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# Efficacy of Polyherbal Unani Formulation in *ehtebas-e-haiz* [amenorrhoea]-a Randomised Single Blind Study

Shaik Akeefa Nousheen\*

Govt. Nizamia Tibbi College, Charminar, Hyderabad, India



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# ABSTRACT

Introduction: Amenorrhoea denotes absence of menstruation. Primary amenorrhoea refers to failure of onset of menstruation beyond the age of 16 years regardless development of secondary sexual characters. Secondary amenorrhoea refers to failure to occurrence of menstruation for 6 months or longer in women who have previously menstruated Primary amenorrhoea is rare about 0.3%, whereas secondary amenorrhoea is about 30-40%. According to Shaik ur Rayees Bu Ali Sena in his book "Al Qanoon Fit Tibb" amenorrhoea is cessation of menstrual flow which may be due to uterine pathology or due to altered temperament of the body.Hk Ashrafuddin Ismail Jurjani in his book Zaqir-e-Qarzam Shahi stated that any imbalance in humours(khilt) will lead to change in temperament of body which causes amenorrhoea. He stated that the hot temperament leads to dryness and constriction of the blood vessels and cold temperament causes increase in the viscosity of the blood which leads to ehtebas e haiz. Objective: To see the efficacy of unani formulation in patients with ehtebas-e-haiz. Methodology: Study was conducted in Dept of Amraze Niswan at Govt Nizamia Tibbi College and hospital, Hyderabad. 100 patients of reproductive were selected. An inclusion criterion includes women of age group  $1\overline{1}$ -40 years with delayed peiods for 2-6 months. Exclusion criteria were pregnant women, menopause, and women with congenital anomalies, systemic disease and genetic disorders. A polyherbal unani formulation was made which consist of single drugs in the form of joshanda(tukhme karafs, aneesun, badiyan, pudina khushk, mishktaramsheey, abhal, parsiaoshaan),Qurs (Murmaki, pudina khushk, barge sadab, mishktaramsheey, majeeth, heeng, jaosheer, sakbeenj, each 3 gms) and humool (Zafraan,Ood-e-shireen, Nagarmotha) was given for 10 days for three consecutive cycles.

Results: Primary outcome was withdrawal bleeding which was seen in 63 patients out of 100 patients and secondary outcome was regularisation of cycle which was seen in 37 patients in first cycle.

Conclusion: The study proved efficacy of unani formulation with good results without any side effects. The formulation can also be used as an alternate to the OCP which are used for withdrawal in conventional medicine.

#### 1. Introduction

Amenorrhoea denotes absence of menstruation. It is a symptom not a disease entity. Initiation of menstruation is an important milestone in the reproductive lives of women. Amenorrhoea denotes absence of menstruation. It may be physiological or pathological. Its onset may be primary or secondary. Physiological amenorrhoea naturally prevails

\*Corresponding Author: Shaik Akeefa Nousheen E-mail Address: nousheen972@gmail.com DOI: 10.46890/SL.2020.v01i04.005

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prior to the onset of puberty, during pregnancy and lactation and after menopause. Pathological amenorrhoea is the result of genetic factors, systemic. Diseases, endocrinopathies, disturbance of the hypothalamic-pituitary-ovarian-uterine axis, gynatresia, nutritional factors, drug usage, psychological factors and other rare causes primary amenorrhoea refers to the failure of onset of menstruation beyond the age of 16 years regardless of development of secondary sexual characters. Secondary amenorrhoea refers to the failure of occurrence of menstruation for 6 months or longer in women who have previously menstruated.

According to *sahib-e-kamil* [Hakeem Kabeeruddin], menarche is attained at the age of 10-14 years and the cycle lasts upto the age of 36-60 years and then ceases and later stops at the age of 60 years. Intersexual women

do not menstruate. In classical unani text, *ehtebas-e-haiz* menstruation either it varies from scanty flow to complete cessation or it is defined as cessation of menstruation at interval of  $\geq 2$  months. Duration of intermenstrual period ranges from 20 to 60 days and if it exceeds, above this level then, it is considered as abnormal and called as *ehtebas-e-haiz*. It usually occurs in women having *balghami mizaj* and fair complexion and such women generally suffer from *usr-e-tams* as heavy menstrual bleeding may occur after a long period of amenorrhea.

