

# A herbal treatment approach for the management of clinical, hormonal and ultrasound parameters in reproductive age group women with polycystic ovarian syndrome: A randomized clinical trial

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**Abstract:** Around fifteen percent women of reproductive age have been effected by Polycystic Ovarian Syndrome (PCOS); a complicated disorder; and apparently there is no standard therapy available. Considering this lack, we design present work; for the assessment of a herbal medicine (Femitex-SP<sub>4</sub>) in managing PCOs. During 2016-17; this study was carried out at Abbasi Shaheed hospital, Karachi, Pakistan. A total of 150 patients aged between 18–44 years were included as per Rotterdam criteria. Patients received 500 mg of powdered herbs in capsule form twice daily. The primary outcomes were regular menstruation and ovulation plus change in fasting blood sugar levels. Changes in free testosterone levels and ovarian morphology was secondary outcome measures. Continuous outcomes before and after treatment were compared by Student's *t*-test (one tailed, independent). *P* = 0.05 was considered as significant. Women menstrual cycle was considerably improved. Fasting blood sugar levels did not change (*p*=0.103392). Progesterone levels were same at the starting point and after treatment (*P*=0.318322). With complete recovery in 6 patients; a notable change was found in ovarian size. Free testosterone levels were also dropped significantly (*p*<0.00001). Our main success was drastic improvement in normalizing menstrual cycle during therapy. Herbal treatment is proven to be clinically effective in most of the patients; particularly PCOs patients with menstrual irregularities. Hence, Femitex-SP<sub>4</sub> can be taken as a better treatment for PCOs.

**Keywords:** PCOs, menstrual cycle, fasting blood sugar, progesterone, ovarian size.

## INTRODUCTION

PCOS is a varied ailment frequently resulting in sterility and total wellbeing (Legro *et al.*, 2014; Sills *et al.*, 2001). This varied nature complicates both diagnosis and handling of the disorder. With the concept of completely incurable (currently); genes are thought to be its biggest cause (Garad *et al.*, 2011; Messinis, 2005). A massive population with PCOS show hyperinsulinemia.

To obscure, menstrual irregularities; most doctors advise oral contraceptive pills and for infertile, they recommend clomiphene citrate (Clomiphene). But PCOs women have shown adverse effects with OCP and despite of the fact that clomiphene has successfully induced ovulation, the rates are not very impressive, specifically low in obsess patients (around 30%) (Kousta *et al.*, 1997; Polson *et al.*, 1989). For controlling hyperandrogenism, anti-diabetics and anti-androgens drugs have been recommended. Even though metformin has shown great tendency in reducing hyperinsulinemia and increase androgens, but at the same time, associated with number of side effects like vomiting, sickness and gastrointestinal problems.(ESHRE

and Group, 2008; Tang *et al.*, 2005). PCOs has been one of the greatest dilemma of medical field; already affected around five to ten million women around the globe. (Thatcher, 2000). And its incidence is increasingly drastically in Pakistan also.

keeping in view the above picture; women have strongly started focusing towards complementary medicine, in last ten years and the ratio is between twenty six percent to ninety one percent (Holden *et al.*, 2014; Lunny and Fraser, 2010). Herbal medicine is above all of them (Grant and Ramasamy, 2012). Their active components have shown tremendous physiological effects on female reproductive system plus helpful in reducing the occurrences of number of health issues (Francis *et al.*, 2002; Grant and Ramasamy, 2012; Whitten and Naftolin, 1998; Wolff *et al.*, 2010). Henceforth, to estimate the efficacy of our formulation in PCOs; a randomized study has been arranged.

The medicine was formulated in powdered form from 4 curative herbs (i.e. Plant-1 *Saraca indica L.*, Plant-2 *Vitex agnus castus L.*, Plant-3 *Embelica officinalis L.*, and Plant-4 *Symplocos racemosa Roxb.*). Proven in studies, that phytoestrogenic herbs are very effective in treating

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diverse parameters of PCOs (Kamel, 2013); and herbs used in our formulation strongly possess these effects (Goyal *et al.*, 2021; Khani *et al.*, 2011).

*Saraca indica* is found to be useful in treating fibroids induced menorrhagia, leucorrhoea, and has a positive effect on the endometrium and ovarian tissue. Its phenolic glycosides have revealed strong oxytocic action (Pachiappan *et al.*, 2020; Pankaj 2003; Singh *et al.*, 2015).

*Vitex agnus castus* have beneficial effect on the pituitary gland; increasing number of luteinizing hormones; which ultimately helps to normalize a female cycle. It also regulate prolactin levels; and by this it may benefit infertile women by decreasing excessive prolactin level (Haerifar *et al.*, 2020; Lauritzen *et al.*, 1997).

