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Clinical Study of Polycystic Ovarian Syndrome with a Unani Formulation: A randomized single-blind placebo controlled study

Shabir Ahmad Bhat[1*], Aysha Raza[2], Paraswani[3], M.Shahabuddin[4]
1. PG scholar Dept of Obstetrics & Gynecology, A&U Tibbia College & Hospital (Delhi University), Karolbagh, New Delhi.
2. Associate Professor Dept of Obstetrics & Gynecology A&U Tibbia College & Hospital (Delhi University), Karolbagh, New Delhi.
3. Lecturer Department of Preventive and Social medicine,A&U Tibbia College & Hospital, Karolbagh (Delhi University),NewDelhi.
4. PG scholar D/O Pharmacology, A&U Tibbia College & Hospital Karolbagh (Delhi University), New Delhi.

ABSTRACT

Main objective of the study was to evaluate the efficacy and safety of a Unani formulation in the management of *Marz Akyas Khusyatur Rehm* (Polycystic Ovarian Syndrome) and to provide the safe, economic and effective alternative therapy for the patients of *Marz Akyas Khusyatur Rehm (*Polycystic Ovarian Syndrome). A randomized single blind, placebo controlled trial was carried out on 70 patients was at A&U Tibbia College and Hospital Karol Bagh New Delhi. After obtaining ethical clearance, 70 eligible patients was randomly assigned into test and control groups. Test group was administered with 6 gm of Unani formulation orally in the morning and same dose in the evening for three months while control group was given placebo for the same period of time as that of test drug. Written informed consent was sought from every subject before inclusion in the study. Present study was completed within a period of one year. Response was measured by the assessment of pictorial blood loss of assessment, acne, obesity, Hirsutism staging score (Ferrimans Gallewey Score), Acanthosis Nigrican grading, BMI, Serum LH, Serum FSH, LH/FSH ratio, Serum Testosterone and Serum Prolactin. Patient was called for follow up on every 15th day. The result was statistically analyzed by applying 't'test, χ^2 test and one way Annova. Test group showed strongly significant decrease in LH/FSH ratio ($p<0.0001$), decrease in Serum LH concentration ($p<0.0001$), F.G score ($P=0.0440$), USG study after 3 month is normal in 17 patients out of 35 patients and PBACscore ($p<0.0001$). The study revealed that test drug appeared to be beneficial in PCOS patients by decreasing LH/FSH ratio, improving PBAC score, decreasing F.G score and increasing fertility rate without any adverse reaction hence can be safely recommended in PCOS patients.

Keywords: Unani Medicine, Polycystic Ovarian Syndrome, Herbal medicine, *Marz Akyas Khusyatur Rehm.*

*Corresponding Author Email: drbhatshabir55@gmail.com
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INTRODUCTION

The *Marz Akyas Khusyatur Rehm* (Polycystic Ovarian Syndrome) is one of the most common causes of oligo-ovulatory infertility[1] and it is the most common endocrinopathy affecting premenopausal women.[2,3] It starts appearing at 15 to 25 years of age & it may take years for its clinical presentation to appear. Over all incidence of *Marz Akyas Khusyatur Rehm* (Polycystic Ovarian Syndrome) is 4% to 22% in women & 50% of women seen at infertility clinics. [4,5] It is an incompletely understood enigmatic disease of heterogeneous nature. It is characterized by oligomenorrhoea, obesity, hyperandrogenism and infertility. The condition appears to have a genetic component [6,7,8,9] and those affected often have been both male and female relatives with adult onset diabetes, obesity, elevated blood triglyceride, high blood pressure and female relative with infertility, hirsutism and menstrual problem.[10]The editors coroner of infertility and sterility (June 1995) suggested that hyperandrogenemic chronic anovulation (HCA) is the correct name for this disease as the most consistent features are hyperandogenemia and chronic anovulation.[11] During the reproductive years, PCOS is associated with increased morbidity including abnormal bleeding, infertility, increased pregnancy loss and other complications of pregnancy such as gestational diabetes mellitus.[12] Women with PCOS also have an increased risk of endometrial carcinoma because of long standing unopposed estrogen stimulation[13]. Although PCOS is known to be associated with reproductive morbidity, diagnosis is especially important because PCOS is now thought to increase metabolic and cardiovascular risks such as atherosclerosis, coronary artery disease, myocardial infarction, these risks are strongly linked to insulin resistance and subsequent hyperinsulinemia and are compounded by the common occurrence of obesity, although insulin resistance and its associated risks are also present in non obese women.[14-19] Women with PCOS are at increased risk of impaired glucose tolerance, type 2 diabetes mellitus and hypertension.[20-22] Hence PCOS must be diagnosed and treated at any point of time irrespective of the desire to conceive. There is a wide spectrum of clinical manifestation of *Marz Akyas Khusyatur Rehm* (Polycystic Ovarian Syndrome); these may vary from skin changes such as acne, hirsutism, or alopecia to menstrual abnormalities as dysfunctional uterine bleeding, oligomenorrhea, recurrent miscarriage and infertility. Clinically the most common symptoms associated with PCOS are menstrual irregularities (90%), hirsutism (50-80%) depending upon 5α reductase activity in skin, infertility (75%) and obesity in approximately 50-60% of subjects. PCOS is essentially biochemical diagnosis with either hypergonadotropic or hyperinsulinemic state, since the advent of endovaginalsonography is more practical approach to morphological

