International Journal of Medical and Health Research
ISSN: 2454-9142, Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 3; Issue 4; April 2017; Page No. 125-133

Efficacy of Unani formulation in infertility among obese women: A clinical study

[1] Saba Khan, [2] Ismath Shameem, [3] Suhail Sahibole, [4] Aafreen Siddiqui

[1, 2] Dept. of Ilmul Qabalat wa Amraze Niswan (OBG), National Institute of Unani Medicine, Bengaluru, Karnataka. India
[3] Dept. of Ilmul Jarahat (Surgery), National Institute of Unani Medicine, Bengaluru, Karnataka. India
[4] Dept. of Molajat (Medicine), National Institute of Unani Medicine, Bengaluru, Karnataka. India

Abstract

Background and objectives: Obesity represents a rapidly growing threat to the health of populations which has detrimental effect on fertility by disrupting the neuroendocrinal and ovulatory functions. The aim of the study was to evaluate the efficacy of Unani formulation in infertility among obese women.

Methods: A single blind non-randomized pre and post observational study was carried out at National Institute of Unani Medicine Hospital, Bengaluru. Infertile women (n=30) in the age group of 18-40 years, with Body Mass Index 30-40 kg/m^2, menstrual irregularities, controlled thyroid dysfunction and spouse normal seminogram were included in the study. Patients with systemic illnesses and those on weight reduction in last 3 months were excluded. 12.5 gm of Unani formulation (*Tukhme Karafs, Tukhme Anisoon, Tukhme Ajwain Desi, Tukhme Hulba, Asaroon*) was administered orally twice daily in the form of decoction for two consecutive months. Primary outcome measures (weight reduction, menstrual regulation and conception) and secondary outcome measures (changes in BMI, lipid profile and fasting insulin) were assessed for improvement. Data were analyzed using paired Student 't' test.

Results: Weight loss (7% reduction of body weight) was achieved in 80% patients with significant reduction (P<0.001) in BMI and waist to hip ratio, Menstrual regulation was achieved in 66.7% with significant reduction (P=0.081) in duration of cycle. The conception rate was 0% during the study period, but 10% patients conceived after 2 months of completion of study. Changes in lipid profile (on fixing 5% reduction) were achieved in 40% patients clinically (P>0.05). Changes in fasting insulin were achieved in 20% patients (P=0.004).

Interpretation and conclusion: Unani formulation may be used as an effective alternative in infertility among obese women with PCOD.

Keywords: Infertility, Obesity, PCOD, Conception, Unani formulation

Introduction

Infertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. (WHO) [1] It affects approximately one in six couples during their lifetime. [2] In 2010, an estimated 45-52.6 million couples were infertile globally. [3] The prevalence of obesity are increasing which has detrimental influences on reproductive health. [4] One quarter of all obese infertile couples have an ovulatory disorder[5] and 90% of those women with an ovulatory disorder have PCOS. [5]

In classical Unani literature, it is mentioned that obesity is associated with infertility. [6] Unani physicians has given a well-established correlation between visceral obesity (deposition of fat on omentum), [7] amenorrhoea, anovulation and infertility which can be correlated with polycystic ovarian disease. [8] In obese infertile women qualitative and quantitative derangement of normal equilibrium of *akhlat* leads to excessive production of *phlegm* which causes *zo'afe jigar* [9] and *zo'afe quwwate tawleede mani* [10, 11] resulting in chronic anovulation. [7] *Zo'afe quwwate masika rahim* prevents implantation [9] and increases the risk of miscarriage. [12] It forms *sudda* in uterine blood vessels leading to amenorrhoea. [6, 13] Hence, treatment of obesity (weight reduction with diet restriction and exercise), [14] itself should be the primary aim in obese infertile women before embarking on ovulation-induction drugs (clomiphene citrate, metformin, gonadotropin etc) or assisted reproductive techniques. [15] Studies have shown that, obese women require higher doses of ovulation inducing drugs and has poor outcome with ART. [5] Unfortunately, pharmacological treatment of obesity despite short-term benefits are often associated with rebound weight gain after the cessation of drug use, side effects of medication and the potential for drug abuse. [16] These pharmacological and surgical interventions are associated with complications such as ovarian hyper stimulation syndrome, [17] reduce ovarian reserve and pelvic adhesions. [18] Hence, there is a need for alternate therapy which is to be safe, effective, easily available and free from side effects.

In Unani system of medicine, principle of treatment includes elimination of the cause of infertility that is obesity [6, 19] through diet restriction or regimens, *tanqia badan* with use of *munzij wa mushile balgham*, [6, 20] menstrual regulation with *mudirre haiz* (emmenogogue) drugs having *mufattih sudad* (deobstruent) property [6, 10] and use of *muwallide mani* (ovulation inducing) and *mu'ine haml advia* [6] for conception. Numerous single drugs and compound formulations are available for the treatment of infertility in obese women. *Tukhme Karafs (Apium graveolans), Anisoon (Pimpinella anisum), Ajwain desi (Ptychotis ajowan), Tukhme Hulba (Trigonella foenum), Asaroon (Valeriana wallichii)* was selected as a Unani formulation due to presence of aforementioned properties. Pharmacological studies suggest

that the ingredients of this formulation act as insulin sensitizer, [21] hypolipidemic, [22-28] diuretic, emmenagogue [29] and are known to contain phytohormones as well as obesity suppressing active substances. [30] Hence, this Unani formulation may help in conception by weight reduction, menstrual regulation and ovulation.The study was conducted to test the hypothesis that the treatment of infertility among obese women with Unani formulation is likely to result in conception. The study was planned with an objective to evaluate clinically the efficacy and safety of Unani formulation in infertility among obese women.

