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Clinical Evaluation of Furostanolic Saponins and Flavanoids in Polycystic Ovarian Syndrome (Pcos) Patients

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Abstract:

PCOS affects approximately 4-12% women of reproductive age. For such a common syndrome, there is surprisingly a lack of well-defined diagnostic criteria, making it confusing to doctors. Furthermore, the symptoms of PCOS range from physical to psychological and can also lead to infertility. It was thus, pertinent to deliberate upon more ways of managing PCOS and so the objective of the study was to find out the effect of Standardized Fenugreek seed Extract on reduction in ovarian volume and the number of ovarian cysts.

An open labeled, single armed, single-centric and noncomparative study on 107 female patients suffering from PCOS was conducted using a novel fenugreek seed extract for a period of 12 weeks to determine its efficacy in reduction of ovary volume and number of ovarian cysts.

On completion of the study, significant decrease was noticed in both the ovaries' volume (p-value 0.0001). More than 65% of the patients showed reduction in cyst size in both left & right ovaries. 15 patients got pregnant by the end of the study and HOMA Index was reduced in 75.67% of the study population. 79.5% of the study population had regular menstrual cycles at the completion of the study and prolactin levels were significantly reduced. Hirsutism score was significantly reduced (p=0.002) at the end of 12 weeks of treatment. No changes were observed on LFT, KFT & Haemogram level.

The fenugreek seeds extract was proven to be safe and effective in treating PCOS in women of reproductive age by reducing the cyst volume in both ovaries as well as cyst sizes.

1. Introduction

Polycystic ovary syndrome (PCOS) is an ovarian disorder, on the rise. It involves development of multiple cysts, whether small or large, in the ovaries of affecting females. These cysts start affecting the ovarian function of female reproductive system. PCOS targets the primary functions of female reproductive tract, which results in **[1]**:

- Infertility

- Disturbed menstrual cycle
- Hirsutism
- Unstable hormonal profile
- Increased risk of type 2 diabetes
- Thyroid
- Hyperlipidemia, etc.

These major outcomes of PCOS are due to the hormonal disturbance inside body. As the androgen hormone starts producing in excess amount inside ovaries, they play a major role in follicle development and growth. These follicles are in fluid lump form and detected clearly in ultrasonographic scan of ovaries. When the growth of follicles is stopped by excess androgens, then, they take form of ovarian cysts with reduced cell death. This causes anovulation and thus, infertility as well as a disturbed menstrual cycle. It has been observed from the in-vitro studies that androgen levels are increased due to an increase in circulating LH levels and decrease in FSH levels. These results in imbalanced LH: FSH ratio **[2]**. It has been observed that increase in androgen levels and cyst development causes increase in body weight. This is the major reason that PCOS-affecting females start observing an increase in their body weight. Beside this, if a woman is obese, then, she is more prevalent to PCOS as obesity is a major contributor in PCOS. The increase in body weight and PCOS causes disturbance in insulin hormone and as more is the body weight; more will be the circulating insulin levels. Excess insulin levels further cause insulin resistance. Being a major cause of type 2 diabetes, PCOS-affecting females start experiencing increase in blood sugar levels, too. This whole process of obesity, PCOS, hyperandrogenism and insulin resistance converts to a cycle. One indication produces another and another indication promotes the previous indication to much higher level **[2, 3].** PCOS has been observed to have risen due to lifestyle changes and increase in obesity. Worldwide unhealthy eating habits of urban women have contributed to raise the incidence of PCOS. As India is taken into picture, there has been 30% rise in PCOS in Indian adolescent girls due to lifestyle changes. In U.S., there are total 80% women affected with PCOS from which around 11% of the females are of reproductive age and adolescent girls with PCOS are much higher than India i.e. 50%. If we consider marital status of females, it has been seen that 16.4% of married women and 24% of unmarried women suffers from PCOS **[4].** This prevalence of PCOS is increasing day-by-day. Many management strategies like lifestyle modifications and medications are applied to lower the risk of PCOS or to control such prevalence but the number is increasing progressively worldwide.

