had history of in-vitro fertilization or intra-uterine insemination (IVF/IUI) failure and miscarriage (22%).

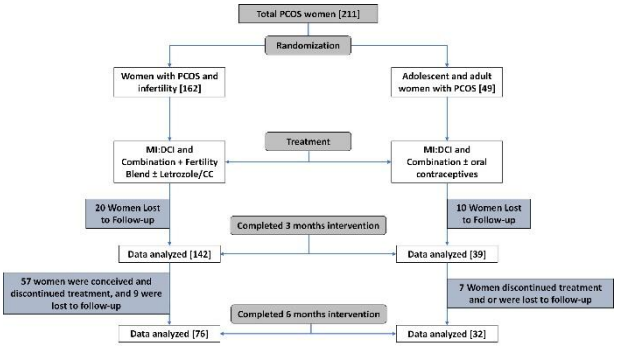

Figure 1: Flowchart illustrates the availability of medical records at 3 and 6 months of treatment, corresponding to patient follow-up visits.

Table 2: Baseline characteristics.

Parameters	ALL (n=211) (%)	Lean (n=33) (%)	Obese (n=178) (%)
Age (years)	27.4±4.8	26.85±4.26	27.5±4.92
≤20	19 (9)	1 (3.03)	18 (10.11)
21-25	51 (24.17)	13 (39.39)	38 (21.34)
26-35	130 (61.62)	18 (54.55)	112 (62.93)
>35	11 (5.21)	1 (3.03)	10 (5.62)
Body weight (kg)	66.97±12.34	49.02±4.27	69.22±10.44
BMI (kg/m^2)	27.97±5.31	20.81±1.74	29.34±4.56
Waist circumference	86.65±19.91	77.90±8.22	88.27±21.0
Waist hip ratio	0.89±0.37	0.84±0.15	0.90±0.40
Number of adolescent women	13 (6.16)	1 (3.03)	12 (6.75)
Number of married women	162	25 (15.44)	137 (84.56)
Number of unmarried women	49	8 (16.32%)	41 (83.68)
Number of adult women	198 (93.84)	32 (96.97)	166 (93.25)
Occupation			
Student	22 (10.42)	2 (6.07)	20 (11.23)
Working	78 (36.97)	15 (45.45)	63 (35.39)
Housewife	111 (52.61)	16 (48.48)	95 (53.38)
No. of patients with infertility	162 (76.78)	25 (57.7)	137 (76.9)
Primary	115 (70.99)	22 (88)	93 (67.89)
Secondary	47 (29.01)	3 (12%)	44 (32.11)
Duration of infertility (years)	3.58±1.28	3.52±2.67	3.59±2.62
No. of patients with history of IUI/IVF failure	47 (22.27)	3 (9.09)	44 (24.71)
Average number of cysts	13.25±1.30	13.12±4.62	13.27±4.26
Average cyst size	7.57±0.75	7.55±2.39	7.57±2.22
Acne score	15.07±1.68	17.18±9.99	14.68±9.81
Hirsutism score	1.37±0.07	1.55±0.97	1.34±0.95

Data are presented as mean±SD. At baseline (first visit), all patients (n=211) were divided into two groups: obese (n=178) and non-obese/lean (n=33). IVF, in-vitro fertilization; IUI, intra-uterine insemination; BMI, body mass index.

Table 3: Composition of therapeutic interventions for patients undergoing 3-6 months of treatment.

Intervention-1 (Ova-BD™)	Intervention-2 (Dreamfert-F™)
Myo inositol (550 mg), D-chiroinositol (15 mg), N-acetylcysteine (300 mg), vitamin D_3 (1000 IU), berberine (277.25 mg), grape seed extract (42.5 mg), chasteberry extract (50 mg), fenugreek extract (250 mg), chromium picolinate (201.5 µg), L-methyl folate (0.5 mg)	L-Arginine (200 mg), Coenzyme Q 10 (25 mg), green tea extract (100 mg), melatonin (3.0 mg), berberine (25 mg), lycopene (20 mg), chasteberry extract (100 mg), fenugreek extract (100 mg), astaxanthin (10 mg), L-methyl folate (1 mg), benfotiamine (25 mg), zinc sulphate (12 mg), magnesium trisilicate (350 mg), sodium selenate (40 µg)

Table 4: Comparison of clinical and anthropometric parameters pre- and post-intervention in obese and non-obese/lean PCOS patients.

