The Effect of Using Combined Oral Ethinyl Estradiol and Levonorgestrel in the Resolution of Menstrual Pattern Disorder and Functional Ovarian Cyst

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ABSTRACT

Objectives: To evaluate the usefulness of combined oral contraceptives (ethinyl estradiol and levonorgestrel) in resolving menstrual pattern disorder in reproductive-age women with a functional ovarian cyst in Iraq.

Method: A longitudinal (before and after) , interventional study was used. Data were collected at a single obstetrics and gynaecology outpatient clinic in Mosul City, Iraq. Participants: A sample of 96 women aged between 15 and 45 years participated in the study. Participants diagnosed with ovarian cysts were treated using an oral administration of contraceptive pills (combination of ethinyl estradiol, 0.03 mg, and levonorgestrel, 0.15 mg) on a daily basis for a treatment duration of 2 months. The Outcome Measures are Menstrual pattern disorders (dysmenorrhea, irregular menstrual cycle, and amenorrhea) and cyst dimensions were recorded.

Results: After one therapy cycle, a statistically significant disappearance of menstrual pattern disorder was observed (p=0.000). Cyst resolution was observed in 89.58% of the patients (n=86), while mean ovarian cyst size fell from 4.452 ± 1.0603 cm at the start of therapy to 0 .451 ± 1.5613 cm(p = 0.000). 5 of the 10 persistent cysts disappeared after the second cycle (2 months after the start of therapy) and complete cyst resolution was 94.8% (n = 91) after two cycles. This indicated a further significant reduction of mean ovarian cyst size to 0.335 ± 1.4684 cm. However, no significant difference was observed between mean cyst size in the first and second months of treatment (p=0.329).

Conclusion: Combined oral contraceptives (ethinyl estradiol and levonorgestrel pills) are effective in relieving dysmenorrhea, irregular menstrual cycle, and amenorrhea. They also hasten the disappearance of functional ovarian cysts, and are associated with high rates of success in patients with functional ovarian cysts.

Keywords: Combined oral contraceptives pill's, functional ovarian cysts.

تأثير استخدام حبوب منع الحمل الفمويه المركبه إيثينيل استراديول وليفونورجستريل في حل اضطراب نمط الحيض واالكيس المبيضي الوظيفي

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الخلاصة

الهدف من الدراسة: تهدف هذه الدراسة إلى تقييم فائدة حبوب منع الحمل الفموية المركبة (إيثينيل استراديول وليفونورجستريل) في حل اضطراب نمط الحيض لدى النساء اللاتي في سن الإنجاب المصابات بالكيس المبيضي الوظيفي في العراق.

الطريقة: تم استخدام دراسة طولية (قبل وبعد)، تداخلية. تم جمع البيانات في عيادة خارجية لأمراض النساء والتوليد في مدينة الموصل ، العراق. المشاركات: عينة من 96 امرأة تتراوح أعمارهن بين 15 و 45 سنة شاركن في الدراسة. تم علاج المشاركات المصابات بالأكياس المبيضية باستخدام حبوب منع الحمل الفموية المركبة (إيثينيل استراديول ، 0.03 ملغ ، و ليفونورجيستريل، 0.15 ملغ) يوميا لمدة شهرين. مقاييس النتائج هي اضطرابات نمط الحيض (عسر الطمث، الدورة الشهرية غير المنتظمة ، وانقطاع الطمث) وتم تسجيل أبعاد الكيس.