2. Investigational Product- Furocyst®

Fenugreek is an important condiment in India as well as in tolerance and insulin-sensitivity, thereby promoting weight loss and moderation of androgen levels in blood. Fenugreek seeds extract helps in PCOS management. Fenugreek is already known to promote excellent glucose metabolism in the body. It improves glucose-tolerance and insulin-sensitivity by targeting insulin receptor sites. The fenugreek seed extract-based Furocyst used in the present study contains bioactive components such as furostanolic saponins. These substances are known to lower blood lipid levels and play valuable role in insulin promotion, which further helps to reduce PCOS and its symptoms. The extract is a group of furostanolic saponins, derived from fenugreek seeds *(TRIGONELLA FOENUM GRAECUM) by* innovative process. It contains rich variety of saponins and flavonoids. Fenugreek seeds have been found to contain at least a dozen different saponins. All of these substances are known to lower blood lipid level and play valuable role in improving insulin sensitivity, which plays an important role in the management of the PCOS. Such efficacious action against PCOS has also been observed in the previous clinical as well as preclinical studies on Furocyst **[5].**

3. Aims and Objectives

The aim of the study was to evaluate the effect of Furocyst in patients suffering from PCOS. This effect was evaluated by considering following objectives:

3.1. Primary objective

- To evaluate decrease in ovarian volume
- To evaluate decrease in number of cysts and cyst size.

3.2. Secondary objective

- To determine safety of Furocyst in patients suffering from PCOS.

4. Materials and Methods

This was an open labeled, single armed, non-comparative and single centric study, which was carried out on Indian population suffering from PCOS. The study was carried out at King George's

Medical University situated at Lucknow, Uttar Pradesh in India. The patients with PCOS were screened on the basis of inclusion criteria and exclusion criteria and the eligible patients were enrolled afterwards. Laboratory analysis was done for each enrolled patient to generate baseline data and then, they were given investigational product (Furocyst), advised to be consumed as BD dosage for 12 weeks. Patients were instructed to visit hospital at the intervals of 4 weeks, 8 weeks and 12 weeks of IP consumption till 12 weeks for clinical and laboratory analysis. Key inclusion and exclusion criteria were as follows:

4.1. Inclusion Criteria

- Premenopausal women between 18-45 years of age and BMI less than 42.
- Diagnosed with PCOS by Rotterdam Criteria.
- Adequate hepatic, renal, cardiac and hematological functions.
- Patients willing to participate and give informed consent in writing for the study.
- Stable weight for last two months (Change of weight <3 kg).

4.2. Exclusion Criteria

- Male.
- Postmenopausal women.
- Women with hysterectomy.
- Hyperprolactinemia.
- Patients with congenital adrenal hyperplasia.
- Patients suffering from Cushing's syndrome.
- Acute or chronic Medical illness including Hepatic, Cardiac or renal insufficiency, COPD, Gastrointestinal disorders.
- Uncontrolled Hypertensive or known diabetics on drugs.
- Use of oral contraceptives or HRT for last three months.
- Smoking or drug addicts or with psychiatric illness.
- Patients diagnosed with androgen secreting tumors.
- Patients with thyroid dysfunction (T3, T4 level is higher than that in normal women of reproductive age).
- Patients with Hypo-gonadotropic and Hypogonadism (central origin of ovarian dysfunction).
- Pregnant or lactating mothers.

The subjects were screened for the clinical study on the basis of given inclusion and exclusion criteria. The investigational product was allotted after screening & enrolment of the study patients. The subjects were followed up after 4 weeks, 8 weeks and 12 weeks. Safety was assessed at each follow-up visit. Subjects complaining of significant symptoms following administration of investigational product were planned to be evaluated for objective parameters of adverse drug reactions. Investigational product was to be discontinued in case of any serious adverse drug reaction. 500 mg of investigational product capsules were decided to be given to the subjects in the form of BD dosage. This dose was chosen on the basis of toxicity study in animals as well as previous clinical studies on humans. Those studies proved the safety of investigational product in animals and humans. The efficacy of investigational product (Furocyst) in PCOS patients was evaluated by the laboratory investigations. The following investigations were done at baseline, follow-up month (4 weeks and 8 weeks) and end of the study (12 weeks) for efficacy analysis**.**