Parameters	Obese (n=155)			Lean (n=26)		
	Baseline	3 months after intervention	6 months after intervention	Baseline	3 months after intervention	6 months after intervention
Body weight (kg)	69.48±10.59	67.82±10.03	60.39±5.39*	49.02±4.27	48.97±3.85	48.17±3.54
BMI (kg/m^2)	29.47±4.60	28.77±4.36	25.51±2.29*	20.81±1.74	20.79±1.61	20.37±1.64
Waist circumference (cm)	89.49±18.16	86.74±18.12	84.60±17.11*	81.58±9.36	79.58±8.82	78.47±8.65
Waist hip ratio	0.91±0.29	0.89±0.27	0.85±0.19	0.85±0.24	0.82±0.23	0.82±0.18
Ovulation (% patients)	0 (0)	62 (40)	125 (80.65)	0 (0)	11 (42.30)	18 (69.23)
Oligo-ovulation/ anovulation (% patients)	155 (100)	93 (60)	30 (19.35)	26 (100)	15 (57.70)	8 (30.77)
Clinical pregnancy (% patients)	0 (0)	57 (36.78)	101 (65.16)	0 (0)	10 (38.46)	14 (53.84)
Acne score	14.66±9.98	11.89±7.36*	10.14±5.87**	17.27±10.26	14.12±7.45	9.57±6.84*
Hirsutism score	1.35±0.94	1.19±0.77	0.95±0.58**	1.50±0.99	1.38±0.63	1.13±0.74*

Patients were divided into two groups: obese (n=155) and non-obese/lean (n=26). All participants received OVA-BD™ and/or Dreamfert-F™ at a dosage of two tablets per day for a period of three to six months. Parameters including body weight, body mass index (BMI), waist and hip circumference, menstrual cycle regularity, clinical pregnancy rates, acne, and hirsutism were compared before and after the intervention. Data are presented as mean ± standard deviation (SD). Differences between baseline and post-intervention values within each group were analyzed using one-way analysis of variance (ANOVA) followed by Bonferroni post-hoc multiple comparisons test. *p<0.05, **p <0.01, ***p <0.001 versus before intervention. BMI, body mass index.

Table 5: Effect of therapeutic interventions on polycystic ovarian morphology in obese and non-obese/lean PCOS patients.

Parameters	Obese (n=155)			Lean (n=26)		
	Baseline	3 months after intervention	6 months after intervention	Baseline	3 months after intervention	6 months after intervention
Number of cysts	13.04±4.27	11.73±3.32*	9.26±4.17***	11.38±2.59	8.38±2.16*	7.73±2.45**
Size of cysts (mm)	7.58±2.20	6.34±2.24***	5.68±3.21***	7.40±2.17	6.14±1.85*	5.71±1.79***
Complete cyst dissolution (% patients)	NA	11 (7.09)	38 (24.51)	NA	4 (15.38)	7 (26.92)
Reduced cyst size (% patients)		54 (34.84)	95 (61.3)		7 (26.93)	12 (46.15)
No change in cyst size (% patients)		101 (65.16)	60 (38.7)		19 (73.07)	14 (53.85)

Improvement in clinical parameters

The pre- and post-intervention data assessing the efficacy of therapeutic interventions (1 and 2) on clinical parameters in obese and lean subjects are presented in Table 4.