*Embelica officinalis* stands out as a powerful revitalizing herb; by having high content of Vitamin C. It helps increasing reproductive fluids and applied for the treatment of ulcers and hyperacidity. By creating a positive nitrogen balance and increasing total protein levels; *Embelica* also expressively decreases the levels of free fatty acids (Kapoor *et al.*, 2020; Sivarajan and Balachandran, 1994).

*Symplocos racemosa* is advised for treating spermatorrhoea, sexual weakness and weakness of uterus. Prescribed for number of female problems (Sharma, 1996; Yadav *et al.*, 2020).

## MATERIALS AND METHODS

### *Study design*

A total number of 150 patients were recruited over 1 year (January 2016-June 2017). from Obstetrics and Gynecology Department at Abbasi Shaheed Hospital, Karachi, Pakistan.

### *Sample size*

The sample size  $n=150$  was calculated on the basis of convenience sampling technique.

### *Inclusion criteria*

As per Rotterdam criteria patients having PCOs were enrolled; aging between 18 to 44 years (both married and unmarried) (Macut *et al.*, 2013). Whereas, expectant and nursing mothers; women suffering from hyperprolactinemia, thyroid problem, any sort of malignancy was excluded from the study. It also includes those patients which were on hormonal therapy for the last three months.

### *Methodology*

Informed consent was sought from patients participating in the study. Randomized, convenience sampling method was used. Consort 2010 flow chart was used for recruiting

patients. The Femitex-SP<sub>4</sub> capsules were prepared manually as they are not commercially available. Each empty capsule was filled with 500 mg of powdered herbs. Patients were advised to take capsule twice a day during meals to avoid gastric complaints. This cycle was repeated for all the clinically assessed patients (Ishaque *et al.*, 2011).

Demographic profile of the recruited patients was also measured and noted. Blood sugar was checked on an empty stomach at baseline and two months afterword to monitor insulin variation. At day 21 of menstrual cycle, progesterone and testosterone levels were checked and repeated two months after words with same protocol. Same methodology was followed for the sonographic findings of the pelvis.

Our primary outcome was the regulation of menstrual cycle (i.e. less than equal to thirty-five days) during the trial and two months after trial of regular intake of Femitex-SP<sub>4</sub> capsules. On first hand, we also looked for the changes in blood glucose levels at fasted state and progesterone levels after treatment. Later, we measured changes in free testosterone levels and ovarian morphology. All findings were documented.

### *Ethical approval*

The study is approved by International Center for Chemical and Biological Sciences (ICCBS), Karachi University, Pakistan; Study# -001-BC-2014; Protocol# UOK-001-BC-2014/protocol/1.0; Version# 1.0; Version Date: 11<sup>th</sup> December, 2014.

## STATISTICAL ANALYSIS

The results were reported as mean  $\pm$  S.E.M. Continuous outcomes, before and after, were compared by Student's *t*-test (one tailed, independent).  $P = 0.05$  was considered as significant. SPSS (version 20) software was used for the analysis (SPSS Inc., Chicago, IL, USA).

## RESULTS

Trial began in January 2016 and lasted till June 2017. During this period, hundred and fifty women were screened; 100 were randomized; and finally 48 women completed the study. The comprehensive enrolment flow chart can be seen in fig. 1.

Only two patients suffered with epigastric burning & belching. Not any serious side effect was reported and all events subsided during the study period.

### *Socio-Demographic profile of patients*

Patient's socio-demographic status (for all 150 patients screened); frequency of body mass index (BMI); educational level; and their marital status is shown in (fig.