Materials and methods

Study design: A single blinded non-randomized pre and post observational study was carried out in the Dept. of *Ilmul Qabalat wa Amraze Niswan* (OBG), National Institute of Unani Medicine, Hospital, Bengaluru during Nov 2014 - March 2016.The study was approved by Institutional ethical committee.
(IEC NO. NIUM/IEC/2013-2014/ANQ/01)

Participants: Total 166 patients were evaluated for eligibility during the trial, out of these, 41 denied for participation and 125 were subjected to investigation; 95 were excluded for not meeting the inclusion criteria and 30 were included in the study (Fig.1).

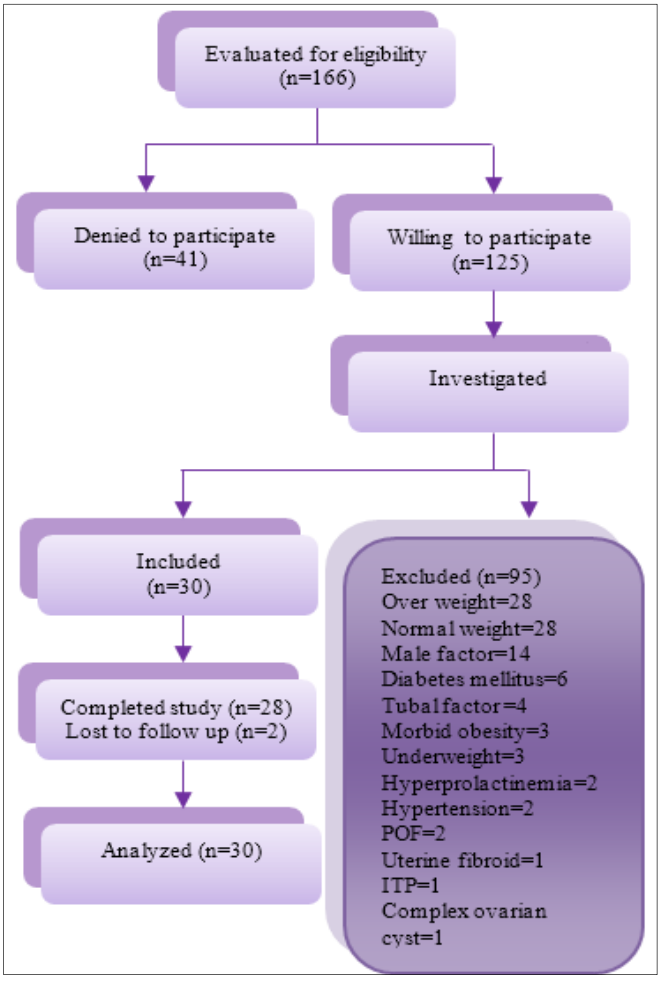

Fig 1: Study flow chart

Sample size calculation: It was determined on the basis of previous study conducted on obese infertile PCOS women with 53.5% of them became pregnant in first 6 months; provided 80% to power with significance level of 5%, the effective sample size of 43 was calculated. [31] However, due to cost effectiveness, practical feasibility and availability of patients in hospital, the sample size of 30 was kept as single group.

Selection criteria: Married women with in the age group of 18-40 years, with infertility (primary and secondary), BMI between 30-40 kg/m^2, menstrual irregularities (oligomenorrhoea and amenorrhoea), controlled hypothyroidism and spouse normal seminogram were included in the study. Patients with systemic illnesses and received treatment for weight reduction in last 3 months were excluded from study.

Study procedure: Patients meeting inclusion criteria were offered study participation and informed consent was obtained. Enrolled patient were evaluated during the early follicular phase after a spontaneous or induced menses. Each patient underwent a detailed history including the duration and type of infertility, previous treatment received for infertility, its outcome, detailed menstrual history (including duration of cycle, duration & amount of flow and history of passing clots). Complete physical examination was performed in all patients and findings were recorded in the case record form designed for the study. BMI, waist hip ratio, hirsutism score and vitals were measured. Assessment of socioeconomic status (Modified Kuppuswamy's Socioeconomic Status Scale), *Mizaj* (as per the parameters mentioned in classical Unani literature), menstrual blood loss (Pictorial blood loss Assessment Chart Scoring System), and hirsutism (Modified Ferriman Gallwey Score) was done in each patient. Following initial screening, patients were advised for routine investigation (complete haemogramm), Biochemical test (SGOT, SGPT, Alkaline phosphatase, Blood Urea, Sr. Creatinine, lipid profile including Sr. Cholesterol, Sr. Triglyceride, HDL-Cholesterol), fasting serum insulin, transvaginal ultrasonography was carried out to know safety and efficacy of Unani formulation.

Intervention: All dried crude drugs *(Tukhme karafs, Tukhme anisoon, Tukhme ajwain desi, Tukhme hulba, Asaroon)*[15] were purchased from local crude drug market of Bengaluru city, and were identified by chief pharmacist Dept. of *Ilmul Advia* NIUM, Bengaluru (Fig.2). Drugs were cleaned, crushed and mixed in equal quantity in NIUM pharmacy. Drugs was dispensed in self-locking packets for two months and advised to use continuously irrespective of cycle days in the form of decoction orally. Patients were instructed to prepare decoction by boiling 12.5gm of drugs in 300 ml of water to make it 100 ml and used twice daily. (300 ml of bottle was given with 100 ml marking for measurement).

Trachyspermum ammi Linn.

Pimpinella anisum Linn.

Apium graveolens Linn.

Trigonella foenum graecum.

Valeriana wallichi DC

Fig 2: Intervention

Duration of the Protocol therapy: 2 months.
Blinding and Compliance to treatment: To ensure blinding, medication was dispensed in self-locking packets to one patient at a time. Compliance with medication was monitored on monthly visit with dispensing packets to receive the remaining treatment.

Assessment cum follow UP: During treatment patients were assessed once in a month for two months. Menstrual regulation, changes in BMI measured on every follow up visit. After treatment patients were followed once in a month for one month. BMI, waist hip ratio, hirsutism and PBAC score was measured and recorded; lipid profile and serum fasting insulin was done to confirm reduction in weight and insulin resistance. If the patient had missed period, then urine for pregnancy test was done to detect pregnancy and TVS was done to confirm the pregnancy.