Anthropometric changes

After 6 months of intervention, obese patients exhibited a statistically significant reduction in body weight ($p<0.05$), BMI ($p<0.05$), and waist circumference ($p<0.05$). Additionally, a decrease in waist-hip ratio was observed, with obese individuals experiencing a reduction of 2.2% in

three months and 5.6% in six months. Lean individuals showed a reduction of 2.3% in three months and 3.6% in six months; however, these changes were not statistically significant. Notably, no significant changes in other anthropometric measures were observed among lean patients.

Menstrual cyclicity

A notable improvement in menstrual regularity was observed across all patients. Among obese women, 40% regained regular menstrual cycles within three months, increasing to 80.56% by the six months. Similarly, among lean patients, menstrual regularity was achieved in 42.30% at 3 months and 69.23% at 6 months.

Ovulatory function

The treatment with therapeutic interventions used in the present study significantly improved ovulatory function, as reflected by a substantial reduction in oligo/anovulation prevalence. Among obese women, the prevalence of oligo/anovulation decreased to 60% after three months and further declined to 19.35% by six months treatment. A similar trend was noted in lean patients, with the prevalence reducing to 57.70% at 3 months and 30.77% at 6 months.

Clinical pregnancy rates

A progressive increase in clinical pregnancy rates was observed with combination therapy (intervention 1 and 2). Among obese patients, clinical pregnancies were reported in 36.78% in three months and 65.16% at six months. In lean women, pregnancy rates were 38.46% and 53.84% at the corresponding time points. At the three-month evaluation, 3 pregnancies among obese women were attributed to IUI. By six months, the number increased to 8 cases, with 1 additional case resulting from IVF. Among lean patients, 1 pregnancy was linked to IUI.

Dermatological improvements (hyperandrogenism manifestations)

Significant improvements were noted in acne and hirsutism scores, indicating a reduction in hyperandrogenic symptoms. Obese patients showed a significant reduction in acne after three months ($p<0.05$), which further decreased after six months ($p<0.01$). Similarly, lean patients exhibited a significant reduction in acne after six months ($p<0.05$). Both obese ($p<0.01$) and lean ($p<0.05$) women experienced a statistically significant reduction after six months.

Effect on ovarian cysts

The efficacy of therapeutic interventions (1 and 2) in reducing ovarian cysts among obese and lean patients is summarized in Table 5. The combination therapy led to a progressive improvement in PCOM over time. At three months post-intervention, a significant reduction in the number of ovarian cysts was observed in both obese ($p<0.05$) and lean ($p<0.05$) patients, accompanied by a notable decrease in cyst size in obese ($p<0.001$) and lean ($p<0.05$) women.

By six months, ovarian cyst-related parameters showed further improvement, with a highly significant decline in cyst number among obese ($p<0.001$) and lean ($p<0.01$) patients. Similarly, cyst size was significantly reduced in obese ($p<0.001$) and lean ($p<0.001$) women. Specifically, cyst size reduction was observed in 34.84% of obese patients at three months and 61.3% at six months. Among lean patients, cyst size reduction occurred in 26.93% at three months and 46.15% women at six months. Additionally, complete dissolution of ovarian cysts was noted in 7.09% and 24.51% of obese patients after three and six months, respectively. A similar trend was observed among lean patients, with complete dissolution in 15.38% in three months and 26.92% at six months.

Despite these improvements, the subset of patients showed no significant change in cyst size. Among obese women, 65.16% exhibited no alteration at three months and 38.7% at six months. Likewise, in lean patients, 73.07% remained unchanged for three months, and 53.85% in six months. These findings indicate a gradual yet significant reduction in both the number and size of ovarian cysts, particularly in obese individuals, highlighting the therapeutic potential of these interventions in managing PCOM.

Effect on biochemical parameters

The efficacy of therapeutic interventions on various biochemical parameters among obese and lean patients is summarized in Table 6. Significant changes in fasting glucose levels were observed across all subjects, particularly after six months of intervention. Among obese patients, fasting blood glucose levels showed a notable reduction ($p<0.01$), accompanied by a significant decrease in fasting blood insulin levels ($p<0.05$) and the HOMA index ($p<0.001$). Similarly, in lean individuals, a significant decline was observed in fasting blood glucose levels ($p<0.05$) and the HOMA index ($p<0.05$), indicating improved insulin sensitivity.

