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Comparison of two drospirenone-containing oral contraceptives for their effect on the ovary, menstrual cycle, acne, and side-effect profile: 20 µg ethinylestradiol/3 mg drospirenone (24/4) versus 30 µg ethinylestradiol/3 mg drospirenone (21/7)

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Ethics Committee Approval
Ethics committee approval for the study was obtained from the Ethics Committee of Health Sciences University Etlik Zübeyde Hanım Gynecology Training and Research Hospital (Decision no:127).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Serious side effects, depending on the length of the hormone-free interval and the estrogen dose, cause the discontinuation of combined oral contraceptives (COCs). Therefore, it is important to identify COCs with minimal side effects which provide effective contraception. This study aimed to compare the effects of two different drospirenone-containing oral contraceptives (COCs) on ovarian suppression, cycle control, premenstrual symptoms, pain, acne, and the incidence of side-effects.
Methods: This prospective randomized controlled study was conducted with eighty women aged between 17-40 years. Patients were randomized to either 3mg drospirenone/30mcg ethinylestradiol (21/7 tablets) (Group 1) or 3mg drospirenone/20mcg ethinylestradiol (24/4 tablets) (Group 2) COCs. On Day-3 of the pre-treatment cycle, menstrual cycle patterns, serum hormone and lipid levels, menstrual complaints were recorded, followed by an evaluation of Day-21 progesterone levels, sonographic evaluation of endometrial thickness and the ovaries. Same assessment was repeated after pill use and the findings of the two cycles were compared.
Results: Both COC formulations suppressed serum hormone levels, decreased endometrial thickness and reduced incidence of dysmenorrhea-dyspareunia, and acne while serum HDL-cholesterol level was increased. Progesterone, FSH and endometrial thickness were lower, and serum cholesterol level was higher in Group 2 (P=0.007, P=0.044, P<0.001, P=0.035; respectively). Breast tenderness was significantly less in Group 2 (P=0.02). The incidence of follicular development, menstrual irregularity, and a headache was higher in Group 1, but the difference was not significant except for headaches (P=0.027).
Conclusion: 24/4 tablets might be a better alternative to 21/7 tablets with the advantage of tolerability as well as providing effective contraception.

Keywords: Combined oral contraceptive, Ovarian suppression, Premenstrual disorders, Side-effects

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Introduction

Combined oral contraceptives (COCs) are widely used all over the world and almost 16 to 30% of women of reproductive age have used COCs at one stage of their lives [1, 2]. The primary mechanism of action of COC use is to suppress dominant follicle development, and thus inhibit ovulation by suppressing follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and preventing fertilization besides preventing implantation by thickening the cervical mucus and making the endometrium thinner [3].

The progestin component suppresses ovulation while the estrogen component is added for cycle control [4]. Estrogen also has an additive effect on suppression of the follicular development while preventing spotting and decreasing menstrual blood loss [5, 6]. With the improvement of contraceptive technology, new forms, formulations, and regimens have been developed to decrease the incidence of side-effects and increase users' compliances. Estrogen-related complaints such as fluid retention, nausea, mood changes, and breast tenderness are common reasons for COC discontinuation [7]. Estrogen in COCs has been reduced from 150 µg Mestranol to 20-30 µg estradiol (EE) with dose adjustment studies. Lower estrogen dosages that still have a suppressive effect on follicular growth and maintain cycle control are preferred to reduce the risk of venous thrombosis besides estrogen-related side effects. Different progestins with anti-androgenic, anti-glucocorticoid properties that stabilize the endometrium efficiently are developed and added to COC formulations. Hormonal fluctuations that cause irregular bleeding patterns and poor cycle control during COC use negatively impact patient compliance. To provide better suppression besides decreasing hormonal fluctuations, new regimens with the shorter hormone-free period or extended-formulations have been developed [8].

We aimed to compare the follicular suppression, cycle control, incidence of premenstrual symptoms, and side-effects encountered in a 21/7 tablet COC, which contains 30 µg ethynyl estradiol (EE) + 3 mg of drospirenone, with a 24/4 tablet COC regimen with 20µg EE + 3 mg of drospirenone.

