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"CLINICAL EVALUATION OF STANDARDIZED FENUGREEK SEED EXTRACT AS FUROSTENOLIC SAPONINS (FUROCYST) IN POLYCYSTIC OVARY SYNDOME PATIENTS."

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ABSTRACT

Background: Polycystic Ovarian Syndrome (PCOS) is one of the most common endocrine conditions affecting women of reproductive age Group with prevalence of approximately 7-10% worldwide. **Objective:** The objectives of the study were to find out the effect of Standardized Fenugreek Seed extract as Furostenolic Saponins (FUROCYST) on reduction in ovarian volume and the number of ovarian cysts. **Method:** An open labeled, Multicentric, single-arm and non-comparative study was planned on 50 female patients suffering from PCOS. Patients were enrolled as per inclusion i.e. Premenopausal women between 18-45 years of age, BMI less than 42, diagnosed with PCOS, with adequate hepatic, renal and haematological functions. Patients willing to give informed consent in writing Patients with Hysterectomy/Congenital adrenal Hyperplasia/Cushing's Syndrome/Androgen secreting tumour/ Thyroid-dysfunction/ Hypo-gonadism were excluded. Women were allocated to receive Furocyst and were assesed on parameters of USG & hormonal on second day of cycle before and every 4 weeks within treatment period of 12 weeks **Result**: After treatment for 3 months with Furocyst caused significant reduction in ovary Volume (p 0.000), 46% of study population showed reduction in cyst size who had bigger cyst, 36% study population showed complete dissolution of cyst who had small cyst, 12% study population got pregnent and 71% patients reported regular menstrual cycle on completion of treatment and LH: FSH ratio was also reduced to normal. Overall 94% of patients reported positively or got benefitted from Standarized Fenugreek seed extract (FUROCYST) dosing. No changes were observed in

LFT, KFT and Haemogram level. **Conclusions:** Present Study indicates that Standardized Fenugreek seed extract as Furostenolic Saponins (FUROCYST) is very effective and safe in the management of Poly Cystic Ovary Syndrome in women of reproductive age Group.

KEYWORDS:

INTRODUCTION

Polycystic ovary syndrome is considered as clinical and public health consequence involving increase in number of cysts in women at reproductive age. These cysts are under-developed sacs in which eggs are developed. In PCOS, these sacs are unable to release an egg which means ovulation doesn't take place.[1, 2]

The estimated 5-10% prevalence of PCOS is reported in women of reproductive age. A study from Spain also reported that 28.3% prevalence rate of PCOS is among 113 overweight or obese women who were referred to an endocrinology clinic for weight loss. This data was compared with a previously reported prevalence of 6.5% which suggests that the prevalence of PCOS might be markedly increasing with obesity.[3, 4]

PCOS impacts significantly on various hormonal cycles. With PCOS, luteinizing hormone (LH) levels become higher than follicle stimulating hormone (FSH) levels. Because of this increase in LH levels, the LH surge does not take place and ovulation doesn’t carry out which results in irregular menstrual cycle. The irregular menstrual period produces oligomenorrhea (few menstrual periods) or amenorrhea (no menstrual periods) and infertility due to irregular or lack of ovulation. PCOS also produces high levels of masculinizing hormones with symptoms of acne and hirsutism, hypermenorrhea involving heavy and prolonged menstrual periods and androgenic alopecia (increase hair thinning and diffused hair loss). The other metabolic syndromes associated with PCOS are increased risk of type 2 diabetes, high cholesterol levels and obesity.[5]

These complications arise because of the genetically determined cause of the PCOS *i.e.* hyper- secretion of androgens from the ovary which favours excess luteinizing hormone (LH) secretion and insulin resistance. However, insulin resistance with or without a genetic mutation may be the initiator, followed by hyper-androgenism. Thus, insulin resistance is an important contributing factor to abnormal steroidogenesis in PCOS because hyper-insulinemia stimulates the pathway of insulin like growth factor-I (IGF-I) in theca cells of the

ovary by cross-reacting with the receptors of IGF. Stimulation of the ovarian theca cells increases the production of androgens (eg, testosterone, androstenedione) which in turn, blocks the down-regulation of androgens by LH surge and leads to the hyper-androgenic environment in the ovary. Because of a decreased level of FSH relative to LH, the ovarian granulosa cells cannot aromatize the androgens to estrogens, which lead to decreased estrogen levels and results in anovulation.[6, 7]

Treatments for PCOS are chosen based on woman's symptoms, age and future pregnancy plans which may include birth control pills to regulate menstruation, insulin-sensitizing medications, ovulation induction to treat infertility, androgen-blocking medications, topical anti-hair-growth medications, etc.[8]