Subjective parameters: Infertility was defined as failure to conceive after one year or more of a regular unprotected sexual intercourse. Menstrual irregularities (oligomenorrhoea and amenorrhoea) was assessed through duration of cycle (days), duration of flow (days) and amount of flow (pads/cycle). Weight gain was assessed by weight check up with same weighing scale and BMI was calculated and recorded. Reduction in body weight of at least 5-10% is considered as change in weight.

Objective parameters: Urine for pregnancy test was done for detection of pregnancy. Transvaginal Ultrasonograph was done for confirmation of pregnancy by the presence of gestational sac. Body Mass Index (BMI) was measured for 5% reduction. Lipid profile [total cholesterol (Normal level: 120-250 mg/dl), triglycerides (Normal level: 40-165 mg/dl) and HDL- cholesterol (Normal level: 30-70 mg/dl)] were measured to observe 5% reduction. Serum fasting insulin was measured to observe for reduction. **(**Normal level: 2.6-24.9 µIU/ml, Fully automated chemi luminescent assay).[170] The modified Ferriman-Gallwey score was measured during the study period to note reduction. Total score range from 0-36. A score of 8-16, 17-24 and >24 was considered as mild hirsutism, moderate hirsutism and severe hirsutism. Waist circumference was measured with a stretch resistance tape wrapped around the subject at a level parallel to the floor, midpoint between the lower margin of last palpable rib and top of the iliac crest in the mid axillary line and hip circumference around the widest portion of the buttocks. It was measured on every follow up visit to note reduction in its ratio.WHO cut-off points of waist circumference and WHR[166] were considered as >88 cm & ≥0.85 respectively for determination of abdominal obesity. Pictorial Blood Loss Assessment Chart measured on every follow up visit to observe for improvement.

Outcome measures: Primary outcome measures were weight loss, menstrual regulation, and conception. Secondary outcome measures were reduction in BMI, reduction in lipid profile & serum insulin.

Adverse effects documentation: Stomatitis and gastritis was observed in four patients initially, later on patients were instructed to continue the medicine with *gulqand* which is considered as *musleh.*
Statistical analysis: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale before and after treatment. [32-34] The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Results: Total 30 patients were enrolled in the study out of which 2 patients were loss to follow up after treatment, and had not turned up for post-test but included in statistical analysis by last observation carry forward method. (Fig.No.1)

Table 1: Demographic data

Demographic data	Results
Age (Years)	27.17±4.84
Age at marriage	19.87±3.79
Married Life (years)	
Type of infertility	6.93±4.13
Primary	17 (56.7%)
Secondary	13 (43.3%)
Duration of infertility	4.80±3.69
Socio Economic Status	
Lower Middle	9 (30.0%)
Upper	2 (6.7%)
Upper Lower	11(36.7%)
Upper Middle	8 (26.7%)
Mizaj	
Balghami	25(83.3%)
Damvi	5(16.7%)

Data were presented as mean ±SD and number (percentage); Student t test (two tailed, dependent)

Subjective Parameters

Table 2 (a): Comparison of nature of menstrual cycle

Nature of cycle	Before Treatment	After 1st month treatment	After 2nd month treatment	After Treatment	% change
Irregular	17(56.7%)	13(43.3%)	8(26.7%)	10(33.3%)	-23.4
Regular	13(43.3%)	15(50%)	20(66.7%)	19(63.3%)	20.0
NP	0(0%)	2(6.7%)	2(6.7%)	1(3.3%)	3.3%
Total	30(100%)	30(100%)	30(100%)	30(100%)	-

Data were presented as number (percentage); NP- no period

Table 2 (b): Comparison of menstrual cycle pattern and weight reduction

Menstrual cycle pattern	Before treatment	After 1st month treatment	After 2nd month treatment	After Treatment
Duration of cycle (days)	59.57±38.76	51.16±33.34 (P=0.461)	35.52±11.851 (P=0.024*)	44.11±27.6 P=0.081+
Duration of flow (days)	5.53±5.46	4.60±2.40 (P=0.383)	4.26±2.09 (P=0.875)	4.33±1.96 P=0.242
Amount of flow (pads/cycle)	7.60±6.36	7.80±4.43 (P=0.681)	7.74±4.19 (P=0.952)	8.93±4.7 P=0.333
Weight reduction (Kg)	75.93±7.5	72.93±7.8 p<0.001**	70.87±8.13 P<0.001**	70.60±8.P<0.001**

Data were presented as mean ±SD; Student t test (two tailed, dependent); + Suggestive significance (P value: 0.05<P<0.10)
*Moderately significant (P value: 0.01<P ≤ 0.05); **Strongly significant (P value: P≤0.01)

Table 2 (c): Comparison of conception

Conception	Before Treatment	After 1st month treatment	After 2nd month treatment	After Treatment	% change
No	30(100%)	30(100%)	30(100%)	30(100%)	0.0%
Yes	0(0%)	0(0%)	0(0%)	0(0%)	0.0%
Total	30(100%)	30(100%)	30(100%)	30(100%)	-

Data were presented as number (percentage)

Objective parameters

Table 3 (a): Comparison of objective parameters

Objective parameters	Before Treatment	After Treatment	% change
UPT			
NO	30(100%)	30(100%)	0.0%
YES	0(0%)	0(0%)	
PCOD			
Negative	16(53.3%)	19(63.3%)	10.0%
Positive	14(46.7%)	11(36.7%)	-10.0%
Gestational sac			
Negative	30(100%)	30(100%)	0.0%
Positive	0(0%)	0(0%)	0.0%

Data were presented as number (percentage); UPT- urine for pregnancy test, PCOD- polycystic ovarian disease