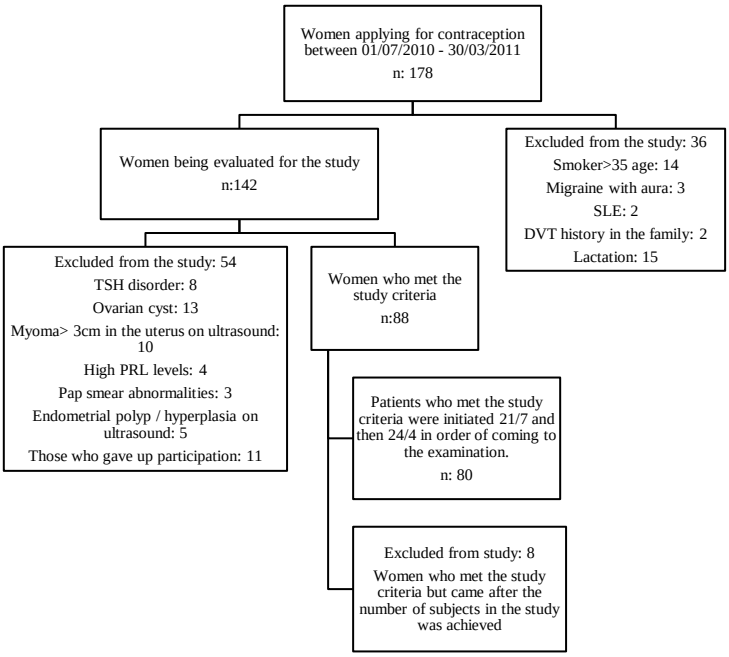
Materials and methods

The study was conducted at the Family Planning Clinic of a tertiary center. Ethics committee approval for the study was obtained from the Ethics Committee of Health Sciences University Etlik Zübeyde Hanım Gynecology Training and Research Hospital (Decision no:127). The study was conducted according to the Helsinki Declaration principles. The study group consisted of women who visited Etlik Zübeyde Hanım Gynecology Training and Research Hospital for contraception between July 1, 2010, and March 30, 2011 and requested combined oral contraceptives after comprehensive counseling for family planning methods. The medical eligibility for COC use for the recruitment of the women was based on the recommendations of the WHO eligibility criteria [9].

Inclusion criteria included 1) Being a non-smoker aged 17-40 years, 2) Not being pregnant or lactating, 3) Not having any organic gynecologic pathologies, 4) Having a Body Mass Index (BMI)< 30kg/m^2, 5) Not using hormonal contraception during the last six months.

The exclusion criteria were as follows: Smokers over the age of 35, query of pregnancy or a malignancy, having migraines, endocrine disorders (diabetes mellitus, thyroid dysfunction vs.), unexplained vaginal bleeding, using drugs that could interact with COCs (barbiturate, rifampin, hydantoin), having a history of deep venous thrombosis (DVT) or pulmonary embolus, women with SLE, hepatic, or renal disease, and an abnormal pap smear within the last year. All volunteering women received comprehensive counseling for COC use and signed informed consent forms. The patients were evaluated on the second month of the COC use. The flowchart of the study is shown in Figure 1.

Figure 1: Flow-chart of the study



Two groups were formed: Group 1: 40 patients who met these criteria received COC containing 3mg drospirenone/30mcg ethinyl estradiol (21/7, Yasmin, Bayer Germany) and Group 2: 40 patients were given 3mg drospirenone/20mcg ethinyl estradiol (24/4, Yazz, Bayer, Germany) COC. To avoid bias in the study, oral contraceptives were started randomly on the 2nd or 3rd day of the menstrual cycle. Randomization was done by assigning tablets sequentially: the 21/7 tablet for the first patient and the 24/4 tablet for the subsequent patient until the groups were completed.