- Sonographic scan
- Hirsutism score
- Menstrual cycle
- Body weight
- BMI
- Height
- Blood pressure
- Waist Circumference
- LH
- FSH
- LH/FSH ratio
- TSH
- Prolactin
- Fasting insulin
- Fasting glucose
- HOMA index
- Free testosterone
- 2 hour GTT
- DHEAS

5. Results

This study enrolled only female patients suffering from PCOS and the average age of study population was 25.94 years. The average height of the study population was 153.3 cm and the average pulse rate of the study population was 74.10 per minute **(Figure 1).**

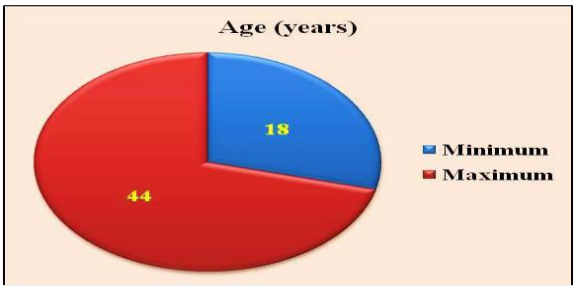

Figure 1: Efficacy Evaluation.

5.1. Ovary Volume

- Left Ovary Volume
- The mean left ovary volume of the study population decreased significantly from baseline levels of 12.36 cc to 9.42 cc on completion of the treatment (p-value 0.0001**). It was observed that the decrease in left ovary volume was up to 23.78% in the study population.
- The Left ovary volume was decreased in 90% of the patients.
- Right Ovary Volume
- The mean right ovary volume of the study population decreased significantly from baseline levels of 12.72 cc to 8.99 cc on completion of the treatment (p-value 0.0001**). The decrease in right ovary volume was up to 29.32% in the study population.
- Right ovary volume was decreased in 96.7% of subjects **(Figure 2).**

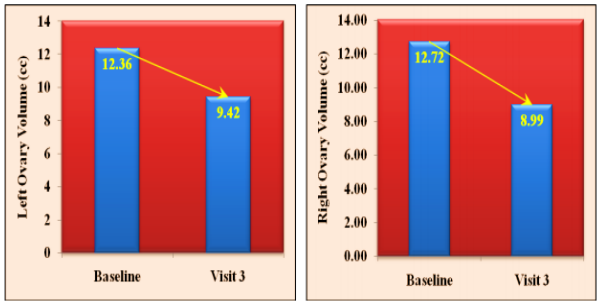

Figure 2: Mean ovary volume of the study population.

5.2. Cyst Size

- **In Right Ovaries**

The mean cyst size in the right ovaries of study population was decreased significantly from 6.35 mm at baseline to 3.71 mm on completion of the treatment.

The decrease in mean cyst size of right ovary was up to 41.57% in the study population till completion of the treatment.

- **In Left Ovaries**

The mean cyst size in the left ovaries of the study population was decreased significantly from 6.50 mm at baseline to 3.58 mm on completion of the treatment. The decrease in mean cyst size of left ovary was up to 44.92% in the study population till completion of the treatment **(Figure 3).**

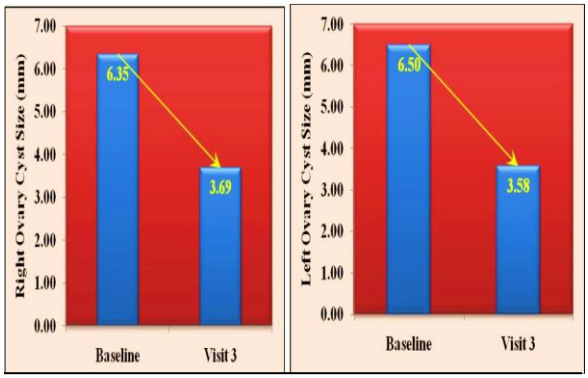

Figure 3: Mean cyst size of the study population.

