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Evaluating the Effect of Chamomile on Ovulation Induction in Women With Polycystic Ovary Syndrome: A Clinical Trial

Malihe Afiat[1], Naghmeh Khorsand[1], Azam Akbari Lor[2], Mona Najaf Najafi[3], Masumeh Ghazanfarpour[4*]

Abstract

Objectives: Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases among women, causing oligomenorrhea and symptoms of hyperandrogenism. This study aimed to evaluate the effect of chamomile on ovulation induction in patients with PCOS.

Materials and Methods: This randomized clinical trial included 70 patients with a diagnosis of PCOS according to the Rotterdam criteria. The samples were selected from patients referred to a specialty clinic in Mashhad, Iran from 2017 to 2018R. Patients were randomly assigned into two groups of intervention and control. While the intervention group received two chamomile capsules (500 mg) daily for three months, the control group received two placebo capsules daily for three months. Both groups underwent ultrasounds on days 3 and 12 of the first and third cycles. The collected data were analyzed using SPSS software version 20.

Results: The mean age of patients in the control and intervention groups was 28.06 ± 5.71 and 25.43 ± 5.58 years, respectively. There was no significant difference between the two groups in terms of age and body mass index (BMI) before treatment. Ovarian volume on day 12 of the third cycle was significantly lower in the intervention group ($P=0.01$). The number of dominant follicles in the intervention group was significantly higher after treatment ($P=0.02$). While hirsutism improved in the chamomile group ($P=0.028$), there was no significant difference between the two groups in terms of testosterone levels ($P=0.894$).

Conclusions: According to our results, chamomile treatment regimen could increase the dominant follicle, and thus affect the induction of ovulation in patients with PCOS.

Keywords: Polycystic ovary syndrome, Chamomile, Ovulation induction

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women. Women with PCOS have common symptoms such as oligomenorrhea and hyperandrogenism (hirsutism and acne, hair loss, and infertility) (1). According to the evidence, 6%-10% of women suffer from this disorder worldwide (2-4). Although the etiology of PCOS is still unknown (5,6), genetic and environmental factors have been introduced as the possible causes.

Many contradictory recommendations have been made about the role of diet in weight control (7). Treatments for hyperandrogenism and PCOS depend on the patient's goals. These treatments include weight loss, birth control pills, medroxyprogesterone acetate, gonadotropin-releasing hormone (GnRH) agonists, glucocorticoids, ketoconazole, spironolactone, cyproterone acetate, flutamide, cimetidine, finasteride (sensitizer 1), and herbal medicines.

Chamomile plant, with the scientific name *Matricaria chamomilla*, has anti-inflammatory (8) and anti-diabetic properties (9), and it can regulate menstrual periods (10). Chamomile flowers contain tannin, phytosterol, and also a bitter substance called anthemic acid (11). Chamomile grows easily in most parts of Iran and it does not have the side effects of chemical drugs.

A literature review showed that two studies have assessed the effect of chamomile on PCOS (7,12). The first study was conducted on animal models (13) and the second one assessed the effect of chamomile on lipid- and hormonal-related parameters (12). However, no study has investigated the effect of chamomile on ovulation induction in patients with PCOS. Therefore, this study aimed to evaluate the effect of chamomile on ovulation induction and testosterone change in women with PCOS.

Materials and Methods

This randomized controlled clinical trial was performed on 70 patients with PCOS referred to a specialty clinic in Mashhad, Iran from 2017 to 2018. Considering a 20%

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[1]Milad Infertility Center, Mashhad University of Medical Sciences, Mashhad, Iran. [2]Department of Obstetrics and Gynecology, Gonabad University of Medical Sciences, Gonabad, Iran. [3]Imam Reza Clinical Research Units, Mashhad University of Medical Sciences, Mashhad, Iran. [4]Department of Nursing and Midwifery, Kerman University of Medical Sciences, Kerman, Iran.
*Corresponding Author: Masumeh Ghazanfarpour, Email: masumeh.ghazanfarpour@yahoo.com

Key Messages

- Chamomile treatment regimen could increase the dominant follicle, and thus affect the induction of ovulation in patients with PCOS.

effect of chamomile in the intervention group, $\alpha = 0.05$, $\beta = 0.2$, and an attrition rate of 10%, the sample size in each group was calculated as 35 individuals using the PASS software.

PCOS was diagnosed based on the Rotterdam criteria (14), according to which it is necessary to have at least two of the following criteria: 1) Low ovulation or no ovulation, which usually manifests as oligomenorrhea, amenorrhea, and polymenorrhea, 2) Increase in levels of androgen, hirsutism, and 3) Polycystic ovaries observed on ultrasonography. The diagnosis of PCOS was made after ruling out secondary hyper-endogenous causes, including hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, and androgen-secreting ovarian tumors.

