Comparison of Low-Dose Monophasic Oral Contraceptive Pills and Expectant Management in Treatment of Functional Ovarian Cysts

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Objective: *To compare the effectiveness of low-dose monophasic oral contraceptive pills in the treatment of spontaneously occurring functional ovarian cyst detected by ultrasonography compared with expectant management.*
Material and Method: *A total of 70 women in their reproductive period with functional ovarian cysts detected by means of ultrasonography were randomized to low-dose monophasic Oral Contraceptive pills (OC) or to expectant management and followed up at one month with a second ultrasonography. If the ovarian cysts were still present, the women were followed for another month while on the same treatment.*
Results: *At the first month, the remission rates of ovarian cyst were 63.6% in low-dose monophasic OC and 52.9% in expectant groups. At the second month, the cumulative remission rates increased up to 72.7% in low-dose monophasic OC and 67.6% in expectant groups. There was no statistically significant difference between the two groups at both the first and second month of treatment. The most common side effect in women using OC was acne (18%).*
Conclusion: *Low-dose monophasic OC were no more effective than expectant management in the treatment of spontaneously occurring functional ovarian cysts.*

Keywords: *Oral contraceptive pills, Functional ovarian cyst, Expectant management, Remission rate*

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Ovarian cysts are a common gynecological problem. In women of reproductive age, the prevalence of ovarian cysts is around 7%[1]. Most of these cysts (80-85%) are benign[2], particularly functional ovarian cysts[3]. Functional (physiological) ovarian cysts include both follicular and corpus luteum cysts[4]. Many previous studies have indicated that the use of Oral Contraceptive pills (OC) is associated with a lower risk of occurrence of functional ovarian cysts[5-15]. However, few studies have considered the treatment effect of OC on functional ovarian cysts. In current clinical practice, gynecologists treat functional ovarian cysts with either OC or expectant management alone. Several randomized controlled trials have shown no significant difference in the resolution of functional ovarian cysts treated with OC over expectant management alone[16-21]. Some of these studies were conducted in women receiving ovulation-inducing drugs and high dose OC[16,17], which are not commonly used now for contraception because of more adverse effects than low-dose OC. Only a few recent studies have used low-dose OC compared with observation alone[18-21]. The primary objective of this prospective randomized controlled trial study was to compare the remission rates of spontaneously occurring functional ovarian cysts between treatment with low-dose OC and expectant management at 1 and 2 months.

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Material and Method

Subjects

The women in their reproductive period who attended the outpatient gynecologic clinics for their annual pelvic examination or because of any gynecologic problems in Songklanagarind and Hatyai Hospitals in Songkhla province, Southern Thailand, between August 2003 and April 2005 and were found to have a functional ovarian cyst by ultrasonography were enrolled in the present study. Exclusion criteria were premenarche, postmenopause, history of ovulation induction within three months prior to the study, current user of OC or other hormonal drugs, those having contraindication from OC use, conditions requiring adnexal surgery before the end of the study, history of bilateral oophorectomy, gynecologic malignancy, or pelvic inflammatory disease.

Sample size calculation

There have been a few published randomized controlled trials comparing the effectiveness of OC with expectant management in the treatment of a natural functional ovarian cyst. The sample size was calculated to show a difference of 30% between the remission rates of OC and expectant management with the assumption of remission rate 90% in OC compared with 60% in expectant management. A sample of 32 women in each group was needed with 80% power and α at 0.05.

Study Design

This was an open-label randomized controlled trial conducted in two hospitals. The Ethics Committee of each institute gave approval in August 2003. Women who had a functional ovarian cyst detected by ultrasonography and did not meet any exclusion criteria were informed about the study. If they were willing to enroll in the study, informed consent was obtained, and personal obstetric and gynecological histories were obtained through an interview by one of the authors. They were then allocated to one or other of the treatment groups (OC or expectant management) using block randomization. In the OC group, the women received one package of OC (Microgest ED; ethinyl estradiol 0.03 mg + levonorgestrel 0.15 mg, Schering, Indonesia) and were counseled about how to take OC and informed of possible side effects. They also received a diary card for recording OC intake to be returned to the physician on the day of the next visit. An appointment for the women in both groups was scheduled at 1 month of treatment for the second ultrasonography. If the ovarian cyst did not show remission, the woman continued the same treatment and was followed up in another month by the third ultrasonography. If the ovarian cyst still persisted or had progressed at the second month, the woman was referred to a responsible gynecologist for further management or surgical evaluation.