diagnosis has been popular. A gradation of thecal hyperplasia has been encountered in PCOS subjects, since both LH and insulin act at the thecal compartment of ovary to cause hyperandrogenemia. Morover, the small and intermediate follicle predominate the PCOS scenario and the gradually proceed to atresia rather than the follicular dominance.[23] These two entities namely homogenous polyfollicular enlargement and thecal hyperplasia are well definable endosonographic landmarks of PCOS ovaries. More over the state of endometrial stimulation, proliferation of hyperplasia will also be evaluated at pelvic scan. In Unani system of Medicine Polycystic Ovarian Syndrome is mentioned under the headings of Amenorrhea, Obesity and other phlegmatic disorders. (Eminent Unani physicians have attributed *Marz Akyas Khusyatur Rehm* (Polycystic Ovarian Syndrome) with Clinical features like amenorrhea, obesity, oligomenohoea as phlegmatic disorder). Zakaria Razi (860-925AD) described that women with PCOS can present with the clinical features of amenorrhea, hoarseness of voice and hirutism[24]. Unani physicians attributed *Marz Akyas Khusyatur Rehm* (Polycystic Ovarian Syndrome) to dominance of *Balgham* (phelgm). Ibn-e-Rushed described that *Marz Akyas Khusyatur Rehm* is a disease of cold and moist nature and arises due to change in quantity and quality of balgham. Buqrat (Hippocrates), Ibn-e- Habal Bagdadi, Ali Ibn-e- Abas Majoosi , Rabban Tabri attributed PCOS due to pathology in liver (*Sue Mizaj Kabid)* liver dysfunction which may lead to abnormal production of *Balgham* (phelgm).[25-27]. Abnormal form of *Balgham* is divided on the basis of consistency and taste. On the basis of consistency one type is *Balgham Mayi* which is responsible for causing the *Marz Akyas Khusyatur Rehm* (Polycystic Ovarian Syndrome). So it can be concluded that PCOS arise due to predominance of *Balgham* in the body which leads to the cyst formation in the ovaries, amenorrhea and obesity. Seeing on current trends, *Marz Akyas Khusyatur Rehm* (Polycystic Ovarian Syndrome) will become a major cause of infertility, therefore the need for an effective treatment protocol is becoming increasingly urgent. In conventional medicine treatment of PCOS is adapted according to a specific cause; goals of therapy include ameliorating hyperandrogenic symptoms by use of anti-androgen drugs, inducing ovulation, regulating menstruation and preventing cardio-metabolic complications.[21] All these therapies are being used for treating PCOS but they have their own limitations. Most of these drugs are costly, having potential side effects and producing only symptomatic relief. Most of the drugs used for the induction of ovulation are having serious manifestations like Ovarian Hyper Stimulation Syndrome, multiple pregnancies, ascites, and thromboembolism.[11]

