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Title: Effect of *Foeniculum vulgare* essence on symptoms of Polycystic ovarian syndrome (PCOS): A Randomized Double-Blind, Placebo-Controlled Trial

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Effect of *Foeniculum vulgare* essence on symptoms of Polycystic ovarian syndrome (PCOS):

A Randomized Double-Blind, Placebo-Controlled Trial

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Abstract:

**Background:** Polycystic ovarian syndrome (PCOS) is the most common cause of ovulatory infertility with an endocrine origin. An alternative therapy for PCOS is complementary medicine (CM), with herbal medicine becoming the most popular during the past ten years. The fennel plant
(Foeniculum Vulgare Mill) belongs to the flowering plant of the fennel Apiaceae family. It is a medicinal plant that is commonly recommended by practitioners of Iranian traditional medicine for ovarian or unknown infertility in women because it has an estrogenic effect. The effects of fennel (FOEVU: Foeniculum vulgare Mill essence of fennel seeds) on PCOS has yet to be investigated. Therefore, the main objective of our study was to investigate and evaluate the effects of fennel essential oil capsules on PCOS symptoms.

**Subjects and Methods:** This study was a double-blinded, randomized controlled study. Our subjects were thirty female students who were selected from the age range of 20-35 and met the Rotterdam diagnostic criteria for PCOS. The subjects were randomly assigned to two groups: fennel (study) and placebo (control). The ultrasonography assessments, body mass index, biochemical, and hirsutism variables were measured individually before and after three months usage of the fennel and placebo as our main outcome measurements. The comparison between the quantitative data obtained for the two studied groups was carried out using the Man-Whitney and chi-square tests.

Results: The comparison of menstruation cycle, hirsutism, BMI, biochemical, and ultrasonography measurements revealed that the interventions did not cause significant differences in the two groups, except in the dehydroepiandrosterone sulphate (DHEAS) and ovarian volume (p<0.05).

**Conclusion:** Fennel was not effective in alleviating the ovarian cyst symptoms in polycystic women but since the sample size calculation in our small study was based on very large effect sizes, the study might not be powered enough to detect smaller effects.

Key words: fennel, PCOS, treatment, polycystic ovarian syndrome
BACKGROUND:

Polycystic ovarian syndrome (PCOS) is of endocrine origin and is the most common cause of ovulatory infertility. It is also a major factor for metabolic syndrome, cardiovascular disease, and type 2 diabetes mellitus. Clinical symptoms of PCOS such as acne, hirsutism, obesity, and alopecia can also cause psychological problems, especially for adolescents (Beltadze and Barbakadze, 2015). PCOS is usually associated with hormonal abnormalities through changes in the concentrations of the luteinizing hormone (LH), prolactin, estrogen, and serum androgens (testosterone and androstenedione) (Jalilian et al., 2015). Two principal components to clinically diagnose this syndrome are menstrual dysfunction and clinical or laboratory hyperandrogenism, (Taghavi and Fatemi 2008). Hormonal measurements indicate that many women with PCOS have an increased LH/FSH ratio. Therefore, the ratio of 2 to 1 and sometimes 2.5 to 1 of LH/FSH is considered as the biochemical measurement for diagnosing this disease (Jalilian et al., 2015).

In addition, the economic and psychological burden of this syndrome is potentially significant for public providers, health caregivers and patients (Azziz, 2005; Barry, 2011). Despite the potential public health impact of PCOS, estimates regarding its prevalence are surprisingly scarce, with a wide range from 2.2% to as high as 26% (Ramezani Tehrani et al., 2011). Moreover, the prevalence of this syndrome has been estimated among different populations in various studies (Mehrabian et al., 2011). The prevalence of PCOS based on the National Institute of Child Health and Human Development of the U.S has been reported as 6.8%. However, based on the Rotterdam diagnostic criteria it has been reported as 19.5% and based on ultrasound reports it has been reported as 4.41% (Jalilian et al., 2015).
Weight loss and metformin administration have been shown to improve hyperandrogenic signs and symptoms of PCOS, and this may be due to lowered androgen levels. Others have demonstrated that changing dietary habits, even without any significant weight loss, may also improve endocrine features and reproductive functions in this group of patients (Firouzabadi et al., 2012). The Rotterdam diagnostic criteria was presented by the Fertility and Embryology Association of Europe and the America Fertility Society in the Rotterdam Conference in 2003, and they have determined that two of these three criteria (oligoovulation, hyperandrogenism, or the presence of polycystic ovaries on pelvic ultrasound) as a criteria for diagnosing PCOS (Rahmanpour et al., 2009).

