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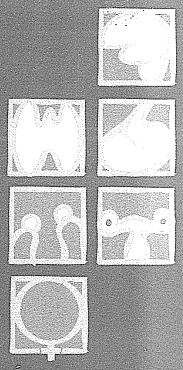

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The influence of the dose of ethinylestradiol in oral contraceptives on follicle growth

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ABSTRACT

This prospective, randomized comparative clinical study involving 416 women investigated follicle development over a period of 12 oral contraceptive treatment cycles. Women were allocated to two groups, one group (n = 207) received a preparation containing 30 μg ethinylestradiol and 75 μg gestodene daily, and the other group (n = 209) received 20 μg ethinylestradiol and 150 μg desogestrel, daily. Follicular development was monitored by transvaginal ultrasonography of the ovaries, during days 18–21 in the pretreatment cycle and in treatment cycles 1, 3, 6, 9 and 12.

Follicular development was found to be twice as frequent in the group receiving 20 μg ethinylestradiol/ desogestrel as in the group receiving 30 μg ethinylestradiol/ gestodene. For all cycles, follicles of 10–30 mm were found in 18% of women in the desogestrel group, compared with 9.7% in the gestodene group, whilst follicles with a diameter of > 30 mm were present in 5% of the desogestrel group compared with 1.9% of the gestodene group. The difference between the treatment groups with respect to follicle diameters of 10–30 mm and > 30 mm was statistically significant ($p < 0.05$ and $p < 0.001$, respectively). No ruptured follicles were observed in either group throughout the study, suggesting that there was no escape ovulation, however, there was one pregnancy in the desogestrel group that could not be explained either by drug interactions or missed pills.

It can be concluded that the ethinylestradiol dose in an oral contraceptive has a significant effect on follicular ovarian activity, and that reducing the dose to 20 μg is associated with a significant increase in follicle size.

INTRODUCTION

There has been no essential change in the principle behind the inhibition of ovulation since the introduction of combined oral contraceptives in 1959. However, a number of new progestogens have been developed which have differing endocrinological profiles, and there have been reductions in both progestogen and estrogen dose. The reduction in estrogen dosage was chiefly in response to the epidemiological finding of an association between the use of oral contraceptives and thromboembolic complications. The estrogen dose used in modern oral contraceptives has been reduced to

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approximately 30 μg per day, but a recently introduced oral contraceptive has further reduced the ethinylestradiol dose to 20 μg per day.

Results from a large number of studies indicate that reducing the steroid dose in oral contraceptives, together with the introduction of new progestogens, has led to a reduction in metabolic impact and a decrease in the incidence of serious side-effects, particularly thromboembolism, stroke and myocardial infarction[1]. Most clinical studies also demonstrate that the low-dose oral contraceptives are not associated with any significant reduction in either contraceptive efficacy or cycle control[2]. There is, however, some clinical evidence from studies with oral contraceptive preparations containing 20 μg ethinylestradiol combined with 150 μg desogestrel that cycle control is impaired[3], a finding that may reflect the decreased estrogen dose.

In order to further investigate the effect on ovulation inhibition, suppression of ovarian activity, cycle control and the incidence of adverse events, of reducing the ethinylestradiol dose to 20 μg per day, a prospective, randomized, clinical study has been performed which compared two oral contraceptive preparations, one containing 30 μg ethinylestradiol/ 75 μg gestodene and the other 20 μg ethinylestradiol/ 150 μg desogestrel.

Although the two preparations contained different progestogens, the two progestogens are similar with respect to biological activity[4,5], particularly antigonadotropic activity. In addition, both progestogens have high progestogenic activity, no glucocorticoid activity, no antiandrogenic activity and a low level of androgenic activity. Because of the broad similarity between the two progestogens there is a high probability that the findings of this study will reflect the difference in ethinylestradiol dose and not the difference in progestogen.

This paper focuses on the effects of the two oral contraceptive preparations on ovarian activity. Analysis of cycle control data and the incidence of adverse events will be reported in a separate communication.

SUBJECTS AND METHODS

Subjects

Healthy, sexually active women between 19 and 40 years of age who requested oral contraception and had a regular cycle (24–36 days) were considered for this study. After receiving detailed written and verbal information, the subjects signed informed consent forms. The decision to include individual subjects in the study was made on the basis of a gynecological and laboratory examination (normal range of fasting triglyceride and cholesterol levels, plus a negative urinary glucose test). Body weight of subjects was not allowed to exceed the normal range by more than 20%. Women regularly taking long-term medication were excluded from the study, as were women who had taken any hormonal medication during the previous 8 weeks. Smokers were not allowed to participate in the study. The generally accepted contraindications for oral contraceptives were strictly observed.