According to unani physicians, the disease is caused by the of *Khilt e balgham* and *sauda*. According to *Avicenna* (Al-Qanoon), *Jurjani* (Zakheer-e-Quarzam shah), *Abbas majoosi* (Kamil-us-sana), *Raban tabri* (Firdous-ul-Hikmat), *Akbar Arzani* (Tibb-e-Abar) the major causes of *Ehtebas-e-haiz* are *su-e-mizaj barid*, *akhlat-e-ghaliz*, *zof-e-jigar*.. Aim of present study is to prove efficacy of some of the classical unani drugs in *Ehtebas-e-haiz*, To find out safe effective and easily available remedy for *Ehtebas-e-haiz*.

# 2. MATERIAL AND METHODS

#### **Study Design**

A randomized single blind, study was conducted from 2016 to 2018 in Post Graduate Dept of *Ilmul Qabalat Wa Amraz-e-Niswan*, Government Nizamia Tibbi College and General Hospital, Charminar, Hyderabad. Ethical clearance certificate obtained from institutional ethical committee.

## Sample Size

Sample size of 100 patients were taken for the study. Total 250 patients were evaluated for the study 25 patients did not meet the inclusion criteria and 45 patients denied participation 80 patients had irregular follow ups and left in between. Hence were excluded.

#### **Inclusion Criteria**

Married and unmarried women of age group 11 to 40 years. Women with complaints of delayed and irregular menstrual cycle FOR 2-6 months. Patients with normal secondary sexual characteristics and not attained menarche at the age of 16 years. Patients with amenorrhoea due to hypothyroidism, hyperprolactinemia were also included.

## **Exclusion Criteria**

Pregnant women and women who have attained menopause Women with systemic illness, malignancies and metabolic disorders. Patients with developmental defects of genital organs and genetic disorders, CAH, POF. Patients with big uterine fibroids and polyps.

# **Pharmacognosy**

Drugs which are cost effective, easily available in the market and with least side effects were selected. Drugs were coded and given in the form of *Joshanda* (Decoction), *Qurs* (Tablet). Single group was planned for the study.

#### Joshanda-e-abhal

Tukhm-e-karafs, Anisoon, Badiyaan, Pudina khushk, mishktaramsheh, abhal, parsiyaoshan,each 6gms. Soak the above drugs in 200ml of water overnight, and boil in the morning till it becomes half. Filter it and give in the morning on empty stomach for 10 days with *Qurs-e-murmaki*.

#### Qurs-e-murmaki

Murrmaki, pudina khusk, Barg-e-sadab, Mishktaramsheeh, Majeeth, Heeng, Jaosheer, Sakbeenaj, each 3gms. The above drugs in equal quantity are taken and cleaned, then grinded into fine powder and made into tablet form. 4 tablets per day (2 in the morning and 2 in the night) given for 10 days.

#### Follow up

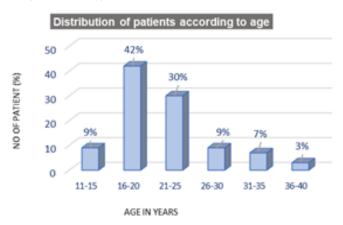
Patients were instructed to start therapy 10 days before menstrual cycle every month. Urine for Pregnancy test was done in patients with the history of amenorrhoea before starting the treatment. If the patient had withdrawal bleeding, they were followed up on every 1<sup>st</sup> day of mc to know the flow and the duration of cycle. Patients were also enquired for any adverse effect of test drugs during the trial.

# **Subjective parameters**

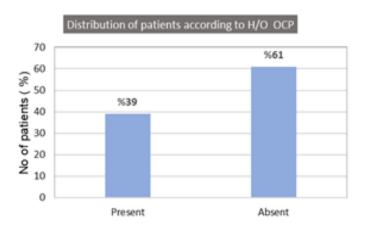
Nature of cycle, Duration of cycle, length of the cycle, and amount of flow [PBAC] were used to assess.

# **Objective parameters**

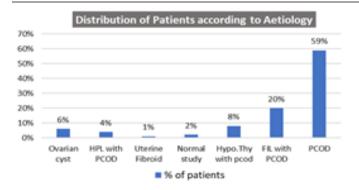
BMI, PBAC score, ultrasound



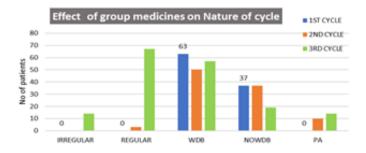
Graph no: 1



Graph no: 2



## Graph no: 3



#### Graph no: 4

**RESULT:** Outcome measures: Primary outcome measure was withdrawal bleeding. Secondary outcome measure was regularisation of menstrual cycle.