Assessment

The ovarian cysts were measured on the day that the participants visited the outpatient gynecologic clinic by transvaginal or transabdominal (in the case of the transvaginal route being inaccessible) ultrasonography in 3 dimensions (length x width x height) by a well-standardized gynecological staff member who serviced gynecological patients on a regular basis and did not know the study group. For each woman, the follow-up ultrasonography was performed via the same route as the previous measurement by the same person as the first time.

A functional ovarian cyst is defined as largest dimension between 2-8 cm in diameter, unilateral, uniloculated, thin-walled, anechogenic and has distal acoustic enhancement with none of the following: solid parts, papillary formations, peritoneal masses, intra-abdominal lymph node enlargement or ascites[2,22,23].

The following definitions of outcomes were used: 1. Remission**,** the main outcome measure**,** was defined as ultrasonographic examination being unable to detect the ovarian cyst or the cyst being less than 2 centimeters in the largest dimension; 2. Regression was defined as ultrasonographic examination being able to detect the same ovarian cyst at more than 2 centimeters in size, but with the largest dimension having decreased more than 50% of the pre-treatment measurement; 3. Progression was defined as ultrasonographic examination being able to detect the same ovarian cyst with the largest dimension having increased more than 25% of the pre-treatment measurement; 4. Persistence was defined as ultrasonographic examination being able to detect the same ovarian cyst with the same size or with a decrease in the largest dimension of less then 50% or an increase in the largest dimension of less than 25% of the pre-treatment measurement.

Data analysis

Data were collected and analyzed using SPSS for Windows version 12.0 software. This was an intention-to-treat analysis. The results of the two groups were compared using the chi-square test and

student's t-test as appropriate. Comparisons with $p \leq 0.05$ were considered statistically significant.

Results

Data from 70 subjects were included in the present study. Three subjects were lost to follow up during the study, 2 in the OC group and 1 in the expectant group. This resulted in 67 subjects included in the analysis, 33 in the OC group and 34 in the expectant group (Fig. 1). Only one woman in the OC group discontinued taking the pills during the first month because of difficulty in remembering to take the pills everyday.

The mean ages of women in the OC and expectant groups were 36.7 and 39.1 years, respectively. The mean largest dimensions of the ovarian cysts in the OC and expectant groups were 3.98 and 3.29 centimeters, respectively, which were not statistically significantly different. Other baseline data are shown in Table 1.

After the first month of treatment, the cysts were found to have remission in 21 of the 33 (63.6%) women in the OC group, and in 18 of the 34 (52.9%) women in the expectant group. The difference was not statistically significant (Table 2). One woman in the OC group showed regression. Five women each in the OC and expectant groups, 15.2% and 14.7% respectively, showed progression. Five (15.2%) women in the OC group and 11 (32.4%) women in the expectant group showed persistence. None of these differences were statistically significant (Table 2).

Following the second month, in the OC group, an additional 3 of the remaining women had remission of the ovarian cyst. One was a woman with a progressive ovarian cyst, another was a woman who had had regression of her ovarian cyst in the first month, and the other was a woman who had continued using OC for the 2 months but had been unavailable for the first month checkup. In the expectant group, an additional 5 women had remission. All had shown persistent cysts in the first month. This resulted in cumulative remission rates in the OC and expectant groups in the second month of 72.7% and 67.6%, respectively. Again, the difference was not statistically significant.

The differences in regression, persistence and progression rates at the second month between OC and expectant groups were also not statistically significant. Two women were lost to follow-up at 2 months

Table 1. Baseline characteristics

Characteristics	OC group (n = 35)	Expectant group (n = 35)
Mean age ± SD (yr)	36.7 ±10.1	39.1 ± 6.5
Mean largest dimension ± SD (cm)	3.98 ± 1.54	3.29 ± 0.98
Gravidity(%)		
0	28.6	20.0
1	25.7	17.1
≥ 2	45.7	62.9
Previous OC use (%)	17.0	25.0
Duration (yr), mean ± SD	4.0 ± 2.0	2.0 ± 1.0
Time since last use (mo), mean ± SD	89.0 ± 59.0	121.0 ± 81.0
Current non-hormonal contraception (%)	37.1	40.0

OC = oral contraceptive pills

Table 2. Remission rates in OC and expectant groups at 1 and 2 months

Month(s) of treatment	Remission rate No. (%)		p-value
	OC (n = 33)	Expectant (n = 34)	
1 month	21 (63.6)	18 (52.9)	0.37
2 months	24 (72.7)	23 (67.6)	0.65

OC = oral contraceptive pills
p-value was calculated by chi-squared test

Table 3. Histopathologic results of non-remission ovarian cyst after 2 months in oral contraceptive pills (OC) and expectant groups