النتائج: بعد دورة علاج واحدة، لوحظ اختفاء ذي دلالة إحصائية لاضطراب نمط الحيض (القيمة الاحتمالية = 0.000). لوحظ انحلال الكيس في 89.58 ٪ من المرضى (عدد =86) ، في حين انخفض متوسط حجم كيس المبيض من 4.452 ± 1.0603 سم في بداية العلاج إلى 0451 ± 1.5613 سم (القيمة الاحتمالية = 0.000). اختفت 5 من أصل 10 اكياس موجوده بعد الدورة الثانية (شهرين بعد بدء العلاج) وكان الانحلال الكامل للكيس 94.8 ٪ (عدد = 91) بعد دورتين. هذا يشير إلى انخفاض كبير آخر في متوسط حجم كيس المبيض إلى 0.335 ± 1.4684 سم. ومع ذلك ، لم يلاحظ أي فرق كبير بين متوسط حجم كيس في الأشهر الأولى والثانية من العلاج (القيمة الاحتمالية=0.329)

الاستنتاج: تعتبر حبوب منع الحمل الفموية المركبة إيثينيل استراديول وليفونورجستريل فعالة في تخفيف عسر الطمث ، الدورة الشهرية غير المنتظمة ، وانقطاع الطمث. كما أنها تسرع اختفاء اكياس المبيض الوظيفية ، وترتبط بمعدلات نجاح عالية في المريضات اللاتي يعانين من الاكياس المبيضية الوظيفية.

الكلمات المفتاحية: حبوب منع حمل فمويه مركبه ، أكياس مبيض وظيفية.

INTRODUCTION

Due to the emergence of periodic physical assessments and ultrasonography, the diagnosis of ovarian cysts, which are classified as fluid-filled sacs located within an ovary containing either a liquid or semiliquid substance, has become a more straightforward task1,2. Almost all ovarian cysts identified in reproductive-age females are physiological (functional) rather than pathological, a category which can be subdivided into the following two types: firstly, follicular cysts; and secondly, cystic corpus luteum3. In pre-and post-menopausal females, Greenlee, Kessel4, found that reports of ovarian cyst prevalence vary significantly from 8% to 18%, while Grimes, Jones5, identified ovarian cysts as a fundamental gynaecological concern for reproductive-age females globally.

In terms of the cause of follicular cysts, the evidence indicates that over the menstrual cycle's early proliferative phase, a collection of follicles grows in response to the secretion of follicle-stimulating hormone and luteinising hormone. In turn, a single follicle emerges as dominant, continually expanding until it reaches around 2.5 cm to 3.0 cm. In the event that fluids in a follicle other than the dominant one are not resorbed and continually grow, this is classified as a follicular cyst. As visualised by ultrasonographic assessment, follicular cysts are characterised by thin walls, their vascular nature, and a single chamber, which contains anechoic fluid which leads to posterior acoustic enhancement6. Follicular cysts can range from 3cm to 8cm, and when these cysts grow rapidly, rupture, or haemorrhage, this can produce discomfort and pain. The formation and slow involution of the corpus luteum takes place 6 weeks after ovulation, the latter process lasting the course of the menstrual cycle until menstruation. In certain cases, fluid may remain and continue to gather inside the corpus luteum, thus giving rise to a corpus luteal cyst. According to Dupuis and Kim7 , corpus luteal cysts are dissimilar to follicular cysts in that they are characterised by comparatively thick, irregular walls.

While public health initiatives such as screening and period physical assessments have improved diagnosis rates for ovarian cysts, along with the

development of ultrasonography2, surgical interventions are necessary for the removal of persistent, painful, or large cysts, which can in turn lead to oophorectomy5. As noted by Bottomley and Bourne8 , it is worth emphasising that the majority of ovarian cysts are identified by chance, typically as a result of routine pelvic or ultrasonographic evaluation. Despite the fact that simple ovarian cysts cannot be considered precursor lesions to malignant ovarian cancer, it is necessary to conduct effective assessments to confirm the lack of solid or papillary structures prior to the diagnosis of an ovarian cyst as a simple ovarian cyst. Although progression to malignancy is rare, follow-up examinations are essential9,10.

The combined oral contraceptive pill (COCP), frequently referred to as the birth control pill (or simply “the pill”), contains small doses of a progestin and an oestrogen-like hormone, comparable to the naturally-occurring progesterone and oestrogen produced by the female body. The COCP is regularly administered as a preventive agent, and according to some healthcare professionals, the medication represents an effective treatment agent for ovarian cysts10. Due to this, birth control pills were introduced into joint clinical practice at the beginning of the 1970s5. As noted by Bottomley and Bourne8, certain ovarian cysts are linked to both acute and chronic complications, and so the role played by the COCP as a treatment agent for gynaecological conditions is important to recognise11.