Table 3 (b): Comparison of objective parameters

Objective parameters	Before Treatment	After Treatment	P value
Lipid Profile			
Serum Cholesterol (mg/dl)	166.27±25.17	163.17±29.06	0.566
Triglyceride(mg/dl)	125.43±41.33	122.60±41.27	0.719
HDL (mg/dl)	43.53±7.35	43.57±7.26	0.984
Fasting Insulin μIU/ml	12.99±4.88	16.22±6.09	0.004**
BMI (kg/m^2)	32.83±2.72	30.43±3.14	<0.001**
Hirsutism	14.35±5.31	13.94±5.18	0.030*
WHR	0.90±0.03	0.88±0.04	<0.001**
PBAC	107.43±115.02	171.59±120.18	<0.001**

Data were presented as Mean±SD**;** Student t test (two tailed, dependent); * Moderately significant (P value: 0.01<P ≤ 0.05);
** Strongly significant (P value: P≤0.01)

Table 4: Comparison of primary outcome measures

Primary outcome measures	No. of patients (n=30)	%
Weight loss		
No	6	20.0
Yes	24	80.0
Menstrual regulation		
No	10	33.3
Yes	20	66.7
Conception		
No	30	100.0
Yes	0	0.0

Data were presented as number (percentage)

Table 5: Comparison of secondary outcome measures

Secondary outcome measures	No. of patients (n=30)	%
Reduction in BMI		
No	6	20.0
Yes	24	80.0
Improvement in Lipid Profile		
No	18	60.0
Yes	12	40.0
Improvement in Fasting Insulin		
No	24	80.0
Yes	6	20.0

Data were presented as number (percentage)

Discussion: In the present study, it was observed that out of 30 patients, none of the patient conceived during the study period; but 3 (10%) patients conceived after 2 months of completion of study probably due to the long term effect of research drug as literature report says that if an infertile women received treatment for infertility, she has to be followed for 6 months without giving any further treatment. Weight loss was achieved in 80% and menstrual regulation in 66.7% of patients. The mechanism can be postulated based on earlier experimental studies.

Demographic data: Maximum patients 83.3% were in the age group of 20-30 years which is consistent with the study of Dhaliwal LK *et al.* [35] reported 83% and SF Majeedi *et al.* [36] reported 77.5%. Mean age of patients were 27.17±4.84; which is in conformance with Athar R *et al.* [37] reported 27.55±5.6, Abuelghar WM *et al.* [38] reported 27.63±4.05, Karimzadeh MA *et al.* [39] reported 27.4±2.38. Most of the patients (56.7%) suffered from primary infertility and 43.3% from secondary infertility. This finding is in accordance with the study of Abuelghar WM *et al.* [38, 40] reported 66.7% and 33.3%, SF Majeedi *et al.* [36] reported 65% and 35%. Literature report says that the incidence of primary infertility is more than compared to secondary infertility. [41] Mean±SD of duration of infertility were 4.80±3.69 years. These findings is in conformance with the study conducted by Tang T *et al.* [42] reported 4.9±2.9, Elkadi MA *et al.* [39] reported 4.2±2.83 years and Serour GI *et al.* [43] reported 4.0±2.53 years as duration of infertility. Maximum patients 36.7% were from upper lower class which is in conformance with the study of SF Majeedi *et al.* [36] reported 55% from upper lower class. Most of the patients (83.3%) possessed *balghami mizaj*; which is in compatible with the study of SF Majeedi *et al.* [36] and Kafeel G *et al.* [44] both reported 77.5% patients with *balghami mizaj*. Further, this observed results are in accordance with theory proposed by Unani physicians, who states that in obese women infertility is mainly caused by the dominance of *khilte balgham* which causes *zo'afe jigar* [9] and *zo'afe quwwate tawleede mani* [10, 11] resulting in chronic anovulation; *zo'afe quwwate masika* of *Rahim* [7, 19] which prevents implantation [6] and increases the risk of miscarriage (Table 1). [12, 21]

Subjective parameters

Menstrual regulation: At base line, 43.3% patients reported regular cycles and 56.7% irregular cycles; which gets regular in 63.3% after treatment with % change of 20%. Menstrual cycles remain irregular in 33.3% patients. These findings is consistent with the studies of Qayyum B *et al.* [45] reported 73% patients had regular cycles and 26% had persistent irregular cycles and Tang T *et al.* [42] reported menstrual regulation in 58% and 52% patients(Table 2a). Mean±SD duration of cycle before treatment, after 1st and 2nd month of treatment and after treatment follow up was 59.57±38.76, 51.16±33.34, 35.52±11.85, 44.11±27.68 respectively. Significant reduction in duration of cycle was observed from baseline to after 2nd month of treatment (P=0.024) and even after treatment follow up (P=0.081). No significant difference in duration and amount of flow was observed during the study period. The improvement in menstrual cyclicity is defined as a change from irregular to regular cycles. Further, this improvement in duration and nature of cycle is credited to *mudirre haiz, mufattih sudad* [46-50] and *muqawwi jigar* [13, 41] properties of Unani formulation which helps in menstrual regulation.

Weight reduction: Mean±SD of weight reduction at baseline 75.93±7.54 and after treatment follow up was 70.60±8.05 respectively; 5 kg of weight loss with 7 % reduction of initial

body weight was observed over a period of 3 months, which was strongly significant (P<0.001). These findings is in conformance with the studies of Mahalwar V *et al.* [51] conducted a clinical trial on management of hypomenorrhoea in obese women by a herbal compound (Test group: *Zingiber officinale, Piper longum, Piper nigrum, Embelia ribes, Cinnamomum zeylanica, Commiphora mukul* and control group: physical exercise with diet restriction) reported weight reduction from 69.8±2.9 to 64.87±2.6 with 7.02 % reduction in Test group and 68±1.29 to 65.6±1.27 with 3.52% reduction in control group over a period of 3 month (P<0.001) and Trivedi VR *et al.* [52] reported weight reduction from 80.13±11.47 to 76.89±11.88 (P<0.01)(Table 2b). Moreover, reduction in weight was the most significant predictor for improvement in menstrual cyclicity.

Conception: None of the patient conceived during the study period (Table 2c).