Complementary medicine (CM) is an alternative or natural therapy that includes taking dietary supplements such as herbs like cinnamon (Wang et al., 2007), vitamins such as vitamin D (Irani et al., 2017), minerals such as chromium (Fazelian et al., 2017), or nutritional supplements such as fish oil (Sadeghi et al., 2017). The use of these treatments by women has increased during the last ten years (Smith et al., 2013), with rates of use ranging between 26% and 91% (Bishop et al., 2011). A popular form of complementary medicine is herbal medicine. Herbal medicines are known to contain pharmacologically active constituents with physiological effects on the female endocrine system, and have been positively associated with reduced incidences of breast cancer, osteoporosis, and cardiovascular disease (Grant and Ramasamy 2012).

The use of plants accompanied by synthetic drugs, on the other hand, is also effective in treating certain diseases. In Iran, herbal remedies (such as fennel, chamomile, and marigold) are traditionally used for treating dysmenorrhea. Both the seed and extract of fennel (Foeniculum vulgare Mill), which is an umbelliferous plant, are commonly used by the many tribes of Iran and are appetizing, useful for digestive and menstrual disorders, and are diuretic, anti-spasmodic,
laxative (Nasehi et al., 2013) and lactogenic (Ghasemi et al., 2015). Fennel has also been traditionally used for treating ovarian cysts (Bokaie et al., 2013). This plant has an estrogenic effect, and has been shown to have anti-inflammatory, anti-spasmodic, analgesic, carminative, and expectorant effects. Also, because of its anti-oxidative effects it is also useful for nervous disorders (Delaram et al., 2011).

The fennel plant (Foeniculum vulgare Mill) belongs to the flowering plant of the fennel Apiaceous family. Foeniculum vulgare seeds contain volatile oil composed largely of anethole, which is a phytoestrogen, as well as fenchone, estragole, 1,8-cineole (eucalyptol), and other constituents (Bajan et al., 2011), and is helpful in treating colic as well as having a slight pain-reducing potentiality for dysmenorrhea (Bokaie, Farajkhoda et al. 2013). Fennel is also useful for weight loss and can affect the BMI (Abdelaaty et al., 2012). It is believed that this is one way fennel helps in treating PCOS, because weight reduction is an important treatment target in individuals who have PCOS associated with obesity (Lass et al., 2011).

The decrease of androgen levels, especially testosterone, is another way to treat PCOS. Mirseyed et al. evaluated the effects of fennel in male rat spermatogenesis and showed a significant decreasing trend in terms of testosterone hormones such as LH and FSH (Mirseyed et al., 2008). Another study done on the aqueous extract of fennel seed showed the beneficial effect on renal function in PCOS rats (Zeraati et al., 2014).

To the authors’ knowledge no similar study has been carried out to evaluate the effects of fennel on PCOS. Therefore, the main objective of this study was to investigate the effects of fennel on biochemical levels, hirsutism, and menstruation cycles of Iranian women diagnosed with PCOS.
Subjects and Methods:

Study design: This was a double-blinded, single-center, and prospective randomized controlled parallel study conducted at the Jahrom University of Medical Sciences, Iran. This study was registered in the Iranian registry of clinical trials. (Registration number: IRCT2016040427207N1). The scientific review committee and institutional ethics committee of the Jahrom University of Medical Sciences approved the present study.

Participants: Female students were asked if they had clinical signs of hyperandrogenism or oligomenorrhea.

