



RESEARCH ARTICLE

COMPARATIVE STUDY OF THE EFFECTS OF TREATMENT WITH HERBAL PRODUCT SHILANUM AND HIGH-DOSE CONTRACEPTIVE PILLS ON FUNCTIONAL OVARIAN CYSTS

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ABSTRACT

Background: Functional ovary cysts (FOC) are among the most common problems in women of reproductive age. Present treatment consists of either high-dose birth control pills or surgery while preserving ovarian tissue. Recent studies have questioned the effectiveness of birth control pills, with some studies even showing them to be ineffectual. The incidences of side effects, therapeutic failure, and unnecessary surgeries for ovarian functional cysts have led us to perform this study comparing the effects of an herbal product of jujube and high-dose birth control pills on FOC regression.

Materials and Methods: Sixty women of childbearing age with functional ovarian cysts with diameters of 2-6 cm were randomly divided into two groups that received either high-dose contraceptive pills or Shil anum capsules, a herbal product with an extract of jujube as its active ingredient. Cyst regression was evaluated by transvaginal ultrasound examinations on the second or third day of the second menstrual cycle or after one month and repeated the following month in the case of persisting cysts. Data were analyzed using Chi-square and t-tests as well as other analytical tests where necessary.

Results: Sixty patients with a diagnosis of functional ovarian cyst were enrolled. However, at the end of the study, given that some patients failed to refer for further ultrasound evaluation and were inaccessible, data from 26 subjects in the high-dose birth control pill (HD) group and 27 in the Shil anum group were analyzed. Baseline characteristics such as education, professional status, and medication intake were similar. The average age of all participants was 32.61±7.35 years, all of whom were married. Average cyst size before treatment was 27±7mm in the HD group and 39±14mm in the Shil anum group. After treatment, cysts regressed in all patients except for two patients in each group.

Conclusion: The Shil anum herbal product with an extract of jujube as its active ingredient was effective on the regression of functional ovarian cysts in more than 90% of cases without any side effects. Since its effect was similar to HD pills, it can be suggested as an alternative to oral contraceptive pills (OCPs) in treating functional ovarian cysts. However, due to the fact that this is the first study with this combination, further studies with larger sample sizes are recommended.

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INTRODUCTION

Functional ovary cysts (FOC) (follicular cysts and corpus luteum cysts) are among the most common problems in women of reproductive age all over the world. Routine ultrasound scanning in gynecologic examinations has led to increased cases of diagnosis. According to recent reports, annually

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250,000 women are diagnosed with functional ovarian cysts (Bottomley and Bourne, 2009; Christensen et al., 2002). A significant problem in comparative studies of FOC pertains to differing definitions in terms of cyst size (Christensen et al., 2002; Kozak et al., 2005). These cysts are usually on one side, have a single mass with smooth, uniform walls with sizes ranging from 2-8 cm (Kozak et al., 2005; Whiteside and Keup, 2009). Such cysts disappear 65% of the time in the subsequent menstruation cycle with only 35% persisting in later examinations (Christensen et al., 2002; Kozak et al., 2005). While many of these physiologic cysts disappear on their own,

as a result of stability, pain, discomfort, risk of underlying cancer, and such complications such as hemorrhage, rupture, or torsion, some cysts require surgical intervention (Bottomley and Bourne, 2009; Whiteside and Keup, 2009; Grimes *et al.*, 2014). Surgery is reported to be performed in 15-30% of FOC cases since diagnostic measures, specifically ultrasound-guided aspiration, cannot differentiate between organic and functional cysts. In one study, over 60% of patients suspected of organic cysts received unnecessary surgery (Grimes *et al.*, 2014; Spanos, 1973). The most common types of organic cysts during the reproductive ages include endometrioma, teratoma, and cystadenoma (Spanos, 1973). Since it has been observed that oral contraceptive pills (OCPs) with high doses of estrogen reduce the prevalence of functional ovarian cysts, many physicians have concluded that contraceptive pills are effective in the treatment of such cysts and they have thus been utilized as a common clinical treatment since 1970 (Bottomley and Bourne, 2009). In a study of 29 women having FOC with an average cyst size of 2-3 cm and a maximum size of 5.7 cm, it was determined that monophasic low-dose OCPs play a preventive role against emergence of FOCs (Curtin, 1994). Also another study demonstrated the greater effect of OCPs in regression of FOCs compared to monitoring of patients without any treatment (Whiteside and Keup, 2009). Recent epidemiologic studies report an inverse relationship between use of OCPs and emergence of FOCs leading to surgery.

