Research Article

Effects of Flax Seeds Supplementation in PolyCystic Ovarian Syndrome

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ABSTRACT

The objective of this study is to assess the effects of flax seed powder on ovarian morphology, menstrual cycle, hirsutism and blood sugar in PCOS. 32 women with PCOS who fulfilled the selection criteria were included in this open label interventional study. Menstrual history, measurement of body weight, BMI, random blood sugar, ultrasound abdomen and Ferriman Galleway scoring for hirsutism were done at baseline. The subjects were given 15 grams of flax seed powder to be taken as a single dose in milk every morning for 3 months.30 subjects completed the study. The above parameters were measured every month for three months. The results were analyzed using paired T test. A significant reduction in mean ovarian volume and number of follicles was observed after flax seed therapy. The mean reduction in right and left ovarian volume was -3.35 c.mm and -2.383 c.mm and the mean difference in number of follicles was -4.259, -4.519 for right and left ovaries respectively (p value <0.01). After flax seed treatment 17 (56.7 %) subjects did not have peripheral follicles and 16(53.3 %) had normal ovarian echogenicity. 12 subjects (40%) had improved menstrual cycle and 3(10%) became pregnant. There was no significant change in hirsutism and blood sugar level after treatment. Flax seed supplementation has caused significant reduction in ovarian volume and number of follicles in polycystic ovaries, improved the menstrual cycles and not altered the body weight, blood sugar and hirsutism. Hence flax seed can be further explored as an alternative source of new drug for PCOS.

Keywords: PCOS - flax seed –lignan - ultrasound

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a heterogeneous syndrome characterised by menstrual dysfunction, chronic anovulation, hyperandrogenism and polycystic ovaries. It commonly affects women of child bearing age; about 7 to 10 percent worldwide.[1] The co-morbidities such as infertility, hirsutism and insulin resistant diabetes are often associated with PCOS.

Multifactorial causes have been implicated for PCOS. Abnormalities in the hypothalamic-pituitary axis, hyperandrogenism, hyperinsulinaemia, chronic inflammation, environmental, genetic factors and obesity, play a significant role in the pathogenesis of this disorder.[2-5] Obesity is becoming a worldwide epidemic and it can be an important contributing factor for PCOS.

Bearing in mind the diversity of presentation of the disease, a multidisciplinary approach from various specialities like obstetrics and gynaecology, reproductive medicine, dermatology, medicine and nutrition is required to treat the individual as a whole. There is no proven drug therapy that can cure PCOS. Several natural products have been used in traditional medicine for PCOS, some of which are chaste berry, white peony, cinnamon, Tribulus terrestris, saw palmetto, dandelion root, gymnema, black cohosh, flax seed and many more.[6,7] Among these numerous agents advocated, flax seeds have been used for treating menstrual irregularities since ancient times.[6,7]

Archaeological findings reveal that flax (Linum Usitatissimuman) has been cultivated since the Mesopotamian civilization, 6000BC and has been extensively used in Ayurvedic medicine for various diseases.[8]

Linum Usitatissimuman in Latin means "very useful". Flax plant is native to the region extending from the eastern mediterranean, through western Asia and the Middle East, to India.

Flax seed is often taken as whole or crushed and the powder is incorporated into food products like breads, muffins, juices, milk, dry pasta, dairy and meat products.[9]

Flaxseed contains several biologically active compounds like alpha- linolenic acid (ALA), lignans (secoisolariciresinol diglycoside-SDG), soluble flaxseed fibre mucilage (d-Xylose, L-Galactose, LRhamnose, d-galacturonic acid) which have significant health benefits.[10]

Flaxseed and its products have been reported to have laxative[9], antidiabetic[11], cholesterol lowering[12], antimalarial[13], antioxidant[14], anti-arrhythmic[15], anti-inflammatory[16], hepatoprotective, anticancer actions[17,18] and others.

It is reported that "Flax seeds have the highest content of dietary lignan" and the most important lignan present is secoisolariciresinol diglucoside (SDG).[19] Lignans seem to reduce the excess testosterone which plays a key role in the pathogenesis of PCOS.[20,21]

As hyperandrogenemia is an important contributory factor for PCOS, any compound that can reduce androgens will be useful in PCOS. Based on this assumption the present study was conducted to find out the effect of flax seeds in PCOS.

SUBJECTS AND METHODS

This study was a prospective, open label, interventional study. It was conducted after approval from Institutional Human Ethics Committee. Letter No: IHEC/05/2013/Desp no 262 – 27/11/2013.

Thirty two women with PCOS, between 18 to 35 years were selected based on Rotterdam criteria i.e. presence of two out of the three features: Oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, or polycystic ovaries (ovarian volume>10cc, 12 or more peripherally located follicles 2-9 mm in diameter or hypoechoic enlarged ovaries with hyperechoic central stroma in USG).