#### 2.1 Interpretation

# Withdrawal bleeding %

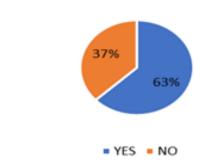


Figure no: 1

# Menstrual regulation %

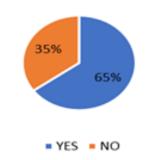


Figure no: 2

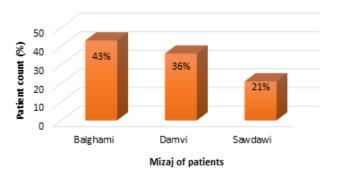
#### **Statistical Analysis**

A total of 250 patients were screened for the study, out of which 50 patients denied participation and 150 were evaluated through investigation, 30 were excluded for not meeting inclusion criteria, and 120 were enrolled in the study. Among 120, 20 patients were lost in the follow ups and not visited again.

In the present study, it was observed that withdrawal bleeding was achieved in 63% patients, while 37% patients had no bleeding. Out of 100 patients menstrual regulation was achieved by group medicines in nearly 58% of patients and the remaining patients that is 42% of patients had persistent irregular menstruation.

The data shows the majority of patients with amenorrhoea were in the age group ranging 15-30yrs, Kouser *et al* reported 46.66%. Mean age of patients was 21.8  $\pm$  5.56 which is in accordance the study of Elkind-Hirsch K *et al* reported 28.2  $\pm$ 1.1, 27.7

Mean age of menarche was 12.2  $\pm$  1.71 which is in conformance with the study of Dahlgren E *et al* reported 12.7  $\pm$  1.2, 12.3  $\pm$  1.7, Parveen *et al* reported 13.45 $\pm$  1.09, Balikci A. *et al* reported 12.9  $\pm$  1.0 and 13.0  $\pm$  0.8, Dahlgren E *et al* reported 12.7  $\pm$  1.2, 12.3 $\pm$  1.7.



Graph no: 5

Distribution according to temperament in the analysis shows the majority of patients with amenorrhea was Balghami [phlegmatic] i.e, 43%, followed by Damvi, 36%, and then Saudavi, i.e. 21%. Kouser et al reported balghami, damvi and saudavi in 71.11%, 20%, and 8.8% of patients respectively, which is consistent with the present study. It proves the theories mentioned by eminent Unani physicians in pathophysiology of amenorrhoea, as it is caused by abnormal production of balgham, which inturn causes zo'afe-jigar resulting in ehtebas-e-haiz. It is described in Ghina Mina that obstruction of uterine and ovarian blood vessels due to Sue Mizaj e Barid prevents the passage of blood leading to ehtebas-e-haiz.

Analysis of the patients based upon the history of hormonal replacement therapy shows that 39% of patients had the same for amenorrhoea for duration ranging from 3 months to nearly 4-5yrs of period which differs from patient to patient. The patients who were on long duration of treatment with hormonal therapy had difficulty in having withdrawal bleeding in the first two consecutive cycles. Unmarried and married women both had the H/O OCP for withdrawal bleeding and regularisation of menstruation.

Amenorrhoea itself had numerous aetiologies. The analysis shows the majority of the patients i.e. 59% had PCOD as the root cause of amenorrhea and the other associated

disorders like PCOD with Hyperprolactinemia 4%, PCOD with hypothyroidism 8%, PCOD with Fatty infiltration of liver 20%. The remaining patients had Uterine fibroid 1% and 2% of patients had normal study.

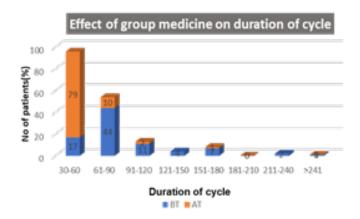
The patients reported for the study were having irregular periods of varying durations i.e. 100% of the patients had irregular cycles. Analysis shows 67% and 58% patients had regular cycles in  $3^{\rm rd}$  cycle after treatment whereas only 3% and 10% of patients had regular cycles after  $1^{\rm st}$  cycle and  $2^{\rm nd}$  cycles.

Withdrawal bleeding in the first cycle was seen in 63% of patients. 50% and 57% of patients were having withdrawal in the subsequent  $2^{\rm nd}$  and  $3^{\rm rd}$  cycles respectively. While, 37% of patients in  $1^{\rm st}$  and  $2^{\rm nd}$  cycles had no withdrawal bleeding. The patients who had no withdrawal bleeding within first three cycles were extended for 3 more consecutive months for treatment. Among them 3% of patients responded after 6 cycles and were having withdrawal in  $4^{\rm th}$  and  $5^{\rm th}$  cycles. 2 patients had regular menstruation after 6 cycles. Regularity of menstrual bleeding is consistent with the study of Qayyum B.et al reported 73% patients had regular cycles and 26% had persistent irregular cycles.