Following this finding, it was reasoned that OCPs are just as effective in treatment of FOCs as they are in their prevention. Even though recent studies have not shown a relationship between use of OCPs and regression of functional ovarian cysts, OCPs are still used for their treatment (Bottomley and Bourne, 2009). Some studies have used of high-dose OCP formulas for treatment of FOCs. The risk to benefit ratio of such medications must be evaluated (Curtin, 1994). Regardless of numerous studies showing conflicting opinions in this regard, many physicians prescribe high-dose OCPs for treatment of functional ovarian cysts. When surgery is indicated, the treatment of choice is removal of the ovarian cyst(s) while preserving ovarian tissue (Holt *et al.*, 1992). Some indications for surgery include large cysts, multiple cysts, existence of septa, presence of solid areas, torsion, and intra-abdominal hemorrhage. In other cases and where the cyst is suspected of being functional, use of analgesics is preferred over surgery to prevent surgical complications such as adhesions and subsequent infertility (Lanes *et al.*, 1992). In this regard, medicinal plants have long been considered as alternative treatment methods. Availability, history of use, natural origins, and relative safety of medicinal plants as well as side effects of synthetic medicines are among the reasons for renewed interest in such plants. Therefore, in the past two decades, researchers have started to reevaluate medications with natural origins. Nowadays, natural-based medications are becoming much more commonplace, and the use of medicinal plants is encouraged by the WHO Traditional Medicine Strategy 2014–2023 which has been developed and launched in response to the World Health Assembly resolution on traditional medicine (World Health Assembly, 2014). It is not appropriate to examine thousands of synthetic substances developed by researching students to discover the possible effects on a particular disease. Furthermore, synthetic production of some active biologic substances is not possible due to unknown or complex chemical structures. It is therefore necessary to resort to natural resources in order to utilize such medications. Accordingly, the correct methodology for rapid

scientific discovery of new medications is to perform research on materials and plants with relatively known effects. Ovarian cysts are among a group of disorders that are collectively entitled “*sal’eh*” in Persian traditional medicine, which is included in the category of ‘cold edemas’. According to traditional medicine, jujube is neutral in nature (neither warm nor cold), has anti-ulcer and anti-inflammatory properties, and dissolves and expels harmful substances from the body. Therefore, it may be helpful in treating such cysts. Considering its properties as well as the disease mechanisms, this natural medication has been utilized for possible treatment of functional ovarian cysts in Persian traditional medicine (Zargari and GiahaneDaru’I, 1991). *Shilanum* is a plant-based product produced from the jujube plant. The medicinal part of the *Ziziphusjuzuba* Mill plant consists of an edible, fleshy, oval-shaped fruit named jujube. In English, it is also called red date and Chinese date. It is a bit sweet with a smooth consistency. It includes phenolics, carbohydrates, proteins (about 2.73-6.43%), organic minerals and vitamin C (Zargari and GiahaneDaru’I, 1991). High quantities of cAMP and cGMP have been identified in the jujube fruit (Cyong, 1981). Oleic acid is the predominant fatty acid in the fruit. Sitosterol, stigmasterol, and desmasterol have also been found in the fruit (Al-Khatib *et al.*, 1987). Jujube is consumed as a laxative and sedative (Gong Cheng *et al.*, 2000). It is used in the treatment of atherosclerosis and asthma, for strengthening the teeth and throat, cleansing and generating blood, reducing inflammation and warm nature, treatment of liver, kidney, bladder, edemas, and rashes (AlaviKhorassani, 2007). It is also used to counter plaque and caries (Zargari and GiahaneDaru’i, 1991). In Persian traditional medicine sources, it is cited that jujube dissolves or purges cardinal humors, soothes the chest and viscera and eliminates ferocity. The fruit of the jujube has nucleic acids, vitamin A, vitamin C, and zinc sulfate is used to prevent infection, cancer, and AIDS (Prepn, 2016). In addition, the jujube fruit contains active ingredients that gather free radicals and is therefore considered an antioxidant. Moreover, it has anticoagulant, anti-inflammatory, and anti-histamine effects (Agata Maria Pawlowska *et al.*, 2009; Tahergorabi *et al.*, 2015). Its anti-inflammatory and antioxidant effects have been utilized in facilitating response to ovarian cancer treatments (Agata Maria Pawlowska *et al.*, 2009; Ray and Dewanjee, 2015; Gupta, 2004). The jujube fruit is effective in controlling the flow of ions across cell membranes. Its local anesthetic and muscle relaxant effects are due to this property. Furthermore, this fruit exerts inhibitory effects on neuronal membrane hyperexcitability, which justifies its sedative effects (Hill, 1995). It stimulates nitric oxide release, reduces blood pressure by increasing renal blood flow, and has antinephritic effects (Kim *et al.*, 1996). The high incidence of functional ovarian cysts, lack of definitive treatment, side effects of available treatment methods, risk of persistence of cysts leading to unnecessary surgeries, and surgical complications such as infertility as well as the increasing orientation of patients toward complementary medicine and herbal products has led us to examine the effects of the plant-based oral capsule, *Shilanum*, in regression of functional ovarian cysts.