Exclusion criteria: pregnant and lactating women, those with signs and symptoms of PCOS but showing normal ovaries on ultrasound, those on oral contraceptive pills, metformin, antiandrogens like flutamide, spironolactone, clomiphene citrate, women on antiplatelet and fibrinolytic drugs, those with ovarian hyperstimulation syndrome, simple/complex ovarian cyst on ultrasound and those with history of allergy to flax seeds.

The study was conducted from January to August 2014. The subjects were recruited from the department of obstetrics/gynaecology and radiology department, Chettinad hospital and Research institute. The participants were explained about the details of the study and informed consent was obtained. A total of 32 subjects were recruited. Two subjects had dropped out, one due to inability to travel long distance to the hospital and the other due to IVF treatment for infertility. Detailed menstrual history was taken and height, body weight, BMI, random blood sugar was measured and ultrasound abdomen, modified Ferriman Galleway scoring for hirsutism were done before initiation of the study. Menstrual cycle details included age at menarche, frequency, duration and severity of menstrual flow and history of dysmenorrhea.

In addition, information on marital status, parity and history of difficulty in conception was collected. They were then provided with flax seed powder in 450 gm packets and instructed to take orally 15 grams of flax seed powder with a spoon provided, in milk before food, everyday morning for 3 months. Compliance to the treatment was confirmed by regular phone calls and marking on daily calendar for every successful intake which the patient had to bring on the next monthly visit.

Most patients did not complain of any adverse effect except transient nausea by a few. Patients were reviewed every month for three months and all the above parameters were measured at each visit.

A reduction in the number of follicles and ovarian volume, improvement in menstrual cycle and reduction in body weight were considered positive outcome.

Ultrasonography Procedure

Subjects were evaluated by transabdominal ultrasonography using GE Voluson 730 expert or Philips HD7 ultrasound machines with 6-12MHZ transducer. Ovaries were scanned from their inner to outer margins and the ovarian volume, ovarian echogenicity, number and location of follicles were noted each time. Ovarian volume was obtained by measuring the craniocaudal, transverse and anteroposterior diameters. The images were stored in PACS (picture archiving and communication system) for offline viewing.

Statistical Methods

Detailed descriptive analysis of socio-demographic and clinical parameters was done. The quantitative variables were presented as mean ± standard deviation and the categorical variables were presented as frequency and percentage. Ovarian volume, number of follicles and duration of menstrual cycle were taken as outcome variables. The mean difference or percentage differences in the outcome parameters, before and after treatment were calculated. Paired t-test was used to assess the statistical significance of these differences and 95% CI of the differences were also calculated. Microsoft Excel and IBM SPSS version 21 were used for statistical analysis. STATA version 13 was used for sample size calculation.

RESULTS

A total of 30 women with PCOS were included in the final analysis as in (Fig 1). There were 13 (43.3%) married and 17 (57.7%) unmarried women. The mean body weight was 61.43 kg and the mean BMI, 25.86 kg/m^2. The complete descriptive analysis of anthropometric parameters is presented in (Table 1).

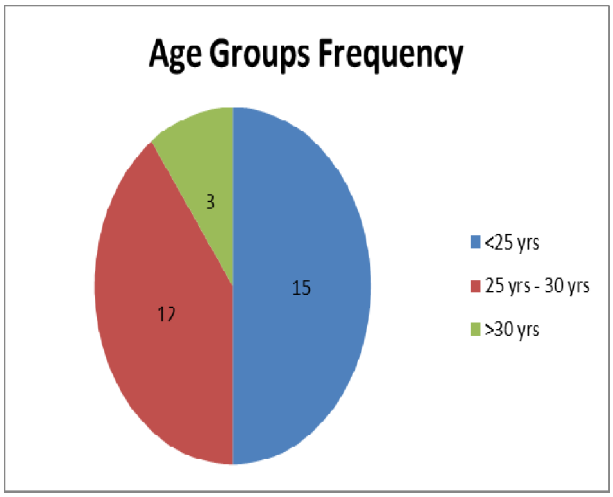

Figure 1: Age group frequency

Effect on Mean Ovarian Volume

There was a statistically significant difference in the mean ovarian volume, before and after treatment, p-value <

0.001. The mean reduction in the right ovarian volume was -3.35 c.mm (-3.35, 95% CI -4.16 to -2.54) and left ovarian volume was -2.383 c.mm (-2.383, 95% CI -3.049 to -1.716) by the end of 3 months of treatment.

The details of monthly mean reductions of ovarian volume are shown in (Table 2).