Objective parameters

Urine for pregnancy test & gestational sac: Urine for pregnancy test and e/o gestational sac on USG Pelvis was negative, as no patient conceived during the study period.

Polycystic ovarian disease: At base line, 46.7% patients had PCOD on USG Pelvis which persists in 36.7% on post treatment scan with percentage change of 10%. (Table 3a) An Association between insulin resistance, compensatory hyperinsulinaemia and hyperandrogenism has provided insight into the pathogenesis of PCOD. [42] Chronic inflammation has been implicated as a cause of PCOD and several studies have reported the presence of inflammatory markers in PCOD. [53] In vitro study on rats has shown that *Tukhme Karafs* improve insulin sensitivity due to presence of phenolic compounds, alkaloid and flavonoids. *Tukhme Hulba* also exhibits same effect due to presence of Amino acid (*4-hydroxyisoleucine*). [21] Pharmacological studies has reported that Unani formulation possess anti-inflammatory properties due to presence of flavonoids in *Tukhme Ajwain,* [13, 22] *Tukhme Anisoon*,[54] *Asaroon*; [55] apigenin and luteolin in *Tukhme Karafs* [56] and glycoside and steroidal compound - saponin in *Tukhme Hulba*. Thus, useful in PCOD.

Lipid profile: Before and after treatment, Mean±SD of serum cholesterol was 166.27±25.17 and 163.17±29.06, triglyceride was 125.43±41.33 and 122.60±41.27 and HDL was 43.53±7.35 and 43.57±7.26 respectively. Cholesterol and triglyceride slightly decreased (P-not significant), while HDL remains unchanged during the study period.

Fasting insulin: Before and after treatment, Mean±SD of fasting insulin was 12.99±4.88 and 16.22±6.09 respectively; statistically strongly significant (P=0.004) difference in fasting insulin was observed, though the values were in normal range only and perhaps signs of insulin resistance was not observed in patients clinically during the study period.

BMI: Before and after treatment, Mean±SD of BMI was 32.83±2.72 and 30.43±3.14 respectively. Strongly significant (P<0.001) change in BMI was observed over a period of 3 months. This findings is consistent with the study of Parham M *et al.* [57] (conducted RCT on effect of pistachio nut supplementation in type 2 diabetes) reported reduction in BMI from 30.1 ± 0.4 to 28.8 ± 0.4 over period of 3 months, Trivedi VR *et al.* [52] reported reduction in BMI from 30.93± 2.69 to 29.71±3.07 (P<0.01) over a period of 3 months, Fanghanel G *et al.* [58] reported reduction in BMI from 36.14±5.07 to 33.56±4.78 (P<0.05) over period of 2 months. Halpern *et al.* [59] reported reduction in BMI from 36.7±6 to 34±6.3 (P<0.01) over a period of 3 months. Strongly significant reduction in BMI is attributed to hypolipidemic and anti-obesity effect of Unani formulation. [21, 25, 30, 60, 61]

Hirsutism: Before and after treatment, Mean±SD of hirsutism was 14.35±5.31 and 13.94±5.18 respectively. Significant difference (P=0.030) in hirsutism was observed during the study period. Dodin S *et al.* [62] reported reduction in hirsutism score from 16.9±1.6 to 14.2±1.7 (P<0.01), 15.6±0.8 to 11.9±0.8 (P<0.01), Ciotta L *et al.* [63] reported 19.07±0.73 to 18.47±0.73 and 20.93±0.99 to 20.07±0.93 (P<0.05). The result of present study is compatable with most of the above studies. Inverse relationship exist between the weight and sex hormone binding globulin (SHBG); probably Unani formulation may act as insulin sensitizer, increases SHBG through weight reduction and decreases androgen levels which in turn causes reduction in hirsutism score. [21, 28]

Waist to hip ratio: Before and after treatment, Mean±SD of waist to hip ratio was 0.90±0.03 and 0.88±0.04 respectively. Strongly significant change (P<0.001) was observed during the study period. Fanghanel G *et al.* [58] reported change in waist to hip ratio from 0.88±0.08 to 0.86±0.06 and from 0.89±0.08 to 0.87±0.06 (P<0.05) over a period of 2 months which is in agreement with the present study. This effect is ascribed to hypolipidemic, hypoglycemic and insulin sensitizing activities of Unani formulation. [21, 25, 47, 61]

PBAC: Strongly significant difference (P<0.001) in Mean±SD of PBAC score was observed before (107.43±115.02) and after treatment (171.59±120.18) during the study period. This effect is credited to *mufattih sudad*, *mulattif*, *qawi mudirre haiz* [46-50] and *muqawwi jigar* [13] properties of Unani formulation (Table 3b).

Primary outcome measures: Weight loss was achieved in 80% patients and even statistical analysis has proved significant reduction (P<0.001) in weight and BMI, with 7% reduction of body weight over a period of 3 months. Fanghanel G *et al.* [58] reported weight loss in 72.5% of patients. Pasquali *et al.,* Kiddy *et al.,* Huber-Buchholz *et al.,* Clark *et al.* [42] suggested that weight loss improves endocrine profile, menstrual cyclicity, frequency of ovulation and chances of pregnancy. Despres *et al.* suggest 5–10% weight loss result in approximately 30% loss of visceral adipose tissue, which can improve metabolic and reproductive functions. [42] Significant change in weight loss in the present study is credited to the medicinal properties of Unani formulation such as *mujaffif, mulattif, mu'arriq, musakhkhin, muhallil, munzije balgham* and *mudirre bawl* [46-50] thereby it reduces the obesity. Moreover, the ingredients of Unani formulation consist of obesity suppressing active substance diosgenin [30, 61] and camphene [26]

