# Effect of Aslagh Capsule, an Herbal Product on Oligomenorrhea in Polycystic Ovary Syndrome: A Three-Group Randomized Clinical Trial

# Abstract

**Background:** Oligomenorrhea is a common complaint in patients with PCOS. There are some useful medicinal recommendations such as “Aslagh” in Iranian traditional medicine for the treatment of oligomenorrhea in PCOS and this study was conducted to compare it with metformin.

**Materials and Methods:** In this randomized clinical trial, 150 women aged between 18-43 years with oligomenorrhea due to PCOS were randomly assigned into Aslagh, metformin and Aslagh + metformin groups. The occurrence of menstrual bleeding was considered as the primary outcome. Menstrual cyclicity, duration and volume of the bleeding were evaluated as well. . Data were analyzed using chi-square or one-way ANOVA.

**Results:** Occurrence of menstrual bleeding was 87.2% in all patients,with no significant difference between the three groups (*p*> 0.05). Menstrual cyclicity significantly improved from baseline in Aslagh and Aslagh + metformin groups (*p*=0.02). Duration of menstrual bleeding was significantly higher in Aslagh group in the first and the second menstrual bleeding compared to the other two groups (*p*<0.05). There was no significant change in the volume of the menstrual bleeding after the intervention in any of the three groups. The occurrence of menstrual bleeding in Aslagh was significantly higher than the other two groups in the fourth month (drug-free) (*p=*0.03).

**Conclusions:** Aslagh capsule showed similar beneficial effects to metformin in the treatment of oligomenorrhea in PCOS women. This herbal product may be used as an alternative treatment in these patients.

Key Words: Aslagh, Polycystic ovary syndrome, Iranian Traditional Medicine, herb, oligomenorrhea.

# Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder which affects women of reproductive age, and has a prevalence of 5–10% [[1](#_ENREF_1)]. It is commonly characterized by polycystic ovaries, chronic anovulation and hyperandrogenism, irregular menstrual cycles, hirsutism, acne and infertility [[2](#_ENREF_2), [3](#_ENREF_3), [1](#_ENREF_1), [4](#_ENREF_4)]. About 50% of women with PCOS have oligomenorrhoea and approximately 20% have amenorrhea [[5](#_ENREF_5), [6](#_ENREF_6)]. Menstrual irregularity in PCOS is associated with impaired insulin sensitivity, cardiovascular diseases, type-2 diabetes mellitus, chronic anovulation, high risk of endometrial hyperplasia and carcinoma [[7-10](#_ENREF_7)]. Improvement in menstrual cyclicity may reduce some of these complications [[10](#_ENREF_10), [11](#_ENREF_11)].

Primary care management typically includes oral contraceptives and insulin-sensitizing agents. Metformin is one of the best treatments in the therapy for reproductive and metabolic disorders caused by PCOS [[12](#_ENREF_12), [13](#_ENREF_13)]. Each of these therapies has been associated with adverse effects, for example oral contraceptives may increase the risk of cardiovascular diseases, and metformin may cause gastrointestinal side effects [[1](#_ENREF_1), [14-16](#_ENREF_14)]. Therefore, it is necessary to find some new drugs that could be targeted to treat the disease.

In Iranian Traditional Medicine (Persian Medicine), no disease has been expressed with the title of PCOS, but the symptoms of PCOS have been told in different parts of ITM encyclopedia such as canon of medicine. “Al-Qanon fi Al-Tibb” or “Canon of Medicine” is the chief medical book of Ibn –Sina or Avicenna (980 – 1037 A.D). The twenty-first chapter of the third book of “Canon of Medicine” principally discusses various kinds of uterine diseases. In this section, amenorrhea and oligomenorrhea are described under the title: “Ehtebas Tams” [[17](#_ENREF_17), [18](#_ENREF_18)].

One of the herbal medicines used for the treatment of PCOS symptoms [[19-21](#_ENREF_19)] is Aslagh capsule. Aslagh (Raha) capsule is made of *Vitex agnus-castus* [L.](https://en.wikipedia.org/wiki/Carl_Linnaeus) (Verbenaceae), *Foeniculum vulgare* Mill. (Apiaceae), and *Daucus carota* (Apiaceae). It is used for the management of oligomenorrhea and amenorrhea in ITM [[22](#_ENREF_22), [18](#_ENREF_18)].