MATERIALS AND METHODS

A randomized single blind, placebo controlled study was at A&U Tibbia College and Hospital Karol Bagh New Delhi over a period of one year from March2013- February 2014. This study was carried out strictly according to guide lines of good clinical practices, embodying the principles mentioned in declaration of Helsinki. Informed consent was obtained from all participants & approval from the institutional Review Board was obtained. After ethical clearance patient were questioned and screened for inclusion and exclusion criteria. Detailed information about the study was explained to the participants and written informed consent was taken from all the eligible participants before starting the treatment schedule. Women's aged between 18-45 years (both Married and Unmarried), BMI greater than or equal to 25, a medical diagnosis of polycystic ovary syndrome. Together with irregular menses (fewer than 6 cycles per year), participants must also have at least one of the following characteristics. a)Presence of polycystic ovaries on transvaginal ultrasound, b)Clinical manifestations (hirsutism) examined by the PI at the screening visit or biochemical evidence (elevated testosterone or free androgen index) of hyperandrogenism, determined by fasting blood sample collected during the screening visit were included in the present study. Individuals with a history of cardiovascular disease or an elevated blood pressure above 160/90 mmHg, Diabetes (Type 1 or Type 2), Kidney, Liver or Heart disease, untreated thyroid disease, pregnant or lactating mothers, and subjects with local pathology like uterine Synechae, Uterine Fibroid, Endometriosis, cervical carcinoma etc.were excluded during enrolment. In this study, all the participants attending Obstetrics and Gynecology OPD of the hospital were screened. Patients were selected on the basis of inclusion and exclusion criteria from OPD of A&U Tibbia College and Hospital Karol Bagh New Delhi. To minimize the selection bias participants fulfilling the inclusion criteria and willing to participate in the study were randomly divided into test and control group. Due to time constrain head and coin method was used for randomization. Written informed consent was obtained from the study subjects before enrolment in the study. The patients were examined every fortnightly for twelve weeks, during which clinical evaluation of the disease and treatment related sign and symptoms, menstrual activity and the information about concomitant medication was also obtained. The assessment of menstrual functions, obesity and acne was done at baseline and after every fifteenth day. The assessment of dysmenorrhea if present was done following every menstrual cycle for three months by the patient herself. Assessment of menstrual dysfunctions (amenorrhea, oligomenorrhoea and DUB) was done by the patient herself in terms of the

duration of cycle, number of days of menstruation (duration of flow) and number of pads (amount of flow) used per day during the menstruation. A total 85 patients with routine gynecological problems were selected. 15 patients drop out during present study. Test group was administrated with 6 grams of Unani formulation[30] (Formulation containing *Barg-e-sudab* (Ruta graveolans), *Abhal*(Junipers communis), *Parshiaushiaya* (Adiatum capillus), *Afsanteen* (Artemisia abseinthium), *Darchini* (Cinnamomum zeyanicum), *Brinjasif* (Artemisiavulgaris), *Methidana* (Trrigonellafoenium), *Charaita* (Swerita charasta) in the form of powder orally along with *Arq-e-Kasni* 25 ml twice daily after meal for three months. While control group was given placebo for the same period of time as that of test drug. Patients were particularly advised to take their medicine timely and regularly. Before starting the treatment, detailed information about the patient including signs and symptoms were recorded in the case record form. Efficacy in both groups was assessed on the following parameters.

a) Clinical parameters:

1. Pictorial blood loss amount

It was first described by Higham et al. in 1990. The scoring was based on the no. of sanitary pads used each day and their degree of soiling. The number and size of any clot passed were also taken into account and scored. It is simple to use and at present the best practical tool available for the assessment of menstrual blood loss. The method has been reported to have a sensitivity of 86% and a specificity of 89%

PBAC Score used to assess the amount of bleeding was a follow

PBAC score	Inference
1-10	Spotting
11-30	Hypomenorrhea
30-100	Eumenorrhea
>100	Menorrhagia

2)Acne

3)Obesity

b)Objective Parameters:

1) Acanthosis Nigricans grading by using Gold Standard Scale[23]. Staging acanthosis (neck severity) is as follows:

- ✓ Absent (0) - Not detectable on close inspection
- ✓ Present (1) - Clearly present on close visual inspection, not visible to the casual observer, extent not measurable

- ✓ Mild (2) - Limited to the base of the skull, usually does not extend to the lateral margins of the neck
- ✓ Moderate (3) - Extends to the lateral margins of the neck but not visible anteriorly
- ✓ Severe (4) - Visible anteriorly
- ✓ Severe (5) - Circumferential

2) Hirsutism staging score (Ferrimans Gallewey Score)

The Ferriman–Gallwey scoring system is an easily and the most widely used tool for the evaluation and quantification of hirsutism in women used in which the whole body was divide into twelve different areas of the body, grading each part as 0,1,2 and 3 according to the presence and density of hair.