Dysmenorrhea refers to the uncomfortable cramping that originates within the uterus over the course of menstruation. The condition is a prevalent cause of pelvic pain and menstrual disorder, and it stems from the secretion of prostaglandins which induce uterine muscle contractions12. In the case of primary dysmenorrhea, the condition is classified as uncomfortable menses for females with healthy pelvic anatomy, and it typically begins during adolescence. Contrastingly, secondary dysmenorrhea, which can start long after menarche, is classified as menstrual pain arising from a health condition (e.g., pelvic inflammatory disease, intrauterine devices, endometriosis, infertility issues, ovarian cysts, adenomyosis, irregular cycles, uterine myomas, cervical stenosis, or intrauterine adhesions)13. According to Sanghera, Roberts14, certain contraceptive medications containing hormones are associated with reduction of dysmenorrhea.

The landscape of public health in Iraq, a developing country, is affected by a range of political considerations. Nevertheless, the literature is scarce in Iraq regarding the utility of combined oral contraceptive administration for the improvement of menstrual pattern disorder for reproductive-age females suffering from functional ovarian cysts. Therefore, this study evaluates the usefulness of combined oral contraceptives (ethinyl estradiol and levonorgestrel) in resolving menstrual pattern disorder in women of reproductive age with a functional ovarian cyst in Iraq.

PATINTS AND METHODS

Design

Alongitudinal(before and after study) interventional study design was adopted to evaluate the usefulness of combined oral contraceptives(ethinyl estradiol and levonorgestrel) in menstrual pattern disorder for reproductive-age women with a functional ovarian cyst in Mosul City, Iraq.

Selection and Description of Participants

This study was conducted at a single obstetrics and gynaecology outpatient clinic in Mosul City, Iraq. A convenience sample comprising 105 reproductive-age females was recruited for the study. Only 96 women were eligible and willing to participate over the study period, with a response rate of 90%. The inclusion criteria for the participants were as follows:(a) Reproductive age (15-45 years); (b) Currently suffering from dysmenorrhea, irregular menstrual cycle, or amenorrhea; (c) Diagnosed with ovarian cysts; (d) No evidence of renal, liver, or cardiovascular disease; (e) Not hypertensive; (f) Not receiving any medication at the time of the study; and (g) Neither a smoker nor an alcoholic.

Technical Information

Data were collected between 1 December 2017 and 1 December 2018. The participants were recruited during visits to an obstetrics and gynaecology outpatient clinic in Mosul City, Iraq. The diagnosis of prospective participants’ ovarian

cysts took place over the course of the following phases: firstly, a physical assessment was performed to facilitate a clinical diagnosis; and secondly, transvaginal ultrasonography was performed as expectant management for two months with no resolution of the gynaecological issue and no disappearance of the ovarian cyst. Combined oral contraceptive pills(COCPs) containing ethinyl estradiol(0.03 mg) and levonorgestrel(0.15 mg) were administered on a daily basis for a 2-month period. Over the treatment duration, patients received baseline (pre-treatment) and monthly ultrasonography assessments involving transvaginal ultrasound to assess changes in size, resolution, or complications.

Ethics

The purpose of the study was explained to each prospective participant in order to ensure voluntary and informed consent. Further to this, information sheets and recruitment pamphlets relating to the details of the study were distributed during the meeting. Prospective participants were assured that their participation would have no effect on their treatment, and that they would not be exposed to harm.

Statistical Analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) (version 25). Descriptive statistics were applied to determine the mean and standard deviation (M ± SD) for quantitative data, while non-parametric variables were expressed as counts and percentages. The McNemar test was used to test significance for non-parametric variable, while X was used to test significance for quantitative variables. A probability value (p value) of less than 0.05 was considered statistically significant.