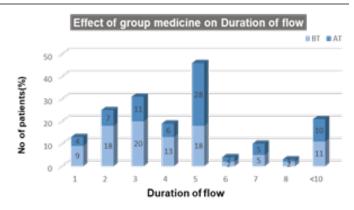
The majority of the patients who had withdrawal bleeding in the first cycle did not have PCOD in their aetiology and the patients with hypothyroidism and ovarian cyst responded to the group medicines and were having regular cycles in their  $1^{\text{st}}$  and  $2^{\text{nd}}$  cycles of treatment.

Table no: 1

Nature Of Cycle	ВТ	1st Cycle	2nd Cycle	3rd Cycle	AT
IRREGULAR	100	-	32	15	29
REGULAR	-	-	6	24	65
WDB	-	63	50	46	-
NOWDB	-	37	-	-	-
PA	-	-	12	15	6
TOTAL	100	100	100	100	100



Graph no: 6



Graph no: 7

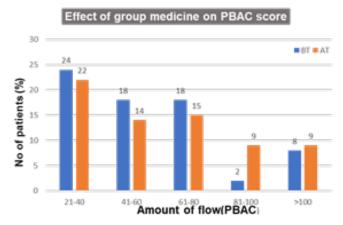
#### Effect of group medicine on Duration of cycle

Analysis of duration of cycle before and after the treatment to know the efficacy of the drugs. Mean  $\pm$  SD of duration of cycle before treatment, after 1<sup>st</sup> cycle, 2<sup>nd</sup> cycle, 3<sup>rd</sup> cycle and after treatment was 97.2  $\pm$  42. 7, 85.5 $\pm$  48.8, 68.3 $\pm$  45.11, 62.5 $\pm$  44.05, 47.4 $\pm$  25.8 respectively.

#### **Duration of flow**

Data represented in the form of Mean  $\pm$  SD, to know the effect of drugs on duration of flow. Mean  $\pm$  SD of duration of flow before treatment, after 1st cycle, 2nd cycle, 3rd cycle and after treatment was 5.5  $\pm$  6.3, 5.56  $\pm$  4.9, 6.05  $\pm$  5.1,6.38 $\pm$ 6.37, 5.9  $\pm$  4.91 respectively. Duration of flow remains nearly same in the first cycle as before treatment later in the next subsequent cycles the duration flow is increased, where as it remains same in the 3rd cycle and after treatment.

The patients who had withdrawal bleeding in the first and second cycles had a small duration which was increased in the next two cycles.



Graph no: 8

# **Amount of flow**

Mean  $\pm$  SD of amount of flow before treatment, after  $1^{st}$  cycle,  $2^{nd}$  cycle,  $3^{rd}$  cycle during treatment and after treatment was  $48.9 \pm 41.2$ ,  $40.52 \pm 45.01$ ,  $40.18 \pm 46.9$ ,  $49.18 \pm 49.9$ ,  $52.9 \pm 50.9$  respectively.

Amount of flow was decreased in 1<sup>st</sup> cycle of treatment and then remains static in the subsequent cycles of treatment. Patients who had the history of hypothyroidism had PBAC score more than 100 during their withdrawal bleeding. One patient had the history of menorrhagia in her past,

later she had irregular cycles with complain of 6 months amenorrhoea, her USG and hormonal profile was normal. During her withdrawal bleeding after  $1^{\rm st}$  cycle she has PBAC score >100. She has the same score in her 2 consecutive cycles.

A patient who had chronic PCOD with H/o long term HRT was given group medicine for amenorrhea of 6 months duration she had withdrawal bleeding with PBAC score less than 10, later after completion of 6 cycles her PBAC score was improved to 100.

# 2.2 OBJECTIVE PARAMETER

#### **BMI**

Mean ± SD of BMI before and after treatment was from 29.12± 4.2 to 28.14 ±4.10 There was a significant change in BMI during treatment. These findings are consistent with the study of El-Halwagy A.et al reported reduction from  $27.5\pm5.2$ , to  $27.0\pm$  4.5,  $28.0\pm5.1$  to  $27.3\pm4.5$ ,  $25.8\pm5.7$  to 25.3±5.0, in three groups in 6 months. Nazari T.et al reported reduction from 27.5±4.4 to 26.6±4.1 in 6 months. Angik R. et al reported reduction from 24.10±4.13 to 23.97±3.02, 23.23±2.65 to 23.22±3.51 in 6 months. Highly significant reduction in BMI is attributed to munaffis wa mukhrij-ebalgham, and mudirr-e-baul wa haiz drugs according to research done by Rehana khatoon et al reported reduction from  $29.71\pm3.87$  to  $28.89\pm3.75$ . The group medicine has murr [commiphora myrrha] which has the properties of antihyperlipidemic, anti-inflammatory, and anti-oxidant, which helps in the reduction of body weight which is very essential for improvement of menstrual regulation.