More than 65% of the patient showed reduction in cyst size in both left & right ovaries.

Fifteen patients got pregnant during the study & complete dissolution of cysts was observed in 8 patients.

5.3. Menstrual Cycle

Delayed Menstrual Cycle At baseline, the menstrual cycle was observed to be delayed in 75.9% of the study population, which decreased to 52.9% of the study population after treatment with investigational product for 4 weeks (Visit 1). On Visit 2, the delayed menstrual cycle remained only in 33.3% of the study population, which was further decreased to only 12.3% of the study population after 12 weeks of the treatment with investigational product i.e. on completion of the treatment. Irregular Menstrual Cycle At baseline, irregular menstrual

cycle was observed in 23% of the study population which decreased to 18.8% of the study population after treatment with investigational product for 4 weeks (Visit 1). On Visit 2, only 12.8% of the study population had irregular menstrual cycle which was further decreased to only 8.2% of the study population on completion of the treatment. Regular Menstrual Cycle At baseline, menstrual cycle was regular in only 1.1% of the study population and after 4 weeks of the treatment with investigational product, regularity in menstrual cycle was observed in 28.2% of the study population. On Visit 2, the study population with regular menstrual cycle was increased to 53.8% which was further increased to 79.5% of the study population on completion of the treatment **(Figure 4)**.

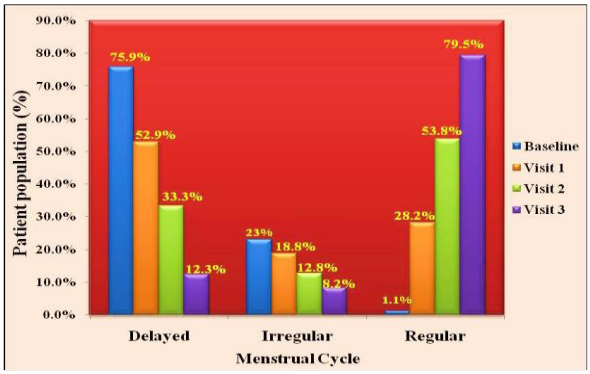

Figure 4: Study population with menstrual cycle.

5.4. Hirsutism Score

Hirsutism score was analyzed using wilcoxon signed rank tests. Hirsutism score was significantly reduced after 8 weeks (p = .038*) and 12 weeks (p= .002**) of the treatment.

5.5. Luteinizing Hormones (LH) Levels

The mean LH levels of the study population were 10.91 mIU/ml at baseline, which were significantly decreased to 8.62 mIU/ml after 4 weeks of the treatment with investigational product (p-value 0.001**). On Visit 2, the mean LH levels decreased significantly to 7.94 mIU/ml as compared to the baseline levels (p-value 0.002**). On Visit 3, the mean LH levels significantly decreased further to 6.23 mIU/ml on completion of the treatment as compared to the baseline levels (p-value 0.0001**) **(Figure 5).**

It was observed that the LH levels decreased up to 42.89% in the study population on completion of the treatment.

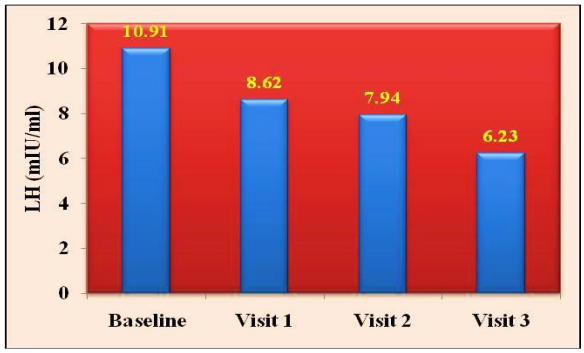

Figure 5: Mean LH Levels of the Study Population.

5.6. Follicle Stimulating Hormones (FSH) Levels

The mean FSH levels of the study population were 7.30 mIU/ml at baseline, which were non-significantly increased slightly to 7.34 mIU/ml after 4 weeks of the treatment with investigational product (p-value 0.918). On Visit 2, the mean FSH levels decreased to 7.21 mIU/ml. On Visit 3, the mean FSH levels significantly increased to 7.42 mIU/ml on completion of the treatment as compared to the baseline levels (p-value 0.0001**) **(Figure 6)**.