During the cycle before using the pill

Pre-pill Day 2-3: Age, parity, educational status, smoking, lactation, previous pelvic surgery, chronic disease, PAP smear results, menstrual pattern, premenstrual symptoms, dysmenorrhea-dyspareunia complaints (the severity of dysmenorrhea and dyspareunia was evaluated with the visual analog scale (VAS)), acne and other skin manifestations of the women in both groups were questioned and recorded. After physical examination and recording of the blood pressure, height and weight measurements, organic pathologies that could cause abnormal bleeding were excluded by gynecological examination and transvaginal ultrasonography (TVUSG). Evaluation of the ovaries and endometrial thickness were noted. In the morning, fasting blood samples were collected and FSH, LH, estradiol

(E2), prolactin (PLR), thyroid stimulating hormone (TSH) levels, fasting blood sugar, blood lipid (triglyceride (TG), low-density lipid (LDL), very low-density lipid (VLDL), high-density lipid (HDL), total cholesterol) levels, liver (alanine aminotransferase (ALT), aspartate aminotransferase (AST)) and kidney (blood urea nitrogen (BUN), creatinine) function tests were requested and the results were recorded.

Pre-pill Day-21: Blood samples were collected for serum progesterone (P) level, and ovaries and endometrial thickness were re-evaluated by TVUSG.

In the cycle following one month of pill use

Post-pill Day 2-3: Analysis of serum hormone and lipid levels, transvaginal ultrasonographic evaluation of the ovaries and the endometrium were conducted.

Post-pill Day-21: Serum P level assessment, TVUSG for evaluation of follicular development and measurement of endometrial thickness were conducted. Menstrual patterns, presence of premenstrual symptoms and skin findings, signs of deep vein thrombosis and side effects due to pill use (breast tenderness, nausea, headache) were questioned, and the severity of dysmenorrhea and dyspareunia was re-evaluated with the VAS score.

BMI and blood pressure were recorded at each visit. Premenstrual symptoms included breast tenderness, anxiety, increased appetite, and sleep disturbance. Symptoms that occurred for at least two cycles, began within five days before menstruation, disappeared with menstruation and caused distress in daily social or work-related activities were considered premenstrual symptoms [10].

In terms of menstrual pattern, cycles lasting 4-7 days, with 21-35-day intervals and bleeding up to 35-80 ml were considered regular cycles.

A Logiq P5 ultrasonography device was used for TVUSG. Blood hormone samples were analyzed with the E170 device using kits from Roche, and blood lipid samples were analyzed with dry chemistry kits with the Vitros Fusion 5.1 device.

Power analysis

Sample size was determined with the G Power 3.1 program. In the study of Krol et al. [11], considering that the rate of side effects in women using oral contraceptives between 18-35 years of age was 9.0%, 0.70 effect size (d = 0.70) was calculated according to the double-tailed hypothesis method. The confidence interval was 90% and the margin of error was 5%. Thirty-six women were needed in the control group, and 36 women were required in the study group. Considering possible data loss, the study was completed with 80 women, 40 women in each group.

Statistical analysis

Data were analyzed using the SPSS 21.0 program. Mann-Whitney U test and Wilcoxon signed-rank test were used to compare variables not conforming to normal distribution. In cases with normal distribution, Independent Sample T-Test and Paired Sample T-Test were used. Chi-square test or Fisher's exact probability test were used to determine whether frequency distributions of categorical variables were homogeneously distributed among the groups. Results with $P<0.05$ were considered statistically significant.

Results

Both groups were homogeneous in terms of demographic characteristics (Table 1).

When compared with the pre-pill values, in both groups, post-pill serum FSH, LH, E2 and P levels were significantly suppressed, and endometrial thickness was decreased ($P<0.05$). However, serum FSH and P levels and endometrial thickness were lower with 24/4 tablets than 21/7 tablets. With 21/7 tablets, seven patients had follicular development (follicle diameter 11-16mm), while in the 24/4 group only two had follicles (diameter 12 and 14 mm). However, this was not statistically significant ($P>0.05$) (Table 2).