Sample size estimation: There was no previous comparable study on which to base data for a sample size calculation. To estimate an acceptable sample size, the following formula was used: a significance level of 0.05, a power level of 0.80, an effect size of 1.5 based on blood testosterone changes and SD=2. The minimum sample size for this study was 15 in each group. They were selected by consecutive sampling from students aged 20-35 who met the study's inclusion criteria.

Procedure: The inclusion criteria of the subjects were based on the Rotterdam diagnostic criteria for PCOS (Table 1). The exclusion criteria of the subjects were as follows:

1- Use of any medications to treat PCOS, such as oral hormonal contraceptive during treatment.
2- Rule out other causes such as thyroid dysfunction, pituitary dysfunction and adrenal dysfunction.
3- History of renal or liver disease.
4- Any allergy to herbal or suspected contraindication to herbal remedies.
5- History of major pelvic surgery, seizures, stress factors in the last 6 months, severe gastrointestinal disorders, or any diseases that might interfere with the conduct of the study or the interpretation of the results.

Students who satisfied the inclusion criteria and wanted to participate in this trial were asked to read and accept the conditions of the study and then sign an informed consent form. Secondly, the questionnaires about demographic characteristics, general health, menstrual health, and regularity of menstruation were distributed between the selected subjects, and they were asked to fill out the questionnaires. The researchers requested the subjects to not use any drugs for the next three months. In this study one person from the placebo group discontinued use of the study drug in the second month of intervention.

Randomization and blinding: The manufacturer produced 15 fennel boxes that contain 168 capsules (46mg) and 15 placebo boxes. The subjects were requested to use that drug for 12 weeks, twice a day (each 12 hours) after meals. Each box was assigned a number from 1 to 30 and each participant received one box according to table randomization. The researchers were not informed about which of the capsules was the drug or placebo. The subjects and researchers were blinded as to whether the given drug was fennel or the placebo. The manufacturer provided a list that showed which number assigned to each drug was fennel or the placebo. Only the operator who performed the statistical analysis received that list and had information about the numbers and the nature of each drug.

The major components of fennel essential oils included Trans-Anethole, Fenchone and Estragole (Methylchavicol). Fennelin soft capsules were supplied by the Barij Essence Pharmaceutical Company, Mashhad Ardehal, Kashan, Iran, (http://barijessence.com/en/product/fennelin-softcap/)
*Foeniculum vulgare* Mill essence was produced by distilling the fennel seeds with water vapor (Barij Essence Co, Iran produced the drug and placebo) and then for this study they were formed into pearl-shaped pills (46 mg). Fennel drug toxicity was assessed in a past study and its safety had been reported (Badgajar et al., 2014). The placebo contained 100 mg soya produced by the Barij Essence Company. In order to isotropy, each pearl was placed inside a capsule and was coded.

**Assessment tools:** The following variables were measured on each individual before and after three months of drug usage as the main outcome measures (clinical, biochemical and ultrasonographic assessment)

**Clinical measurements**

The degree of hirsutism was assessed by using the modified Ferriman-Gallwey method before and after the trial. The modified method measures hair growth in these sites: upper lip, chin and sides of the face, it has five grades, and the scores range from zero to four for each site (Amiri and Ramezani Tehran 2017).

Height and weight of the subjects were measured before and after the intervention and BMIs were calculated for each of them as follows: BMI (kg/m²) = weight (kg)/ height² (m²). When the subjects used their assigned drugs (fennel or placebo) for a period of three months and then the variables were measured, the study was terminated.

Duration of menstruation cycles were measured from the first day of one menstrual cycle to the first day of the next period according to Patient report.
Biochemical measurements

A venous blood sample was obtained from the studied population to evaluate the changes in the level of biochemical factors. Testosterone (reference number: 411712), DEHAS (reference number: 1705357), Prolactin (reference number: 725090), TSH (reference number: 411712), FSH (reference number: 1655137), and LH (reference number: 1616732) were measured by using the enzyme-linked immune sorbent assay method using the Eliza Kit (Monobind Inc., Germany).

Ultrasonographic assessments

Ovarian transabdominal sonography was performed for all the subjects at their mid cycle (according to the regular menstrual cycle and time intervals of 21-35 days) by one sonographer to evaluate the evidence of ovulation, endometrial thickness, right and left ovarian volume, and right and left ovarian follicular number. Presence of the dominant follicle >14 mm was considered as an evidence of ovulation.