Standardized fenugreek (*Trigonella foenum graecum)* seed extract (FUROCYST) plays an important role in the management of PCOS. FUROCYST improves glucose-tolerance and insulin-sensitivity, thereby promoting weight loss and moderation of androgen levels in the blood. Standardized fenugreek seeds extract (FUROCYST) contains a group of furostanolic saponins, derived from fenugreek seeds by an innovative process. It contains rich variety of saponins and flavonoids which have been known to lower the blood lipid levels and play valuable role in improving insulin sensitivity. Standardized fenugreek seeds extract (FUROCYST) is a dual mode insulin-sensitizer. In the presence of high fiber furostanolic saponins, cells become more sensitive to insulin & an increase in number of insulin receptor sites occurs. These receptor sites are responsive to insulin to stimulate the cells ability to burn glucose. This decrease in insulin resistance helps in the management of PCOS.[9]

Considering the beneficial effects of standardized fenugreek seed extract (FUROCYST), present study was conducted to evaluate the efficacy of standardized fenugreek seeds extract (FUROCYST) in patients with poly cystic ovary syndrome by assessing reduction in ovarian volume and decrease in the number of ovarian cysts.

METHODOLOGY

This was an open label**,** multi-centric, single arm and post-marketing study conducted in 50 female patients suffering from poly cystic ovary syndrome. The population taken for the 12 week study had age of 18 to 45 years. The subjects were screened for the enrolment on the basis of following inclusion & exclusion criteria.

Inclusion criteria

- The premenopausal women having age between 18-45 years.
- The patient having BMI less than 42.
- The patient diagnosed with PCOS.
- The patient having adequate hepatic, renal and haematological functions.
- Patient willing to give informed consent in writing.

Exclusion criteria

- Males
- Women with post menopausal.
- Women with hysterectomy.
- Patients with congenital adrenal hyperplasia.
- Patients suffering from Cushing's syndrome.
- Patients diagnosed with androgen secreting tumor.
- Patients with thyroid dysfunction (T3, T4 level is higher than that in normal women of reproductive age).
- Patients with Hypogonadism (central origin of ovarian dysfunction).
- Pregnant or lactating mothers.

The subjects were screened for the clinical study on the basis of above inclusion/exclusion criteria. The allocation of the product was done after screening. Investigational product was consumed by the patients for three months during which capsules of Furocyst (500mg BD) were given orally to the enrolled subjects. No instructions were issued to enrolled subjects to change their routine physical activity schedules while treatment with investigational product.

Efficacy evaluation

The following listed investigations were done (after intervals of 4 weeks) with each enrolled subject to assess the efficacy of Furocyst:

1. At baseline
2. Clinical examination
3. Laboratory evaluations

- Sonographic scan
- Luteinizing hormone levels
- Follicle stimulating hormone levels
- LH/FSH ratio

- Waist circumference
- Triglycerides level
- HDL levels
- Fasting glucose level
- Liver function tests (AST, ALT, ALP)
- Renal function tests (Urea and Creatinine)
- Haematogram (Using routine methods)

Safety evaluation

Safety was assessed as each follow-up visit and following laboratory parameters were evaluated:

- Haemoglobin level
- Total leukocyte count
- Serum glutamic oxaloacetic transaminase (SGOT) activity
- Serum glutamic pyruvic transaminase (SGPT) activity
- Alkaline phosphatase (ALP) activity
- Blood urea nitrogen (BUN) level
- Serum creatinine level
- Serum triglyceride level
- HDL cholesterol level

RESULTS

The mean age of the study population was 24.06 ± 5.35 years. The average height, weight, and waist size of study population were 157.01 cm, 58.98 Kg and 54.42 cm, respectively. Mean systolic blood pressure, diastolic blood pressure and pulse rate were 116.78 mmHg, 75.32 mmHg, and 76.49 per min, respectively. The average BMI of the study population was 23.88. 62% of the patients had BMI ≤25 and 38 % of the patient had BMI more than 25.

Efficacy data

1. Effect on the pregnancy

A significant percent of population got pregnant during the treatment. It was observed that 12% of the study population got pregnant during which three pregnancies were observed one each after 30 days, 39 days, 70 days & 84 days of the treatment.

2. Effect on ovary volume

As compared to baseline data, subjects showed significant reduction in ovary volume at the end of the study. Left ovary volume was decreased by 17.82% and right ovary volume was decreased by 28.25% as shown in table 1.

Table 1: Change in the ovary volume (cm^3).

