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Comparison of Hormone Therapy with Expectant Management in the Clinical Management of Functional Ovarian Cysts: A Randomized Clinical Trial

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Abstract

Introduction: The current study aimed at comparing the effect of oral contraceptive pills (OCPs) with expectant management in treatment of functional ovarian cysts. The study was conduct to compare the effect of hormone therapy with expectant management in the treatment of functional ovarian cysts. Hormone therapy for functional cysts is widely used in clinical practices, but the efficacy of this treatment is not determined.

Methods: The current randomized, clinical trial was performed on 50 females with functional ovarian cysts (40 to 95 mm in diameter) in reproductive age, within the age range of 18 to 48 years, referred to the Clinic of Gynecological Diseases in a private hospital as outpatient from May 2015 to September 2016. The cysts were identified by transvaginal ultrasonography. All the patients had stable vital sign, mild to moderate abdominal discomfort. The patients were randomly divided into two equal groups and followed for eight consecutive weeks. Group A (n= 25) was observed without hormone therapy, only with some analgesics if needed, and the Group B (n=25) received OCPs. After follow-up period, cysts improvement status was compared between the groups.

Results: Although nonsignificant, the chance of recovery reduced in patients with each passing year [(odds ratio (OR) =0.985; 95% confidence interval (CI): 0.902-1.077]. In addition to the insignificant results, the odds of improvement in the severe and moderate pain groups were 0.777 and 2.023 times higher than that of the mild pain group. The feeling of heaviness increased the odds of improvement by 1.161. As well, the patients who had cysts for more than three months were 1.264 times more prone to recovery than the ones with younger cysts. Nausea and the absence of internal echo inside the cysts decreased the odds of improvement. However, the impact of none of the abovementioned factors was significant on the treatment of cysts.

Conclusions: Based on the results of the current study, the expectant management is as effective as OCPs for the treatment of functional ovarian cysts; in other words, the rate of disappearance of functional ovarian cyst was not affected by OCP use. However, further studies with larger sample sizes are needed to increase the study power and obtain more conclusive results.

INTRODUCTION

Ovarian cyst is a blister-like sac, which is formed on the surface of ovary during or after ovulation [1]. Most of them are made in reproductive age and are harmless [2]; these cysts do not cause any symptom and are resolved without treatment [3], but sometimes they cause health problems that require special attention, and even may lead to infertility [4]. Normal function of ovary is the periodic release of eggs and the production of the steroid hormones of estradiol and progesterone [5]. Both activities are integrated in the continuous repetitive process of follicle maturation, ovulation, and corpus luteum formation and regression. Mature follicle is ruptured and releases egg during ovulation and corpus luteum is produced from empty follicle [6]; if pregnancy

does not occur corpus luteum is regressed, due to the absence of hCG (human chorionic gonadotropin). Sometimes this procedure does not happen normally, which results in the formation of ovarian cysts [7]. Therefore, functional ovarian cysts are different from ovarian growths induced by other pathological problems [8]; most of them regress spontaneously in two or three cycles [9], but if a cyst gets large, it can twist, be ruptured, or bleed and become very painful [10]. A functional type of ovarian cyst forms because of slight changes in the way of making or releasing an egg by the ovary [11]. There are two types of such cysts: 1. The follicular cyst, which occurs when the sac on ovary does not release an egg and the sac swells up with fluid, 2. The luteal cyst, which is formed when the sac releases an egg and then reseals and fills with fluid [12]. Most functional ovarian cysts are asymptomatic [13], the larger the cyst, the more likely the symptom. The symptoms are pain or aching in lower abdomen, menstrual irregularity, vaginal bleeding, dyspareunia, etc.; sometimes the cyst is ruptured and causes peritoneal irritation with presentations such as nausea and vomiting or sudden onset of pain, hemorrhagic cyst, intra-abdominal bleeding, and emergency conditions [14]. Some other manifestations such as nausea and vomiting may be felt before the occurrence of such events [15]. Regular pelvic examination is recommended for some patients with the history of such cysts; they also may need regular sonography [16]. Oral contraceptive pills (OCPs) are prescribed by some physician to shrink the cyst, if it is persistent and makes discomfort [17]. Although it seems that they are not effective enough compared with close observation, and even some researchers reported no benefits for OCPs, some others prescribed them before any surgical practices [18]; therefore, the current study aimed at evaluating this issue. For this purpose, some patients who referred to a private clinic were selected in order to compare the effect of OCPs with close observation in the clinical management of functional ovarian cysts.