The inclusion criteria were history of normal puberty, thyroid test in the normal range (0.5-5), age in the range of 18-35 years, no recent history of surgical treatment for PCOS or any kind of treatment for PCOS, not using sex steroids (such as birth control pills, hormone therapy, and androgen drugs), not using chemical or herbal medicines, and not using tobacco products.

After explaining the objectives of the study, observance of ethical issues under the Helsinki Declaration, and assuring the confidentiality of patients' information, a written consent was obtained from all participants.

Participants were free to withdraw from the study in any stage. A demographic questionnaire was completed for all participants, and they were requested to refer for a transvaginal ultrasound if they had a menstruation on days 3 to 5 or amenorrhea after bleeding (following daily administration of 10 mg/d progesterone for seven days). Patients referred to the gynecological clinics with the results of their ultrasound and biochemical tests. Next, the patients were randomly assigned into two groups of intervention and control using a random allocation list.

The capsules were provided to the patients based on a checklist. The effective dose was determined as 500 mg according to previous studies (7,12). We used chamomile capsules made by Barij Essence Pharmaceutical Company (Iran). While the intervention group received two capsules per day for three months, the control group received two placebo capsules per day for three months. The drugs were packaged and numbered by an unrelated person to the study. In this way, chamomile and placebo tablets, which were completely similar in appearance, were taken by a colleague in two envelopes A and B, and for each patient, the selection of the envelope was done randomly by a site. The facilitators and patients were unaware of the contents of the envelope. Thus, the study was performed in a double-blind manner. Also, on day 12 of the third cycle and in case of menstruation at the end of day 90, the patients were referred for a transvaginal ultrasound to evaluate the effect of the drug on the volume and follicles of the ovaries.

Statistical Analysis

The data were analyzed by SPSS software version 23. Descriptive statistics, including central indicators, dispersion, and frequency distribution were used to present the characteristics of the subjects. Independent *t* test was used to compare quantitative variables for normal data, and Mann-Whitney test was used for non-normal data. The chi-square test and Fisher exact test were used to compare qualitative variables. In all the analyses, *P* value equal to 0.05 was considered as statistically significant.

Results

In this study, 70 patients were randomly assigned into two equal groups of intervention and control (n=35 in each) (Figure 1). In the intervention group, two patients were excluded due to gastrointestinal complications and three patients due to incomplete drug use. Meanwhile, five patients in the placebo group were excluded from the study due to incomplete drug use. Finally, the collected data from 60 patients (30 in the intervention and 30 in the placebo) were analyzed.

The mean age of patients in the intervention and placebo groups was 25.4 ± 5.58 and 28.06 ± 5.71 years, respectively (P=0.076). The body mass index (BMI) before treatment was 25.28 ± 4.98 and 25.58 ± 5.98 kg/m^2 in the intervention and placebo groups, respectively, indicating no significant difference between the two groups ($P = 0.831$). Marital status, history of pregnancy, and history of infertility were assessed in both groups. Chi-square test was used to compare marital status ($P = 0.436$) and Fisher's exact test was used for the history of infertility (P<0.99) and pregnancy ($P = 0.898$). The results showed no significant difference between the two groups.

Using the chi-square test and Fisher's exact test, we examined the dominant follicle and ovarian volume before treatment, on day 12 of the first cycle, and on day 12 of the third cycle in both placebo and intervention groups. The results indicated significantly lower levels in the intervention group ($P = 0.018$) (Table 1).

Using the Mann-Whitney test, dominant follicles were examined before treatment, on day 12 of the first cycle, and on day 12 of the third cycle. According to the results, the number of dominant follicles in the intervention group was significantly higher in the dominant follicle of the third cycle ($P = 0.027$) (Table 2).