Vitexis a popular herbal treatment, predominantly used for a range of female reproductive conditions [[23](#_ENREF_23)]. It is effective in premenstrual syndrome [[24](#_ENREF_24)], improvement of irregularities of the menstrual cycle [[23](#_ENREF_23), [25](#_ENREF_25), [26](#_ENREF_26)], corpus luteum formation, infertility [[23](#_ENREF_23)] and hyperprolactinemia [[3](#_ENREF_3)].

Fennel is a well-known plant with a mild estrogenic effect [[27](#_ENREF_27)]. It is used in resolving primary dysmenorrhea [[28-30](#_ENREF_28)] and reducing spasms in smooth muscles [[31](#_ENREF_31)]. It is also used to induce menstrual bleeding in women with amenorrhea and oligomenorrhea in folk remedies [[27](#_ENREF_27)].

Carrot is a very popular vegetable used as diet worldwide. It is rich in beta-carotene, a plant form of vitamin and anthocyanin, which contributes to many health benefits [[32](#_ENREF_32)]. Carrot has hepatoprotective [[33](#_ENREF_33), [34](#_ENREF_34)] and antioxidant activities [[35](#_ENREF_35), [36](#_ENREF_36)]. Various parts of the plant have also been used in folk medicine; e.g. carrot seeds are diuretic and carminative and are used for the stimulation of menstruation [[37](#_ENREF_37)].

According to the beneficial effects of herbal medicines in Aslagh capsule on menstruation and its usage for the treatment of oligomenorrhea in ITM, we aimed to examine the effect of Aslagh capsule on oligomenorrhea in PCOS. Moreover, the effect of Aslagh capsule has been compared with metformin and Aslagh + metformin combination.

# Materials and Methods

### **Patients**

This was a randomized clinical trial with three groups. Sample size calculation was performed by a statistician. One hundred and fifty patients aged between 18-43 years with oligomenorrhea due to PCOS (based on the Rotterdam criteria) [[38](#_ENREF_38)] who visited the gynecologist in Tehran and Qom cities, were selected for the study between December 2014 and March 2016. Patients with a diagnosis of concomitant hypothyroidism, hyperprolactinemia, diabetes mellitus, renal or adrenal insufficiency and history of drug use for PCOS for the past three months, were not included. Women with suspected pregnancy, breastfeeding with an infant younger than 6 months, intending to have a child in the following 3 months and known sensitivity to specific drugs or medical plants (especially the plants of Apiaceae) were excluded.

### **Recruitment and randomization**

After obtaining permission from the ethics and research committees of Shahid Beheshti University of Medical Sciences (SBMU.REC.1394.81) and registering the trial in the Iranian registry of clinical trial (code IRCT2015042521937N1), 150 patients were enrolled in the study with personal satisfaction and an informed consent. Researcher enrolled participants and assigned them to intervention. Then, the patients were randomly assigned into 3 groups (Aslagh, metformin and Aslagh + metformin) using block randomization with a block size of 6 and an allocation ratio of 1:1:1. Random allocation sequence was generated by the nurse.

### Intervention

Patients were randomized into three groups. Group 1 received Aslagh, 4 caps daily divided in 2 doses, in the morning on an empty stomach and at night before bed, except during the period; group 2 received metformin, 1 tab TDS after meals; group 3 received Aslagh, 4 caps daily divided in 2 doses, plus metformin 1 tab TDS. All the groups received the mentioned treatment for three months and were followed in the 4th month (drug-free) for the occurrence of menstrual bleeding in each month. For all patients in metformin group, the initial dose was 500 mg after dinner for at least 1 week and gradually it increased to a final dose of 500 mg TDS to reduce the incidence and severity of gastrointestinal side effects. Patients were advised to use barrier contraception. The subjects were not allowed to receive other PCOS management and were asked to keep to their existing diet and lifestyle during the study period. All subjects were free to withdraw at any time during the course of the study.