Histopathology	No. (%)	
	OC (n = 6)	Expectant (n = 3)
Serous cystadenoma	3 (33%)	1 (11%)
Endometrioma	2 (22%)	1 (11%)
Par-ovarian cyst	1 (11%)	-
Follicular cyst	-	1 (11%)

and could not be contacted by telephone or letter. The women who did not have remission of the ovarian cyst at the second month underwent a laparotomy or laparoscopy. The histopathologic results were reported to be serous cystadenomas in 4 women, endometriotic cysts in 3 women, follicular cyst in 1 woman and par-ovarian cyst in 1 woman (Table 3). The other eight women were followed up further with the gynecologists in our hospital. Most of them were lost to follow-up eventually, whereas 2 women preferred to be treated at a local hospital near their home.

Side effects of low-dose OC were found in 14 of the 33 (42%) women. These were acne 18%, increased body weight 12%, abnormal vaginal bleeding 9%, nausea and vomiting 6%, breast tenderness 6%, and headache 3%.

Discussion

This randomized, prospective, controlled trial failed to provide evidence of superiority of low-dose OC, commonly used in reproductive women for contraception, over expectant management for the treatment of functional ovarian cysts. A large number of ovarian cysts in both groups resolved within one month of treatment and most resolved by the second month, with no statistically significant difference between the two groups. The present study accurately represented the real treatment of functional ovarian cysts in general gynecological practice because the authors enrolled women who had visited an outpatient gynecological clinic for an annual pelvic examination or because of any related symptoms and were found to have a functional ovarian cyst by ultrasonographic criteria. In addition, these women had not received any ovarian stimulation medications and also underwent ultrasonography irrespective of menstrual cycles. This means that the ovarian cysts in the present study could have been either a follicular cyst or a corpus luteum cyst. On the other hand, most previous studies were conducted under conditions wherein the women had received ovulation-inducing drugs[16,17] or had functional ovarian cysts detected by ultrasonography within several days after their last menstrual period[19], and therefore were only follicular cysts. However, when using ultrasonographic criteria to diagnose a functional ovarian cyst, some other types of benign ovarian cysts with features similar to a functional ovarian cyst can lead to misdiagnosis and delay of optimal treatment. In the present study, the authors found the non-remission ovarian cysts after 2 months to be serous cystadenoma, endometrioma and par-ovarian cyst. Only one woman had a persistent follicular cyst. This is consistent with the previous studies by De Guia et al[25] and Bayer et al[24]. They performed surgery when the ovarian cyst persisted more than 6 months. The histopathologic results showed that all were benign and a number of them were also functional ovarian cysts[24]. Therefore, in a case having persistent functional ovarian cyst after detection by ultrasonography more than 2 months, the benign ovarian tumors should be suspected. However, a persistent follicular or corpus luteum cyst is still possible and should be kept in mind. In the current study, the largest dimension, instead of mean diameter, of the cyst was used to assess the resolution in order to make sure that when identifying cases of remission, all dimensions were less than 2 centimeters, which is the cutoff size for diagnosis of a functional ovarian cyst.

Epidemiological data have suggested that oral contraceptive pills suppress the development of functional ovarian cysts[14], even low-dose monophasic OC[12], by means of reduction in the frequency of ovulation[14]. In turn, it has also been claimed that OC hastens the resolution of functional ovarian cysts formed during the menstrual cycle either by suppression of pituitary gonadotropin release or by a direct effect on the gonad[25]. However, two earlier randomized controlled trials on the effect of high-dose OC on resolu-

tion of functional ovarian cysts which were formed in a program of ovulation induction compared with that of expectant management found that a similar number of functional cysts had resolved within one month[17,18]. Moreover, all the remaining cysts resolved after 2 months, including a study of MacKenna et al[17] in which the cysts did not receive any treatment in the second cycle. This differs from the findings of the present study. The higher resolution rate than that of the present study may have been due to the higher doses of estrogen and progestogen components in the OC and the smaller mean diameters of the cysts. Chiaffarino et al[10] reviewed the epidemiologic data on the relationship between OC use and functional ovarian cysts and concluded that low-dose monophasic OC could not suppress follicular activity. However, Turan et al[18] showed that the disappearance rates of spontaneously formed functional ovarian cysts, either at 5 or 10 weeks of therapy with OC, were not statistically different among women using high-dose, low-dose monophasic or multiphasic OC and were similar to that of expectant management. At 5 weeks of therapy, the functional ovarian cysts disappeared in 88.9% of women using low-dose monophasic OC and in 76% of women on expectant management. At 10 weeks of therapy, the disappearance rates were more similar, 100% and 94.1%, respectively. The lack of statistical significance was ascribed to an insufficient number of subjects enrolled in the study. Nevertheless, their disappearance rates of functional ovarian cysts were higher than those of the Preent study despite the same kinds and doses of estrogen and progestin in low-dose monophasic OC as in the present study.

