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EVALUATION OF EFFICACY AND SAFETY OF SAMSHEE SYRUP IN MENSTRUAL IRREGULARITIES: A MULTICENTRIC, POST MARKETING SURVEILLANCE STUDY

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ABSTRACT

Menstrual problems are generally perceived as only minor health concern and thus irrelevant to the public health agenda particularly for women in developing countries who may face life threatening condition. Hence the present study was conducted to evaluate the clinical efficacy and safety of *Samshee* Syrup in the treatment of menstrual irregularities. The present study includes 1,000 female patients aged between 18-45 years with menstrual irregularities and those willing to give informed consent were included in this multicentric, post marketing surveillance study. At the initial visit, a detailed medical history, symptomatic evaluation and gynecological evaluation was carried out in all the patients. Out of the 1,000 patients, 342 had dysmenorrhea, 416 had menorrhagia and 242 patients had oligomenorrhea. Each patient was administered Samshee Syrup at a dose of 15 ml, twice-daily for a period of three months. Results of the study were statistically analyzed. At the end of treatment in 342 patients suffering from dysmenorrhea, 18 had slight abdominal pain and 324 of them had total absence of symptoms. In patients with menorrhagia, significant reduction was observed in the mean score of duration of menstruation, quantity of blood loss, character of blood flow changed from clot to flow after treatment with *Samshee* Syrup. At the end of three months of treatment, 236 patients had normal menstruation, normal duration and character of blood flow was normal in oligomenorrhea. No significant complication or adverse effects of drug administration was noticed during the study. The results of the present study showing clinical benefit of *Samshee* Syrup appear promising in the management of menstrual irregularities.

Keywords: *Samshee* Syrup, Dysmenorrhea, Menorrhagia, Oligomenorrhea,

INTRODUCTION

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Menstrual cycle is normal physiological process that is characterized by periodic and cyclic shedding of progestetional endometrium accompanied by loss of blood which is a vital sign and a powerful tool for the assessment of normal development and the exclusion of pathological conditions in woman[1]. Range of menstrual disturbances occurs due to disruption of a regulated sequence of molecular, cellular and vascular events. Age of menarche varies globally,

especially in the less developed countries. The age of menarche is determined by general health, genetic, socio-economic and nutritional factors. The median menstrual cycle length is 28 ± 3 days and the average duration of menstrual flow is 5 ± 2 days with a blood loss averaging 130 ml.[2] This cyclical process is regulated in part by complex changes in the concentrations of five hormones: gonadotropin-releasing hormone (GnRH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol and progesterone. Menstrual cycles are often irregular through adolescence, particularly the interval from the first to the second cycle. Early menstrual life is characterized by anovulatory cycles and the ovulation frequency is related to time since menarche as well as age at menarche. Menstrual irregularities can be caused by disturbance of the central GnRH pulse generator as well as by significant weight loss, strenuous exercise, substantial changes in sleeping or eating habits and severe stressors. Chronic diseases, such as poorly-controlled diabetes mellitus, genetic and congenital conditions, such as Turner syndrome and other forms of gonadal dysgenesis can also be a cause.[3]

Menorrhagia is the medical term for menstrual periods with prolonged bleeding i.e longer than seven days or abnormally heavy i.e amount exceeding 80 ml from normal secretory endometrium after normal ovulation.[4] It affects 10-30% of the menstruating women and may occur at some time during the perimenopause in upto 50% of the women. Metrorrhagia is uterine bleeding at irregular intervals, particularly between the expected menstrual periods. The bleeding is usually light, although it can range from staining to hemorrhage. Polymenorrhea is the medical term for cycles with intervals of 21 days or fewer. Oligomenorrhea is an abnormally infrequent menstrual bleeding characterized by menstrual periods occurring at intervals of greater than 35 days. When menstrual bleeding does occur, it can be profuse and prolonged or decreased in amount. Primary amenorrhea should be considered for any adolescent who has not reached menarche by the age of 15 years or has not done so within three years of thelarche. There are three types of dysmenorrhea: Primary, secondary and membranous. Primary dysmenorrhea is characterized by the absence of an organic etiology, while secondary dysmenorrhea is associated with specific diseases or disorders, such as endometriosis, ovarian cysts, pelvic inflammatory disease, adenomyosis, cervical stenosis, fibroid polyps and possibly uterine displacement with fixation. Membranous dysmenorrheal (uterine cast) is rare and causes intense cramping pain due to the passage of the intact endometrial cast through an undilated cervix.[5] In women with dysmenorrhea, the concentrations of prostaglandins (PG), both PGF2α and PGE2, in menstrual blood are significantly increased compared to those in women without dysmenorrhea as a result of endometrial synthesis and release of PGs.[6,7] It is, therefore, logical that in the clinical management of both primary and secondary dysmenorrhea, nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit PG synthesis, offer a valid treatment. However, the treatment is less effective if the intake of the drug is delayed until the pain is more severe. Also side effects can occur, especially in women with asthma and allergic disorders and peptic ulcers.[8] Oral contraceptives (OCs) are still used very often as treatment, especially in young women who also require contraception. They reduce uterine contractility, induce endometrial atrophy and reduce endometrial PG concentrations. But, side effects and potential of adverse drug reactions may limit their use in some women. Other treatments (e.g., danazol, GnRH agonists) have either too many side effects, are too invasive (e.g., surgical methods), or are ineffective for the treatment of an accompanying disorder, and cannot, therefore, be considered for routine treatment of dysmenorrhea. Samshee Syrup is a polyherbal formulation and various clinical studies have observed the beneficial effect in the management of uterine disorders. This study was planned to evaluate the efficacy and safety Samshee Syrup in menstrual irregularities.