### Preparation of the drug

Materials of Aslagh capsule were purchased from a local market (Tehran, Iran). Aslagh (Raha) capsule is made up of *Vitex agnus-castus* [L.](https://en.wikipedia.org/wiki/Carl_Linnaeus) (Verbenaceae), *Foeniculum vulgare* Mill. (Apiaceae), and *Daucus carota* (Apiaceae). After identification, verification and performing of quality control tests on the samples in Traditional Medicine and Material Medical Research Center, Shahid Beheshti University of Medical Sciences, the samples were powdered and sieved to obtain a fine powder. They were mixed in the ratio of 1: 1: 1. The capsules were standardized based on total essential oil contained in each capsule. The powder was placed into long “0” capsules (500 mg). Metformin 500 mg tablets were bought from an Iranian Pharmaceutical company (Aria).

### Outcomes

The present study was designed to evaluate the efficacy of Aslagh, metformin and Aslagh + metformin on the occurrence of menstrual bleeding (primary outcome) and the volume and duration of menstrual bleeding (secondary outcome) in women who had oligomenorrhea due to PCOS. Occurrence of three times menstruation during the intervention period was considered as regular menses. Menstrual cyclicity (number of cycles/month) was calculated by dividing 30 by the days between two menstrual bleedings [[39](#_ENREF_39), [40](#_ENREF_40)]. Menstrual cyclicity was compared in the intervening months, and between the baseline and the third month in each group. Considering the significant difference in BMI between the three groups at the beginning of the study, ANCOVA test was used to control the BMI’s confounding effect. The Higham chart (Pictorial blood loss assessment chart, PBAC) was used to determine the volume of menstrual bleedings. This tool assesses the menstrual blood loss with 89% accuracy [[41](#_ENREF_41)]. It was interpreted as a positive result in inducing menstrual bleeding. Based on the chart, there was at least 10 ml blood losses in at least two consecutive days.

### Data collection

At the beginning of intervention, each patient was examined clinically, and their demographic, menstrual and medical histories were recorded by the researcher. Body weight was measured with individuals minimally clothed without shoes and recorded to the nearest 100 g by using a weighing scale (Soehnie, Germany). Height was measured in a standing position without shoes, using tape meter while shoulders were in a normal alignment and recorded to the nearest 1 cm. BMI (Body Mass Index) was calculated according to the formula: BMI=body weight (BW) /squared height (kg/m2). Waist circumference was measured at the level of umbilicus and hip circumference was measured at the level of greater trochanter using a non-stretchable tape and the waist-hip ratio was calculated. Each participant received a drug pack along with the form including the Higham chart. Patients were followed through telephone calls every two weeks and in every month and were asked about their menstruation. Higham charts and the remaining capsules and pills were taken in monthly visits. A patient who missed more than 20% of the total dose of prescribed treatment was considered non-compliance and was excluded from the study. Upon the occurrence of any major side effect, the participants were asked to stop using the drugs and to contact the researcher. The related side effects were assessed based on the self- report symptoms and also a checklist. At the end of the intervention, the patients were asked to express their satisfaction with the medication in a 10-point visual analogue scale scoring from 1-10. Patients in group 3 (Aslagh + metformin) were told to score each of the two drugs separately. Then, a comparison was carried out between Aslagh and metformin scores.

### Statistical analysis

The analysis was done using the SPSS version 16. Qualitative variables were presented as number (%) and compared among the three groups using the Chi-square test. Quantitative variables were presented as mean ± standard deviation (SD) and compared among the groups using one-way ANOVA or Kruskal-Wallis tests. The Paired t-test was used to compare patients’ satisfaction with two medications. A p-value < 0.05 was considered as statistically significant.

# Results

### Quality control of plants and products

Total ash, loss on drying and total essential oil were found to be 8.5, 4 and 2% for *Foeniculum vulgare,* 9.5, 4.9 and 2% for *Dacus carota* and 4.95, 7.45 and 2% for *Vitex agnus-castus*, respectively. The obtained data and microbial level of the plants were in agreement with the requirements [[42](#_ENREF_42)]. The total amount of essential oil was 0.01 ml per capsule.