Statistical analysis

Obtained data were analyzed using SPSS version 21 (SPSS Inc., Chicago, IL, U.S.A.) software. Quantitative variables were presented as the mean ± standard deviation (SD). After using the normality test we decided to use the Mann-Whitney and the Wilcoxon tests for the comparison of quantitative data between the two studied groups. P values less than 0.05 were considered significant.
Results:

**Participant flow:** From 30 subjects (15 in the study group and 15 in the control group) who entered the study, 29 women completed the study (Figure 1).

**Baseline characteristics:** Eleven subjects in the study group (73.3%) and nine subjects in the control group (64.3%) were unmarried. The mean ages in this study were 23.60 ± 2.32 years in the fennel group and 23.14 ± 2.7 years in the control groups, respectively.

**Primary outcome:**

The degree of hirsutism before the intervention was not significantly different between the two groups. The rate of hair growth was not reduced significantly in the two groups after the intervention \((P > 0.05)\) (table 2)

Before the intervention, the Mean ± SD of the BMI in the fennel group was 23.50±.03, and in the placebo group it was 25.27±.49, although this different was not significant \((p=0.290)\). After the intervention, the Mean ± SD of the BMI in the fennel group was 22.97±4.55, and in the placebo group it was 25.24±4.64; however, this difference was not statistically significant \((p=0.172)\) (Figure 2).

The duration of the menstruation cycle when compared before \((p \text{ value } = 0.359)\) and after \((p \text{ value } = 0.588)\) the intervention in the two groups was not significantly different.

Biochemical measurements (TSH, FSH, LH, DHEAS, PROLACTIN, and free testosterone) before the intervention were not significantly different between the two groups. The comparison of the
biochemical blood test after the intervention showed that there was no significant difference between the two groups ($p > 0.05$) (table 3).

Ultrasonography factors (endometrial thickness and ovarian volume) were compared in both groups before the intervention and it was shown that endometrial thickness and ovarian volume was not different between the placebo and fennel groups; however, the left ovarian follicular number ($p=0.05$) and right ovarian follicular number ($p=0.00$) were significantly different between the two groups. Ultrasonography factors in both groups after the intervention were not significant, except for the right and left ovarian follicular number which was significantly different between the two groups (Table 4).

**Discussion:**

In this study there was no significant difference between the ovarian cyst symptoms in the fennel and control groups, although other studies have shown that fennel might be effective in primary dysmenorrhea (Bokaie et al., 2013; Nasehi et al., 2013), and in decreasing the intensity of infantile colic (Alexandrovich et al., 2003).

To the authors’ knowledge there has been no study that has evaluated the effects of fennel in patients with PCOS. Only one animal study has shown that the use of fennel can decrease the levels of LH/FSH/testosterone hormones significantly (Modaress Nejad & Asadipour, 2006). Aqueous extract of fennel seed has also shown the beneficial effects on renal function in PCOS rats (Zeraati et al., 2014).

In this study, although herbal treatment was not effective in ovarian cyst symptoms, the ovarian follicular number before and after the intervention was significantly different, which may be due
to trans-abdominal sonographic assessment that is less accurate than trans-vaginal sonography measurement.

Most of the PCOS women with a normal gonadotropin ratio belonged to a group of patients suffering from hyperinsulinemia and obesity. Patients with hyperinsulinemia and excess LH constitute a selected and distinct subgroup with increased adrenal androgenic activity (Banaszewska et al., 2003). Cimicifuga Racemosa was found to decrease the level of LH (Arentz et al., 2014), and another clinical study has shown elevated FSH following treatment with tribulus terrestris (Ghosian Moghaddam et al., 2013).

Although our study showed that there was no significant difference between the effects of fennel in the hirsutism score, in another double blind study, idiopathic hirsutism patients were treated with creams containing 1% and 2% fennel extract over 12 weeks with no adverse effects (Javidnia et al., 2003).