Aim and Objectives of the Study

1. To evaluate the clinical efficacy of Samshee Syrup in the management of menstrual irregularities.
2. To evaluate the safety of Samshee Syrup in the management of menstrual irregularities.

DRUG REVIEW

Samshee syrup includes ingredients which tones the uterus, each 10 ml of it contains aqueous extract of Ashok (500mg), Lodra (350mg), *Shatavari* (160mg), *Daruharidra* (160mg), *Palashpushpa* (160mg), *Vidarikand* (160mg), *Manjakani* (160mg), *Dashamula* (900mg), *Jirak* (100mg) and Sodium Benzoate (0.1%). It is prepared as authentic method mentioned for the preparation of syrup in SKM Herboceuticals (A GMP and ISO 9001:2008 Certified Company), Sonepat, Haryana and Marketed by Samriddhi Herbal Industries, Farrukhabad, UP.

MATERIAL AND METHODS

The present study was open clinical trial on 1000 patients which were properly diagnosed with menstrual irregularities like Dysmenorrhea, Menorrhagia and Oligomenorrhea. The study was a multicentric, post marketing surveillance study. The study was conducted in accordance with regulatory standards of good clinical practice.

Study Design:

Each patient was administered Samshee Syrup at a dose of 15 ml, twice-daily for a period of three months. All patients were followed up every month till the end of treatment. Symptomatic evaluation and clinical examination was done. If any adverse events (AEs) found, were recorded.

Before starting the trial a detailed medical history, symptomatic evaluation and gynecological evaluation was carried out in all the patients. Out of the 1000 patients, 342 had dysmenorrhea, 416 had menorrhagia and 242 patients had oligomenorrhea (Table 1). Most of the patients with oligomenorrhea had scanty and irregular menstruation. The protocol of the study was as per the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines and the patients were free to withdraw from the study if they so desired. During intervention no other medication was allowed for these patients. Patient was followed up for 6 months after the study period.

Inclusion criteria:

- Female patients aged between 18-45 years.
- Female patients with menstrual irregularities like Dysmenorrhea, Menorrhagia and Oligomenorrhea.
- Patients those who were given written informed consent, were only included.

Exclusion criteria:

- Women of childbearing age, who were not willing to follow the adequate contraceptive method and lactating women were also excluded from the trial.
- Patients with history of recent delivery or abortion
- Patients who had systemic disorders like Diabetes Mellitus, Hypertension, Renal disease, Tuberculosis, Hepatic disease, Coagulation disorder etc.
- Patients who had any disorder of the reproductive tract, especially any benign or malignant growth, extensive cervical erosion, cervical polyps, endometriosis, tubercular endometritis and acute infective disorder.
- Patients who refused to give informed consent.

Assessment Parameters:

For Dysmenorrhea: Painful menstruation, associated symptoms like Bloating, Loose motions, Fever, Headache, Vomiting and Nausea.

For Menorrhagia: Duration of Menstruation, Quantity of blood loss, Character of Blood flow and consistency of blood.

For Oligomenorrhea: Menstrual irregularities (Interval between periods).

Investigations:

Complete blood count and ultrasound scans were done for all patients before and after treatment. Hormonal levels of the patients and other investigations were done, whenever necessary.