Menstrual regulation was achieved in 66.7% of patients. Rezai M *et al.* reported 73.9% and 54.1%, Hanjalic-Beck A *et*

al. [64] reported 70% and 78%, Ciotta L *et al.* [63] reported 60%, Karimzadeh MA *et al.* [39] reported 66.6%, 62.5%, 55.5%, 66.6% improvement in menstrual disorders. The result of present study is compatible with most of the above studies. Significant improvement in menstrual regulation is attributed to *mufattih sudad, qawi mudirre haiz* [46-50] and *muqawwi jigar* [13] properties of Unani formulation. Moreover, the ingredients of Unani formulation contains phytohormones like flavonoids, [13, 22] saponins [65] and glycosides which helps in menstrual regulation. [66] It seems that menstrual regulation is associated with weight loss, secretion of SHBG, free androgen reduction, and improvement in ovarian function. [67] Further, improvement in menstrual regularity is an indication of improvement of potential fecundity. [68] Conception rate in the present study was 0% than those reported by others (El Gharib MN *et al.* [69] reported 2.22% and Athar R *et al.* [37] reported 3.2%), the probable reason could be short duration of intervention (as minimum 3 months treatment is required to conceive), [52, 58] short follow up (as minimum 6 month is required to restore reproductive function after weight loss). [70] The patients could have conceived, if the treatment was continued for one more month and follow up for 2 more months (Table 4).

Secondary outcome measures: Changes in BMI was achieved in 80% patients over a period of 3 months. On fixing 5% reduction in lipid profile, clinically change was achieved in 40% patients which was not significant statistically. Changes in fasting insulin were achieved in 20% patients, although pre and post test values were normal(Table 6).

Safety profile: Unani formulation was proved to be safe as all safety parameters were within normal limits with no adverse clinical manifestation during the study period, thus validating the safety of Unani formulation.

Finally, it can be inferred that Unani formulation may be an effective treatment option in infertile patients with obesity and PCOD, as it has significant effect on weight reduction and menstrual regulation and added benefit of improving metabolic parameters such as lipid profile and serum insulin (slightly); however, the definite effect on conception was not achieved during the study period but 10% patients conceived after 2 months of completion of study.

Limitation: Short duration of intervention, loss of long term follow up, TVS was not performed as a routine to monitor follicular development and ovulation, SHBG, Serum DHEA and total testosterone was not done during the study period.

Future Recommendation

Further research is required with exact dosage of Unani formulation for longer duration to assess fertility with long term follow up. Additional research is needed by comparing Unani drug formulation in one group with life style modification in another group on large sample size at least for six months for better treatment outcome. Additional research is needed on large sample size; combining Unani drug formulation with life style modification to enhance reduction of central adiposity in obese PCOD patients.

Conclusion: Finally, it can be inferred that Unani formulation may be used as an alternate therapy in infertile patients with obesity and PCOD, as it has significant effect on weight reduction, menstrual regulation and BMI; slight effect on lipid profile and fasting insulin and no effect on conception during the study period but 10% patients conceived after 2 months of completion of study. Unani formulation was effective to reduce obesity and menstrual regulation, due to hypolipidemic, insulin sensitizer, diuretic, emmenagogue, and ovulation inducing properties. Moreover, Unani formulation consist of obesity suppressing active substance (diosgenin and camphene) as well as phytohormones like flavonoids, saponins, and glycosides which helps in menstrual regulation and conception.

Acknowledgement: The authors are thankful to the Director, National institute of Unani medicine; Bengaluru for providing all facilities to complete the research and Dr. KP Suresh, Scientist (Biostatistics), National Institute of Animal Nutrition and Physiology, Bengaluru for performing the statistical analysis.

Conflict of interest: none declared

References

1. http://www.who.int/reproductivehealth/topics/infertility/definitions/en/21stMar, 2017.
2. Wilkes S, Murdoch A. Obesity and female fertility: A primary care perspective. J Fam Plann Reprod Health Care. 2009; 35(3):181-5.
3. Mascarenhas MN, Flaxman S, Boerma T, Vanderpoel S, Stevens GA. National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLOS. 2012; 9(12):1- 42.
4. Beall SA, Decherney A. The history and challenges surrounding ovarian stimulation in the treatment of infertility. Fertil Steril. 2012; 97(4):795-801.
5. Harrison CL, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: A systematic review. Human Reproduction Update. 2011; 17(2):171-83.
6. Majoosi ABA. Kamilus Sana'a (Urdu translation by Kantoori GH). Vol I. New Delhi: Idarae Kitabul Shifa. 2010; 40:155-337-534-538-9.
7. Tabri AR. Firdausul Hikmat (Urdu translation by Shah MA). New Delhi: Idarae Kiatabul Shifa. 2010; 112-3-125-6-254-257-259-261-471.
8. Khan AA. Akseere Azam. New Delhi: Idarae Kitabul Shifa. 2011; 798-801, 806-819-20.
9. Khan HA. Haziq. Karachi: Madina Publishing company. 1983; 296-462-4-468-470.
10. Ibn Sina Al, Qanoon Fil Tibb. (Urdu translation by Kantoori GH). New Delhi: Idarae Kitabul Shifa; 2010; 40: 155, 337, 534, 538-9, 1065-66, 1069-70, 1088-89, 1095-98, 1445-47.
11. Khan AA. Akseere Azam. New Delhi: Idarae Kitabul Shifa. 2011; 798-801, 806-819-20.
12. Qurrah S. Zakheera Sabit Bin Qurrah (Urdu translation by Ali SA). Aligarh: Leethu Colour Printers. 1987; 301-303, 311-2.
13. Kabeeruddin M. Bayaze Kabeer. New Delhi: Idarae Kitabul Shifa. 2010, 207-8.
14. Allahbadia, Merchant R. Polycystic Ovary Syndrome and Impact on Health. Middle East Fertility Society Journal. 2011; 16:19-37.