The right and left ovarian volume in the fennel group decreased after the intervention, however, this difference was not significant. Although Morin-Papunen et al. reported that the mean volumes of the right and left ovary did not change after metformin therapy (Morin-Papunen et al., 1998), in another research the mean ovarian volume significantly decreased after three months of metformin administration (Farimani Sanoee et al., 2011). Similarly, Bayrak et al. showed that one week of metformin therapy (850 mg/day) was associated with a significant improvement in PCO morphology (Bayrak et al., 2007).

In our study, the change of BMI in the two groups before and after the intervention was not significant, and this is likely to be related to the use duration of the fennel, which was three months. However, based on recent PCOS international guidelines, a six month intervention duration is
optimal to reduce the BMI in PCOS women (Teede et al., 2018). Current evidence suggests that following a healthy lifestyle that reduces body weight and abdominal fat, can in turn reduce testosterone, and improve hair growth and insulin resistance. However, there was no evidence that a healthy lifestyle improved cholesterol or glucose levels in women with PCOS (Sirmans and Pate 2014). In this trial, the level of DHEAS and prolactin were increased insignificantly in the fennel group after treatment. Several articles have concluded that PCOS is not associated with the higher levels of prolactin measured in daily profiles (Szosland et al., 2015). Milewicz's study has shown that a statistically significant correlation was found between the mean prolactin concentrations and mean plasma DHEAS concentration (Milewicz, 1984). Regular exercise and calorie restriction are known to increase DHEAS production in the primate’s body and this increase is appropriate for the general health of the body (Mattison et al., 2003; Moore et al., 2007). Although the effects of herbal substances are unknown, some foods such as wild yam, maca root and rose root can increase DHEAS levels (Boroch, 2007).

In this study, fennel was not effective on the length of the menstruation cycle in PCOS women, and this could be related to the dosage and duration of treatment. However, the use of another phytoestrogen such as vitex has been effective for oligomenorrhea treatment (Arentz et al., 2014).

Some of the limitations of this study were small sample size, poor generalizability and the duration of treatment. Thus, we suggest a greater sample size with a longer treatment time for future studies to evaluate this herbal drug. According to budget limitations the effect size which the authors used might be too high so the study was unable to detect small differences.
In this article satisfaction of subjects was not evaluated. Although our subjects did not inform us whether the given drug was fennel or placebo, some of the subjects in the fennel group showed satisfaction after the intervention. We recommend that future studies should evaluate the satisfaction of PCOS patients who use fennel. If future studies show therapeutic effects and satisfaction after using fennel, this herbal drug will be considered for PCOS patients.

**Conclusion:**

Fennel was not effective in improving ovarian cyst symptoms in polycystic women. but since the sample size calculation in our small study was based on very large effect sizes, the study might not be powered enough to detect smaller effects.

**List of abbreviations**

PCOS: polycystic ovarian syndrome

LH: Luteinizing hormone

FSH: Follicle-stimulating hormone

CM: Complementary medicine

PRL: Prolactin

DHEAS: Dehydroepiandrosterone sulphate

**Declarations**

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
This study protocol was approved by the ethics committee of the Jahrom University of Medical Sciences and after explaining the study aims, the informed consent forms were signed by the participants who desired to be included in our study.

- Consent for publication

  Not applicable

- Availability of data and material

  The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

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Full trial protocol can be accessed as follow:

IRCT registration number: IRCT2016040427207N1    date of registration: 04/04/2016

Acknowledgments

The authors would like to thank the research department of the Jahrom University of Medical Sciences and Barij Essence Company.
References:


Arentz, S., J. A. Abbott, C. A. Smith and A. Bensoussan.,2014. "Herbal medicine for the management of polycystic ovary syndrome (PCOS) and associated oligo/amenorrhea and hyperandrogenism; a review of the laboratory evidence for effects with corroborative clinical findings." BMC Complementary and Alternative Medicine 14: 511.