- ✓ 0-3 No hirsutism (absent)
- ✓ 4-11 Mild
- ✓ 12-22 Moderate
- ✓ 23-33 Severe

3) Body mass index

Body mass index is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in the adults. The international classification of adult underweight, overweight and obesity according to BMI

BMI	Inference
Underweight	≥18.50
Normal range	18.50-24.99
Overweight	≥25.5
Obese	≥30.00

4) Hormonal assays: LH/FSH ratio, Serum Prolactin, Serum Testosterone,

5) USG pelvis

The efficacy of the Test and Placebo control was assessed by observing the change in the rating score (grade) of the subjective symptoms and decrease below the diagnostic criteria in the score of objective scales. Thus in LH/FSH ratio, the reduction of value at ≤3 was considered normal. In S.testosterone the reduction below the ≥2.8ng/ml was considered normal. In USG pelvis the normal scan with resolution of polycystic ovaries following therapy showed the efficacy of drug. In case of Acanthosis Nigricans, the decrease in grading of "Neck severity" (Golden standard scale) was considered efficacious and incase of Hirsutism the decrease in Ferriman Gallwey scores was considered effective. Result were recorded on case report form and put for statistical analysis at

the end of the study. For safety evaluation of the drug, LFT, KFT and blood sugar were carried out at baseline and at the end of the treatment.

Statistical Methods

Descriptive and inferential statistical analysis was carried out in the present study. Result on continues measurements were presented by Mean±SD (Min-Max) and result on categorical measurements were presented in number(%) Paired 't' test , Chi square test and One Way Anova were used. A 0.05 level was used to define statistical significance. The statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, Med Calc 9.0.1, Systat12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft and Excel have been used to generate tables.

Significant figures

+Suggestive significance (p value:0.05<p<0.10); moderately significant (P value:0.01<P≤0.05);**strongly significant (P value;P≤0.0001)*** were used for the conncotation of the significant differences.

RESULTS AND DISCUSSIONS

Table 1:-In current study the mean age was 23.55±0.762 among test group and 23.6±1.110 among control group. Range was 14-36 years among the test group and 14-35 years among the control group. The highest prevalence of PCOS was found in the age group of 21-25years in both test and control group. An overall 18 patients out of 40 i.e. 45% were between the age group of 21-25 years followed by 10 patients i.e.25% from the age group of 26-30 years while 9 patients i.e.22.5% in16-20 years, 1patients i.e. 2.5% in 31-35years,1 patients i.e.2.5% in ≤15 years and 1 patients i.e.2.5% in 36-40 years among test group. In control group 9 patients out of 30 i.e. 30% were between the age group of 21-25 years while 7 patients i.e. 23.34% in 16-20 years ,7 patients i.e.23.34% in 26-30 years,4 patientsi.e.13.33% in ≤15 years and 3 patients i.e.10% in 31-35. Age distribution analysis revealed that the prevalence of this disease decreases with increases in age as no case was observed above 36 years. In present study maximum patients were adolescents and young adults. It is in accordance to Ryan Kenneth j[28].which states that "onset of this disease is prepubertal". In our study the maximum number of patients belonged to middle and lower class in test group (45%) and among control group 60% in middle class followed by 33.34% in lower class. Although PCOS is a life style disorders and obesity is the predisposing cause for it therefore it should be prevalent in upper class and middle class but in our study it was more prevalent in middle class which was contradictory to the study conducted by Sharon Stein

Merkin [29], who found that maximum number of patients belonged to the lower class. Regarding lifestyle distribution 75% of patients was observed in sedentary life style followed by 20% hardworking and 15% veryhardworking among test group.In control group 63.3% of patients in sedentary, 23.3% in hardworking and 14% in very hard working. This result is coinciding with the statement of Ibn Sina and Kabiruudin[30,31]. According to Ibn Sina rest is always cooling and moistening in nature. It is cooling because of which there is no excitation of heat and there is an inward collection and aggregation of waste matter. In the present study out of 70 patients with suspected polycystic ovarian syndrome most (54.28%) of them were married compared to unmarried (45.72%). This observation was same from the results of the study conducted by Luciando GN[32], out of 120 patients of PCOS most of these patients were married and 24% patients were unmarried. In current study, it was observed that only 12 patients i.e. 17.14% had family history of PCOS. This observation in accordance with the study done by Kahsar-Miller [33] that there is high risk of developing this disease among first degree female relatives with reported percentage of 24-34%.Regarding the temperament, most of the patients had Balghami temperament. In test group out of 40 patients 32 (80%) had Balghami temperament and 8 (20%) patients had Damwi temperament. In control group 24 (80%) had Balghami temperament and 6(20%) patients had Damwi temperament. This observation validates the claims of Razi that amenorrhea and obesity is usually seen in the women with Phlegmatic temperament[24]. In the present study 78.5% of patients had irregular periods particularly oligomenorrhoea. The other main complaints of the patients were obesity which was found about 61.4%% of the patient followed by 45.7%% of infertility, hirsutism 30%, amenorrhea 18.5% and DUB 2.8%. Study by Nagamani peri et al on 245 patients with PCOS, 146 showed menstrual irregularities, 38 had hirsutism and 15 had infertility.[4]