### Demographic Characteristics

One hundred and fifty patients were enrolled in the clinical trial and were randomly assigned into three groups, (50 patients in each group) (Figure 1). The age of the patients ranged from 18 to 43 years. Their mean age was 24.61±5.10 years; their mean age at menarche was 13.23±1.35. ANOVA and chi-square tests showed no significant differences in these variables among the three groups. The demographic data, body mass index and waist-hip ratio are presented in Table 1.

### Menstrual bleeding

The occurrence of menstrual bleeding was (102) 87.2% in all patients during the intervention period (three months). This rate was (32) 86.5% in the Aslagh group, (35) 89.7% in the metformin group and (35) 85.4% in the Aslagh + metformin group. There was no significant difference between the three groups in the occurrence of the period (p> 0.05). Regular menses occurred in 16 (13.7%) patients. Although the regular menses was higher in Aslagh group (6, 16.2%) compared to metformin (4, 10.3%) and Aslagh + metformin (6, 14.6%), this difference was not significant. The occurrence of menstrual bleeding in the groups is presented in Table 2.

### Menstrual cyclicity before and during intervention

Baseline menstrual cyclicity was 0.43±0.16 in Aslagh group, 0.36±0.14 in metformin group and 0.34±0.13 in Aslagh + metformin group. Menstrual cyclicity increased with treatment in all groups. Menstrual cyclicity was 0.52±0.24 in Aslagh group, 0.49±0.23 in metformin group and 0.44±0.20 in Aslagh + metformin group in the first cycle. In the second cycle, menstrual cyclicity was 0.83±0.15 in Aslagh group, 0.87±0.16 in metformin group and 0.80±0.18 in Aslagh + metformin group. In the third cycle, menstrual cyclicity was 0.90±0.13 in Aslagh group, 0.89±0.20 in metformin group and 0.89±0.13 in Aslagh + metformin group. There was no statistically significant difference between the groups in each month (Kruskal-Wallis test).

### Menstrual cyclicity in the third month and baseline

Menstrual cyclicity significantly improved from 0.43±0.16 in baseline to 0.90±0.13 in Aslagh group (*p*=0.02, Paired t-test) and from 0.34±0.13 to 0.89±0.13 in Aslagh + metformin group (*p*=0.02, Paired t-test). In metformin group, menstrual cyclicity improved from 0.36±0.14 in baseline to 0.89±0.20, but this shift was not statistically significant (*p*=0.06, Paired t-test). Menstrual cyclicity in the third month and baseline in the three groups are shown in Figure 2.

### Duration and volume of menstrual bleeding

The duration of menstrual bleeding was significantly higher in the Aslagh group compared to the other groups in the first (*p*=0.03) and second (*p*=0.03) menses after intervention. The total volumeof menstrual bleeding had no significant change in the three months of the intervention in any of the groups (Table 3).

### Follow-up

The dropped out of the study in the three months was (33, 22%) in all patients, (13, 26% in Aslagh group compared to 11, 22% in metformin group and 9, 18% in Aslagh + metformin group), (Chi-Square Tests *p*=0.6).

After discontinuation of the drug, in the fourth month, occurrence of menstrual bleeding in Aslagh group (21, 56.8%) was significantly higher compared to metformin group (9, 23.1%) and Aslagh + metformin group (14, 34.1%), (Chi-Square Test, *p*= 0.03)

### Side effects of the drugs

The most frequently observed side effects included nausea (10 patients in metformin group and 13 patients in Aslagh + metformin group) and diarrhea (4 patients in metformin group and 1 patient in Aslagh + metformin group). The most common side effect of Aslagh was rash (2 patients in Aslagh group). The intensity of these side effects was not so severe and did not result in the discontinuation of the medicine.

### Patients satisfaction of interventions

Patients’ satisfaction score in the Aslagh group was significantly higher compared to metformin (7.69±1.67 in Aslagh versus 6.96±1.94 in metformin, *p*=0.01).