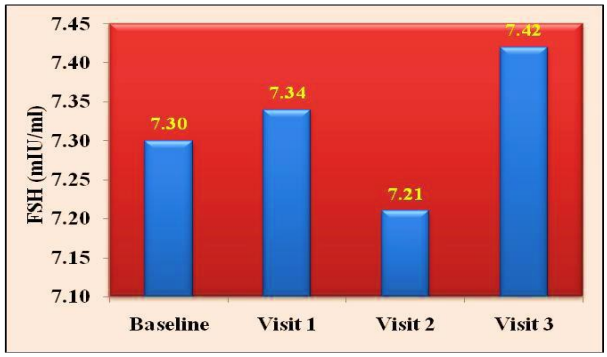

Figure 6: Mean FSH levels of the study population.

5.7. LH/FSH ratio

The mean LH/FSH ratio of the study population was 1.73 at baseline, which was decreased significantly to 1.28 on Visit 1 (p-value 0.001**). On Visit 2, the LH/FSH ratio decreased significantly to 1.18 as compared to the baseline levels (p-value 0.0001**), which was decreased significantly further to 0.90 on completion of the treatment (p-value 0.0001**) **(Figure 7)**.

It was observed that the LH/FSH ratio decreased up to 47.97% in the study population on completion of the treatment.

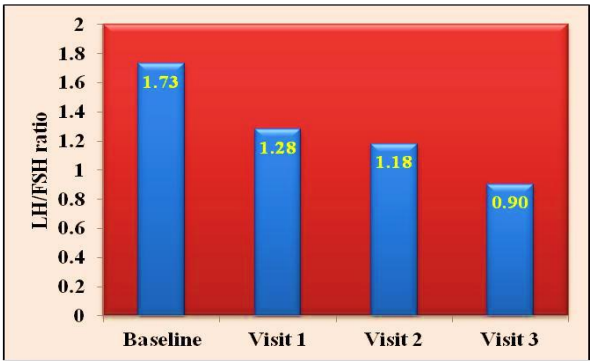

Figure 7: Mean LH/FSH ratio of the study population.

5.8. Thyroid Stimulating Hormone (TSH) Levels

There was non-significant change in mean TSH levels of the study population.

- **Prolactin Levels**

The mean prolactin levels at baseline were 13.40 ng/ml, which were decreased significantly to 10.50 ng/ml on completion of the treatment (p-value 0.0001**) **(Figure 8)**.

It was observed that the prolactin levels decreased up to 21.64% in the study population on completion of the treatment.

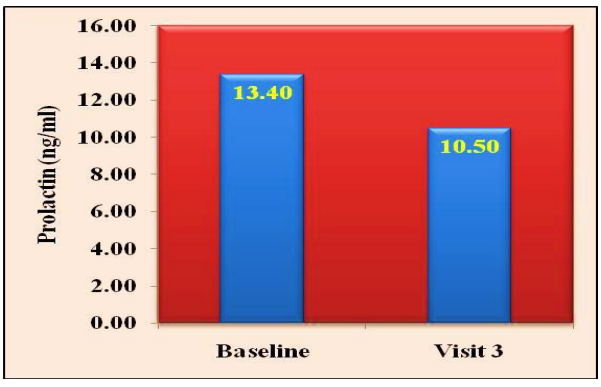

Figure 8: Mean prolactin levels of the study population.

5.9. Fasting insulin

The fasting insulin levels of the study population were 14.98 µU/ml at the baseline, which were significantly decreased to 8.22 µU/ml on completion of the treatment with investigational product (p-value 0.0001**).

These fasting insulin levels were decreased up to 45.12% in the study population on completion of the treatment **(Figure 9)**.