STATISTICAL ANALYSIS

Results were analyzed statistically by repeated measures of ANOVA and Friedman's test followed by Dunnett's multiple comparison tests for evaluation of symptomatic scores. The

minimum level of significance was fixed at 95% limit and a 2-sided p value of <0.05 was considered significant. Statistical analysis was performed using GraphPad Prism Software, Version 4.03.

OBSERVATIONS OF THE STUDY:

Table 1: Distribution of Patients with Various Clinical Diagnosis of Menstrual Abnormalities (n = 1,000)

Clinical diagnosis	No. of patients	Age(years)
Dysmenorrhea	342	22.60±4.42
Menorrhagia	416	30.22±6.14
Oligomenorrhea	242	24.00±7.24

The mean age of the patients in dysmenorrhea group was 22.60 ± 4.42; it was 30.22 ± 6.14 in menorrhagia group and 24.00 ± 7.24 in the oligomenorrhea.

Adverse Events

All Adverse events (AE), either reported or observed by patients, were recorded with information about severity, date of onset, duration and action taken regarding the trial drug. Relation of Adverse events to the study medication was predefined as 'Unrelated' (follows a reasonable temporal sequence from the administration of the drug), 'Possible' (follows a known response pattern to the suspected drug, but could have been produced by the patient's clinical state or other modes of therapy administered to the patient) and 'Probable' (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient's clinical state). Patients were allowed to voluntarily withdraw from the study, if they so desired without assigning reasons. Efforts were made to ascertain the reason for dropout in such patients. Noncompliance (defined as failure to take <80% of the medication) was not regarded as treatment failure and reasons for noncompliance were noted.

RESULTS OF THE STUDY

After 3 months of clinical study results were assessed on the basis of changes in symptoms recorded. One thousand patients were enrolled into the trial and all the patients completed the study.

Effect of *Samshee* Syrup in Dysmenorrhea

Three hundred Forty-two patients presented with clinical diagnosis of dysmenorrhea. The results of the study are shown in Table 2. A partial absence of symptoms was observed in 130 patients at second month and complete absence of symptoms in 12 patients. At the end of treatment, 18 had slight abdominal pain and 324 of them had total absence of symptoms ($p < 0.001$). No clinically significant adverse drug reactions were reported except for two patients had nausea and it did not require additional treatment or withdrawal of drug.

Table 2: Effect of *Samshee* on Symptomatic Relief in Patients with Dysmenorrhea (n = 342)

Menstrual Irregularity	Duration of Treatment	No. of cases showing recovery		
		Complete	Partial	Persistent
Dysmenorrhea	1st month	0	16	326
	2nd month	12	130	200
	3rd month	324	18	0

*$p < 0.001$ as compared to at entry values.

Effect of Samshee Syrup in Menorrhagia

The clinical diagnosis of menorrhagia was made in 416 patients. The results of the study are shown in Table 3. Treatment with *Samshee* therapy showed a significant ($p < 0.001$) reduction in the mean score of duration of menstruation,

quantity of blood loss (number of pads changed per day) and blood flow loss (graded as profuse to normal) at the end of treatment. Reduction in the symptoms was evident from the second month of therapy itself. Duration of menstruation was 11.80 ± 0.32at baseline and significantly reduced to 6.72 ± 0.46 ($p < 0.05$) and 5.18 ± 0.72 ($p < 0.001$) at the end of second and third months of treatment, respectively. There was a significant change in the mean score of character of blood flow from clot or flow at the end of 3-month treatment with *Samshee* ($p < 0.05$). No adverse drug reactions were reported except for one patient who had symptoms of gaseous distension at third month of treatment and it did not require additional treatment or drug withdrawal.

Effect of Samshee Syrup in Oligomenorrhea

Two hundred forty patients had a clinical diagnosis of oligomenorrhea. The results of the study are shown in

Table 3: Effect of *Samshee* on Symptomatic Relief in Patients with Menorrhagia (n = 416)

Parameter	Duration of treatment	Score	Significance
Duration of menstruation(No. of days)	Baseline	11.80 ± 0.32	-
	1st month	9.60 ± 0.72	NS
	2nd month	6.72 ± 0.46	$p < 0.05$
	3rd month	5.18 ± 0.72	$p < 0.001$
Quantity of blood loss (No. of pads changed/day)	Baseline	6.46 ± 0.12	-
	1st month	5.14 ± 0.20	NS
	2nd month	3.82 ± 0.12	$p < 0.05$
	3rd month	3.18 ± 0.36	$p < 0.001$
Character of Blood flow (normal to profuse)	Baseline	1.82 ± 0.12	-
	1st month	1.34 ± 0.14	NS
	2nd month	0.96 ± 0.16	NS
	3rd month	0.74 ± 0.12	$p < 0.001$
Consistency of blood (with Clot or without clot)	Baseline	1.24 ± 0.12	-
	1st month	0.92 ± 0.18	NS
	2nd month	0.68 ± 0.16	NS
	3rd month	0.56 ± 0.12	$p < 0.05$

Statistical analysis was carried out using repeated ANOVA test and Friedman test followed by Dunnett's multiple comparison tests. NS: Not significant.