Table1: Distribution based on Demographic variables

Characteristic	Test Group (n=40)	Control Group (n=30)
Age (in years		
<15	01 (2.5%)	04 (13.33%)
16-20	09 (22.5%)	07 (23.34%)
21-24	18 (45%)	09 (30%)
25-30	10 (25%)	07 (23.34%)
31-35	01 (2.5%)	03 (10%)
36-40	01 (2.5%)	0 (0%)
41-45	0 (0%)	0 (0%)
Socio economic status		
Upper class	04 (10%)	02 (6.66%)
Middle class	18 (45%)	18 (60%)

Lower class	18 (45%)	10 (34.34%)
Life style		
Sedentary	30 (75%)	19 (63.33%)
Hardworking	08 (20%)	07 (23%)
Very hardworking	02 (15%)	04 (14%)
Marital history		
Married	22 (55%)	16 (53.34%)
Unmarried	18(45%)	14 (46.66%)
History of PCOS		
Present	07 (17.5%)	05 (16.66%)
Absent	33 (82.5%)	25 (83.34)
History of Temperament		
Damavi	8 (20%)	6 (20%)
Phelgmatic	32 (80%)	24 (80%)
Safaravi	0 (0%)	0 (0%)
Saudavi	0 (0%)	0 (0%)
Based on Chief complaint		
Amenorrhea	9	4
Oligomenorrhoea	30	25
Infertility	18	14
Obesity	30	18
DUB	1	1
Hirsuitism	11	10

Table:2 In the present study majority (37.14%) of the patients belongs to the group of 21-25 kg/m^2 followed by 31.42% belong to the group of 26-30 kg/m^2 i.e. overweight , 24.28% were obese, 4 patients were severely obese (5.71%) and 1.42% were ≤20 kg/m^2. While as the study done by Insler V and Shoham Z[34] showed 50% of patients were obese with BMI greater than 25kg/m^2. Regarding the distribution of acne 28 patients in test group had no acne i.e. 70% followed by 7 patients had mild acne i.e. 17.5%, 3 patients had moderate acne i.e. 7.5% and 2 patients had severe acne i.e. 5%. In control group 22 patients had no acne i.e. 73.33% followed by 4 patients had mild acne i.e. 13.33%, 2 patients had moderate acne i.e. 6.66% and 2 patients had severe acne i.e. 6.66%.Over all patients that had complaint of acne in both test and control group was 20 i.e. 28.57%.Similar study done by Servet Hacivelioglu[35] found a majority of mild cases of acne. In our study 40% of patients had a score of ≥8 and 60% of patients had a score of <8 by applying a Ferriman Gallwey scale. Previous study done by Balen et al in [36], found that 66% of patients had FG score ≥8 and 34% of patients had<8 score.In our study 16 patient out of 40 i.e. 40% had a zero AN score and 24 patients i.e. 60% had a score of ≥1-4 among test group. In control group 13 patients i.e. 43.33% had a zero AN score and 17 patients i.e. 56.66% had a score ≥ 1-4. Overall patients that had complaint of acanthosis nigrican was 41 among both test

and control group i.e. 58.5%. Study done by Balen et al [36] found 2.5% of patient was acanthosis nigrican.

Table 2: Distribution based on Clinical Parameters

Characteristics	Test Group (n=40)	Control Group (n=30)
Body mass index(in Kg's)		
≤ 20	0	0
21-25	14	12
26-30	11	11
31-35	13	04
36-40	02	02
41-45	0	0
Acne		
No acne	28	22
Mild acne	07	04
Moderate acne	03	02
Severe acne	02	02
F.G Score		
<8	27	15
≥8	13	15
A.N Score		
0	16	13
>1-4	24	17

Table 3: Analysis of Test drug on Clinical Parameters

Variables N= 40	Before Treatment		After Treatment		Difference of mean before and after Treatment	P Value
	Mean	S.D.	Mean	S.D.		
Weight	65.45	12.49	63.7	11.501	1.750	<0.0001**
BMI	28.41	0.74	27.55	0.6847	0.8543	<0.0001**
FG-Score	5.55	3.59	4.95	3.412	0.5750	<0.0001**
A N - Score	1.07	0.99	0.95	1.011	0.1250	0.1684
Acne	1.1	0.81	1.2	0.9392	-0.1000	0.3523

Table:3 Effect of test on weight, BMI and FGI score was statistically significant (P value <0.0001**, <0.0001**,<0.0001** respectively).