Figure 1: Consort Flow Diagram of the study
Figure 2: Mean of BMI factor in patients treated with Fennel and placebo before and after intervention.
Table 1. Rotterdam diagnostic criteria for PCOS

<table>
<thead>
<tr>
<th>Rotterdam (2003) Diagnostic criteria for PCOS - two out of three of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Hyperandrogenism (Ferriman-Gallwey Score &gt;8) or</td>
</tr>
<tr>
<td>Biochemical Hyperandrogenism (Elevated Total/Free Testosterone)</td>
</tr>
<tr>
<td>Oligomenorrhea (Less Than 6-9 Menses per Year) or Oligo-Ovulation</td>
</tr>
<tr>
<td>Polycystic Ovaries on Ultrasound (&gt;= 12 Antral Follicles in One Ovary or Ovarian Volume &gt;= 10 cm3)</td>
</tr>
</tbody>
</table>
Table 2: Mean, standard deviation and p. values of Ferriman-Gallwey values in patients treated with Fennel and placebo before and after intervention.

<table>
<thead>
<tr>
<th>Variable Area</th>
<th>Placebo group</th>
<th>Fennel group</th>
<th>P. value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Chin</td>
<td>Before intervention</td>
<td>2.07 ± 1.67</td>
<td>2.43 ± 1.40</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>1.53 ± 1.41</td>
<td>1.93 ± 1.59</td>
</tr>
<tr>
<td>Upper lip</td>
<td>Before intervention</td>
<td>0.8 ± 1.32</td>
<td>0.21 ± 0.58</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>0.67 ± 1.23</td>
<td>0.21 ± 0.58</td>
</tr>
<tr>
<td>Chest</td>
<td>Before intervention</td>
<td>2.00 ± 1.77</td>
<td>0.93 ± 1.00</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>1.47 ± 1.41</td>
<td>1.14 ± 1.35</td>
</tr>
<tr>
<td>Upper abdominal</td>
<td>Before intervention</td>
<td>1.53 ± 1.77</td>
<td>1.07 ± 1.54</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>1.47 ± 1.66</td>
<td>0.86 ± 1.46</td>
</tr>
<tr>
<td>Lower abdominal</td>
<td>Before intervention</td>
<td>1.73 ± 1.62</td>
<td>0.93 ± 1.54</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>1.27 ± 1.53</td>
<td>1.21 ± 1.63</td>
</tr>
<tr>
<td>Upper back</td>
<td>Before intervention</td>
<td>0.60 ± 1.30</td>
<td>0.43 ± 1.16</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>0.47 ± 1.13</td>
<td>0.14 ± 0.53</td>
</tr>
<tr>
<td>Lower back</td>
<td>Before intervention</td>
<td>0.53 ± 1.13</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>0.20 ± 0.41</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Upper arm</td>
<td>Before intervention</td>
<td>0.27 ± 1.03</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>0.31 ± 0.35</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Leg</td>
<td>Before intervention</td>
<td>1.00 ± 1.51</td>
<td>0.86 ± 1.46</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>0.67 ± 1.11</td>
<td>1.00 ± 1.57</td>
</tr>
</tbody>
</table>

* Mann-Whitney
Table 3. Mean, standard deviation and p. values of biochemical factors in patients treated with Fennel and placebo before and after intervention.