The pre-pill menstrual pattern in Group 1 was as follows: All women had regular cycles, 3 had spotting, and one woman had heavy menstrual bleeding (HMB). After pill use, the patient with HMB improved. However, five patients developed spotting episodes, and menstrual irregularity was observed in three patients. These differences in bleeding patterns before and after pill use were not significant ($P>0.05$) (Table 2).

Table 1: Comparison of the groups in terms of demographic characteristics (age, BMI, parity, educational status, chronic disease, previous surgery), smoking status, systolic and diastolic blood pressures before pill use, serum TSH and PRL levels

		21/7 Tablet n (40)	24/4 Tablet n (40)	*P*-value
Age (year)		26.55 (4.04)	27.38 (3.76)	0.348
BMI (kg/m2)		25.45 (3.12)	25.30 (2.84)	0.531
Education	Primary school	5 (12.5%)	2 (5.0%)	0.587
	Middle school	6 (15.0%)	5 (12.5%)	
	High School	22 (55.0%)	23 (57.5%)	
	University	7 (17.5%)	10 (25.0%)	
Parity	Nulliparous	3 (7.5%)	5 (12.5%)	0.712
	Multiparous	37 (92.5%)	35 (87.5%)	
Previous operation		9 (22.5%)	7 (17.5%)	0.576
Chronic disease		4 (10.0%)	6 (15.0%)	0.499
Smoking		12 (30.0%)	7 (17.5%)	0.189
TSH (mIU / L)		2.22 (1.72)	1.88 (1.05)	0.806
PRL (mlU/ml)		11.02 (4.85)	9.93 (3.50)	0.285

P-values were calculated with the independent T test (age), Mann Whitney U Test (BMI, TSH, PRL), and Chi-Square Test, PRL: Prolactin, TSH: Thyroid stimulating hormone

Table 2: Comparison of the effects of 21/7 and 24/4 tablets on ovarian suppression and cycle control

	Before the 21/7 tablet n (40)	After the 21/7 tablet	*P*-value	Before the 24/4 tablet n (40)	After the 24/4 tablet	*P*-value	Difference with the 21/7 tablet n (40)	Difference with the 24/4 tablet n (40)	*P*-value
FSH (U/L) (D3)	5.07 (2.21)	1.62 (1.00)	<0.001	5.82 (1.99)	1.67 (1.80)	<0.001	3.45 (2.18)	4.15 (2.46)	0.044
LH (U/L) (D3)	5.87 (3.14)	1.60 (1.15)	<0.001	6.55 (3.20)	1.87 (1.38)	<0.001	4.27 (3.50)	4.67 (3.56)	0.581
E2 (pg/ml) (D3)	89.10 (146.94)	17.35 (20.52)	0.004	65.00 (33.48)	14.92 (10.27)	<0.001	71.75 (150.14)	50.07 (37.36)	0.248
P (ng/ml) (D21)	4.65 (4.01)	0.32 (0.21)	<0.001	6.49 (4.11)	0.25 (0.19)	<0.001	4.32 (3.94)	6.23 (4.14)	0.007
ET (mm) (D21)	11.65 (3.72)	4.02 (0.99)	<0.001	16.60 (2.56)	3.25 (1.12)	<0.001	7.62 (3.69)	13.35 (2.86)	<0.001
Follicle development (D21)	-	7 (17.5%)	-	-	2 (5.0%)	-	7 (17.5%)	2 (5.0%)	0.077
Menstrual cycle	n (%)	n (%)	*P*	n (%)	n (%)	*P*	n (%)	n (%)	*P*
Regular	40 (100.0)	37 (92.5)	0.241	40(100.0)	39(97.5)	1.00	37 (92.5)	39 (97.5)	0.615
Spotting*	3 (7.5)	8 (20.0)	0.105	0 (0.0)	3 (7.5)	0.241	5** (12.5)	3 (7.5)	0.712
Menorrhagia*	1 (2.5)	0 (0.0)	1.00	1 (2.5)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	-
Amenorrhea	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Irregularity	0 (0.0)	3 (7.5)	0.241	0 (0.0)	1 (2.5)	1.00	3 (7.5)	1 (2.5)	0.615

P-values were calculated with Paired Sample T Test and Wilcoxon Test in dependent groups and Chi-Square Test. ET: Endometrial thickness, *: with regular cycles, **: new spotting complaint, D3-D21: 3rd and 21st day of the menstrual cycle.

