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Effects of an oral contraceptive combination containing 0.150 mg desogestrel plus 0.020 mg ethinyl estradiol on healthy premenopausal women

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Summary. Twenty-six healthy premenopausal outpatients from the Menopause Clinic of the University of Bologna were treated with a combination pill containing 0.020 mg of ethinyl estradiol and 0.150 mg of desogestrel for one year. Throughout the treatment period, clinical and laboratory monitoring was periodically performed, and women were asked about the occurrence of climacteric symptoms. This formulation relieved climacteric symptoms, and did not adversely affect lipids and clotting factors, except for a slight increase in serum triglycerides. Laboratory data also suggest a beneficial effect on bone metabolism.

Key words: Oral contraceptives – Premenopause – Climacteric syndrome

Introduction

Contraception in the few years before the menopause still is a matter of concern. The combined contraceptive pill, being a very effective contraceptive method, would be advisable. In premenopausal women, these preparations should control climacteric symptoms and also protect against osteoporosis (de Aloysio et al. 1990).

Yet many consider that the combined oral contraceptive pill should not be prescribed to women over 35, because of their negative effect on cardiovascular risk. We believe that this effect is dose-related and can be eliminated by using low-dose combined preparations (Bottiglioni et al. 1991).

The aim of this study was to assess the clinical and metabolic effects of a low-dosage combined oral contraceptive therapy in premenopausal women.

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Subjects and methods

After the study protocol had been approved by the local Ethical Commitee, 35 healthy premenopausal women agreed to take part in the study, and gave oral informed consent. The patients were selected from the Menopause Clinic of Bologna if they fulfilled the following criteria:

- Age between 45 and 50 years with irregular menstrual cycles or over 50 years with both regular and irregular cycles (de Aloysio et al. 1983);
- Absence of contraindications to use of oral contraceptives and of cardiovascular risk factors: smokers of less than 5 cigarettes per day were included in the first part of the study;
- Absence of drugs likely to interfere with clotting mechanism or with steroid metabolism.

The study group's mean age 47.4 ± 3.0 (S.D.) years and 79.8% had never used contraception previously.

Women were treated with a combination of 20 mcg of ethinyl estradiol and 150 mcg of desogestrel for 12 months: tablets were taken daily for three weeks followed by a 7-day treatment-free period.

At baseline and at three-month intervals during the treatment, women were asked about the occurrence of climacteric symptoms, gynecologic and breast examinations were performed, and body weight and blood pressure were measured. We used only the presence or absence of each climacteric complaint before and during the treatment, without any specification of the intensity of symptoms in our assessments (de Aloysio et al. 1989).

At baseline and at month 6 and 12 of treatment (on days 18–21 of the therapeutic cycle), a cervical smear was taken and blood samples were drawn for the measurement of fasting lipids, clotting factors, and parameters of bone metabolism.

Measurements relating to lipids and bone metabolism were performed by the Central Laboratory of St. Orsola Hospital (Bologna); clotting factors were tested by the Center for Coagulation Study of Bologna University. Methods and errors in measurements were provided, as described (de Aloysio et al. 1983).

Women were asked to report the duration and intensity of withdrawal bleeding and the occurrence of breakthrough bleeding or other side effects.

Statistical evaluation was performed using analysis of variance for quantitative variables and chi-square for qualitative variables.

Results

One patient discontinued the treatment after two months because of a venous thrombosis associated with immobilization of a fractured leg in plaster. She was excluded from the study as were two other women who smoked (albeit less than 5 cigarettes per day).

Six women discontinued the treatment after 6 months: in one case alterations in coagulation factors (increase in blood platelets and fibrinogen) were detected; one patient requested removal from the study because of frequent intermenstrual spotting; the remaining 4 patients withdrew for personal non-medical reasons.

Twenty-six women thus completed 12 months of treatment.

Clinical data

Gynecologic and breast examinations were consistently negative throughout treatment. There were no pregnancies and no significant changes in body weight and blood pressure.