MATERIALS AND METHODS

The study is a double-blind clinical trial with a sample of 60 women of reproductive age (18-45 years old) suffering from functional ovarian cysts. Patients with cysts sizes between 2-6 cm were entered into the study after filling out informed consent forms.

Table 1. Underlying variables of the two groups

Profile	High-dose OCP Group (A)	Shil anum (B)	P-Value
Age:	31.64±7.25	32.36±6.34	0.569
Education:			0.443
1. Below high-school diploma	10 (38.5%)	4 (14.8%)	
2. High-school diploma or above	16 (61.5%)	23 (83.2%)	
Employment:			0.375
1. Housewife	21 (80.7%)	22 (81.5%)	
2. Employed	5 (19.3%)	5 (18.5%)	
Medication History:			0.133
1. Positive	15 (55%)	20 (77%)	
2. Negative	11 (45%)	7 (23%)	

Table 2. Cyst size prior to treatment and response in the two groups

Profile	High-dose OCP Group (A)	Shil anum (B)	P-Value
Cyst size prior to treatment (mm)	27±7	39±14	0.0001
Patients with complete response to treatment (cyst regression)	24 (92.3%)	25 (92.5%)	0.813
Patients with lack of response to treatment	2 (7.7%)	2 (7.5%)	

All participants were approved in terms of negative cyst history, lack of hormonal disorders (TSH and prolactin tests), and benignity of cysts based on patient history, examination, ultrasound, and evaluation of markers such as CA125. Participants were selected from among patients of the infertility clinic of Imam Khomeini Hospital. After cysts were confirmed through ultrasound, patients were randomly (using random numbers) entered into two groups: group A (HD OCPs) and group B (Shil anum plant-based product). In each group there were 30 participants. Both physicians and patients were unaware of treatment type provided to each group. For one month, patients in group A were treated with high-dose oral contraceptive pills once every day, and group B was treated with the oral plant-based product, Shil anum, obtained from the extract of jujube. Medications were given to patients in each group in the form of identical capsules. After completion of the treatment period, cyst sizes were examined using ultrasound, and results were recorded in prepared forms. Also if the cyst had not regressed in the first cycle the patient was afforded with 30 more pills and reexamined by ultrasound after completing treatment, during the following menses. Data from examination, observation, and ultrasound before and after treatment period were gathered in questionnaires. Data included age, duration of disease, patient hormone chart, and cyst size prior and subsequent to treatment. Primary and secondary outcomes included cyst regression and side effects of medications, respectively. After collection, data were entered into SPSS version 19 and analyzed based on study aims using descriptive and analytical statistics including the chi-square test and t-test. Finally, the results were analyzed and the therapeutic effects of Shil anum were evaluated and compared with the effects of high-dose OCPs. Statistical confidence and power were 95% ($P < 0.05$) and 80% respectively.