# Discussion

The results of this study indicated that the menstrual cyclicity increased significantly in the third month compared to the base in Aslagh and Aslagh + metformin groups. The effect of Aslagh capsule on the occurrence of menstrual bleeding was equivalent to the effect of metformin. The volume and days of menstrual bleeding increased with Aslagh capsule and did not have a significant difference with metformin. The third group did not obtain better results despite the researchers expected. Although we examined the patients' compliance with a pill count, we guess that due to a large number of medications consumed per day, these patients have not consumed their medication properly.

One of the limitations of our study was that it is a short study, and it is suggested that a study with a longer duration should be conducted.

### Menstrual bleeding

Thus far, no study has been conducted on the effect of Aslagh capsule on oligomenorrhea in patients with PCOS. This study however, is similar to the one conducted by Mohebbi-Kian (2014) in Hamadan on menstruation. They compared the effect of fennel, low-dose combined oral contraceptive (LD-COC) and placebo in women with amenorrhea due to DMPA and showed that women who received LD-COC and fennel were significantly menstruating higher than in the placebo group (P<0.05) [[43](#_ENREF_43)].

### Menstrual cyclicity

Menstrual cyclicity increased significantly in the third month compared to the base in Aslagh and Aslagh + metformin groups (*p=*0.02), and this increase was not significant in the metformin group (*p=*0.06). Considering the significant difference in BMI and WHR, between the three groups in the baseline, these results were analyzed by ANCOVA test and it was found that BMI and WHR were not as confounding factors. Essah et al. (2006) compared the effects of short- term (3-6 months) and long- term (more than 6 months) metformin on menstrual cyclicity in patients with PCOS. They reported that the number of menstrual cycles was modified from 0.27 per month to 0.60 (in women who took metformin for less than 6 months) and 0.76 (in women who took metformin for 6 months and more) [[39](#_ENREF_39)]. Kort's study (2014) showed that menstrual cyclicity in patients with PCOS was modified up to 0.75 per month by prescribing cinnamon for 6 months [[40](#_ENREF_40)].

### Volume of menstrual bleeding

In this study, the change of menstrual bleeding volume within three months was not significantly different in any of the groups. In the study conducted by Mohebbi-Kian, the volume of menstrual bleeding in fennel group was significantly more than in LD-COC and placebo groups [[43](#_ENREF_43)]. One of the reasons for the difference between our study and Mohebbi-Kian's study in menstrual bleeding volume might be the fact that in our study, Aslagh capsule is compared with metformin while in their study, fennel is compared with LD- which reduces menstrual bleeding- and placebo.

### Follow-up

Menstruation occurrence after the discontinuation of medication in patients who took Aslagh capsule (26%) was more than the other two groups. In the study carried out by Yavari et al. (2015) in Tehran to compare the effect of sesame and progesterone on menstruation in patients with oligomenorrhea, menstruation occurrence in sesame group (4 patients out of 8 patients were followed, 50%) was significantly higher than in progesterone group at the time of drug withdrawal [[44](#_ENREF_44)]. The total number of patients and the followed patients in our study were more than that of Yavari's study. Our medication is composed of three Emmenagogue drugs whereas they used only sesame.

### Patients satisfaction of interventions

In our study, patients' satisfaction with Aslagh was significantly more than with metformin, which could be due to very low side effects of Aslagh compared to metformin.

The prevalence of metabolic syndrome in women with PCOS is 43-47%, which is approximately almost twice as much as its prevalence in the normal population of women. High BMI and low HDL are the most common components of metabolic syndrome in such patients. The connecting link between PCOS and metabolic syndrome is resistance to insulin. Obesity, dyslipidemia, hypertension, impaired glucose tolerance, high fasting glucose and cardiovascular disorders are the common metabolic disorders in PCOS [[45](#_ENREF_45)]. Metabolic syndrome is associated with an increased risk of diabetes and atherosclerotic vascular disorders [[46](#_ENREF_46)].