RESULTS

Table 1 provides an overview of the participants' demographic characteristics. The participants, all female, were aged 15-45 (30.75 ± 8.36).

Most participants were married (90.6%), relatively few were single (7.3%), and only 2.1% were widowed. Additionally, the majority of the detected cysts were simple and unilateral with mean 4.45 ± 1.06.

Table 1: Participants' demographic characteristics

Total participants (n = 96)	
Age (Years)	Mean ± SD
	30.75 ± 8.36
Marital status (count and percentage)	
Single	7 (7.3%)
Married	87 (90.6%)
Widowed	2 (2.1%)

As shown in Table 2, cysts were categorised based on their size, revealing that most (n = 72) were unilateral with a diameter of 3-5 cm. 24 cysts were more than 5 cm in diameter.

Table 2: Characteristics of ovarian cysts by age group.

Age Group	**Location**			**Size (cm)**	
	Unilateral/ Laterality		Bilateral		
	Right	left		3-5cm	> 5cm
15-25 years	7	18		19	6
26-36 years	10	31		31	10
37-45 years	16	13	1	22	8
Total	33	62	1		

Table 3: Effect of oral contraception on gynaecological condition.

Gynaecological Condition	**Before reatment**	**After Treatment**	**P value**
Dysmenorrhea	43 (44.8%)	1	0.000*(s)
amenorrhea	36 (37.5%)	1	0.000*(s)
Irregular Menstrual cycle	63 (65.6%)	1	0.000*(s)

* McNemar test

The mean difference is significant at the 0.05 level

Forty three participants (44.8%) presented with dysmenorrhea, 36 (37.5%) had menorrhea, and 63 (65.6%) suffered from irregular menstrual cycles. All participants received medical treatment with COCPs (containing ethinyl estradiol, 0.03 mg, and levonorgestrel, 0.15 mg) table 3 .

After a single therapy cycle, a statistically significant disappearance was observed for menstrual pattern disorder (including dysmenorrhea, irregular menstrual cycle, and amenorrhea) (p = 0.000). Ovarian cyst resolution was observed in 86 (89.58%) of the 96 patients Table 4 .

Table 4: Disappearance rates of functional ovarian cysts in management in patients for terminal period

Outcome	Count and Percentage
Disappearance after one therapy cycle	86 (89.58%)
Disappearance after two therapy cycles	5 (5.2%)
Persistence of cyst	5 (5.2%)

Mean ovarian cyst size dropped from 4.452 ± 1.0603 cm at the start of therapy to 0.451 ± 1.5613 after therapy (p = 0.000). 5 of the 10 persistent cysts disappeared after the second cycle (2 months after start of therapy), and complete cyst resolution was observed for 91 participants (94.8%) after two cycles. The mean significant reduction for ovarian cysts was 0.335 ± 1.4684 cm. However, no significant difference was observed between mean cyst sizes in the first and second months of treatment(p=0.329) Tables 5, 6, and 7 .

Table 5: Difference in ovarian cyst size before and after one month of treatment

Ovarian Cyst Size Number of Patients (96)	Mean ± SD	P value
Ovarian Cyst Size Before Treatment	4.452 ± 1.0603	
Ovarian Cyst Size After One Month of Treatment	0.451 ± 1.5613	0.000* (s)

Based on estimated marginal means

*The mean difference is significant at the 0.05 level

Adjustment for multiple comparisons: Bonferroni.