Hormonal parameters also demonstrated significant improvements over time. At three months post-intervention, LH and FSH levels were significantly reduced in obese women ($p<0.05$), with a further decline observed at six months (LH: $p<0.01$; FSH: $p<0.001$). A similar trend was noted among lean patients, where both LH and FSH levels exhibited a significant reduction ($p<0.05$) at six months. The LH:FSH ratio significantly decreased in obese women at three months ($p<0.01$), with a highly significant reduction in both obese ($p<0.001$) and lean ($p<0.01$) patients by six months.

Table 6: Efficacy of therapeutic interventions 1 and 2 on the biochemical parameters in obese and non-obese/lean PCOS patients.

Parameters	Obese (n=50)			Lean (n=15)		
	Baseline	3 months after intervention	6 months after intervention	Baseline	3 months after intervention	6 months after intervention
Fasting glucose (mg/dl)	131.15±13.52	129.63±22.15	117.58±18.51	126.86±21.31	123.71±15.85	119.58±11.54
Fasting insulin (mIU/ml)	15.40±3.52	13.36±2.63	12.33±3.84	12.87±3.65	11.53±2.78	11.02±2.78
HOMA index	4.27±1.52	3.29±1.12	2.81±0.55	3.05±1.18	2.57±0.44	2.39±0.77
LH (mIU/l)	12.95±0.94	9.61±0.87	8.65±0.76	11.92±0.84	10.87±0.67	8.87±0.99
FSH (mIU/l)	4.52±0.95	7.80±0.81	9.18±0.86	4.80±1.10	6.01±0.64	8.20±0.85
LH:FSH ratio	2.87±0.18	1.23±0.11	0.94±0.15	2.48±0.16	1.81±0.12	1.08±0.09
Progesterone (ng/ml)	3.85±1.04	7.14±0.96	9.27±2.12	2.49±0.19	3.08±0.48	6.83±0.81
AMH (ng/ml)	7.88±1.48	6.94±1.27	5.76±1.54	7.67±1.25	6.32±1.17	5.98±1.35
Free testosterone (pmol/l)	24.72±4.44	20.26±2.12	18.63±3.09	19.03±2.36	15.77±2.18	14.43±1.90
SHBG (nmol/l)	119.65±12.55	124.29±15.24	126.36±11.64	115.64±10.18	118.67±12.42	122.36±11.61