Parameters		Mean	Standard deviation	% Decrease	t-value	p-value
Pair 1	Left ovary volume Baseline	12.23	5.13		2.013	0.101
	Left ovary volume Completion of treatment	10.05	4.19	17.82		
Pair 2	Right ovary volume Baseline	14.00	6.27		4.443	0.000**
	Right ovary volume Completion of treatment	10.00	4.19	28.57		

3. Effect on the cysts

Enrolled subjects showed reduction in cyst size. Out of total 50 subjects, 46% of the subjects showed reduced cyst size and 36% of the subjects showed complete dissolution of the cysts at the end of the study. A total of 6 patients got pregnant during the study.

4. Effect on the menstrual cycle

At the time of enrolment, most of the patients had prolonged menstrual cycle (81%) and few of them had irregular cycle (10%). Rest of the patients (10%) had primary infertilities. There was significant improvement in menstrual cycle with consumption of the standardized fenugreek seed extract (FUROCYST). On completion of the last visit, 71% of the patients showed regular cycles, 19% patients reported prolonged cycles and approx. 10% reported primary infertility. None of the patient reported irregular cycle at the end of the standardized fenugreek extract (FUROCYST) dosing schedule.

5. Effect on luteinizing hormone

A significant increase in luteinizing hormone levels was observed on completion of the treatment as compared to baseline levels as given below in table 2.

Table 2: Effect on luteinizing hormone (LH) (mIU/mL).

		Mean	Standard deviation	t-value	Sig.
Pair 1	LH baseline	10.33	7.246	1.189	0.241ns
	LH 1st	8.98	4.929		
Pair 2	LH baseline	10.33	7.246	0.223	0.825ns
	LH 2nd	10.64	7.717		
Pair 3	LH baseline	10.36	7.327	2.069	0.045*
	LH 3rd	13.93	10.144		

6. Effect on follicular stimulating hormone

A significant increase in follicular stimulating hormone levels was observed after 8 weeks and on completion of the treatment as compared to baseline value as given below in table 3.

Table 3: Effect on follicle stimulating hormone (FSH) (mIU/mL).

		Mean	Standard deviation	t-value	Sig.
Pair 1	**FSH baseline**	5.36	1.734	0.473	0.638ns
	FSH 1st	5.49	1.817		
Pair 2	**FSH baseline**	5.36	1.734	2.685	0.010*
	FSH 2nd	6.38	2.367		
Pair 3	**FSH baseline**	5.36	1.753	5.767	0.000**
	FSH 3rd	8.36	3.335		

7. LH/FSH ratio

A reduction in LH/FSH ratio was observed on completion of treatment, which was statistically non-significant. It has been shown in following table 4.

Table 4: Effect on LH/FSH ratio.

		Mean	Standard deviation	t-value	Sig.
Pair 1	**LH/FSH baseline**	3.16	7.983	1.211	0.232ns
	LH/FSH 1st	1.67	1.000		
Pair 2	**LH/FSH baseline**	3.16	7.983	1.300	0.200ns
	LH/FSH 2nd	1.56	0.918		
Pair 3	**LH/FSH baseline**	3.18	8.073	1.291	0.204ns
	LH/FSH 3rd	1.61	0.813		

The overall percent of the study population responding positively to standardized fenugreek extract (FUROCYST) comes out to be 94%. The overall response given by above given efficacy parameters is shown in Figure 1.

Safety data

The response of standardized fenugreek seeds extract (FUROCYST) by patients towards safety parameters is shown below in table 5 and it has been evaluated that significant change was not observed in serum liver function tests and renal function tests. Hemogram was also not changed after the completion of treatment.

Table 5: Response towards safety parameters.

Safety Parameter		Mean	Standard deviation	t-value	Sig.
Hb (g %)	Baseline	12.37	1.047	5.442	.000**
	On completion	13.00	0.926		
TLC (x 10^3/µL)	Baseline	7.37	2.430	1.123	0.268ns
	On completion	8.77	7.901		
SGOT (U/L)	Baseline	30.50	19.673	2.016	0.050*
	On completion	34.18	22.303		
SGPT (U/L)	Baseline	50.50	24.720	1.151	0.256ns
	On completion	53.20	20.946		
ALP (U/L)	Baseline	116.41	27.321	1.816	0.076ns
	On completion	110.57	20.172		
Urea BUN (mg/dL)	Baseline	9.23	3.139	0.237	0.814ns
	On completion	9.32	2.631		
Creatinine (mg/dL)	Baseline	0.909	0.290	0.298	0.767ns
	On completion	0.886	0.386		
Fasting glucose (mg/dL)	Baseline	90.59	14.498	1.776	0.083ns
	On completion	92.48	13.668		
Triglycerides (mg/dL)	Baseline	108.84	48.266	1.505	140ns
	On completion	122.45	52.826		
HDL cholesterol (mg/dL)	At baseline	47.80	13.680	0.188	0.852ns
	On completion	47.45	9.240		