Table 4: Analysis of Test drug on Hormonal Parameters

Variables N=40	Before Treatment		After Treatment		Difference of Mean before & after Treatment	P Value
	Mean	S.D	Mean	S.D.		
LH	20.04	16.76	18.85	16.49	1.190	<0.0001**
FSH	8.39	6.36	10.56	6.23	-2.172	<0.0001**

LH/FSH	2.61	0.91	1.75	0.85	0.8573	<0.0001**
Prolactin	19.33	6.83	18.52	6.93	0.8050	0.00534
Testosterone	2.02	1.73	1.85	1.80	0.1635	0.3027
TSH	3.11	2.02	3.42	1.44	-0.3183	0.2751

Table:4 Effect of test drug on LH, FSH, LH/FSH was significant at the end of three months with P value <0.0001.However there was no effect on Prolactin, testosterone and TSH.

Table 5: Analysis of Test and Control Drug on duration of cycle, duration of flow, PBAC score and dysmenorrhea by applying one way analysis of variance Anova

	Duration of cycle		**Duration of flow**		**PBAC score**		**Dysmenorrhea**	
Assessment	Test Group N(40)	Control Group N (30)	Test Group N(40)	Control Group N (30)	Test Group N(40)	Control Group N (30)	Test Group N(40)	Control Group N (30)
Before Intervention	1.2±0.93	1.2±0.88	1.27±1.8	1.52±1.13	25.25±10.49	28.16±13.0	1.47±1.01	1.13±1.04
Day 1 of ist menstruation During treatment	0.75±0.89	1.16±0.87	1.07±0.99	1.33±1.06	31.15±11.22	27.6±12.2	0.45±0.74	1±0.94
Day 1 of 2nd menstruation During treatment	0.47±0.71	1.16±0.87	0.5±0.78	1.23±1.06	35.5±11.5	16.83±11.85	0.25±0.49	1.06±0.98
Day 1 of 3rd menstruation During	0.2±0.51	1±0.83	0.25±0.63	1.03±0.99	40.87±11.5	27.16±11.19	0.22±0.42	1±1.01

treatment

Table 5: As shown in table mean and SD of duration of cycle in test group before intervention , day one of 1st,2nd, 3rd menstruation were 1.2 ± 0.93, 0.75 ± 0.89, 0.47 ± 0.71 and 0.2 ± 0.51 respectively. There exists a significant decrease in duration of cycle in first assessment with p<0.0001 which is extremely significant. Similarly in control group, mean and SD before intervention, day one of 1st, 2nd, 3rd menstruation during treatment were1.2 ± 0.88, 1.16 ±0.87, 1.16 ± 0.87 and 1±0.83 respectively. There exist a significant decrease in duration of cycle in the 2nd assessment with, p= 0.8196 considered not significant. Mean and SD of duration of flow before intervention, day one of 1st, 2nd, 3rd menstruation during treatment were 1.27±1.8, 1.07±0.99,0.5±0.78 and 0.25±0.63 in test group respectively with p value is 0.001 considered significant and 1.52± 1.13, 1.33±1.06, 1.23±1.06 and 1.03± 0.99 in control group respectively with p value is 0.4712 considered not significant. Intra group comparisons were made. In test group, duration of flow was progressively increased from the first menstruation during treatment, and was statistically significant with p<0.001. The effect of test drug and control drug on PBAC score were assessed, with mean and SD before intervention, day one of 1st, 2nd, 3rd menstruation during treatment were25.25±10.4, 31.15±11.2, 35.5±11.5 and 40.87±11.5 respectively in test group and 28.16±13,27.6±12.2, 16.83±11.85 and 27.16±11.1 respectively in control group. In test group, the PBAC score was progressively increased from the first menstruation during treatment and was extremely statistically significant with p<0.001. In control group, the PBAC score was not increased from the first menstruation during treatment which was significant not statistically at p 0.6758, In the inter group comparison the results were significant with p<0.01, suggesting that the test drug possess better efficacy than the control drug in improving PBAC score. The improvement in the duration of cycle, duration of flow and PBAC score during menstruation in patients treated with test group. The reason of this improvement can be attributed to different therapeutic properties of the test drugs. All drugs in this formulation are emmenogogue (*Mudir-e-haiz*), diuretics (*Mudir-e-boul*) and vasodialator *(Mufateh)* in nature. *Afsanteen*, *Darchini* and *Barinjasif* being the specific drugs for liver are helpful to correct *Ehtebase tams* (amenorrhea) caused by liver disorders like *Zofe kabid,Warm kabid* and cold disease of liver. *Suddab* is the potent resolvent of viscous humours.*Afsanteen, Darchini* and *kasni* has the property to dissolve *Balghami warm* and extract out the bad humours from deep inside the body while *Abhal*, *Persishoyan* and *Suddab* has the property to remove bad and waste product from the body as they are strong diuretics. This is in accordance to *Ibne Baitar*[42]and *Najmul Ghan*[43]. The effect of test drug and control drug on