<table>
<thead>
<tr>
<th>Biochemical factors</th>
<th>Before intervention</th>
<th>After intervention</th>
<th><strong>P. value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fennel group Mean ± SD</td>
<td>Placebo group Mean ± SD</td>
<td>P. value*</td>
</tr>
<tr>
<td>DHEAS (mg/ml)</td>
<td>2.94 ± 0.82</td>
<td>2.38 ± 0.89</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>7.52 ± 19.48</td>
<td>2.70 ± 1.02</td>
<td>0.813</td>
</tr>
<tr>
<td></td>
<td><strong>P. value</strong> 0.158</td>
<td>0.490</td>
<td></td>
</tr>
<tr>
<td>Free testosterone</td>
<td>2.55 ± 1.77</td>
<td>3.85 ± 2.25</td>
<td>0.112</td>
</tr>
<tr>
<td>(pg/ml)</td>
<td>1.76 ± 1.39</td>
<td>2.07 ± 1.59</td>
<td>0.652</td>
</tr>
<tr>
<td></td>
<td><strong>P. value</strong> 0.136</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>FSH (MIU/ml)</td>
<td>5.63 ± 2.20</td>
<td>5.34 ± 2.05</td>
<td>0.715</td>
</tr>
<tr>
<td></td>
<td>5.06 ± 2.39</td>
<td>3.91 ± 1.35</td>
<td>0.123</td>
</tr>
<tr>
<td></td>
<td><strong>P. value</strong> 0.232</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>LH (MIU/ml)</td>
<td>10.93 ± 5.83</td>
<td>7.68 ± 3.93</td>
<td>0.186</td>
</tr>
<tr>
<td></td>
<td>8.76 ± 3.93</td>
<td>7.57 ± 4.58</td>
<td>0.331</td>
</tr>
<tr>
<td></td>
<td><strong>P. value</strong> 0.158</td>
<td>0.925</td>
<td></td>
</tr>
<tr>
<td>TSH (MIU/ml)</td>
<td>2.01 ± 1.33</td>
<td>1.57 ± 0.87</td>
<td>0.252</td>
</tr>
<tr>
<td></td>
<td>2.09 ± 0.90</td>
<td>1.92 ± 0.72</td>
<td>0.505</td>
</tr>
<tr>
<td></td>
<td><strong>P. value</strong> 0.124</td>
<td>0.583</td>
<td></td>
</tr>
<tr>
<td>Prolactin (mg/ml)</td>
<td>18.07 ± 11.74</td>
<td>19.69 ± 7.21</td>
<td>0.451</td>
</tr>
<tr>
<td></td>
<td>20.51 ± 14.33</td>
<td>19.05 ± 14.76</td>
<td>0.949</td>
</tr>
<tr>
<td></td>
<td><strong>P. value</strong> 0.754</td>
<td>0.594</td>
<td></td>
</tr>
</tbody>
</table>

* Mann-Whitney
**Wilcoxon
Table 4. Mean, standard deviation and p. values of ultrasonographic factors in patients treated with Fennel and placebo before and after intervention.

<table>
<thead>
<tr>
<th>Ultrasonographic factors</th>
<th>Fennel group Mean ± SD</th>
<th>Placebo group Mean ± SD</th>
<th>P. value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endometrial thickness(mm)</strong></td>
<td>Before intervention</td>
<td>6.23±1.50</td>
<td>5.46±1.66</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>5.81±1.74</td>
<td>5.82±1.81</td>
</tr>
<tr>
<td></td>
<td>** P. value**</td>
<td>0.414</td>
<td>0.609</td>
</tr>
<tr>
<td><strong>Right ovarian volume(ml)</strong></td>
<td>Before intervention</td>
<td>10.30±2.63</td>
<td>9.04±3.26</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>8.17±3.32</td>
<td>9.91±3.58</td>
</tr>
<tr>
<td></td>
<td>** P. value**</td>
<td>1.000</td>
<td>0.039</td>
</tr>
<tr>
<td><strong>Left ovarian Volume(ml)</strong></td>
<td>Before intervention</td>
<td>10.67±3.02</td>
<td>8.73±2.25</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>8.26±3.06</td>
<td>8.88±3.08</td>
</tr>
<tr>
<td></td>
<td>** P. value**</td>
<td>0.06</td>
<td>0.655</td>
</tr>
<tr>
<td><strong>Right ovarian follicular number</strong></td>
<td>Before intervention</td>
<td>9.70±2.55</td>
<td>11.86±0.77</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>9.06±2.23</td>
<td>11.29±1.20</td>
</tr>
<tr>
<td></td>
<td>** P. value**</td>
<td>0.581</td>
<td>0.145</td>
</tr>
<tr>
<td><strong>Left ovarian follicular number</strong></td>
<td>Before intervention</td>
<td>9.60±2.64</td>
<td>11.93±0.62</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>9.47±2.5</td>
<td>11.07±2.5</td>
</tr>
<tr>
<td></td>
<td>** P. value**</td>
<td>0.889</td>
<td>0.459</td>
</tr>
</tbody>
</table>

* Mann-Whitney
**Wilcoxon