Effect on Mean Follicular Count

There was a mean reduction in the follicular count of -4.25 (p value <0.001, 95% CI -5.58 to -3.0) in right ovary and -4.5 (p value < 0.001, 95% CI -5.58 to -3.45) on left ovary, after treatment. Both these reductions were found to be statistically significant (Table 3).

Table1: Descriptive analysis of anthropometric parameters of study participants (N=30)

Parameter	Mean ± STD	Median	Max	min	95% Confidence interval	
					Lower	Upper
Weight	61.43 ± 12.79	60.00	95.0	35.0	56.658	66.215
Height	154.247 ± 4.848	154.00	165.0	144.00	154.436	156.057
BMI	25.86 ± 5.48	23.72	39.04	15.56	23.809	27.904

Table 2: Effect of flax seed on Ovarian volume (Paired sample t-test) (N=30)

Ovarian Volume	Paired Differences					
	Mean		Mean Difference	P value	95% C.I. of the Difference	
					Lower	Upper
Right Side						
Visit 1 - visit 0	Visit 0	11.789	-1.615	<0.001	-2.331	-0.901
	Visit 1	10.173				
Visit 2 - visit 0	Visit 0	11.789	-2.557	<0.001	-3.303	-1.811
	Visit 2	9.232				
Visit 3 - visit 0	Visit 0	11.789	-3.350	<0.001	-4.159	-2.540
	Visit 3	8.440				
Left side						
Visit 1 - visit 0	Visit 0	10.622	-0.627	0.008	-1.075	-0.179
	Visit 1	9.994				
Visit 2 - visit 0	Visit 0	10.622	-1.406	<0.001	-2.007	-0.805
	Visit 2	9.215				
Visit 3 - visit 0	Visit 0	10.622	-2.383	<0.001	-3.049	-1.716
	Visit 3	8.239				

Table3: Impact of Flax seed on follicular count (N=30)

Follicle count	Paired Differences					
	Mean		Mean Difference	P value	95% C.I.* of the Difference	
					Lower	Upper
Right (Before - after)	Before	11.11	-4.259	<0.001	-5.518	-3.001
	After	6.85				
Left (Before - after)	Before	11.04	-4.519	<0.001	-5.584	-3.453
	After	6.52				

*CI-confidence interval

Effect on location of Follicles and Echogenicity

Before treatment, all the 30 patients (100%) had peripherally located follicles. After treatment only 13 (43.3 %) had peripheral follicles. 24 patients (80%) had hypoechoic ovaries before intervention. After intervention 16 (53.3 %) had normal ovarian echogenicity.

Effect on Menstrual Cycle

As shown in (Figure 2), before therapy only 2 (6.7%) women had normal menstrual cycle. Following flax seed therapy 10 (33.3%) had regularisation of menstrual cycle, 5 (16.7%) improvement in the frequency, 9 (30%) had no change and 3 (10%) became pregnant.

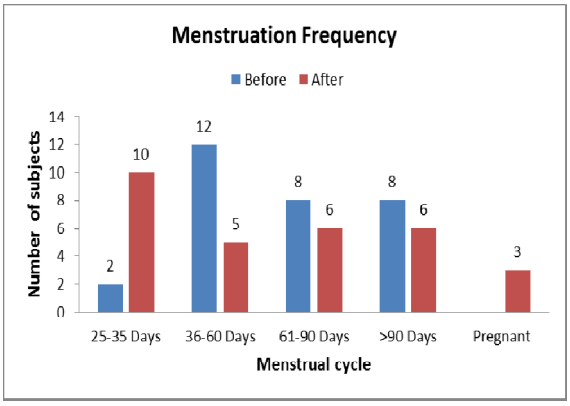

Figure 2: Effect on frequency of Menstrual cycle

Effect on Hirsutism and Random Blood Sugar Level

19 (63.3%) subjects had hirsutism and there was no improvement in hirsutism after treatment. There was no statistical significant difference in the random blood sugar level, before and after treatment. (p value -0.713).

DISCUSSION

This study is the first of its kind, conducted to evaluate the effect of flax seeds on ovarian morphology in PCOS and it has showed that flax seed supplementation significantly reduced the ovarian volume, number of follicles in the ovaries and improved the frequency of menstrual cycles. We did not find any change in hirsutism, blood sugar level and body weight.

An average dose of 15 grams of FSP was chosen based on earlier studies conducted on the effect of flax seed on sex hormone levels.[22-26] At this dose FSP produced a significant reduction in ovarian volume and number of ovarian follicles, improvement in frequency of menstruation. Menstrual cycle was regulated in 33.3% (10subjects).

The exact mechanism for such effects is not known. The mechanism can be postulated based on earlier studies.