In ITM, *Vitex agnus-castus* (VAC) is known as an anti-inflammatory herb which moderate the rigidity of ovaries [[47](#_ENREF_47), [48](#_ENREF_48)]. Therefore, this herb can be effective in PCOS in which ovaries are big and stiff [[10](#_ENREF_10), [49](#_ENREF_49)]. It has dopaminergic effects, as such, it can be connected to DA2 receptors and can have an inhibitory effect on prolactin [[50](#_ENREF_50), [51](#_ENREF_51)]. Since prolactin is a factor for folliculogenesis and oligomenorrhea [[3](#_ENREF_3)], the decrease of its level can be effective in the treatment of PCOS. Moreover, Vitex increases the secretion of melatonin from epiphysis [[52](#_ENREF_52)]. Melatonin is effective in maturation of oocytes and ovulation [[53](#_ENREF_53), [54](#_ENREF_54)]. Since oocyte maturation and ovulation are impaired in such patients [[10](#_ENREF_10)], Vitex can be effective in ovulation in these patients by affecting melatonin. Apigenin in VAC has an inhibitory effect on tumoral cells [[55](#_ENREF_55)] by inhibiting the incidence of oncogenes [[56](#_ENREF_56), [57](#_ENREF_57)]. Since patients with PCOS are at high risks of endometrial hyperplasia and cancer [[21](#_ENREF_21), [10](#_ENREF_10)] and breast cancer [[58](#_ENREF_58)], this herb can be effective in this aspect of PCOS. On the other hand, prescribing progesterone for these patients results in menstrual cycles and the prevention of cancer [[21](#_ENREF_21)]. Therefore, Vitex with its phyto-progesterone property [[59](#_ENREF_59)] leads to menstrual cycles in such patients.

In different studies, fennel has affected various aspects of PCOS. In the study conducted by Ozbek et al. (2003) on rats, fennel essence reduced live enzymes including AST, ALT, ALP and bilirubin, and its hepatoprotective effect was proved [[60](#_ENREF_60)]. Furthermore, fennel enhances hepatic synthesis of SHBG which is bound to testosterone in the blood stream and reduces serum levels of free testosterone [[61](#_ENREF_61)]. Patients with PCOS have lipid profile disorders and many of their symptoms are due to high androgens. Therefore, fennel can be effective in such patients with its hepatoprotective effect and the reduction of androgens [[45](#_ENREF_45), [62](#_ENREF_62)]. Fennel induces menstruation [[47](#_ENREF_47), [43](#_ENREF_43), [60](#_ENREF_60), [63](#_ENREF_63)] because it contains phytoestrogens such as isoflavones, flavonoids and coumestans [[64](#_ENREF_64)]. Phytoestrogens bind with estrogen receptors and have agonist-antagonist effects with estrogen [[65](#_ENREF_65), [66](#_ENREF_66)]. In patients with PCOS, the rate of estrogen is high and is converted to androgens [[67](#_ENREF_67)] and thus phytoestrogens have antagonist effects by binding with estrogen receptors and can set estrogen performance.

Carrot seed eliminates inflammation [[47](#_ENREF_47)] and can be effective in fixing large ovaries and multiple follicles in PCOS. Carrot seed is uterine tonic and can help with pregnancy [[47](#_ENREF_47), [17](#_ENREF_17)]. Therefore, it can be useful in treating infertility which is a common complication of PCOS [[3](#_ENREF_3), [20](#_ENREF_20), [10](#_ENREF_10)]. Carrot seed stimulates Bah (sexuality) [[47](#_ENREF_47)]; it has been used as aphrodite and aphrodisiac since many years ago [[68](#_ENREF_68)]. Studies have shown that carrot extracts inhibit lipid peroxidation and has antioxidant and hepatoprotective effects [[33](#_ENREF_33), [69](#_ENREF_69)]. Carrot is a rich source of carotenoids, particularly alpha and beta carotenes with strong anti-cancer properties which can be used in preventing various kinds of cancer such as breast cancer [[70-72](#_ENREF_70)]. Moreover, carotenoids reduce the risk of diabetes and insulin resistance and can have a useful effect on PCOS which is the main cause of the disease, insulin resistance, and compensatory hyperinsulinemia against it [[45](#_ENREF_45), [73](#_ENREF_73), [74](#_ENREF_74)].