All women in Group 2 had regular cycles before COC use and only one woman had HMB. After pill use, the patient with HMB improved. However, menstrual irregularity developed in one woman and spotting episodes, in three. There was no significant difference in terms of the menstrual pattern changes in Group 2 ($P>0.05$) (Table 2).

Menstrual irregularity and spotting bleeding were more common after 21/7 tablet use compared to 24/4 tablet use, but the difference was not significant ($P>0.05$) (Table 2).

There was a significant decrease in cholesterol and VLDL and a significant increase in HDL after 21/7 tablet use. The decrease in cholesterol levels was more significant in Group 2 while this group also had a significant decrease in HDL levels ($P<0.05$) (Table 3).

In Group 1, the incidence of breast tenderness, nausea, and headache were significantly higher and there was a significant increase in systolic blood pressure. In Group 2, breast tenderness and nausea were significantly high when compared to the pre-pill period. The increase in the incidence of breast tenderness was higher in Group1 when compared to Group 2. No patients had deep vein thrombosis or any other vascular complications (Table 3).

When the effects on premenstrual symptoms were compared, both oral contraceptives positively affected appetite and sleep disturbances, but this did not reach statistical significance ($P>0.05$) (Table 4).

Table 3: Comparison of the side effects of the tablets after use

	Before the 21/7 tablet n (40)	After the 21/7 tablet	*P*-value	Before the 24/4 tablet n (40)	After the 24/4 tablet	*P*-value	Difference with the 21/7 tablet n (40)	Difference with the 24/4 tablet n (40)	*P*-value
FBG (mg/dl) (D3)	94.70 (22.54)	90.72 (16.58)	0.362	91.37 (15.34)	95.90 (16.27)	0.181	3,97 (27.23)	-4.52 (23.60)	0.140
TG (mg/dl) (D3)	131.32 (60.64)	124.00 (52.04)	0.094	108.82 (60.45)	106.15 (44.74)	0.608	7.32 (26.98)	2.67 (32.76)	0.182
Cholesterol (mg/dl) (D3)	166.47 (27.35)	151.55 (26.12)	0.001	160.25 (24.53)	154.65 (22.80)	0.097	14.92 (27.19)	5.60 (20.80)	0.035
HDL (mg/dl) (D3)	53.92 (12.72)	64.52 (11.30)	<0.001	60.05 (12.41)	72.95 (11.67)	<0.001	10.60 (13.04)	12.90 (11.82)	0.927
LDL (mg/dl) (D3)	102.52 (29.25)	103.17 (29.04)	0.850	106.15 (28.87)	101.92 (25.75)	0.246	-0.65 (21.63)	4.22 (22.67)	0.148
VLDL (mg/dl) (D3)	28.40 (13.04)	23.00 (8.38)	0.001	22.32 (14.94)	19.27 (11.64)	0.138	5.40 (9.36)	3.05 (12.74)	0.264
Breast tenderness	0 (0.0%)	15 (37.5%)	<0.001	0 (0.0%)	6 (15.0%)	0.026	15 (37.5%)	6 (15.0%)	0.022
Nausea	0 (0.0%)	12 (30.0%)	<0.001	0 (0.0%)	6 (15.0%)	0.026	12 (30.0%)	6 (15.0%)	0.108
Headache	0 (0.0%)	5 (12.5%)	0.027	0 (0.0%)	2 (5.0%)	0.494	5 (12.5%)	2 (5.0%)	0.432
DVT	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
SBP (mmHg)	110.50 (8.14)	114.00 (10.57)	0.046	112.00 (9.92)	114.00 (0.57)	0.401	3.50 (10.75)	2.00 (14.88)	0.597
DBP (mmHg)	71.00 (7.08)	73.50 (8.33)	0.115	72.50 (6.69)	73.75 (8.06)	0.442	2.50 (9.80)	1.25 (10.17)	0.512

P-values were calculated with the independent T test and Mann Whitney U Test. FBG: Fasting blood glucose, TG: Triglyceride, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, D3: 3rd day of the menstrual cycle, DVT: Deep vein thrombosis.