Over a period of 12 months, a total of 500 women were recruited from the Outpatients Department of the Torun Hospital for Women in Poland. Out of these 500 women, 84 were excluded from the investigation because they had discontinued the study after randomization but before taking the study medication (14 because of pregnancy, three because of a desire to become pregnant, 15 for personal reasons and 52 because they were lost to follow-up). A total of 416 women were included in the study.

Screened subjects were randomly assigned to the two study groups: group A received a preparation containing 21 coated tablets of 30 μg ethinylestradiol plus 75 μg gestodene and group B received a preparation containing 21 coated tablets of 20 μg ethinylestradiol plus 150 μg desogestrel.

Study design

The investigation was designed as a single-center prospective randomized study, conducted in the Women's District Hospital, Torun, Poland. During a 4-week screening period (control cycle 1), subjects' medical histories were recorded and gynecological and laboratory examinations were undertaken, in order to establish which subjects met the inclusion criteria for the study. After a pretreatment phase of one cycle (control cycle 2), subjects received the oral contraceptive preparations according to a randomization list in chronological order, and began the 12-month treatment period. Clinical investigations were carried out between days 18 and 21 in the control cycle 2 and in treatment cycles 1, 3, 6, 9 and 12 (Table 1). The

Table 1 Study design: all procedures listed were performed on day 18–21 of the cycle in control cycle 2 and all treatment cycles

	Control cycle		*Treatment cycle*				
	1	*2*	*1*	*3*	*6*	*9*	*12*
Medical history	●						
Gynecological examination	●				●		●
Randomization		●					
Ultrasonography		●	r	●	●	●	●
Follow-up visit		●	r	●	●	●	●

ultrasound investigations were also performed at these times and recorded photographically. At each visit, bodyweight was recorded and blood pressure was measured after the subject had been sitting for 5 min. Gynecological examinations (including a PAP smear) were repeated during cycles 6 and 12.

Subjects who withdrew from the study before completion were not replaced, regardless of the reason for withdrawal, and subjects were excluded from the control cycle analysis if they did not satisfy prespecified criteria regarding pill taking. The study was performed according to the Declaration of Helsinki (reviewed version, Hong Kong 1975). The proper conduct of the study was ensured by the regular visits of monitors and plausibility checks on the completed study case report forms.

Ultrasound examinations

Vaginal ultrasonography was carried out with a Sono-Diagnost XP 1550 S (Philips, Hamburg, Germany). Mean follicular diameter was calculated by averaging the largest transverse and longitudinal diameters of all follicles with a mean diameter of > 5 mm.

Statistical methods

The following statistical procedures were used to analyze the study results. The χ^2 test was used for the comparison of the frequency distributions in test groups A and B and in subgroups of selected subjects; Student's *t*-test for the comparison of mean values; and Mann–Whitney U-test for the comparison of individual percentage data. A value of $p = 0.05$ was agreed upon as the significance level, and the total probability of error with the use of several target variables was estimated by the method of Bonferroni–Holm.

RESULTS

A total of 207 women received the gestodene preparation containing 30 µg ethinylestradiol (group A) and 209 received the desogestrel preparation containing 20 µg ethinylestradiol (group B). The total number of treatment cycles in group A was 2088, and in group B 2051. At baseline, the two treatment groups were comparable with respect to age, height, weight, cycle length and follicle growth (Table 2). The median age was 26 years in both groups.

Of the 416 subjects who entered the study, 48 (23.2%) in group A and 54 (25.8%) in group B discontinued prior to completion. Of these withdrawals, 18 and 21 respectively, were attributed to adverse events (Table 3). The primary complaints leading to withdrawal were headache, nausea and abdominal pain. Overall, the incidence was similar for the two groups, although more adverse events were cited in group B, the 20 µg

Table 2 Demographic and anamnestic data at baseline (control cycle 2) for group A (30 µg ethinylestradiol/75 µg gestodene) and group B (20 µg ethinylestradiol/150 µg desogestrel)