15. Brewer CJ, Balen AH. The adverse effect of obesity on conception and implantation. Society for Reproduction and Fertility. 2010; 140:347-64.
16. Ranjbar SH, Nayebi N, Larijani B, Abdollahi M. A systematic review of the efficacy and safety of herbal medicines used in the treatment of obesity. World J Gastroenterol. 2009; 15(25):3073-85.
17. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): A review. Human Reproduction Update. 2002; 8(6):559-77.
18. Oriji VK. Laparoscopic ovarian drilling versus medical treatment in management of clomiphene citrate polycystic ovarian syndrome. World Journal of Laproscopic Surgery. 2010; 3(2):99-102.
19. Baghdadi IH. Al Mukhtaraat Fil Tibb. (Urdu translation).Vol IV. New Delhi: CCRUM. 2007; 31-35, 51-55, 59-60, 137-8.
20. Jurjani AH, Zakheerae Khawarzam Shahi. (Urdu translation by Khan HH). New Delhi: Idarae Kitabul Shifa. 2010; 24:27-8, 113, 372-376, 601-606-9.
21. Mullaicharam AR, Deori G, Maheswari U. Medicinal Values of Fenugreek-A Review. RJPBCS. 2013; 4(1):1304-13.
22. Jeet K, Devi N, Narender T, Sunil T, Lalit S, Raneev T. Trachyspermum ammi (Ajwain): A Comprehensive Review. IRJP. 2012; 3(5):133-6.
23. Mansi K, Abushoffa AM, Disi A, Aburjai T. Hypolipidemic effects of seed extract of celery (Apium graveolens) in rats. Phcog Mag. 2009; 5(20):301-5.
24. Jan SA, Shinwari ZK, Zeb A, Khalil AT, Shah SH. Ethnobotany and Research Trends in Trachyspermum ammi L. (Ajowan): A Popular Folklore Remedy. American-Eurasian J. Agric. & Environ. Sci. 2015; 15(1):68-73.
25. Javed I, Iqbal Z, Rahman ZU, Khan FH, Muhammad F, Aslam B *et al.* Comparative antihyperlipidemic efficacy of Trachyspermum Ammi extracts in albino rabbits. Pakistan Vet. J. 2006; 26(1):23-29.
26. Asif HM, Sultana S, Akhtar N. A Panoramic view on Phytochemical, nutritional, ethanobotanical uses and pharmacological values of Trachyspermum ammi Linn. Asian Pac J Trop Biomed. 2014; 4(Suppl 2):545-53.
27. Bairwa R, Sodha RS, Rajawat BS. Trachyspermum ammi. Pharmacogen Rev. 2012; 6(11):56-60.
28. Shojaii A, Fard MA. Review of Pharmacological properties and chemical constituents of Pimpinella anisum. ISRN Pharmaceutics. 2012, 1-8.
29. Moghadam MH, Imenshahidi M, Mohajeri SA. Antihypertensive effect of celery seed on rat blood pressure in chronic administration. J Med Food. 2013; 16(6):558-63.
30. Semalty A, Kumar R, Semalty M. Anti hyperlipidemic and anti obesity activities ethanolic extract of Trigonella foenum graecum (seeds) of Himalyan region in diet induced obese mice. Adv. Biomed. Pharma. 2015; 2(5):229-34.
31. Yanamandra NK, Gundabattula SR. Outcome of ovarian drilling in women with polycystic ovary syndrome. JCDR. 2015; 2(9):1-3.
32. Rosner B. Fundamentals of Biostatistics. 5th ed. Duxbury: Cengage Learning Inc. 2000, 80-240.
33. Riffenb urg RH. Statistics in Medicine. 2nd ed. Amsterdam: Academic press. 2005, 85-125.
34. Suresh KP, Chandrasekhar S. Sample Size estimation and Power analysis for Clinical research studies. Journal of Human Reproductive Sciences. 2012; 5(1):7-13.
35. Dhaliwal LK, Suri V, Gupta KR, Sahdev S. Tamoxifen: An alternative to Clomiphene in Women with Polycystic Ovary Syndrome. J Hum Reprod Sci. 2011; 4(2):76-79.
36. Majeedi SF, Shameem I, Roqaiya M. Efficacy of *Asparagus recemosus* (Satavar) in stimulating follicular growth and ovulation in anovulatory infertility: A randomized controlled trial. Int J Reprod Contracept Obstet Gynecol. 2016; 5(2):310-16.
37. Athar R, Mehrnoosh M, Masoumeh H, Hooshmand F, Fatemeh A. Clomiphene Citrate and Letrozol Versus Tamoxifen and Letrozole as an Infertility Treatment in Women with Polycystic Ovary Syndrome. Pakistan Journal of Biological Sciences. 2015; 18(6):300-3.
38. Abuelghar WM, Elkady OS, Khamees AA. Clomiphene citrate alone, or in combination with metformin or in combination with pioglitazone as first line therapy in induction of ovulation in infertile women with polycystic ovary syndrome- A randomized controlled trial. Middle East Fertility Society Journal. 2013; 18:135-141.
39. Karimzadeh MA, Javedani M. An Assessment of Lifestyle Modification versus Medical Treatment with Clomiphene Citrate, Metformin, and Clomiphene Citrate- Metformin in Patients with Polycystic Ovary Syndrome. Fertility and Sterility. 2010; 94(1):216-20.
40. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. Human Reproduction Update. 2003; 9(4):359-72.
41. Dovom MR, Tehrani FR, Abedini M, Amirshekari G, Hashemi S, Noroozzadeh M. A population based study on infertility and its influencing factors in four selected provinces in Iran (2008-2010). Iran J Reprod Med. 2014; 12(8):561-6.
42. Tang T, Glanville J, Hayden CJ, White D, Barth JL, Balen AH. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo controlled, double blind multicentre study. Human Reproduction. 2006; 21(1):80-89.
43. Serour GI, Aboulghar M, Bahar A, Hugues JN, Esmat K. Phase IV, open label, randomized study of low dose recombinant human follicle stimulating hormone protocols for ovulation induction. RBEG. 2014; 12(52):1-9.
44. Kafeel G, Shameem I, Begum W. Clinical evaluation of Unani formulation in ovulation induction in anovulatory infertility. Journal of AYUSH: Ayurveda, Yoga, Unani, Siddha and Homeopathy. 2013; 2(1):25-32.
45. Qayyum B, Chaudhry SM, Sadaf J. Management of Anovulatory Infertility (Polycystic Ovary Syndrome) with Clomiphene alone and in combination with Metformin. Int. Journal of Surgery Pakistan. 2010; 15(3):135-38.
46. Kabeeruddin M. Ilmul Advia Nafeesi. New Delhi: Ejaz publishing house. 2007; 59(72-3):235-6.
47. Ibn Baitar ZBA. Al Jame ul Mufradat al Advia wal Aghziya (Urdu translation).Vol IV. New Delhi: CCRUM. 2003; 51-4, 139-41, 144, 379-80.
48. Ghani HN. Khazainul Advia. 2nd ed. New Delhi: Idarae Kitabul Shifa. 2011; 202-3, 206-7, 226-293.