dysmenorrhea were assessed with mean and SD before intervention day one of 1st, 2nd, 3rd menstruation during treatment were 1.47±1.01, 0.45±0.74, 0.25±0.49 and 0.22±0.42 respectively in test group which is statistically significant with p value 0.001.In control group 1.13±1.04, 1±0.94, 1.06 ± 0.98 and 1±1.01 respectively with p value 0.9464 considered not significant. The result showed that the test drug was effective in relieving dysmenorrhea which may be due to antispasmodic andanalgesic properties of the test drug. *Suddab and Baranjasif* is described as potent antispasmodic and analgesic. *Afsanteen* is described to relieve neuralgic pain. Thus all of three acts as potent analgesic to relieve dysmenorrhea

Table 6: Analysis of test and control drug on clinical parameters

clinical parameters	Test Group (n=40)	Control Group (n=30)	χ^2 value	P value
BMI			7.25	0.83
≤25	15 (37.5%)	13 (43.34%)		
>25	25 (62.5%)	17 (56.66%)		
F.G score			4.26	0.04*
<8	30(75%)	15(50%)		
≥8	10(25%)	15 (50%)		
AN score			0.076	0.972
0	20 (50%)	16 (53.34%)		
≥1-4	20(50%)	14 (46.66%)		
Acne			4.51	0.03*
No acne	34 (85%)	24 (80%)		
Mild acne	3 (7.5%)	2 (6.67%)		
Moderate acne	2 (5%)	2 (6.67%)		
Severe acne	1 (2.5%)	2 (6.67%)		

Table 6 In the present study mean BMI before and after the study was 27.55±0.68 among test group and 27.72±0.15 among control group with p value 0.0001 which was statistically significant. The intergroup comparison was done; change in BMI in test group and control group was not significant with p value 0.8316. These results of the study were supported by study by Nestler.[11]. The mean and standard deviation of F-G score among test group is 4.95±3.41with p value is <0.001 which is highly significant. In control group the mean and SD is 6.16±3.75 with p value is 0.6903 which is statistically not significant. However on intergroup comparison there result were significant with p value is 0.0440.This may be attributed to medicinal properties of Unani formulation like *Munzig Balgham,mudir haiz* and *mudir boul* etc. which eliminate the cause of hirsutism.In authentic Unani books hirsutism has been mentioned as a complication of *ehtebas tams* associated with virilism due to *sue mizaj barid*. Improvement can be attributed to one of the ingredients of Unani formulation *Darchini (*Cinnamomum zelynicum*)*.Similar findings were depicted in a study by Velazques E. [44] with significant result on hirsutism with p

value 0.001. The mean and standard deviation of AN score among test group is 0.95±1.011with p value is 0.1684 which was not significant. In control group the mean and standard deviation is 0.86±1.00 with p value is 0.325 which was statistically not significant. In the inter group comparison the results were not significant with p value is 0.972. In this study an improvement in acne was statistically not significant among both test and control group, and hirsutism was found statistically significant in test group. However only the improvement in acne appeared to be clinically meaningful. It was observed that in test group 7 patients had mild acne, 3 patients had moderate acne and 2 patients had severe acne and in control group 4 patient had mild acne, 2 patients had moderate acne and 2 patients had severe acne. After completion of trial 3 patient had mild acne, 2 patients had moderate acne and 1 patient had severe acne in test group .In control group 3patients had mild acne, and no change in moderate and severity of acne. The result observed can be due to *Mushile Balgham* and diaphoretic activity of the test drugs. *Suddad* has specific activity to extract the bad humours from deep inside of the body while Chirata is blood purifier remove the waste material from the blood. These findings of drugs are in accordance to *Najmul Ghani. Ibne biatar*[42,43].