Table 4: Comparison of the effects of tablets on premenstrual symptoms, dysmenorrhea-dyspareunia complaints and acne.

		Before the 21/7 tablet n (40)	After the 21/7 tablet	*P*-value	Before the 24/4 tablet n (40)	After the 24/4 tablet	*P*-value	Difference with the 21/7 tablet n (40)	Difference with the 24/4 tablet n (40)	*P*-value
Effects of tablets on premenstrual symptoms								Comparison of patients whose symptoms have improved		
Breast tenderness		5 (12.5%)	4 (10.0%)	0.5	3 (7.5%)	3 (7.5%)	1.00	1 (2.5%)	0 (0.0%)	1.00
Anxiety		4 (10.0%)	4 (10.0%)	1.00	3 (7.5%)	2 (5.0%)	0.5	0 (0.0%)	1 (2.5%)	1.00
Increased appetite		9 (22.5%)	5 (12.5%)	0.130	10 (25.0%)	4 (10.0%)	0.077	4 (10.0%)	6 (15.0%)	0.499
Sleeping disorder		5 (12,5%)	2 (5.0%)	0.216	6 (15%)	3 (7.5%)	0.214	3 (7.5%)	3 (7.5%)	1.00
Comparison of the effects of tablets on dysmenorrhea and dyspareunia in women with VAS scores								Comparison of differences in VAS scores		
Dysmenorrhea	Present	11 (27.5%)	11 (27.5%)		7 (17.5%)	7 (17.5%)		11 (27.5%)	7 (17.5%)	
	VAS	7.30 (1.05)	3.36 (1.02)	<0.001	7.00 (1.41)	3.29 (0.95)	0.002	3.82 (0.98)	3.71 (1.25)	0.846
Dyspareunia	Present	4 (10.0%)	4 (10.0%)		6 (15.0%)	6 (15.0%)		4 (10.0%)	6 (15.0%)	
	VAS	6.75 (1.25)	1.75 (0.50)	<0.001	6.33 (1.63)	3.00 (0.89)	0.003	5.00 (0.81)	3.33 (1.63)	0.099
Effects of tablets on acne and improvement of oily skin in women								Comparison of differences in skin complaints		
Acne and oily skin		4 (10.0%)	3 (7.5%)	0.5	3 (7.5%)	0 (0.0%)	0.120	1 (2.5%)	3 (7.5%)	0.615

P-values were calculated with the Mann Whitney U Test, independent T test and Chi-Square Test. VAS: Visual analog scale scores

In both groups, among women with dysmenorrhea and dyspareunia, pain intensity decreased significantly after using COCs and the results in both groups were similar ($P>0.05$) (Table 4).

Acne and oily skin improved in more women in Group 2 (n:3(7.5%)) when compared to Group 1 (n:1(2.5%)). However, the differences within or between the groups were not significant ($P>0.05$ for both) (Table 4).

Discussion

Although COCs provide effective contraception, compliance and continuity of the method depend on the side-effects' incidence and severity. New formulations aim to minimize the estrogen related side-effects by decreasing the estrogen dosages and using progestin that have favorable metabolic and systemic effects. While decreasing the estrogen dosages, it is important to maintain the suppressive effect of the formulation on ovulation. Hormone free interval (HFI) is another area under investigation with low dose COCs containing <50 mcg ethinyl estradiol (EE) as follicular activity is detected during the HFI [8]. Different regimens with shortened HFI are formulated to suppress ovarian function while using lower doses of EE effectively. In the presented study, we compared two formulations with 20 mcg and 30 mcg EE while the HFI was shorter with the 20-mcg-EE-containing formulation. In the presented study, both formulations suppressed ovulation effectively as proven by the serum levels of Day-3 FSH, Day-21 P values, and TVUSG findings related to follicular growth and endometrial thickness. However, suppression of the serum FSH and P levels and endometrial thickness were lower with 24/4 tablets than the 21/7 tablets, although this was not statistically significant. In the presented study, with the 21/7 tablet, follicles with a diameter of 10 mm or larger are observed and these follicles may easily develop and ovulate if there is a hormone free period [3].