All the three elements in Aslagh capsule are emmenagogue and can affect PCOS through their beneficial effects such as contributing to menstruation, being heptaprotective and enhancing blood circulation in the uterus and ovaries [[17](#_ENREF_17), [47](#_ENREF_47), [48](#_ENREF_48)].

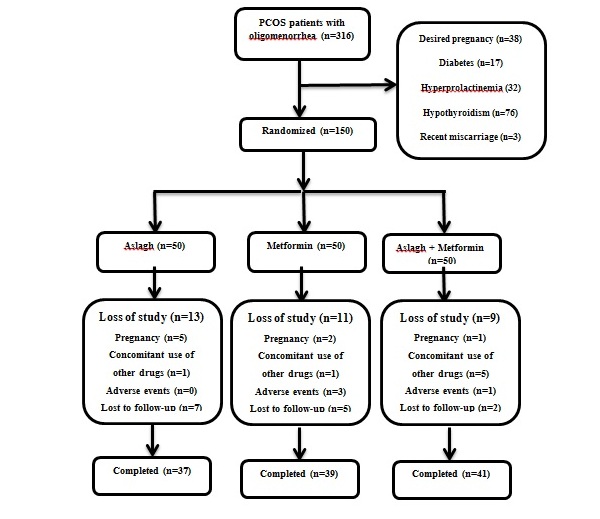
In various studies, metformin has modified clinical and laboratory symptoms in PCOS. Metformin develops and regulates menstrual cycles and removes oligomenorrhea [[12](#_ENREF_12), [75](#_ENREF_75)], reduces BMI and WHR [[75](#_ENREF_75)], lowers blood pressure [[76](#_ENREF_76)], and decreases hyperandrogenism symptoms such as acne and hirsutism [[75](#_ENREF_75)]. Considering laboratory findings, metformin improves insulin sensitivity and glucose tolerance, modifies liver enzymes [[75](#_ENREF_75), [77](#_ENREF_77)] and lipid profile [[78](#_ENREF_78), [76](#_ENREF_76), [79](#_ENREF_79)], reduces serum level of free androgens [[75](#_ENREF_75)], and modifies risk factors for atherosclerosis and cardiovascular events such as plasminogen activator inhibitor-1 (PAI-1) [[80](#_ENREF_80)], endothelin-1 [[13](#_ENREF_13)], and CRP [[81](#_ENREF_81)]. In our study, the effects of Aslagh on the removal of oligomenorrhea were similar to and sometimes better than metformin.

# Conclusion

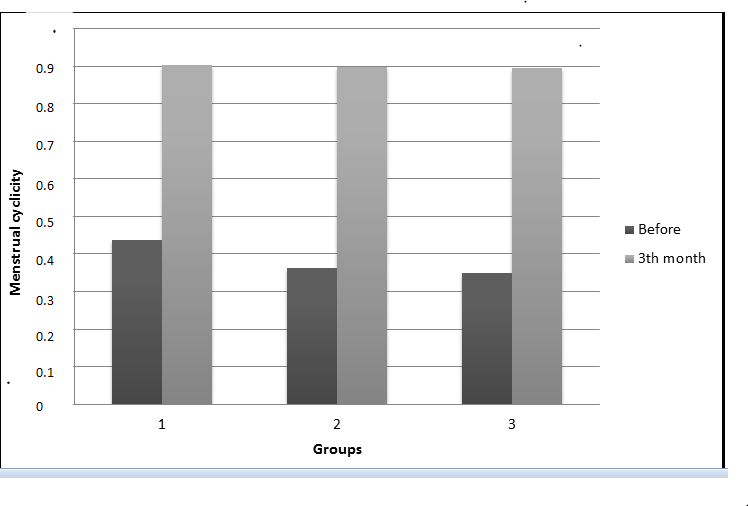
In this study, Aslagh capsule had the same effects as metformin on menstruation and better effects than metformin on menstrual cyclicity and co-administration of the two drugs did not have better results than the individual drugs. It appears that Aslagh capsule can be a good alternative to metformin in treating oligomenorrhea in patients with PCOS. Given the similar effects of metformin and Aslagh on menstruation, it is recommended that future studies plan to investigate the effect of Aslagh on other PCOS symptoms and disorders such as glucose tolerance and insulin resistance disorders, androgen levels in blood and the symptoms of hyperandrogenism, ovulation, and fertility, as well as its effects on lipid profile and liver tests and their comparison with metformin. The short duration of intervention was a limitation of the study. It is recommended to design longer-term studies in future.