METHODS

The current randomized, clinical trial was performed on 215 patients referring to the Gynecology Clinic in Alghadir Hospital as well as private offices in Tehran, Iran, from May 2015 to September 2016. In the current study, 145 patients were excluded due to exaggeration of the symptoms, need for surgery, etc.; therefore, 70 patients participated in the study. All patients were selected randomly based on the computer-generated list. Demographic characteristics of the subjects were collected by a questionnaire; the subjects were defined as outpatient because of stable vital signs and no need for hospitalization; all of them had functional ovarian cysts based on vaginal ultrasound findings performed by the same specialist. The size of ovarian cysts ranged 40 to 95 mm in diameter; most of the patients had mild to severe lower abdominal pain, feeling pressure, dyspareunia, or the cysts may be found accidentally on voluntary sonography without any symptoms. Finally, 20 patients lost to follow-up due to exacerbation of conditions or other reasons; hence, a total of 50 patients were studied for eight weeks. Inclusion criteria were being in reproductive age from 18 to 48 years, euthyroidism, euprolactinemia, normotensive, no history of cystectomy, lack of overweight (body mass index (BMI) < 30 kg/m^2), and having only functional cysts. Exclusion criteria were history of infertility, polycystic ovary (PCO) syndrome, endometrioma, dermoid cysts, and OCPs consumption during the last year. The patients were randomly divided into two equal groups:

Group A were considered as the expectant management group without any medication, and Group B received OCPs. Both groups were followed up for eight consecutive weeks. After history-taking and preliminary examinations, ultrasonography was performed for each patient to confirm the presence of 40-95-mm cysts. Based on the assignments, patients received or not received medication. The participants' demographic and medical data such as age, level of pain, feeling heaviness in pelvis, nausea, duration of cyst formation (± 3 months), and echogenic cysts were recorded and both groups were compared accordingly. Patients attending the clinic on every Wednesday were allocated to either expectant management or OCPs consumption groups. Group A were only given some analgesics, if they had an endurable pain, while group B were given low-dose OCPs for eight consecutive weeks. During follow-up period, all patients had the emergency call number to report any problem and were examined and evaluated weekly. The groups were compared based on the obtained data on nausea, feeling of pressure in the pelvis, echogenic cysts, and mild (a little sense of pressure, no need analgesic), moderate (any discomfort often need to use analgesic), or sever (permanent discomfort that causes continually use of analgesics) pain scored base on VAS (visual analogue scale; a method to measure a characteristic or attitude that is believed to range across a continuum of values).

Statistical Analysis

The descriptive characteristics of the continuous and categorical variables are expressed as mean (standard deviation (SD) and frequency (percentage), respectively. The normality assumption of the continuous variables was assessed by the Kolmogorov-Smirnov test. The comparison between the continuous variables was done by independent samples t test. The cross tables between the categorical variables was analyzed using chi-square test. Logistic regression is a common statistical tool for predicting a binary outcome. In the employed model, the relationship between the independent and dependent variables was a logit function (the natural logarithm of odds), and not a linear one. The model was formulated as

follows: $\text{Log}\left(\frac{\text{p(y=Improvement)}}{\text{p(y=Not improvement)}}\right) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_k X_k + \varepsilon$

In the employed formula, $X_1, X_2, \ldots, X_k$ are the independent variables, and $\alpha, \beta_1, \beta_2, \ldots, \beta_k$ are the regression parameters, which should be estimated through the data. Statistical analysis was performed with SPSS version 16.0 (Chicago, IL, USA). All statistical tests were two-sided, and a P-value < 0.05 was considered the level of significance.

RESULTS

Based on the data obtained from 50 cases, 28 (56%) were improved and the mean (SD) was 30.280 (7.216). The descriptive statistics of the variables in two categories of improvement are shown in Table 2.