Nausea, headaches, bloating, breast tenderness, decreased libido are the common side-effects related to COC use. While breast tenderness and nausea were observed with both tablets, headaches were also significantly more common with 21/7 tablets containing 30 mcg EE. During the HFI, side-effects related to estrogen withdrawal, a.k.a., "hormone-withdrawal-associated symptoms", might arise [12-14]. Similar to the natural cycle, prostaglandins are responsible for these side effects, which are caused by myometrial contractions and shedding of the endometrium and so dysmenorrhea might arise besides headache, nausea and bloating [15]. In our study, side effects were seen less with the 24/4 tablet, which had a shorter HFI when compared to the 21/7 tablet.

Another critical role of estrogen in COCs is providing cycle control and reducing spotting, which is a hormonal breakthrough bleeding. Studies show that spotting and intermittent bleeding are less with shorter HFI formulations when compared to the formulations with the same EE dose but a longer HFI [16]. In a meta-analysis of low-dose estrogen-containing tablets, there was less intermittent bleeding with tablets with a short hormone-free interval [17]. With extended use contraceptives that have a shorter interval, side effects are almost eliminated. Spotting episodes, menstrual irregularities were higher with 21/7 tablets. Hormonal contraceptives are widely used for the treatment of primary dysmenorrhea as they reduce prostaglandin secretion during menstruation and thus improve dysmenorrhea [18]. Drospirenone bearing COCs are effective in the treatment of premenstrual symptoms [19]. When we evaluated the effects on dysmenorrhea and dyspareunia, both

drospirenone containing tablets reduced dysmenorrhea and dyspareunia, but neither was superior. Both tablets had positive effects on premenstrual symptoms, dysmenorrhea, dyspareunia, oily skin, and acne, but only their effects on dysmenorrhea and dyspareunia were significant.

Metabolic side effects of COCs are also important. Drospirenone increases HDL and TG, increases LDL with long-term use. While estrogens increase TG and HDL, they support LDL catabolism [20]. In a study comparing 24/4 tablets containing 20 mcg EE/3mg drospirenone with 21/7 tablets containing 20 mcg EE/150 mcg desogestrel, both tablets increased HDL while decreasing LDL [21]. In our study, both tablets significantly increased HDL but were not superior to each other. The 21/7 tablet also increased systolic blood pressure and reduced cholesterol and LDL. Out of these variables, only the decrease in cholesterol with 21/7 was significant compared to 24/4.

Limitation and strength of the study

As the presented study evaluated the tablets' short-term effects, different results might be encountered after more prolonged use. However, since drospirenone levels become stable after the 8th day of the menstrual cycle with stabilized serum EE levels achieved after the second half of the cycle, making the assessment in the second month of COC use provided sufficient time for evaluation [22].

The strength of our work was the comparison of tablets with a fixed progestin dose (3mg drospirenone) but different EE doses (20mcg-30mcg) and different hormone-free intervals. Studies in the literature have mostly compared the tablets for cycle control and bleeding patterns or only in one aspect [23-25]. The presented study is a comprehensive, multifaceted study of two formulations with two different estradiol doses, including the incidence of side-effects, premenstrual symptoms, dyspareunia and dysmenorrhea pain scores, and effects on acne, together with cycle control.

Conclusion

In summary, among the oral contraceptives that showed efficacy, the 24/4 tablet containing low dose estrogen and having a shorter hormone-free interval can be considered an advantageous option compared to the 21/7 tablet due to relatively fewer side effects (especially breast tenderness), less stray follicle development and less menstrual irregularity in the short term.

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