Hormonal Mechanisms

According to the "two-cell, two-gonadotrophin concept", LH and FSH should work in harmony to ensure follicle development and maturation.[27] LH is responsible for androgen production by theca cells and FSH is responsible for aromatization of these androgens to oestradiol by granulosa cells.[27] Early follicle development is an FSH independent process, however for development of large preovulatory antral follicle FSH is an absolute requirement.[28] The number of follicles, aromatase enzyme activity and estradiol biosynthesis depend on the duration and magnitude of FSH stimulation.[28] During the luteal-follicular transition phase, high levels of FSH will give rise to continued growth of a restricted number of follicles which in turn produce estradiol.[28] Even though estradiol is required for other important physiological processes like endometrial proliferation, induction of mid-cycle LH surge, its role in oocyte maturation is unclear.[28,29] In PCOS the LH to FSH ratio is elevated 3:1 and the imbalances in these hormones contribute to the pathogenesis of PCOS.[20,30]

The excessive androgen in PCOS causes increase in the number of immature follicles. It is found that flax seed reduces serum androgen levels.[21,22] Sturgeon SR observed a decline in testosterone, estradiol and estrone levels especially in overweight/obese women following dietary flax seed supplementation.[22] Debra also reported reduction in total and free testosterone levels following flax seed administration.[21] The decrease in concentration of free circulating testosterone may be due to the lignan content of flax seed which has been found to increase levels of sex hormone binding globulin (SHBG) as described by Adlercreutz.[29] There will be increased binding of testosterone to SHBG and hence the decline in its free level. Reduction in free testosterone may facilitate regularization of menstrual cycle, reduction of hirsutism and improve ovulation.

The lignan secoisolariciresinol diglucoside (SDG) is a phytoestrogen and a precursor of lignans such as enterodiol and enterolactone which are sterically similar to 17β-oestradiol, the most active form of oestrogen in humans.[10,20,31] They compete for oestrogen receptors and cause displacement of endogenous oestrogen. The resultant effect is a rise in the level of circulating estrogen which in turn inhibit hypothalamus-pituitary-gonadal axis by negative feedback mechanism. Reduction in endogenous estrogen level can stimulate the release of FSH and the level of FSH may rise favouring maturation of the follicles.

Insulin resistance and increased ovarian cytochrome P450c17α activity have been attributed to the pathogenesis of PCOS.[32] P450c17α is involved in androgen biosynthesis.[33] Insulin acts indirectly by reducing hepatic biosynthesis of sex hormone binding globulin (SHBG).[33] Studies have reported the inverse relationship between SHBG and insulin levels.[33] SHBG in turn reduces the level of free testosterone by binding to it. Many studies have reported that flax seed has an insulin lowering effect.[8,34] Furthermore Sharon E reported that supplementation of flaxseed or its lignan (SDG) reduces plasma insulin-like growth factor I (IGF-1) levels in rats induced with breast cancer.[35] It has been reported

that IGFs increase LH secretion.[36] Therefore Reduction in plasma IGFs and insulin levels may decrease the LH, increase the SHBG and hence lower testosterone levels. This is the same mechanism by which metformin is useful in PCOS.[37] These could be the reasons for the effects of Flax seed in PCOS.

Non Hormonal Mechanism

Chronic inflammation has been implicated as a cause of PCOS. Several studies have reported presence of elevated levels of CRP, inflammatory markers like soluble intercellular adhesion molecule-1 (sICAM-1) and soluble endothelial leukocyte adhesion molecule-1 (sE-selectin) and other markers of inflammation in PCOS.[3,38]

Flax seed and their products have been reported to have anti-inflammatory effects.[16] Flax seeds are rich in ALA which is found to reduce interleukin-1, tumour necrosis factor and hence useful in reducing inflammation.[18,39] Caughey reported that flaxseed oil given at 14 g/day to human subjects over 4 weeks decreased the levels of tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), and cytokines.[16]

In addition to inflammation, obesity is an important factor that worsens PCOS. Flax seed fibre improves satiety and reduces hunger.[40] Reduction in body weight helps to improve menstrual function and fertility. But in the present study no change in the body weight was observed.

Thus the overall actions of FSP in PCOS can be attributed to, at the hormonal level; reduction in testosterone, circulating oestrogen, LH, insulin levels and increased FSH and the non-hormonal actions include its anti-inflammatory actions.

CONCLUSION

From our study we can conclude that Flax seed supplementation has resulted in significant reduction in ovarian volume and number of follicles in polycystic ovaries, improvement in frequency of menstrual cycles and has no effect on body weight, blood sugar and hirsutism. The positive effect of FSP could be due to reduction in testosterone, oestrogen, LH and insulin levels contributing to follicular maturation and the anti-inflammatory actions to the reduction in ovarian volume. Considering the improvement in ovarian function and menstrual cycle, Flax seeds appear to be an alternative source of future drug development for PCOS.

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