Table 1: Descriptive Statistics of Variables in Different Groups

Variable	Total, N (%)	Group, N (%)		P-value
		A	B	
Age	30.280 (7.216)	30.120(7.031)	30.440(7.539)	0.877
Pain				0.875
Mild	22(44)	12(54.5)	10(45.5)	
Moderate	17(34)	8(47.1)	9(52.9)	
Severe	11(22)	5(45.5)	6(54.5)	
Heaviness				0.377
No	32(64)	14(43.8)	18(56.3)	
Yes	18(36)	11(61.1)	7(38.9)	
Nausea				0.440
No	42(84)	22(52.4)	20(47.6)	
Yes	8(16)	3(37.5)	5(62.5)	
Duration of cyst formation				0.390
< 3 mo	29(58)	13(44.8)	16(55.2)	
> 3 mo	21(42)	12(57.1)	9(42.9)	
Improvement				0.087
No	22(44)	14(63.6)	8(36.4)	
Yes	28(56)	11(39.3)	17(60.7)	
Internal echo inside the cysts				0.306
Yes	11(22)	4(36.4)	7(63.6)	
No	39(78)	21(53.8)	18(46.2)	

Table 2: Descriptive Statistics of Variables in Different Categories of Improvement

Variable	Improvement, N (%)		P-value
	No	Yes	
Age	30.363(7.537)	30.214(7.093)	0.943
Pain			0.319
Mild	11(50)	11(50)	
Moderate	5(29.4)	12(70.6)	
Severe	6(54.5)	5(45.5)	
Heaviness			0.962
No	14(43.8)	18(56.3)	
Yes	8(44.4)	10(55.6)	
Nausea			0.250
No	17(40.5)	25(59.5)	
Yes	5(62.5)	3(37.5)	
Duration of cysts formation			0.890
<3 mo	13(44.8)	16(55.2)	
>3 mo	9(42.9)	12(57.1)	
Internal echo inside cyst			0.912
Yes	5(45.5)	6(54.5)	
No	17(43.6)	22(56.4)	

None of the unadjusted results were significant in Table 2. In other words, the unadjusted effect of the variables on positive/negative improvement was not statistically significant. The results of logistic regression analysis are shown in Table 3.

Table 3: The Results of Logistic Regression assessing Improvement based on Several Variables

Parameter	Estimate	SE	P-value	OR	OR: 95%CI	
					Lower	Higher
Age	-0.015	0.045	0.744	0.985	0.902	1.077
Pain						
Severe to mild	-0.252	0.832	0.762	0.777	0.152	3.972
Moderate to mild	0.705	0.748	0.346	2.023	0.496	8.776
Heaviness (yes)	0.149	0.677	0.826	1.161	0.308	4.384
Nausea (yes)	-0.833	0.920	0.365	0.435	0.072	2.640
Duration(>3 mo)	0.234	0.657	0.722	1.264	0.348	4.586
Internal (yes)	0.047	0.774	0.952	1.048	0.230	4.786
Group (B)	1.186	0.655	0.070	3.275	0.907	11.822

SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval

Although insignificant, chance of recovery is reduced in patients with each passing year (Odds Ratio (OR) = 0.996, 95% Confidence Interval (CI): 0.907-1.094). The chance of improvement is reduced by each millimeter growth of the cyst in length (OR = 0.969, 95% CI: 0.913-1.029); similarly, the chance of improvement is reduced by each millimeter growth of the cyst in width (OR = 0.997; 95%CI: 0.903-1.101). In addition to the insignificant results, the odds of improvement in the severe and moderate pain groups were 0.859 and 1.717 times higher than that of the mild pain group. The feeling of heaviness increases the odds of improvement by OR of 1.019. As well, those who had cysts for more than three months were 1.211 times more prone to experience improvement. Nausea decreased the odds of improvement. However, none of the abovementioned effect sizes were significant. Based on the results, the adjusted effect of group (medicine/expectation) was statistically significant in such an extent that the odds of improvement in the medicine group was 1.581 times higher than that of the expectation group (95%CI: 1.014-23.299). However, none of the variables affected the status of improvement in the adjusted format. Moreover, the results of receiver operating characteristic (ROC) curve showed an acceptable amount of prediction accuracy in the logistic regression model (Fig 1). Table 4 shows the accuracy of tools evaluated the results of the logistic regression and indicated an acceptable accuracy of the predicted values. Table 4 shows the accuracy of the tools evaluated the results of the logistic regression, which indicate an acceptable accuracy for the predicted values.