RESULTS

Of 60 patients, 53 patients remained in the study until the end including 26 in group A and 27 in group B. A total of seven patients were excluded from the study for not referring for ultrasound and lack of access. There was no significant difference between the groups in terms of underlying variables such as education, employment, and medication history. The average age of participants was 32.61 ± 7.35 and all were married (Table 1). Prior to treatment, ovarian cyst size in group

B was significantly higher. Cyst size reached 0 after treatment in both groups with the exception of two patients in each group who had persisting cysts (Table 2).

DISCUSSION

Among women of reproductive age worldwide, FOCs number among the most common ailments. Most patients with ovarian cysts are asymptomatic. Such cysts are usually inadvertently diagnosed during ultrasound or routine examinations of women (Bottomley and Bourne, 2009; Christensen *et al.*, 2002). However, some cysts may be associated with a wide range of symptoms, sometimes severe, such as pain or discomfort in the lower abdomen, left or right side pelvic pain, severe pain caused by torsion or rupture, pain or discomfort caused by intercourse, difficulty having bowel movements, frequent urination, menstrual cycle irregularities, menometrorrhagia, tachycardia, and hypotension caused by cyst rupture (Kozak *et al.*, 2005). While numerous studies and Cochrane Reviews illustrate that these cysts usually regress on their own, OCPs have been used for treatment for many years due to their function in prevention of such cysts (by preventing ovulation). As surgery sometimes becomes necessary, loss of the ovaries is a possibility, and side effects and contraindications of OCPs can be significant, it was necessary to seek out safe and effective alternatives. Three Cochrane Reviews including reviews of eight randomized controlled clinical trials with 668 samples, seven trials studying 500 patients, and four trials examining 227 patients from four countries were examined and all indicated that treatment with combined oral contraceptive pills do not facilitate regression of functional ovarian cysts, whether cysts that occur on their own or incidents that occur after ovulation stimulation. The majority of cysts dissolve on their own within several menstrual cycles. Persisting cysts are usually neoplastic and not physiologic (Grimes *et al.*, 2014; Grimes *et al.*, 2009; Grimes *et al.*, 2006). In a 2004 case study in India, 33 types of plants and traditional remedies having properties similar to contraceptive and ovulation-inducing medications were studied. One of these plants was Ziziphus (from which jujube and Shil anum are derived) which has similar properties to contraceptive medicines with far fewer side effects (Anita Jain *et al.*, 2004). In a different study, it was shown that an extract of this plant can act as a contraceptive due to its inhibitory effect on delta(5)-3beta-hydroxysteroid dehydrogenase (delta(5)-3beta-HSD) and glucose-6-phosphate

dehydrogenase (G-6-PDH), which are the main enzymes involved in ovarian steroidogenesis (Gupta *et al.*, 2004). Similar results have been observed in animal models. By inhibiting the enzymes mentioned above without changing blood profile, significant contraceptive effects of this plant were observed (Gupta *et al.*, 2004). Considering the results of the present study, which corroborates the positive effect of *Shil anum* in regression of ovarian cysts, various mechanisms relating to properties of jujube may be involved including its effects on the cardinal humors in addition to its contraceptive effects. Therefore, if this mechanism is confirmed it seems that, considering *Shil anum*'s lack of side effects, it can be employed both for treatment of cysts and for prevention of pregnancy in patients of advanced age or where there are contraindications for use of OCPs.

Conclusion

Since the plant-based product *Shil anum* (jujube) has effects similar to OCPs in the regression of functional ovarian cysts, due to its lack of side effects it can be proposed as a new medication for treatment of FOCs. Furthermore, since this is the first study of its kind, further research with larger sample sizes are strongly recommended.

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