Table 6: Difference in ovarian cyst size before and after two months of treatment

Ovarian Cyst Size Number of Patients (96)	Mean ± SD	P value
Ovarian Cyst Size Before Treatment	4.452 ± 1.0603	
Ovarian Cyst Size After Two Months of Treatment	0.335 ± 1.4684	0.000

Based on estimated marginal means

* The mean difference is significant at the 0.05 level

Adjustment for multiple comparisons: Bonferroni

Table 7: Difference in ovarian cyst size before and after one and two months of treatment, respectively

Ovarian Cyst Size Number of Patients (96)	Mean ± SD	P value
Size of Ovarian Cyst After One Month of Treatment	0.451 ± 1.5613	
Size of Ovarian Cyst After Two Month of Treatment	0.335 ± 1.4684	0.329

Based on estimated marginal means

*The mean difference is significant at the 0.05 level

Adjustment for multiple comparisons: Bonferroni

For the 5 cysts which were persistent after 2 months of COCP treatment, surgical intervention was undertaken using an open technique (laparotomy) or a minimally invasive technique (laparoscopy). Small incisions were applied, and in the course of operating, pathological cysts were identified in each case.

DISCUSSION

It is well-documented that due to the administration of COCPs, cyst incidence has fallen. This is because COCPs suppress ovulation, thus meaning that eggs are not released from the ovaries[12]. With this in mind, healthcare professionals began to treat cysts with COCPs, understanding that this would hasten the disappearance of the condition[5]. It is also worth noting that because COCP administration abbreviated mean cyst duration, they could be used as valuable pharmacological agents in managing accompanying menstrual conditions[15]. According to Bottomley and Bourne[8], it is possible to safeguard against recurrent cyst rupture or haemorrhage with COCPs administration, and early COCPs were lnked to a lower incidence of functional ovarian cysts[16].

The evidence shows that morbidity and quality of life fall and rise, respectively, with the use of COCPs. One of the principal ways to account for this finding is that COCPs reduce the incidence of ovarian cysts, and as such, prevent the emergence of painful conditions such as menstrual cramps, menstrual bleeding issues, ovulation pain, and endometriosis symptoms(e.g., pelvic pain). As emphasised by Brynhildsen[17], COCPs can be used to treat dysmenorrhea, hirsutism, and acne vulgaris. More specifically, the levonorgestrel-released intrauterine system is a reversible way in which to treat dysmenorrhea and menorrhagia[14]. This study's findings are also consistent with Cochrane reviews addressing the impact of COCPs on functional ovarian cyst resolution. The reviews reported that no significant differences could be observed between therapeutic interventions in functional ovarian cysts and no intervention, noting that cyst resolution occurs spontaneously in almost all case, irrespective of treatment. Nevertheless, it is worth emphasising that these trials included relatively small sample sizes, and a high level of heterogeneity was observed[5,16].

Consistent with Bernardi M ea al [12], this study attests to the statistically significant impact that COCPs administration has on dysmenorrhea, irregular menstrual cycle, and amenorrhea in reproductive-age females suffering from functional ovarian cysts. As reported elsewhere in the literature, COCPs bring rapid relief and regulatory benefits to the pain associated with menstruation, including irregular bleeding and uncomfortable periods, and they can be used to treat symptomatic menorrhagia and primary dysmenorrhea[11,18,19]. The results presented in this study are in agreement with this evidence, and at the same time, show that COCPs can hasten the complete resolution of functional ovarian cysts. However, it is worth noting that several months of watchful waiting could be necessary for the achievement of similar success rates, and this could represent a viable alternative to oral contraceptive therapy. In addition, surgical evaluation of persistent ovarian cysts is essential.

This study's limitations, including its use of the convenience sampling technique and the method used to estimate the sample size, could have affected the generalisability of the findings to other settings. Therefore, future studies should be pursued in which larger sample sizes are utilised. At the same time, probability sampling techniques should be employed to ensure that the study population is representative of the target population. Finally, to determine whether statistically significant differences exist between watchful waiting of cysts and active pharmacological intervention in cyst development through COCP administration, future studies should consider employing control groups in the context of a randomised controlled trial.

CONCLUSION

Combined oral contraceptives (ethinyl estradiol and levonorgestrel pills) are effective in relieving dysmenorrhea, irregular menstrual cycle, and amenorrhea. They also hasten the disappearance of functional ovarian cysts, and are associated with high rates of success in patients with functional ovarian cysts.

DECLARATION OF INTEREST

Statement

The research has no conflict of interest and is not funded from any source.

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