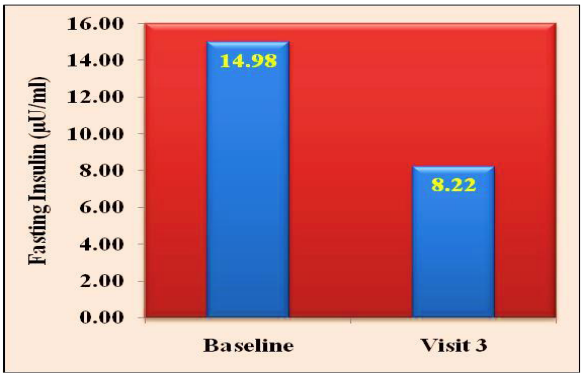

Figure 9: Mean fasting insulin levels of the study population.

5.10. HOMA Index

The mean HOMA index of the study population was 3.33 at baseline, which was decreased significantly to 1.78 on completion of the treatment with investigational product (p-value 0.0001**).

It was observed that the HOMA index was decreased up to 46.54% as compared to baseline value and the decrease was observed in 75.6% of the study population till the completion of the treatment **(Figure 10)**.

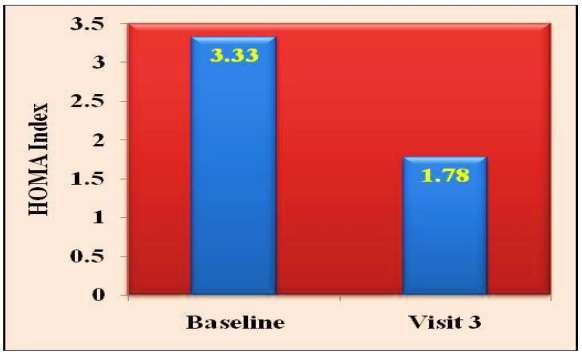

Figure 10: Mean HOMA index of the study population.

5.11. Dihydroepiandrosterone Sulphate (DHEAS)

The mean DHEAS levels of the study population were 164.56 µg/dl at baseline, which were decreased significantly to 157.97 µg/dl on completion of the treatment (p-value 0.006**) **(Figure 11)**.

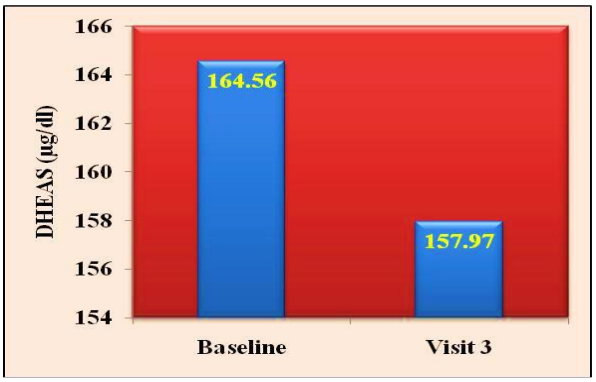

Figure 11: Mean DHEAS levels of the study population.

5.12. Safety Conclusion

On completion of the study, following safety conclusions were made:

- **Liver Function Test (LFT):** There was no significant change in liver function test of the study population except ALT/SGPT activity, which were slightly decreased significantly (p-value 0.007**) but remained under normal range on the completion of the treatment.
- **Renal function test (RFT):** There was non-significant change in urea levels but creatinine levels changed significantly on the completion of the treatment (p-value 0.032*) and remained under normal range.
- **Hemogram:** There was non-significant change in hemoglobin levels and differential leukocyte count (DLC) of the study population on the completion of the treatment. Total leukocyte count (TLC) of the study population significantly decreased slightly on completion of the treatment (p-value 0.002**).
- **Lipid profile:** There was non-significant change in lipid profile including cholesterol levels and triglyceride levels of the study population whereas HDL levels of the study population increased significantly on completion of the treatment (p-value 0.030*).