49. Chughtayi HGM, Chughtayi HF. Rehnumaye Aqaqeer. New Delhi: Aijaz publishing house. 2004; 11-14, 42-47.
50. Rafeequddin M. Kanzul Advia Mufridah. Aligarh: Muslim University Press. 1985, 73-4, 83-4.
51. Mahalwar V, Mahapatra KB, Otta SP. Management of Artavakshaya (Hypomenorrhoea) with obesity by a herbal compound. IJRAP. 2012; 3(6):847-51.
52. Trivedi VR, Satia MC, Deschamps A, Maquet V, Shah RB, Zinzuwadia PH *et al.* Single blind, placebo controlled randomised clinical study of chitosan for body weight reduction. Nutrition Journal. 2016; 15(3):1-12.
53. Fatima FK, Abubacker S, Ruckmani A, Vijayalakshmi K, Karunya LG, Ranjini S. Effect of Flax seeds supplementation in Polycystic Ovarain Syndrome. Int. J. Sci. Rev. 2015; 31(1):113-9.
54. Shobha RI, Rajeshwari CU, Andallu B. Phytoconstituents and lipoxidase and xanthine oxidase inhibitory effects of methanolic extract of aniseeds (Pimpinella anisum L.). Int. J. Pure App. Biosci. 2014; 2(2):81-5.
55. Kour M, Singh H, Kaur J. In vitro anti oxidant and anti inflammatory activities of hydroalcoholic extract of leaves of Valeriana Jatamansi. International archives of integrated medicine (IAIM). 2014; 1(3):18-26.
56. Shanmugapriya R, Ushadevi T. *In vitro* antibacterial and anti inflammatory activity of Apium graveolens seed extract. International Journal of drug Development & Research. 2014, 1-6.
57. Parham M, Heidari S, Khorramirad A, Hozoori M, Hosseinzadeh F, Bakhtyari L *et al.* Effects of Pistachio nut supplementation on blood glucose in patients with type 2 diabetes: A Randomized Crossover Trial. Rev Diabet Stud. 2014; 11(2):190-6.
58. Fanghanel G, Cortinas L, Sanchez Reyes L, Berber A. A Clinical Trial of the Use of Sibutramine for the Treatment of Patients Suffering Essential Obesity. Int J Obes Relat Metab Disord. 2000; 24(2):144-50.
59. Halpern A, Pepe RB, Monegaglia AP, Beyruti M, Melo ME, Mancini MC. Efficacy and Tolerability of the association of Sibutramine and Orlistat for six months in Overweight and Obese Patients. Journal of Obesity. 2010, 1-5.
60. Sreeja S, Anju VS, Sreeja S. *In vitro* estrogenic activities of Fenugreek Trigonella foenum graecum seeds. Indian J Med Res. 2010; 131:814-9.
61. Eidi A, Eidi M, Sokhte M. Effect of fenugreek (Trigonella foenum graecum) seeds on serum parameters in normal and streptozotocin induced diabetic rats. Nutrition Research Elsevier. 2007; 27(11):728-33.
62. Dodin S, Faure N, Cedrin I, Mechain C, Lemay LT, Guy J *et al.* Clinical Efficacy and Safety of Low-Dose Flutamide alone and combined with an Oral Contraceptive for the Treatment of Idiopathic Hirsutism. Clinical Endocrinology. 1995; l43(5):575-82.
63. Ciotta L, Calogero AE, Farina M, Leo VD, Marca AL, Cianci A. Clinical, Endocrine and Metabolic Effects of Acarbose, A-Glucoside Inhibitor, in PCOS Patients with Increased Insulin Response and Normal Glucose Tolerance. Human Reproduction. 2001; 16(10):2066-72.
64. Hanjalic BA, Gabrid B, Schaefe W, Zahradnik H, Schories M, Tempere C *et al.* Metformin versus Acarbose therapy in patient with Polycystic ovarian syndrome: A prospective randomized double blind study. Gynaecological endocrinology. 26(9): 690-97.
65. Sinha1 R, Rauniar GP, Panday DR, Adhikari S. Fenugreek: Pharmacological actions. WJPPS. 2016; 5(6):1481-89.
66. Kokate CK, Purohit AP, Gokhale SB. Pharmacognosy. Chennai: Nirali Prakashan. 2012; 17(19):24-35.
67. Seth B, Arora S, Singh R. Association of Obesity with Hormonal Imbalance in Infertility: A Cross-Sectional Study in North Indian Women. Ind J Clin Biochem. 2013; 28(4):342-7.
68. Dovom MR, Tehrani FR, Abedini M, Amirshekari G, Hashemi S, Noroozzadeh M. A population based study on infertility and its influencing factors in four selected provinces in Iran (2008-2010). Iran J Reprod Med. 2014; 12(8):561-6.
69. EL-Gharib MN, Mahfouz AE, Farahat MA. Comparison of Letrozole versus Tamoxifen Effects in Clomiphen Citrate Resistant Women with Polycystic Ovarian Syndrome. J Reprod Infertil. 2015; 16(1):30-35.
70. https://www.asrm.org. American Society for Reproduction, obesity preventable cause of infertility accessed on 28.3.2016.