	Group A (*n* = 207)	*Group B* (*n* = 209)
Age < 20 years (*n*)	6	9
Age 20–24 years (*n*)	77	65
Age 25–29 years (*n*)	54	62
Age 30–34 years (*n*)	48	45
Age 35–40 years (*n*)	22	28
Median age (years)	26	26
Range of age (years)	19–39	19–40
Mean height (cm) ± SD	163 ± 6	164 ± 6
Mean weight (kg) ± SD	57.8 ± 7.0	58.4 ± 7.7
Cycle length (days)		
Mean ± SD	29.2 ± 2.2	29.2 ± 2.1
Range	24–36	25–35
Follicle diameter		
Diameter < 10 mm (*n*)	109 (52.7%)	105 (50.2%)
Diameter 10–30 mm (*n*)	86 (41.5%)	95 (45.5%)
Diameter > 30 mm (*n*)	10 (4.8%)	7 (3.3%)
Missing data (*n*)	2 (1.0%)	2 (1.0%)

Table 3 Withdrawal of subjects from the study and reasons for discontinuation in group A (30 μg ethinylestradiol/75 μg gestodene) and group B (20 μg ethinylestradiol/150 μg desogestrel)

	Group A (n)	*Group B (n)*
Number of volunteers		
Subjects enrolled	207	209
Subjects completed	159	155
Subjects discontinued	48	54
Reason for discontinuation		
Adverse events	18	21
Desire for pregnancy	4	4
Request of subject	23	28
Protocol violation	3	0
Pregnancy	0	1

Table 4 Adverse events leading to withdrawal from the study of subjects in group A (30 μg ethinylestradiol/75 μg gestodene) and in group B (20 μg ethinylestradiol/150 μg desogestrel)

	Group A (n)	*Group B (n)*
Headache	4	5
Hypertension	0	1
Nausea	4	4
Depressive mood	2	1
Abdominal pain	4	6
Vomiting	1	5
Intermenstrual bleeding	4	3
Dizziness	0	4
Nervousness	0	3
Breast tension	2	1
Pruritus	0	1
Colpitis	1	1
Total number of events	22	35
Total number of women*	18	21

*Some women cited more than one reason for withdrawal

ethinylestradiol/150 μg desogestrel group (35 versus 22). Table 4 gives a breakdown of the adverse events reported by the women who withdrew from the study.

One subject from group B (20 μg ethinylestradiol) became pregnant during treatment. No evidence of any drug interaction or errors in tablet taking was discovered and it was concluded that this was a method failure. Throughout the study there was no difference between the groups with respect to either blood pressure or body weight.

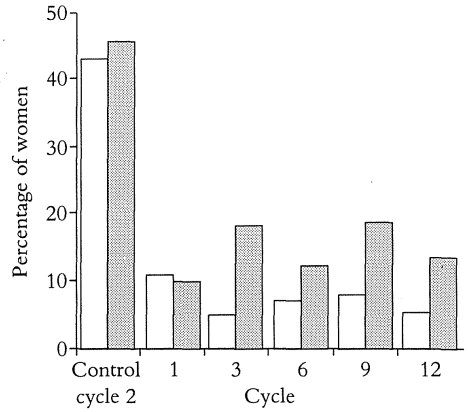

Figure 1 The percentage of women with follicle-like structures of mean diameter 10–30 mm in group A (clear bar; 30 μg ethinylestradiol/75 μg gestodene) and group B (shaded bar; 20 μg ethinylestradiol/150 μg desogestrel) measured in control cycle 2 and treatment cycles 1, 3, 6, 9 and 12.

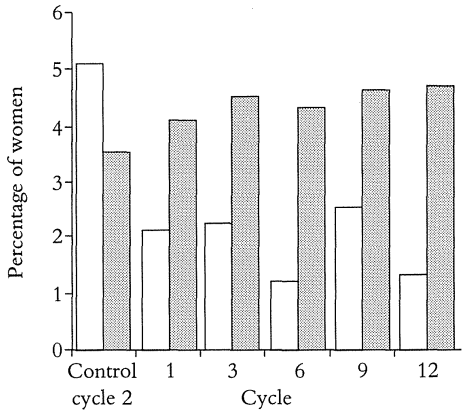

Figure 2 The percentage of women with follicle-like structures of mean diameter > 30 mm in group A (clear bar; 30 μg ethinylestradiol/75 μg gestodene) and group B (shaded bar; 20 μg ethinylestradiol/150 μg desogestrel) measured in control cycle 2 and treatment cycles 1, 3, 6, 9 and 12

One woman withdrew from group B due to hypertension.

At baseline (control cycle 2), the incidences of follicle-like structures with a mean diameter of 10–30 mm and > 30 mm were similar in the two groups. In group A (30 μg ethinylestradiol), 42.6% of women had follicle-like structures with a mean

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