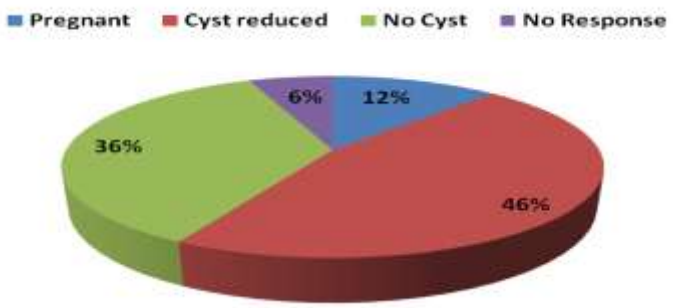

Figure 1: Overall patient response on completion of treatment.

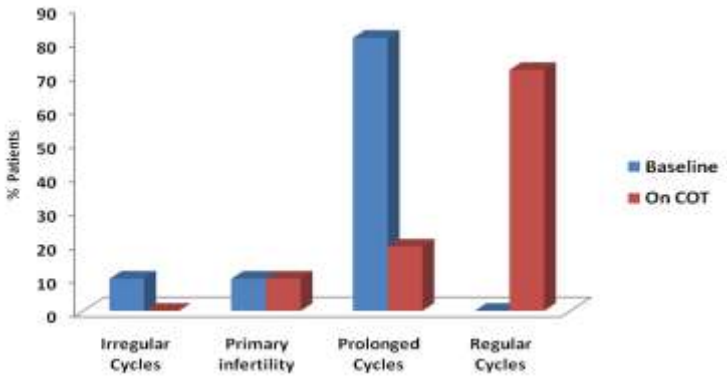

Figure 2: Effect on the menstrual cycle on completion of treatment.

DISCUSSION

Insulin acts directly on ovary, alone or along with luteinizing hormone and enhances ovarian androgen production. It can also increase androgen levels indirectly by reducing hepatic production of sex hormone binding globulin (SHBG) and insulin-like growth factor binding protein-1 (IGFBP-1) and thus elevates free testosterone levels and free IGF-I & II levels. Excess androgen impairs folliculogenesis resulting in menstrual disturbance and development of multiple cysts in the ovary. Insulin resistance increases the risk of development of metabolic disorders including diabetes, hypertension, dyslipidemia and cardiovascular events in women. Hyper secretion of the androgens from the ovary is proposed to be the primary event that leads to the development of PCOS by favouring excess luteinising hormone (LH) secretion and insulin resistance.[10]

FUROCYST regulates the effect of insulin on ovarian androgen biosynthesis, theca cell proliferation and endometrial growth. It improves insulin-mediated glucose disposal in women with PCOS. The presence of insulin-sensitizing compounds *i.e.* saponins and flavonoids in FUROCYST improves insulin sensitivity. These compounds inhibit the ability of insulin to cross-react with the receptors of IGF and blocks the pathway of insulin like growth factor-I (IGF-I) in theca cells of the ovary. This causes the down-regulation of the ovarian theca cells and as a result, decreases the production of androgens (eg, testosterone, androstenedione). This, in turn, causes the normal LH surge. Because of the normal levels of LH in the ovaries, the ovarian granulosa cells aromatize the androgens to produce estrogens, which lead to increased estrogen levels and results in ovulation. This leads to the lackage of androgens in the ovary. Thus, the circulating androgens level is regulated by FUROCYST.[11]

FUROCYST causes the regularity in the menstrual period in the study subjects. This was achieved by making normal LH surge which further signals the ovaries to cause ovulation and release the eggs. This might be regulating ovarian androgen production leading to disappearance or decrease in size and number of cysts.[12, 13]

Increase in LH/FSH ratio has been reported in various studies conducted in PCOS patients. Because of a decreased level of follicle-stimulating hormone (FSH) relative to LH, the ovarian granulosa cells cannot aromatize the androgens to estrogens, which lead to decreased estrogen levels and consequent anovulation. In the present study, a significant decrease in LH/FSH ratio was observed, suggesting the regulated effect of standardized fenugreek seeds extract (FUROCYST).[14]

These findings from the present study depicts that the standardized fenugreek seed extract (FUROCYST) can effectively treat patients with PCOS as observed by decrease in ovary volume and reduction in cyst size. This, in turn, positively contributes towards the regularity in menstrual cycles. Thus, it can be concluded from the present study that standardized fenugreek seed extract (FUROCYST) is effective and safe in the treatment of Poly Cystic Ovary Syndrome in women.

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