Obese women with Polycystic Ovary syndrome have a greater frequency of menstrual disturbance and of hirsutism than lean women with the syndrome. Moderate weight loss during long term calorie restriction is associated with a marked clinical improvement which reflects the reduction in insulin concentrations and reciprocal changes in SHBG.

## Ultrasonography

The USG reports of 59% patients had PCOD which shows the major cause of amenorrhoea, where as 20% of patients had PCOD associated with Fatty infiltration of liver of various grades which differs from patient to patient. 6% of patients USG reports shows ovarian cyst, whereas 1% had Fibroid uterus. Only 2% of patients had no PCOD after treatment.

# 3. Discussion

The classification of plants was done based on the repetition and potency of the plants in the ancient literatures. In present study, emmenagogue plants used to treat amenorrhea were systemically searched. Based on current study, the selected group medicines were proven to be more effective (due to their potency and frequency in ancient literatures) in treatment of amenorrhea. The group had the medicines Apium graveolens [tukhme karafs], Pimpenella anisum [anisoon], Ferula foetida regel [heeng], Foeniculum vulgare [badiyaan], Mentha sylvestris [pudina], Mentha polygium [mishktaramashee], Juniper communis [abhal], Adiantum capillus [parsioshan], Lupinus albus linn [turmus], Rubia

cordifolia (majeeth), Cyperus rotundus linn [nagarmotha], Commiphora myrrha [murrmaki] in the form of decoction (Joshand-e-abhal) before 10 days of last menstrual period, in addition with tablets made of drug like myrrh, Mentha sylvestris, Garden rue, Ruta graveolens [barg-e-sudaab], Mentha polygium, Rubia tinctoria, Ferula persica [sakbinaj] (qurs-e-murmaki). The anti-inflammatory and antioxidative features of the plants have been proposed to play the key role in regulating sex hormones, increasing insulin sensitivity, and modifying lipid profile. It has been reported that some of these plants contain phyto-estrogenic components which lowers LH via a negative feedback process and decreases testosterone.

# Strength of the work

Modern line of treatment includes OCP'S and HRT which has many side effects. By this study we were able to know the efficacy of the *mudirr-e-haiz* drugs in withdrawal bleeding in order to propagate and popularize our medicines in our day to day practice. This result can be utilized in clinical fields, by selecting more efficient, less side effects medicinal plants in Unani medicine. Results of present study can be used as an outline for future studies about the plants found to be effective in Unani medicine.

#### Lacunae of the work

It was difficult to convince the patients particularly the patients who did not have withdrawal bleeding in the first and second cycle of the treatment. The study was limited to some extent. The patients with the history of oral contraceptive pills were not responding to the medicines and the study was not effective in primary amenorrhoea patients. The patients were not satisfied with the odour and taste of the medicines.

#### Recommendations of the further work

The aim of this recommendation is to increase the knowledge and find much more effective medicines than the present study. And with the further research we can decrease the limitation of the study and find much more safe drugs that can reduce the hormonal disturbance and provide healthy reproductive life and decrease the incidence of amenorrhoea and its complications like Infertility associated with anovulation

# 4. Conclusion

Overall, good response was seen on withdrawal bleeding with 63% and 65% on menstrual regularisation of the cycle respectively. The efficacy of group medicine on Duration of cycle before and treatment was 97.2  $\pm$  42.7, 47.4  $\pm$  25.8 respectively. Next the effect of group medicine on Duration of flow before and after treatment was 5.5  $\pm$  6.3, 5.9  $\pm$  4.9 respectively. The effect of group medicines on Amount of flow before and after treatment was 48.9  $\pm$  41.2, 52.9  $\pm$  50.9 respectively.

After treatment 65% patients had regular cycles with 63% of patients had withdrawal bleeding, with significant decrease in duration of cycle. While 6% had persistent amenorrhoea throughout the treatment, and 29% had irregular

menstruation. The result was due to the properties like *Mufatteh sudad, Mudir-e-haiz, mulattif-e-khun, muharrik*, of research medicines. Moreover research drugs contain steroids and flavonoids, Mur contains phytosterol, saponins, terpenoids, lignans, phenolic compounds etc while Abhal contains glycosides and alkaloids as well, which properly exert hormone like action in the body and may help in withdrawal bleeding and menstrual regulation.

Research medicines did not show any adverse or side effects on the patients, and the study were uneventful.

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