Table 4: Effect of *Samshee* on Symptomatic Relief in Patients with Oligomenorrhea (n = 242)

Menstrual Irregularity	Duration of treatment	No. of showing recovery		
		Complete	partial	persistant
Oligomenorrhea	1st month	20	32	190
	2nd month	148	80	14
	3rd month	236	6	0

*$p < 0.001$ as compared to at entry values.

Table 4: At the end of one month, a partial response was seen in 32 patients, they had moderate flow. In 20 patients there was total restoration of normal menstrual flow. At the end of two months, 148 patients had normal flow and 80 patients had moderate flow. At the end of three months, 236 patients had normal menstruation, normal duration and flow with significance of $p < 0.001$ as compared to at entry values. No adverse drug reactions were reported.

DISCUSSION

An extensive review of literature on herbal formulations has provided a list of natural remedies for symptoms related to hormonal and physiological imbalances. Several plants are known to be effective in treating hypogonadism, irregular menses, amenorrhea and other menstrual problems.[9] *Samshee* Syrup is a polyherbal formulation that comprises extracts of *Saraca indica, Symplocos racemosa, Asparagus racemosus, Withania somnifera, Berberis aristata, Butea frondosa, Pueraria tuberosa, Quercus infectoria, Dashamoola, Cuminum cyminum,* Sodium benzoate (preservative). The beneficial results observed in this study could be due to synergistic actions of these herbs in *Samshee* Syrup.

S. indica is rich in tannins, and glycosides, which make it useful in different uterine affections like menorrhagia, dysmenorrhea, postpartum hemorrhage and leukorrhea.[10] Trials have shown that the bark extract of *S. racemosa* reduces the frequency and intensity of the contractions in both pregnant and non pregnant uteri, suggesting its beneficial effect in menstrual irregularities.[11] It is also used in different gynecological problems like menorrhagia, frequent abortions, reduced libido, leukorrhea and vaginal ulcerations.[12] Trials have also suggested its role in renormalizing FSH, LH levels required for women well-being.[13]

Use of *A. racemosus* has been reported in menorrhagia, and threatened abortion.[12] The extract blocks the uterine contraction and spontaneous motility and may also block the pitocin sensitive receptors. This action suggests its use as uterine sedative and in different menstrual problems like dysmenorrhea.[14] glyco-sides also called as with anoloids and sitoindosides and extract of *withania somnifera* has analgesic, mildly sedative, anti –inflammatory and anabolic activities. *Berberis aristata, Butea frondosa Pueraria tuberosa, Quercus infectoria,* has antiinflammatory, analgesic and spasmolytic activities, which are helpful in managing various painful menstrual conditions; it regularizes the menstrual flow.[15] central depressant and vasodilator activities, all of which are of help in premenstrual syndrome, and other painful menstrual conditions.[16,17.]

Dashamoola is an aqueous extract of a combination of 10 plant roots known to be clinically beneficial in various disorders, which may be helpful in variety of conditions related to menstruation.[18] Herbs included in *Dashamoola* like *Clerodendrum phlomidis* and *Premna integrifolia* have tonic and anti-inflammatory activities, which in turn improve the quality-of-life.[19]

CONCLUSION

The results of this multicentric, post marketing surveillance 3-month study show that the clinical benefits of *Samshee* Syrup appear beneficial in the management of menstrual irregularities. In menorrhagia, significant reduction was observed in the mean score of duration of menstruation, quantity of blood loss, blood flow loss and character of blood flow changed from clot to flow after treatment with *Samshee* Syrup. Similarly, patients with oligomenorrhea had normal menstruation, normal duration and flow. No clinically significant adverse drug reactions were reported except for nausea and gaseous distension, which did not require additional treatment or the withdrawal of drug. The beneficial results observed in this study therefore could be due to synergistic actions of the herbs present in Samshee Syrup.

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Figure I: Showing Samshee Syrup Packing

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