# Conflict of interest

Declarations of interest: none.



## **Figure 1. The CONSORT diagram of the study**



## Figure 2. Menstrual cyclicity in the third month and baseline in the three groups

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|  | TABLE 1: Baseline characteristics in patients of study groups | | | |
| P value | Group 3 | Group 2 | Group 1 | Variables |
| 0.19 | 25.30±5.42 | 24.64±4.94 | 23.90±4.95 | Age (years),(mean±SD) |
| 0.00 | 27.14±5.35 | 26.92±5.95 | 23.33±4.15 | BMI (kg/m2), (mean±SD) |
| 0.03 | 0.90±0.06 | 0.92±0.05 | 0.89±0.05 | WHR, (mean±SD) |
| 0.97 | 13.32±1.39 | 13.16±1.20 | 13.22±1.49 | Age at menarche (years), (mean±SD) |
| 0.36 | 5.45±5.05 | 4.07±3.51 | 4.64±3.96 | Duration of disease (years), (mean±SD) |
| Group 1= Aslagh; Group 2= metformin; Group 3= Aslagh + metformin  BMI=, Body mass index; WHR= Waist-hip ratio | | | | |

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| --- | --- | --- | --- | --- |
| TABLE 2: Comparison of the groups on occurrence of menstrual bleeding in three months of intervention | | | | |
| All patients | Group 3 | Group 2 | Group 1 | Occurrence of menstrual bleeding |
| 15 (12.8%) | 6 (14.6) | 4 (10.3) | 5 (13.5%) | No menstrual bleeding, n (%) |
| 35 (29.9%) | 13 (31.7%) | 15 (38.5%) | 7(18.9%) | Once menstrual bleeding, n (%) |
| 51 (43.6%) | 16 (39%) | 16 (41%) | 19 (51.4%) | Twice menstrual bleeding, n (%) |
| 16 (13.7%) | 6 (14.6%) | 4 (10.3%) | 6 (16.2%) | Three times menstrual bleeding, n (%) |
| 117 (100%) | 41 (100%) | 39 (100%) | 37 (100%) | All patients, n (%) |
| Group 1= Aslagh; Group 2= metformin; Group 3= Aslagh + metformin  All comparisons were done using chi-square test, *p*= 0.66 | | | | |

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| --- | --- | --- | --- | --- | --- |
| TABLE 3: Comparison of the groups on characteristics of menstrual bleeding in the three months of intervention | | | | | |
| P value | Group 3 | Group 2 | Group 1 | Characteristics of menstrual bleeding | | |
| 0.03 | 6.85±1.64a | 6.20±1.60b | 7.31±1.90a | The first menstrual bleeding | Duration of menstrual  bleeding\*  (days), mean (SD) | |
| 0.03 | 6.13±1.20b | 6.35±2.05a | 7.28±1.62a | The second menstrual bleeding |
| 0.92 | 6.50±1.04 | 6.25±1.50 | 6.83±1.83 | The third menstrual bleeding |
| 0.16 | 52.51±23.95 | 44.40±15.10 | 52.25±19.72 | The first menstrual bleeding | Volume of menstrual\*\*  bleeding (ml), mean (SD) | |
| 0.26 | 49.95±22.76 | 40.25±17.99 | 44.00±17.20 | The second menstrual bleeding |
| 0.31 | 57.33±22.80 | 37.00±21.11 | 48.83±14.94 | The third menstrual bleeding |
| Group 1= Aslagh; Group 2= metformin; Group 3= Aslagh+metformin  All comparisons were done using one-way ANOVA.  \* Different letters mean a significant difference in each row.  \*\* According to Higham chart. | | | | | |

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