While hirsutism improved in the chamomile group ($P = 0.028$), there was no significant difference between the two groups in terms of testosterone levels (P=0.894). Also, the clinical signs were compared in placebo and

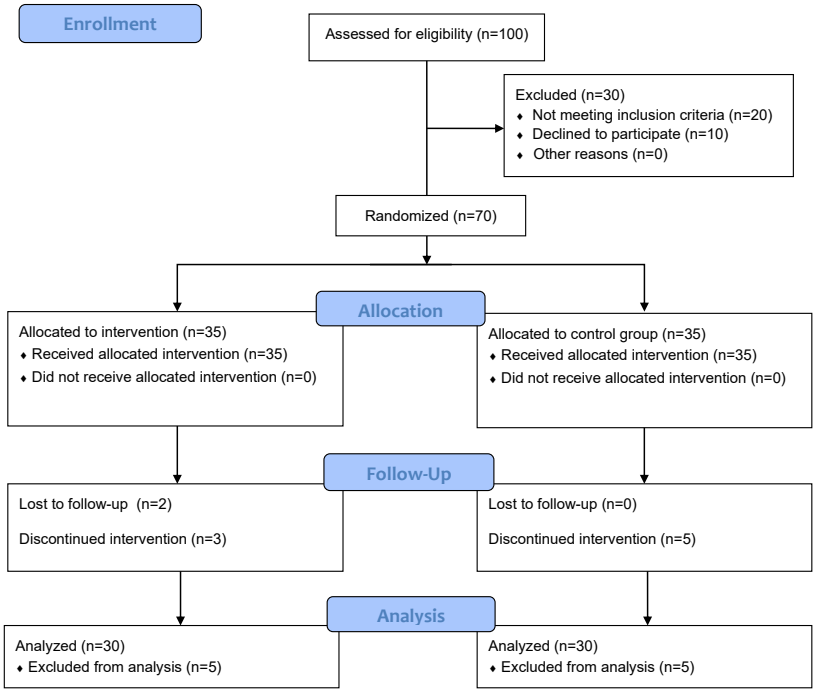

Figure 1. CONSORT Flow Diagram.

intervention groups using the chi-square test. According to the results, oligomenorrhea was borderline significantly decreased in the intervention group after treatment (P=0.069) (Table 3).

Discussion

This is the first study to investigate the effect of chamomile on patients with PCOS. According to the results, the volume of ovaries on day 12 of the third cycle in the chamomile group was significantly lower than the control group. In this study, most follicles were examined before treatment, as well as in the first and third cycles of treatment. There was a statistically significant difference between the two groups only in the third cycle, so that the dominant follicles were higher in the chamomile group.

The exact etiology of PCOS is still unclear. Research showed that in PCOS, some endocrine disorders reinforce each other. These disorders include defects in hypothalamic-pituitary axis function, ovarian function, and adrenal function. PCOS is associated with abnormal secretion of gonadotropins (LH and FSH), increased ovarian steroid secretion, and insulin resistance. Increasing the amount of LH increases the production of androgens. Increased secretion of androgens is one of the most important features of the ovaries in PCOS. In this condition, the ovaries produce large amounts of testosterone, androstenedione, and dehydroepiandrosterone, but elevated serum testosterone is more common (7). PCOS causes histological abnormalities such as bilateral ovarian enlargement, the presence of more than 12 follicles less than 10 mm in size around the central dense stroma, increased follicular sheath thickness, and ovarian stroma due to increased angiogenesis, vasculogenesis, and ovarian blood flow, decreased or no ovulation that becomes chronic and leads to infertility (15). Welschen showed that an increase in LH levels is needed for the final stages of follicular development in adult hypophysectomized rats treated with pregnant mare serum gonadotropin. However, a steady increase in this hormone is a major problem for patients with this syndrome, as egg release

Table 1. Comparison of Ovarian Volume and Dominant Follicle in Placebo and Intervention Groups

Characteristics	Placebo (n=30)	Intervention (n=30)	*P* Value
Ovarian volume on day 3 of the first cycle	15 (50%)	13 (43.3%)	0.605[a]
Ovarian volume on day 12 of the first cycle	16 (53.3%)	13 (43.3%)	0.438[a]
Ovarian volume on day 12 of the third cycle	17 (56.7%)	8 (26.7%)	0.018[a]
Dominant follicle on day 3 of the first cycle	1 (3.3%)	3 (10%)	0.612[b]
Dominant follicle on day 12 of the first cycle	2 (6.7%)	5 (16.7%)	0.424[b]
Dominant follicle on day 12 of the third cycle	9 (30%)	15 (50%)	0.114[a]

[a] Chi-square; [b] Fisher's exact test.

Table 2. Comparison of Dominant Follicles in Placebo and Intervention Groups

Characteristics		Placebo (n=30)	Intervention (n=30)	*P* Value[a]
Dominant follicles before treatment	No	28 (93.3%)	27 (90%)	0.579
	Mono	2 (6.7%)	0 (0%)	
	Multi	0 (0%)	3 (10%)	
Dominant follicles in the first cycle	No	28 (93.3%)	25 (83.3%)	0.184
	Mono	2 (6.7%)	0 (0%)	
	Multi	0 (0%)	5 (16.7%)	
Dominant follicles in the third cycle	No	21 (70%)	15 (50%)	0.027
	Mono	9 (30%)	6 (20%)	
	Multi	0 (0%)	9 (30%)	

[a]Mann Whitney U test.