Table 4: Accuracy of the Tools Assessed the Results of Logistic Regression

	Estimate	95%CI
Sensitivity	0.68	0.45-0.86
Specificity	0.67	0.47-0.84
Positive predictive value	0.62	0.47-0.75
Negative predictive value	0.73	0.58-0.84
Accuracy	0.68	0.53-0.80
Area under curve	0.70	0.55-0.85

DISCUSSION

Since OCPs were associated with a reduced incidence of functional ovarian cysts [19], epidemiologic studies reported adverse relationships between OCPs consumption and surgical remove of functional ovarian cysts [20]. Short-term treatment with OCPs was thus administered for the initial management of ovarian cysts [21]. However, other meta-analyses showed no difference between OCP consumption and placebo treatment outcomes in ovarian cysts; these masses should be monitored expectantly for several menstrual cycles [22]. If a cystic mass does not resolve after this timeframe, it is unlikely to be a functional cyst, and further workup may be indicated [23]. In postmenopausal patients, a persistent simple cyst smaller than 10 cm in the presence of a normal CA125 value may be monitored with serial ultrasonographic examinations [24]. But some authors prescribed hormone therapy base on the patient's characteristics such as age, size of the cyst, pain, and duration of persistent. Alcazar JL. et al., evaluated the results of expectant management of ovarian cysts with benign ultrasound morphology in asymptomatic premenopausal females [25].

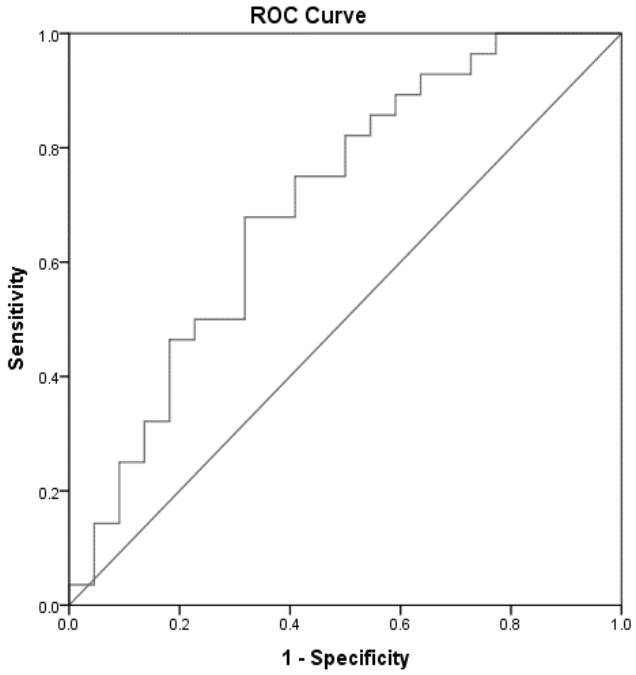

Figure 1: The ROC Curve of the Logistic Regression Results (AUC = 0.70; 95%CI: 0.55-0.85)

In the case of cysts smaller than 80 mm, patients underwent follow-up protocol with transvaginal ultrasound examination with six months intervals for two years, 38.5% resolved spontaneously, 25.5% persisted without change, and 20.8% were surgically removed. They concluded that expectant of cysts with benign morphology is a management option in selected asymptomatic premenopausal females. Also, according to Mackenna's study, 76% of functional ovarian cysts were resolved without any medication in first cycle and the remained ones were treated in the next menstrual cycle; on the other hand, all the persistent cysts were disappeared after the second cycle without any medication [26]. Review of 244 cases of ovarian cysts by Abdulabbar HS in Saudi University showed no benefits for hormone therapy in first and second cycles for resolution of ovarian cysts. Pascual MA conducted a retrospective observational cohort of 408 females with ovarian cysts from 2003 to 2013. During follow-up, 31.8% of females underwent surgery due to physical discomfort and torsion of their cysts. In the current study, authors compared hormone therapy with observation; 56% were improved in the first cycle, although higher proportion in the medicine group were improved (P = 0.087). Ovarian cysts in both groups resolved within two cycles of either expectant management (Group A) or oral contraception (Group B), irrespective of the cyst diameter, feeling of pressure in lower abdomen, and present of internal echogenic cysts. Although the number of patients was small to reach a firm conclusion, the results observed in the current study were in agreement with those reported previously [27]. Steinkampf et al., and Ben–Ami et al., also (Shannon M Grabosch, MD 2017) suggested that the expectant management has the same effectiveness as oral estrogen/progestin therapy for the treatment of functional ovarian cysts [28]. Therefore, it seems unnecessary to prescribe pills to patients with functional ovarian cysts [29]. The authors prescribed low-dose pills, to minimize the possible side effects of OCPs; also the patients showed no interest to use them. Some authors prescribed other hormonal pills and showed resolution of the cysts [30].