6. Discussion

Polycystic ovary syndrome is a hormonal disorder involving development of multiple cysts in the ovaries of female-reproductive system. These cysts develop majorly due to increase in androgen levels in the ovaries and increase in body weight. This ovarian disturbance causes development of cysts of varying sizes, change in menstrual cycle (irregular or delayed menstrual cycle), development of infertility, unwanted body hair growth, insulin resistance (type 2 diabetes), thyroid, acne formation, etc. **[6]**. PCOS has been observed to be developed mostly in the reproductive-age group of the female population**[7]**. In the present study, age group for the inclusion of PCOS patients was 18-45 years where minimum aged patients with PCOS were of 18 years and maximum aged patients were of 44 years. Effect of Furocyst was evaluated in these female patients with PCOS as given below:

6.1. Ovary Volume

As multiple cysts are formed in the ovaries of females due to hyperandrogenism, it leads to increase in the ovary volume too. As observed in the present study, the ovary volume of the study population was higher than normally expected at baseline, which came to be reduced significantly as the study population was treated with Furocyst.

6.2. Cyst size

Ovarian cyst is the collection of fluid surrounded by a very thin wall. The ovarian cyst formation is the confirmatory sign of PCOS as diagnosed by ultrasonography. It is formed due to hyperandrogenism as well as variation in LH and FSH profile. As the efficacy conclusions indicate, the LH and FSH profile has been maintained clearly with Furocyst treatment in PCOS affecting females. This might be the reason behind the management of the cyst formation in the ovaries. The cyst size in left ovaries and right ovaries was reduced significantly up to 44.92% and 41.57% respectively by the completion of the treatment with Furocyst.

6.3. Pregnancy

As the cyst size was reduced, 15 subjects got pregnant. Some got pregnant after 4 weeks of the treatment with Furocyst, some after 8 weeks and some females got pregnant after 12 weeks of the treatment with Furocyst.

6.4. Menstrual Cycle

Being completely dependent upon LH and FSH profile, menstrual cycle is highly affected under PCOS. But as the LH and FSH levels were significantly maintained by the treatment with Furocyst, menstrual cycle was also shown to be regularized in 79.5% of the study population till the completion of the treatment.

6.5. Hirsutism Scoring

The unwanted hair growth is the most depressing symptom of PCOS. It is a major contributor towards reducing the quality of life of females suffering from PCOS. Hirsutism involves the growth of dark hairs in the areas where women typically grow fine hair or no hair at all such as above the lip and on the chin, chest, abdomen and back **[7].** In the present study, extent of hirsutism was evaluated by Ferriman-Gallwey score which included the assignment of score from 0 to 6 according to the increase in severity of body hair growth. 0 score means no hair growth and 6 score means mostly severed hair growth from hirsutism. It was found that Furocyst caused reduction in body hair growth which was proved by decrease in the Ferriman-Gallwey score with the progress in treatment.

6.6. HOMA Index

Type 2 diabetes is very common complication associated with PCOS. The disturbance in hormonal profile in ovaries during PCOS also leads to the disturbance in one more hormone inside body known as insulin. As insulin is the sole hormone associated with balancing blood sugar levels, any disturbance in its biological activity could lead to disturbance in metabolising blood sugar. This results in rise in insulin inside blood which leads to insulin resistance causing type 2 diabetes. In the present study, the effect of Furocyst was also evaluated by measuring HOMA index which is a great indicator of insulin resistance. It was observed that HOMA index was reduced up to 46.54% in the study population. This effect of Furocyst might be due the action of its bioactive components i.e. furostanolic saponins on beta cell function. The insulin receptor sites become more sensitive in the presence of furostanolic saponins and flavonoids which increase the attachment of insulin to its receptors causing increase in flow of sugar from blood to cells for converting it into energy. This could be the mechanism for enhancing insulin sensitity and thus, reduction in HOMA index.

7. Conclusion

These efficacy parameters clearly indicate the beneficial effect of Furocyst in management of PCOS. Besides this, Furocyst was found to be safe in the patients as there was no abnormal change found in the safety parameters in the enrolled patients. These efficacy and safety evaluations signify that Furocyst can be used by the PCOS-affected patients as a natural supplement.

8. Funding

The study was funded by Chemical Resources, Panchkula, Haryana, India.

9. Consent to Publish

All authors have read, consented and approved the final manuscript for publication. This manuscript doesn't contain any individual person's data.

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