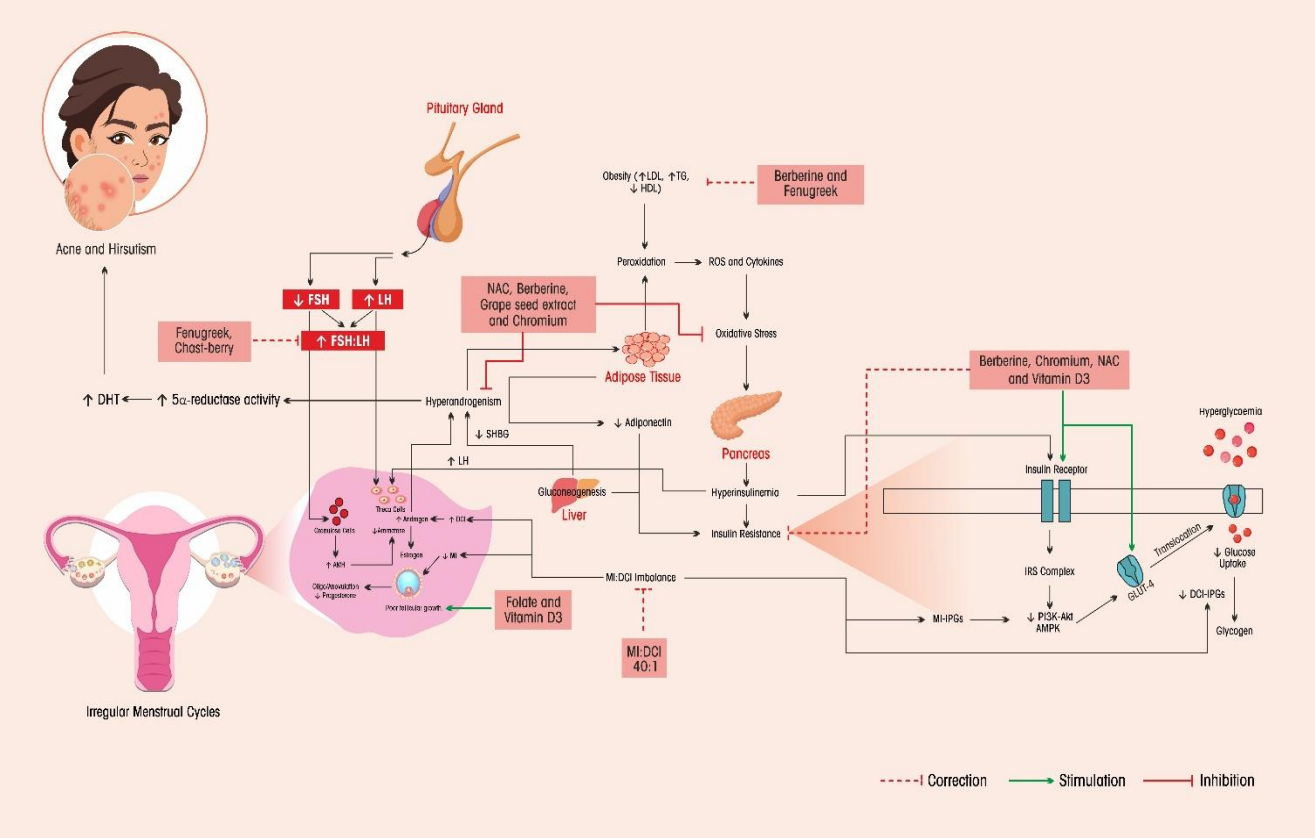

Figure 2: Graphical abstract.

LH, luteinizing hormone; FSH, follicle-stimulating hormone; AMH, Anti-Müllerian Hormone; SHBG, sex hormone-binding globulin; MI, myoinositol; DCI, D-Chiro inositol; DHT, Dihydrotestosterone; LDL, low-density lipoprotein; TG, triglycerides; HDL, high-density lipoprotein; IRS, insulin receptor Substrate; NAC, N-Acetylcysteine; DCI-IPG, D-chiro-inositol-containing inositolphosphoglycan; PI3K-Akt, Phosphoinositide 3-Kinase; MI-IPG, myo-inositol-containing inositolphosphoglycan; AMPK, adenosine monophosphate activated protein kinase; GLUT-4, glucose transporter type 4.