CONCLUSIONS

The study demonstrated no significant differences between two groups in the resolution of functional ovarian cyst. Based on the authors' recommendations, if the patient had stable conditions, it is better to inform the patient about the possibility of spontaneous resolution. A larger sample size is required for future evaluation to get more exact conclusions. According to many articles and text books in gynecology, the first option to treat asymptomatic ovarian cysts is the expectant management.

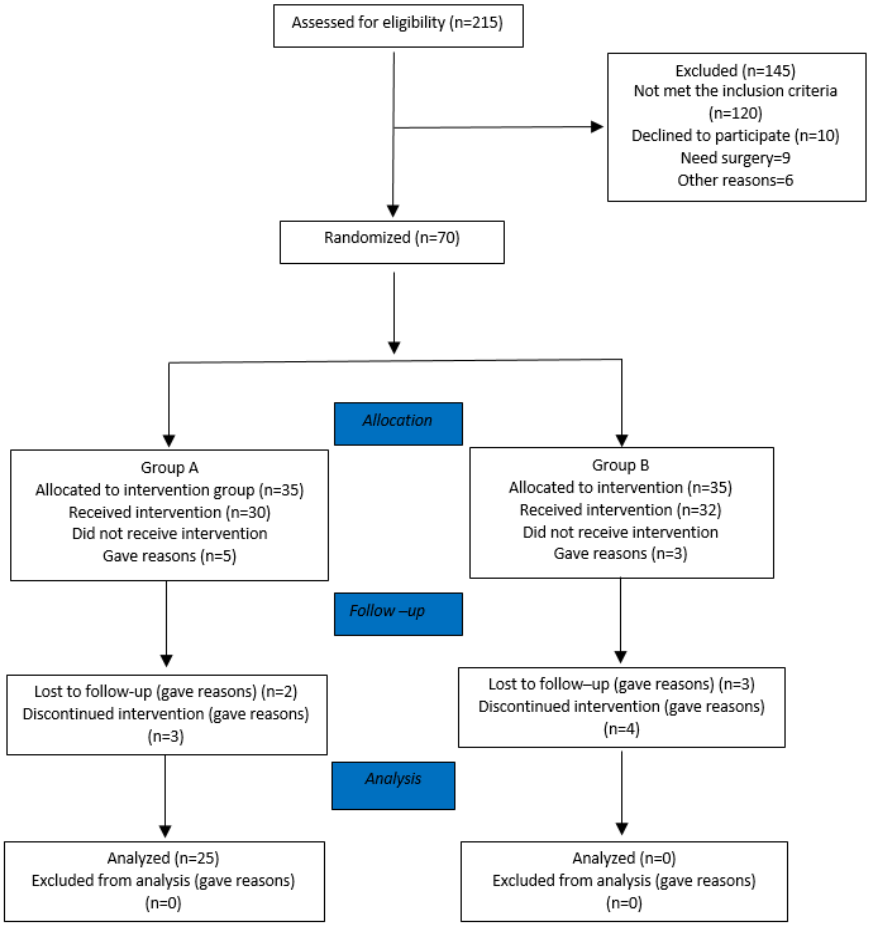

Figure 2: The Flowchart of the Patients' Allocation

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Ethical Consideration

The written informed consent was obtained from eligible woman for participating in the study. The study was approved by the ethics comitte of Shahid Beheshti University of Medical sciences approved under the Code of ethics: IR.SBMU.PHNM.1396.184

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Authors Contribution

Farah Ghasemi developed the original Idea, supervised the study and critically evaluated the manuscript and contributed to the writing process and prepared the final draft. Sanaz Mirzaee was the investigator and carried the study. Payam Amini was the statistical advisor and in volved in data analysis .all authors read and approved the manuscript.

Conflict of Interest

The authors declared no conflict of interest.

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