Similarly, two other randomized controlled trials which also included a small number of subjects in each group found no significant benefit of low-dose monophasic OC on the resolution rate of functional ovarian cysts over that of expectant management[20,26]. A larger randomized controlled trial conducted by De Guia et al[19] examined the effectiveness of low-dose monophasic OC and placebo in the treatment of functional ovarian cysts and included 93 women in each group. The disappearance rates at 4 weeks were 34.4% and 30.1% and at 8 weeks 75.3% and 70.0%, respectively. There were no statistically significant difference. The rates at 4 weeks were much lower than those in previous studies[16-18] and in the present study, but the authors noted that the baseline characteristics of their study population might have been different from other studies. In addition, the report did not mention the mean baseline diameters of the functional ovarian cysts. Nevertheless, the disappearance rates at 8 weeks were very similar to those in the present study.

The present results together with those from the previous studies show no evidence to support the superiority of low-dose monophasic OC in the treatment of functional ovarian cyst over expectant management. McKenna et al[17] added that OC should be used to treat functional ovarian cysts in cases having anovulatory cycles in order to induce the next period and start a new cycle of ovulation induction.

In conclusion, the present results indicate that low-dose monophasic OC is not more effective than expectant management for the treatment of functional ovarian cyst. In addition OC can cause some adverse effects. Therefore, OC administration should be reconsidered in the treatment strategy of functional ovarian cyst.

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การเปรียบเทียบระหว่างยาเม็ดคุมกำเนิดและการเฝ้าติดตามในการรักษาถุงน้ำรังไข่ตามสรีรวิทยา

สุขุมาลย์ เสนอศักดิ์, ศรันญา วัฒนกำธรกุล, ชัชวาล ก่อสกุล

วัตถุประสงค์: *เพื่อเปรียบเทียบประสิทธิผลของยาเม็ดคุมกำเนิดชนิดฮอร์โมนต่ำในการรักษาถุงน้ำรังไข่ตามสรีรวิทยาที่เกิดขึ้นเองซึ่งถูกตรวจพบโดยเครื่องคลื่นเสียงความถี่สูงโดยเปรียบเทียบกับการเฝ้าติดตาม*

วัสดุและวิธีการ: *สตรีวัยเจริญพันธุ์ทั้งหมดจำนวน 70 รายที่มีถุงน้ำรังไข่ตามสรีรวิทยาจากการตรวจพบด้วยเครื่องคลื่นเสียงความถี่สูงได้รับการสุ่มให้อยู่ในกลุ่มที่ได้รับยาเม็ดคุมกำเนิดชนิดฮอร์โมนต่ำหรือกลุ่มที่เฝ้าติดตามอย่างเดียวและติดตามดูถุงน้ำรังไข่ที่ 1 เดือนโดยการตรวจด้วยเครื่องคลื่นเสียงความถี่สูงครั้งที่ 2 ถ้าพบว่าถุงน้ำรังไข่ยังคงอยู่สตรีจะได้รับการติดตามต่ออีก 1 เดือนในขณะที่ยังคงได้รับการรักษาเดิม*

ผลการศึกษา: *อัตราการหายไปของถุงน้ำรังไข่ที่ 1 เดือนคิดเป็นร้อยละ 63.6 ในกลุ่มยาเม็ดคุมกำเนิดและร้อยละ 52.9 ในกลุ่มเฝ้าติดตาม หลังการรักษาที่ 2 เดือนพบอัตราการหายไปเพิ่มขึ้นเป็นร้อยละ 72.7 และ 67.6 ตามลำดับ ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างสองกลุ่มทั้งที่ 1 และ 2 เดือนหลังการรักษา สำหรับในกลุ่มสตรีที่ได้รับยาเม็ดคุมกำเนิดผลข้างเคียงที่พบบ่อยที่สุดคือสิว คิดเป็นร้อยละ 18*

สรุป: *ยาเม็ดคุมกำเนิดชนิดฮอร์โมนต่ำไม่ได้มีประสิทธิผลเหนือกว่าการเฝ้าติดตามในการรักษาถุงน้ำรังไข่ตามสรีรวิทยา*