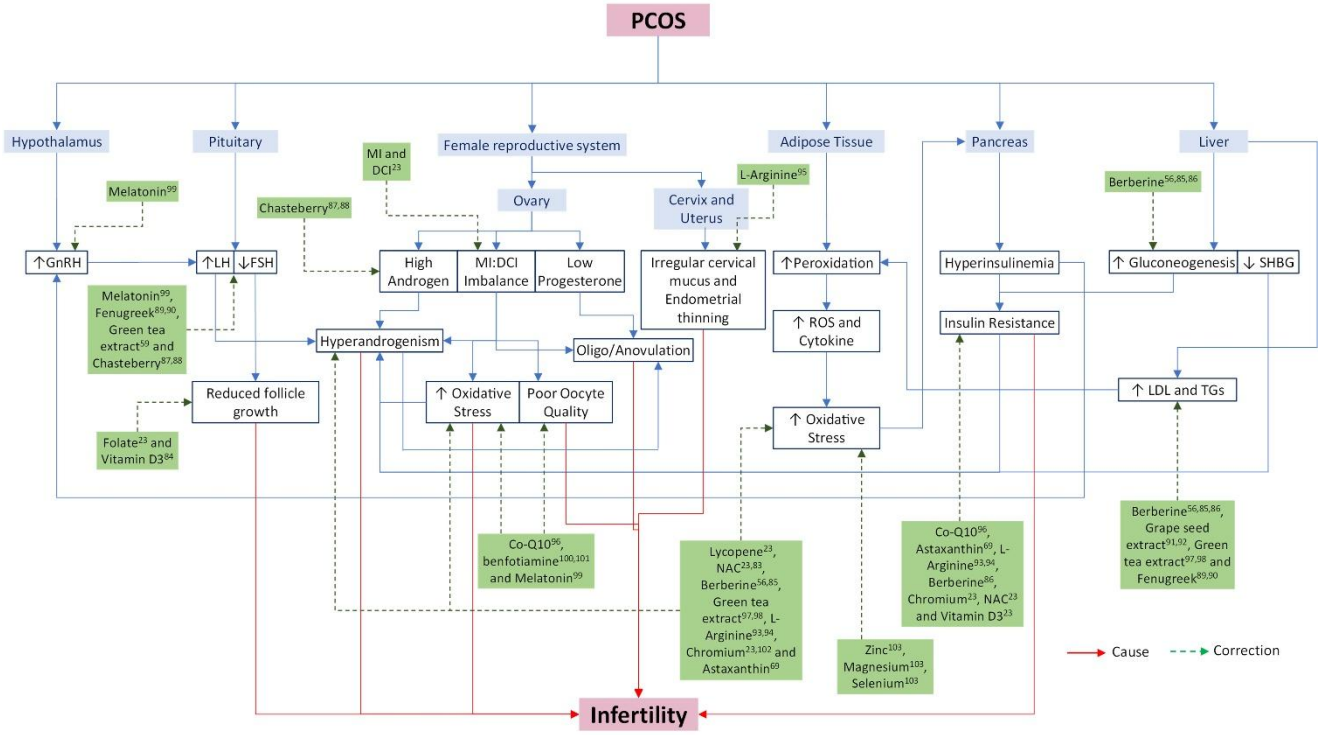

Figure 3: Schematic representation of the proposed mechanism of action of treatment interventions in the management of PCOS.

LH-Luteinizing Hormone; FSH-Follicle-Stimulating Hormone; AMH-Anti-Müllerian Hormone; SHBG-Sex Hormone-Binding Globulin; MI-Myoinositol; DCI-D-Chiro inositol; DHT-Dihydrotestosterone; LDL-Low-Density Lipoprotein; TG-Triglycerides; HDL-High-Density Lipoprotein; IRS-Insulin Receptor Substrate; NAC-N-Acetylcysteine; DCI-IPG-D-Chiro-Inositol-Containing Inositolphosphoglycan; PI3K-Akt-Phosphoinositide 3-Kinase; MI-IPG-Myo-Inositol-Containing Inositolphosphoglycan; AMPK-Adenosine Monophosphate Activated Protein Kinase; GLUT-4-Glucose Transporter Type 4.

Progesterone levels also showed a progressive decline, with a significant reduction in obese women after three ($p<0.05$) months. This reduction became more pronounced at six months, affecting both obese ($p<0.001$) and lean ($p<0.01$) patients. Additionally, AMH levels were significantly decreased at six months in both obese ($p<0.05$) and lean ($p<0.01$) women, indicating an improvement in ovarian function. Free testosterone levels followed a similar pattern, with a notable decline in obese patients at three months ($p<0.05$), followed by a highly significant reduction at six months in both obese ($p<0.001$) and lean ($p<0.05$) women. Furthermore, SHBG levels showed a significant reduction in obese women at three months ($p<0.05$), with a more substantial decline at six months in both obese ($p<0.01$) and lean ($p<0.01$) patients. These findings indicate that the intervention had a profound impact on glucose metabolism and hormonal balance, contributing to overall metabolic and reproductive health improvements.