Table 3. Comparison of Clinical Symptoms and Testosterone Levels Before and After Treatment in Placebo and Intervention Groups

Characteristic	Placebo (n=30)	Intervention (n=30)	*P* Value
Pre-treatment oligomenorrhea	18 (60%)	19 (63.3%)	0.071[a]
Pot-treatment oligomenorrhea	17(56.7%)	10 (33.3%)	0.069[a]
Pre-treatment hirsutism	3 (10%)	23 (76.7%)	<0.001[b]
Pot-treatment hirsutism	3 (10%)	10 (33.3%)	0.028[b]
Intragroup *P* value	<0.001	<0.001	
Pretreatment testosterone	17 (20-64)	30 (25-110.58)	0.346[c]
Post-treatment testosterone	8.5 (20-62)	16.5 (25-57.89)	0.894[c]
Intragroup *P* value	0.005	0.001	

[a] Chi-square; [b] Fisher's exact test; [c]Mann Whitney U test.

requires a sudden increase in LH levels. Accordingly, secondary follicles that form between 28 and 56 days cause a continuous increase in LH concentration and the expansion and stabilization of cysts (13). In the present study, we observed an increase in this series of follicles, which is in line with the results of the study by Welschen.

Zafari et al (16) investigated the effect of chamomile on clinical and biochemical parameters in PCOS patients. In this study, 30 virgin mice were examined, and the control group was treated by intraperitoneal injection at three doses of 75, 50, and 25 mg/kg. The results showed the morphological improvement of ovaries macroscopically and microscopically. The cysts also disappeared significantly and the number of follicles increased. In another study by Johari et al, chamomile significantly decreased estrogen levels but significantly increased progesterone levels. It also significantly reduced the number of graph and primary follicles (11).

In a review study, Arentz et al investigated the effects of treatment and management of PCOS through using herbal medicines. They reviewed 23 studies and a total of 762 women with menstrual disorders were studied. Evidence showed ovulation regulation, improved metabolic hormones, and improved fertility in PCOS patients (17); these results confirm our results.

Chamomile is a phytoestrogen and has anti-estrogenic properties (estrogen reduction). This plant can act as a selective estrogen receptor to regulate endogenous estrogens in people with PCOS and high levels of estrogen (18). Also, chamomile has progestogenic properties that are effective in the treatment of PCOS (19).

The results of current study can pave the way for further studies on the use of chamomile in the treatment of PCOS, so that the ovulation induction and quality of life be improved in these patients. The present study had two major limitations. First, the sample size was relatively low. Second, due to genetic and diet differences, it was not possible to make accurate comparisons.

Conclusions

In general, the chamomile treatment regimen increased the dominant follicle and thus affected the induction of ovulation in patients with PCOS. Therefore, chamomile can be used as a simple, safe, and low-cost drug to treat patients with PCOS. However, further studies are needed to confirm our results.

Authors' Contribution

Conceptualization: Masumeh Ghazanfarpour.
Methodology: Masumeh Ghazanfarpour.
Validation: Malihe Afiat.
Formal analysis: Mona Najaf Najafi.
Investigation: Mona Najaf Najafi.
Resources: Naghmeh Khorsand, Azam Akbari Lor,
Data curation: Azam Akbari Lor.
Writing–original draft: Masumeh Ghazanfarpour,Malihe Afiat
Writing–review and editing: Malihe Afiat, Naghmeh Khorsand, Azam Akbari Lor, Mona Najaf Najafi, Masumeh Ghazanfarpour.
Visualization: Naghmeh Khorsand, Azam Akbari Lor.
Supervision: Malihe Afiat.
Project administration: Malihe Afiat.

Funding acquisition: Malihe Afiat.

Conflict of Interests
Authors declare that they have no conflict of interests.

Ethical Issues
The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Iran (code: IR.MUMS.fm.REC.1396.444) and it was registered in the Iranian Registry of Clinical Trials (identifier: IRCT20170315033085N3).