Table 6: Analysis of test and control drug on Hormonal parameters

Hormonal parameters	Test Group (n=40)	Control Group (n=30)	χ^2Value	P Value
Serum LH			26.7	<0.0001**
≤20	35 (87.5%)	8 (26.64%)		
>20	5 (12.5%)	22 (73.34%)		
Serum FSH			3.35	0.130
<5	4 (10%)	8 (26.66%)		
5-20	36 (90%)	22 (73.34%)		
Serum LH/FSH ratio			19.86	<0.0001**
<3	39(97.5%)	16 (53.33%)		
≥3	1(2.5%)	14 (46.66)		
Serum Prolactin			1.5	0.402
5-25	36 (90%)	24 (80%)		
>25	4 (10%)	6 (20%)		
Serum Testosterone			2.21	0.805
<0.7	4 (10%)	3(10%)		
0.7-2.8	29(72.5%)	22(73.34%)		
≥2.8	7 (17.5%)	5 (16.66%)		

Table:7 The mean value of serum LH in present study was18.85±2.60 among test group with p value is <0.0001 which was extremely significant. In the intergroup comparison the result were extremely significant with p value is <0.0001. Previous study done by Wo Xiao Ka et al [45], found that mean value of serum LH was 10.6±3.3 among test group and 3.9±0.76 among control group with p value < 0.001 which was significant. In current study the effect of test drug on serum FSH was seen 10.56±0.986 with p value is <0.0001which is highly significant. The inter group

comparison was done and the results were not statistically significant with P value is 0.130 which was contradictory to similar studies conducted [45] where the mean value of serum FSH was 4.7±1.1 among test group and 6.4±1.2 among control group with p value < 0.05 which was significant. In present study the mean value of LH/FSH was1.754±0.85 among test group with p value <0.0001which was extremely significant and among control group the mean value of FSH/LH was found 3.303±1.59 with P value is 0.746 which was not significant. The intergroup comparison was done and the result were extremely significant with p value is <0.0001.It was observed that in test group 18 patients out of 40 patients had elevated abnormal LH/FSH ratio i.e. ≥3, while in control group it was observed that 14 patients out of 30 had elevated abnormal level of LH/FSH ratio i.e. ≥3. After completion of trial 17 patients in test group reduced in LH/FSH ratio to normal levels and 1 patient had increase in the LH/FSH ratio. In the control group after completion of trial no patients had reduced the LH/FSH ratio.Wu Xiao Ka [45] found that the distribution of LH/FSH was 2.5±0.30 among test group and 0.75±0.22 among control group with p value of <0.01 which was found to be significant. In present study the distribution of serum prolactin was6.939±1.097 among test group with p value is 0.0053 which is statistically non significant and 23.09±2.036 among control group with p value is 0.062. Intergroup comparison was done and the p value is 0.402 which was not significant. previous study conducted by Wu Xiao Ka et al [45] where the distribution of serum Prolactin was 9.6±3.5 among test group and 8.9±2.9 among control group which was not significant. It was observed that in the test group 3 patients out of total 40 patients and 7 patients in the control group out of 30 patients had elevated abnormal level of serum Prolactin i.e.>25ng/ml .After completion of trial in control group 1 patient had reduced the serum prolactin. While in test group no change was seen after completion of trial. The mean value of serum Testosterone in present study was 1.806±0.285 among test group with p value is 0.302 which was not significant and 23.09±2.036 among control group with p value is0.478 which is statistically not significant. However on intergroup comparison was done with p value is < 0.0035 which was highly significant. Nestler [46] in which the distribution of serum testosterone was 4.69±0.76 among test group and 2.66±0.87 among control group with p value of< 0.001 which was significant. It was observed that 6 patients out of 40 patients had elevated level of serum testosterone than normal i.e.>2.8nmol/L in test group. In control group 5 patient had elevated level of serum testosterone. After completion of trial no change was seen in serum testosterone level in both groups.

CONCLUSION

This trial revealed that this disease is common in *Balghami mizaj* patients of reproductive age. After treatment statistically significant ($p<0.01$) reduction was observed in selected parameters in test group as compared to placebo. We found that this Unani formulation was found effective in inducing menstruation and resolve the ovarian cyst due to its medicinal property *mudir haiz, munzij balgham, mudir boul* etc and are known to contain phytohormones which induce the menstruation by maintaining the normal level of serum LH, FSH, LH/FSH ratio. However no change in seum prolactin, Serum Testosterone, BMI and acanthosis nigrican was observed. However no adverse effect was observed in either group as safety parameters were within normal limit during the study and overall compliance to the treatment was good. On the basis of above observation it may be recommended that this Unani formulation is a safe and effective treatment for PCOS.

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