DISCUSSION

PCOS is a prevalent endocrine disorder affecting reproductive-age women, with a global prevalence ranging from 6% to 20%. It presents as a complex interplay of reproductive, metabolic, and endocrine dysfunctions.[17] Hallmark features include menstrual irregularities, hyperandrogenism, PCOM, and infertility. The multifactorial etiology of PCOS involves genetic, environmental, and lifestyle factors, contributing to IR and oxidative stress, which in turn lead to hormonal imbalance, hyperandrogenism, and follicular dysregulation.[1,18] Chronic anovulation and hyperinsulinemia further stimulate androgen synthesis, manifesting clinically as hirsutism, acne, and metabolic dysfunctions.[2]

Given the pivotal role of IR and oxidative stress in PCOS pathogenesis, therapeutic strategies have increasingly focused on the use of insulin-sensitizing agents, antioxidants, and vitamins to mitigate these underlying mechanisms (Figure 2). Despite the availability of various combinations of these agents, evidence regarding their long-term efficacy and safety remains limited. Insulin sensitizers, such as metformin and inositols, have shown promising improvement in metabolic and reproductive outcomes; however, the optimal therapeutic regimen is yet to be determined.[12] Additionally, antioxidants and vitamins, including vitamin D, vitamin E, and coenzyme Q10, have been proposed to counteract oxidative stress, but further validation through rigorous, evidence-based research is needed.[19] In this context, our multicentric retrospective study evaluated the efficacy of therapeutic interventions comprising inositols, antioxidants, minerals, herbal extracts, and vitamins in women with PCOS. Our

findings provide compelling evidence that multimodal therapy integrating these agents significantly improves clinical and metabolic parameters in both obese and lean women with PCOS.

Insulin resistance is central to the metabolic dysfunction observed in PCOS, with nearly 70% of affected women exhibiting impaired glucose metabolism.[20] In physiological homeostasis, the MI to DCI ratio is approximately 100:1 in follicular fluid and 40:1 in plasma, reflecting the endogenous distribution of these isoforms within healthy ovarian tissue.[21] However, in PCOS, hyperinsulinemia enhances epimerase activity, increasing MI to DCI conversion and disrupting metabolic and reproductive homeostasis.[12] Our study demonstrated that supplementation with MI and DCI, alongside other insulin sensitizers, antioxidants, and vitamins, significantly improved insulin sensitivity, as evidenced by reductions in fasting insulin levels and HOMA-IR scores. These findings align with prior research showing that MI enhances glucose uptake and insulin signalling, while DCI facilitates glycogen synthesis and androgen metabolism.[12]

Obesity is a well-established contributor to PCOS pathophysiology, exacerbating insulin resistance and hyperandrogenism.[21] Between 40-80% of women with PCOS experience obesity, further impairing metabolic and reproductive health.[22] Our study observed significant reductions in body weight, BMI, and waist circumference in obese women following 6 months intervention. These findings align with previous studies supporting the role of MI, DCI, berberine, and NAC in improving metabolic parameters via insulin sensitization and lipid metabolism modulation (Figure 3).[23] Enhanced insulin sensitivity likely facilitated better glucose utilization and reduced lipogenesis, contributing to weight loss.[2] Moreover, the inclusion of chromium picolinate, known for its role in glucose homeostasis, may have further supported metabolic improvements.[24]

Menstrual irregularities and anovulation, driven by hyperinsulinemia-induced hyperandrogenism and disrupted gonadotropin secretion, are hallmark features of PCOS.[25] Up to 85% of women with PCOS experience oligo- or amenorrhea due to elevated LH:FSH ratio.[26] We observed a significant increase in FSH levels, indicating improved follicular recruitment and ovulatory function, while LH levels and the LH:FSH ratio declined, suggesting normalization of gonadotropin dynamics. A substantial reduction in free testosterone and AMH levels further supports the role of interventions in mitigating hyperandrogenism and enhancing ovarian function.[1]