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References
1. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol. 2010;203(3):201.e1-201.e5. doi:10.1016/j.ajog.2010.03.008
2. Antoaneta G, Kamenov Z, Tsakova A. Myeloperoxidase levels in patients with PCOS and/or obesity before and after metformin treatment. Int J Womens Health Reprod Sci. 2015;3(1):21-24. doi:10.15296/ijwhr.2015.04
3. Mehta J, Kamdar V, Dumesic D. Phenotypic expression of polycystic ovary syndrome in South Asian women. Obstet Gynecol Surv. 2013;68(3):228-234. doi:10.1097/OGX.0b013e318280a30f
4. Dumesic DA, Goodarzi MO, Chazenbalk GD, Abbott DH. Intrauterine environment and polycystic ovary syndrome. Semin Reprod Med. 2014;32(3):159-165. doi:10.1055/s-0034-1371087
5. Mohammadi M. Oxidative stress and polycystic ovary syndrome: a brief review. Int J Prev Med. 2019;10:86. doi:10.4103/ijpvm.IJPVM_576_17
6. Tang R, Ding X, Zhu J. Kisspeptin and polycystic ovary syndrome. Front Endocrinol (Lausanne). 2019;10:298. doi:10.3389/fendo.2019.00298
7. Marx TL, Mehta AE. Polycystic ovary syndrome: pathogenesis and treatment over the short and long term. Cleve Clin J Med. 2003;70(1):31-45. doi:10.3949/ccjm.70.1.31
8. Srivastava JK, Pandey M, Gupta S. Chamomile, a novel and selective COX-2 inhibitor with anti-inflammatory activity. Life Sci. 2009;85(19-20):663-669. doi:10.1016/j.lfs.2009.09.007
9. Cemek M, Kağa S, Simşek N, Büyükokuroğlu ME, Konuk M. Antihyperglycemic and antioxidative potential of *Matricaria chamomilla* L. in streptozotocin-induced diabetic rats. J Nat Med. 2008;62(3):284-293. doi:10.1007/s11418-008-0228-1
10. El-Halawany AM, El Dine RS, Chung MH, Nishihara T, Hattori M. Screening for estrogenic and antiestrogenic activities of plants growing in Egypt and Thailand. Pharmacognosy Res. 2011;3(2):107-113. doi:10.4103/0974-8490.81958
11. Johari H, Sharifi E, Mardan M, et al. The effects of a hydroalcoholic extract of *Matricaria chamomilla* flower on the pituitary-gonadal axis and ovaries of rats. Int J Endocrinol Metab. 2011;9(2):330-334. doi:10.5812/kowsar.1726913X.1822
12. Heidary M, Yazdanpanahi Z, Dabbaghmanesh MH, Parsanezhad ME, Emamghoreishi M, Akbarzadeh M. Effect of chamomile capsule on lipid- and hormonal-related parameters among women of reproductive age with polycystic ovary syndrome. J Res Med Sci. 2018;23:33. doi:10.4103/jrms.JRMS_90_17
13. Welschen R. Amounts of gonadotrophins required for normal follicular growth in hypophysectomized adult rats. Acta Endocrinol (Copenh). 1973;72(1):137-155. doi:10.1530/acta.0.0720137
14. Franks S. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: in defense of the Rotterdam criteria. J Clin Endocrinol Metab. 2006;91(3):786-789. doi:10.1210/jc.2005-2501
15. Karimzadeh L, Nabiuni M, Mohseni Kouchesfehani H, Adham H, Bagheri A, Sheikholeslami A. Effect of bee venom on IL-6, COX-2 and VEGF levels in polycystic ovarian syndrome induced in Wistar rats by estradiol valerate. J Venom Anim Toxins Incl Trop Dis. 2013;19(1):32. doi:10.1186/1678-9199-19-32
16. Zafari Zangeneh F, Minaee B, Amirzargar A, Ahangarpour A, Mousavizadeh K. Effects of chamomile extract on biochemical and clinical parameters in a rat model of polycystic ovary syndrome. J Reprod Infertil. 2010;11(3):169-174.
17. Arentz S, Abbott JA, Smith CA, Bensoussan A. Herbal medicine for the management of polycystic ovary syndrome (PCOS) and associated oligo/amenorrhoea and hyperandrogenism; a review of the laboratory evidence for effects with corroborative clinical findings. BMC Complement Altern Med. 2014;14:511. doi:10.1186/1472-6882-14-511
18. Rodriguez-Fragoso L, Reyes-Esparza J, Burchiel SW, Herrera-Ruiz D, Torres E. Risks and benefits of commonly used herbal medicines in Mexico. Toxicol Appl Pharmacol. 2008;227(1):125-135. doi:10.1016/j.taap.2007.10.005
19. Mirzakhani Z, Hosseini SE. Effects of chamomile hydro-alcoholic extract (*Matricaria chamomilla*) on the aborted fetuses, serum sex hormones and ovarian follicles in adult female rats. J Ardabil Univ Med Sci. 2017;17(1):22-31. [Persian].