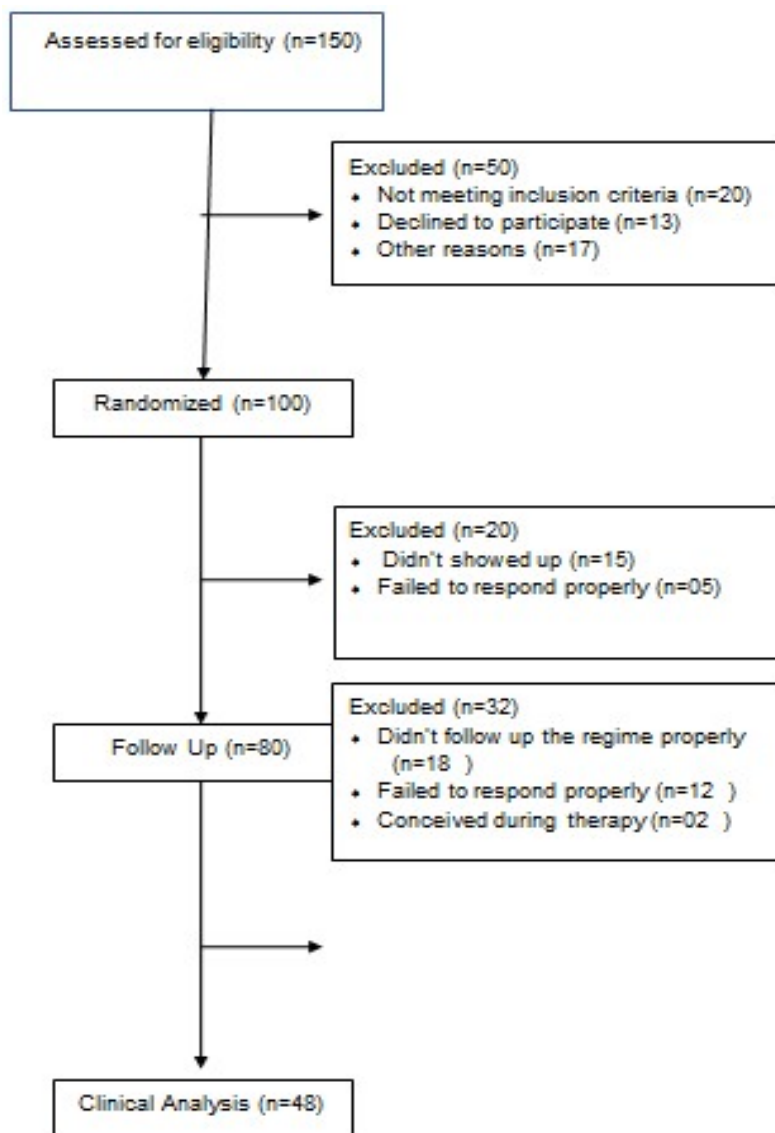


Fig. 1: Patients Flow Chart

Table 1: Duration of menstrual cycle in PCOs patients before and after treatment

	Duration of Cycle (Days)		P Value P<.05	T Test
	Before Treatment (Mean ± SD)	After Treatment (Mean ± SD)		
<b>Test Group</b>	60.6 ± 17.80	30.8 ± 9.22	<0.00001	115.7202

Table 2: Improvement in Fasting Blood Sugar (FBS)

	Fasting Blood Sugar (mg/dl)		P Value P<.05	T Test
	Before Treatment (Mean ± SD)	After Treatment (Mean ± SD)		
<b>Test Group</b>	90.83 ± 9.08	91.26 ± 8.28	0.103392	-1.30081

Table 3: Effect on Serum Progesterone

	Serum progesterone (ng/ml)		P Value P<.05	T Test
	Before Treatment (Mean ± SD)	After Treatment (Mean ± SD)		
<b>Test Group</b>	2.46 ± 6.17	2.42 ± 1.86	0.318322	0.47903

**Table 4:** Free testosterone levels after treatment

	Free Testosterone Levels (ng/ml)		P Value P<.05	T Test
	Before Treatment (Mean ± SD)	After Treatment (Mean ± SD)		
<b>Test Group</b>	1.49 ± 0.87	2.55 ± 0.80	<0.00001	-15.44715

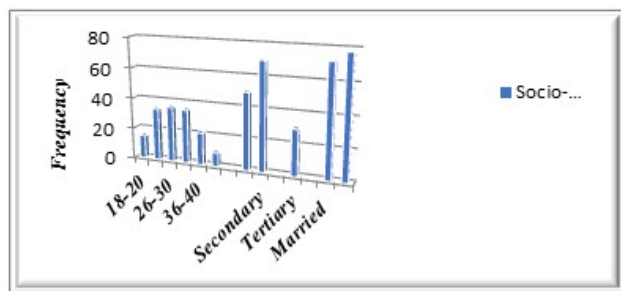
**Table 5:** Improvement in Ovarian morphology

	Sonographic Results		P Value P<.05	T Test
	Before Treatment (Mean ± SD)	After Treatment (Mean ± SD)		
<b>Number of follicles</b>	12.8 ± 1.0	7.6 ± 1.5	<0.00001	18.23036
<b>Stromal thickness (mm)</b>	8.48 ± 0.57	6.04 ± 0.6.0	<0.00001	9.29775
<b>Ovarian volume mm<sup>3</sup></b>	17.39 ± 1.8	10.37 ± 1.0	<0.00001	23.04378

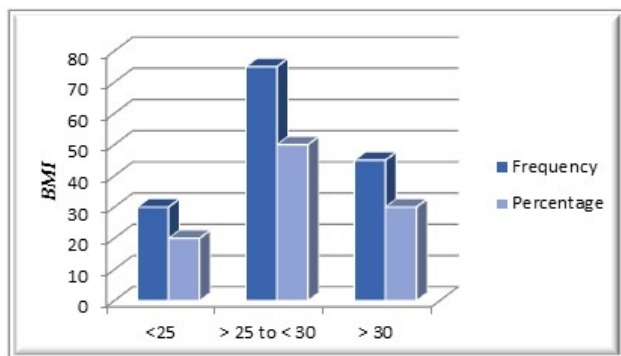
2). Age range was 18-44; and mean was 30.0±9.8 years; and majority of them were in between twenty-six to thirty years of age. About twenty percent had tertiary schooling; while only around 46% have reached only secondary education. Out were single. The BMI of 50% of women was ≥ 25kg/m<sup>2</sup>, while about thirty percent of women were over 30Kg/m<sup>2</sup>. (fig. 3)

**Resumption of menstrual cycle**

Data about period flow was collected at the beginning, during study and one-month post treatment (table 1). There was a noticeable change in menstrual cycle (≤35 days) before and after treatment (mean and standard deviation, 60.6±17.80 v/s 30.8±9.22), and it improved significantly from the baseline after treatment.