Additionally, elevated SHBG levels likely contributed to improved androgen regulation, reducing freely bioavailable testosterone and alleviating hyperandrogenism symptoms such as hirsutism and acne.[27] Coenzyme CoQ10, a key component of the intervention, may have played a role in increasing SHBG levels and supporting insulin sensitivity.[7] The reduction in free testosterone is consistent with DCI's ability to inhibit insulin-stimulated ovarian androgen production.[28]

Ovarian cystogenesis in PCOS is characterized by follicular arrest and increased PCOM.[18] Our study demonstrated a significant reduction in ovarian cyst count and diameter, with some cases reporting complete cyst dissolution. These findings suggest that the intervention improved follicular dynamics, likely via enhanced insulin signalling, hormonal balance, and antioxidant activity. Berberine, green tea, fenugreek extract and astaxanthin have been shown to reduce PCOM by supporting granulosa cell function and steroidogenesis and likely contributed to complete cyst dissolution via their anti-inflammatory and anti-proliferative effects.[29-36]

The interventions used in our study included potent antioxidants such as NAC, CoQ10, astaxanthin, and green tea extract, which collectively modulate oxidative stress pathways. NAC is a known precursor of glutathione and has demonstrated efficacy in significantly reducing oxidative stress markers including AMH and improving insulin sensitivity.[34] Astaxanthin, a carotenoid with strong anti-inflammatory properties, likely contributed to improved ovarian function by reducing inflammatory cytokine activity.[35,36]

Additionally, melatonin, which is found in higher concentrations in follicular fluid than in serum, is recognized for its antioxidant properties. It has been shown to improve oocyte and embryo quality and is associated with increased fertilization and pregnancy rates in patients with prior IVF failures due to poor-quality oocytes and embryos.[35]

The integration of *vitex agnus* likely played a pivotal role in restoring hormonal equilibrium, known to modulate prolactin levels and support progesterone synthesis.[37] Improved progesterone levels, as observed in our study, are crucial for corpus luteum function and endometrial receptivity, directly impacting pregnancy rates in women with PCOS.[38] The restoration of ovulatory function is paramount in PCOS management, particularly for women seeking conception.[39] Our findings indicate a marked improvement in ovulation frequency and menstrual cyclicity, contributing to increased pregnancy rates. Our previous study extensively documented the combined effects of MI and DCI in restoring insulin signalling and reducing ovarian androgen production.[12] The role of NAC in modulating oxidative stress and follicular microenvironment likely contributed to improved oocyte quality and fertilization rates.[12,40]

Unlike other insulin sensitizers, no significant side effects were observed during three to six months of treatment with inositol, antioxidants, amino acid, minerals, herbal extracts and vitamins. Previous studies have also demonstrated the safety of this combination therapy.[12] Taken together, IR, oxidative stress, metabolic and hormonal imbalance contribute to the development and worsening of PCOS.

However, combination therapy incorporating inositols, antioxidants, herbal extracts, vitamins, amino acids, and minerals effectively manage PCOS by improving metabolic function, hormonal balance, and reproductive health.

CONCLUSION

Our findings underscore the efficacy of a comprehensive, non-hormonal, and natural therapeutic approach integrating inositols, antioxidants, minerals, herbal extracts, vitamins, and amino acids in managing PCOS and offering a promising approach for better clinical outcomes in women with PCOS. Given its potential to restore ovulatory function and enhance pregnancy rates, this approach presents a promising alternative to conventional treatments, offering a valuable strategy for managing PCOS. However, future large-scale, randomized, double-blind, placebo-controlled trials with standardized tracking of diet and exercise are necessary to validate the current findings.

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