**Fig. 2:** Socio-demographic status of patients



**Fig. 3:** BMI of patients

**Change in FBS**

No changes were observed in Insulin levels, neither in the beginning nor at the end of treatment cycle (table 2).

**Serum progesterone and testosterone**

There was no change in progesterone (table 3) and androgen values (table 5). While there was a notable reduction in free testosterone levels; but the decrease was not over the normal range (i.e., 1.49±0.87 v/s 2.55±0.80).

**Changes in ovarian morphology**

With complete recovery in 6 patients; a notable change was found in ovarian size and morphology; thus indicating a positive impact of Femitex-SP<sub>4</sub> on ovarian tissues.

**DISCUSSION**

PCOS is one of the most prominent cause of infertility and countless health problems; among the women of reproductive age. Health care professionals are looking after more drastic handlings of PCOs, as current pharmaceutical medicines are only targeted towards symptomatic treatment (Garad *et al.*, 2011; Messinis, 2005; Sills *et al.*, 2001; Tang *et al.*, 2005).

Phytoestrogenic medicinal herbs are of great importance; in treating PCOs. They belong to that class of compounds which have week estrogenic effect, thus protecting PCOs women from metabolic and hormonal abnormalities. Femitex-SP<sub>4</sub> comprised of herbs; that have great phytoestrogenic and anti-oxidant potential (Khani *et al.*, 2011). In this study, we clinically assessed the effectiveness of our formulation in PCOs females and outcomes were tremendous. In our study, 80 patients took two capsules of Femitex-SP<sub>4</sub> twice a day; comprehensive information from 48 patients was received and examined, as shown in fig. 1.

From socio-demographic profile of PCOS women, we concluded that it has mostly effected women in their peak

reproductive years (105/150; were between 21-35 years of age); whereas no significant difference was seen in the incidence in between married (48%) and non-married women (52%). The perception of patients regarding the severity of the symptoms is more important than assessment of medical professional (Ching *et al.*, 2007).

The cycle was normalized in majority of oligomenorrheic patients; improved by 51.9%. The possible cause for this could be the presence of polyphenolic compounds present in the formulation. But the results showed no substantial improvement in insulin levels ( $p=0.899$ ); however, this could be because of the fact that it was assessed only by measuring glucose levels at fasted state.

There progesterone values remain similar before and after treatment ( $P=0.880$ ). As progesterone has a pulsatile secretion manner; and we only took values after 8<sup>th</sup> week; which cannot be related to ovulatory disturbance (Marshall and Dunaif, 2012).

However, there was a significant difference in serum androgen levels before and after treatment; which were assessed by presence of free testosterone. But again, there was no uniform laboratory procedure applied for the testing of free testosterone, so the result may appear variable (Mohan, 2005).

Like resumption of menstrual cycle; one of the most evident outcome was the overall improvement in ovarian morphology; there was a significant reduction in number of follicles present in each ovary ( $12.8\pm 1.0$  v/s  $7.6\pm 1.5$ ), in striatal thickness ( $8.48\pm 0.57$  v/s  $6.04\pm 0.6.0$  mm), and in overall ovarian mass too ( $17.39\pm 1.8$  v/s  $10.37\pm 1.0$  mm<sup>3</sup>). Again, the possible reason is the positive effect of herbs (used in Femitex-SP<sub>4</sub>) on the endometrium and ovarian tissue (Pankaj, 2003; Singh *et al.*, 2015; Sivarajan and Balachandran, 1994).

## CONCLUSION

The most visible change was improvement in the menstrual cycle during the treatment. Unfortunately, a precise mechanism for this effect of Femitex-SP<sub>4</sub> on menstrual cycle was not recognized in our study group. Somehow, post study higher progesterone levels can be associated with this enhancement. Any suspected enhancement in insulin sensitivity was not visible in our study; may be due to FBS, which is not an effective method to measure insulin. Outcomes of this study; supported the fact that, in spite of the minor metabolic and hormonal changes, herbal treatment is proven to be clinically effective in most of the patients; particularly PCOs patients with menstrual irregularities and further studies are suggested in larger population on a longer period of time.

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