Table 1. Climacteric syndrome in healthy premenopausal women treated with oral 0.150 mg desogestrel + 0.020 mg ethinyl estradiol daily for 3 weeks out of 4 for 12 months

Complaints	Pretreatment (%) (n = 32)	After 6 cycles (%) (n = 32)	After 12 cycles (%) (n = 26)
Hot flushes[a]	71.9	18.7***	11.5***
Sweating[a]	71.9	18.7***	11.5***
Headache[b]	43.7	N.S.	N.S.
Insomnia[b]	46.9	28.1**	23.1**
Chest pains[b]	12.5	N.S.	N.S.
Paresthesia[c]	53.1	28.1**	19.2**
Palpitations[c]	56.2	31.2**	19.2***
Dizziness[c]	37.5	21.8*	15.4**
Arthralgia[c]	62.5	50.0*	42.3*
Fatigue[c]	53.1	40.6*	42.3*
Nervousness[c]	62.5	40.6*	38.5*
Depression[c]	43.7	N.S.	23.1*

[a] menopause-dependent; [b] [age-menopause] dependent; [c] age-dependent C.S. complaint (de Aloysio et al. 1989).
* = $P < .05$; ** = $P < .01$; *** = $P < .001$; N.S. = not significant (χ^2: statistical differences between pretreatment and after treatment)

Climacteric syndrome (Table 1). The contraceptive pills were effective in controlling all climacteric complaints except for headache, and chest pains.

Laboratory data

Lipid metabolism (Table 2). A significant increase in serum triglycerides and A and B lipoproteins was found after 6 and 12 months of treatment, while phospholipids, cholesterol and its fractions showed no significant changes.

Table 2. Lipids (x ± S.D.) in healthy premenopausal women treated with oral 0.150 mg desogestrel + 0.020 mg ethinyl estradiol daily for 3 weeks out of 4 for 12 months

mg/100 ml serum	Pretreatment (n = 32)	After 6 cycles (n = 32)	After 12 cycles (n = 26)
Total cholesterol	241.4 ± 39.3	246.3 ± 37.9	233.0 ± 39.0
HDL-cholesterol	54.1 ± 8.8	55.9 ± 9.1	54.6 ± 8.9
LDL-cholesterol	160.2 ± 34.1	160.6 ± 32.5	163.4 ± 35.0
A-lipoprotein	159.9 ± 24.7	166.3 ± 40.1**	186.7 ± 25.9**
B-lipoprotein	113.0 ± 20.1	120.9 ± 19.8*	121.9 ± 19.6*
Phospholipids	244.6 ± 29.1	245.4 ± 34.8	244.4 ± 33.8
Triglycerides	96.8 ± 46.3	134.4 ± 50.0*	130.1 ± 47.4*

* = $P < .05$; ** = $P < .01$

Table 3. Clotting factors (x ± S.D.) in healthy premenopausal women treated with oral 0.150 mg desogestrel + 0.020 mg ethinyl estradiol daily for 3 weeks out of 4 for 12 months

	Pretreatment (n = 32)	After 6 cycles (n = 32)	After 12 cycles (n = 26)
Platelets[b] ($1000/mm^3$)	237.5 ± 57.1	243.0 ± 54.7	239.3 ± 55.6
aPTT[a] (seconds)	29.5 ± 2.8	28.1 ± 2.2	29.4 ± 2.3
Thrombin time[a] (seconds)	18.3 ± 1.1	17.6 ± 1.0	18.0 ± 1.1
Antithrombin III[a] (activity %)	102.9 ± 7.7	100.6 ± 8.0	98.6 ± 8.4
Fibrinogen[a] (mg/100 ml)	292.2 ± 44.7	304.6 ± 47.3	300.1 ± 39.7
Factor VII[a] (activity %)	111.9 ± 37.8	120.5 ± 35.8	122.5 ± 40.2
Factor VIII (AHF) (Ag %)	99.1 ± 23.3	101.9 ± 28.9	101.3 ± 19.8
β_2-Thromboglobulin[a] (ng/ml)	40.8 ± 19.6	37.7 ± 17.9	35.4 ± 18.2

[a] plasma; [b] blood

Clotting factors (Table 3). No significant changes in mean clotting parameters were detected throughout the study.

Bone metabolism (Table 4). Serum alkaline phosphatase and phosphate decrease at the end of the treatment suggesting a beneficial effect on bone metabolism.

Table 4. Bone metabolism parameters (x ± S.D.) in healthy premenopausal women treated with oral 0.150 mg desogestrel + 0.020 mg ethinyl estradiol daily for 3 weeks out of 4 for 12 months

	Pretreatment (n = 32)	After 6 cycles (n = 32)	After 12 cycles (n = 26)
Calcium[a] (mg/100 ml)	9.1 ± 0.6	9.1 ± 0.4	9.1 ± 0.2
Phosphate[a] (mg/100 ml)	3.6 ± 0.6	3.4 ± 0.7	2.7 ± 0.7*
APh[a] (mU/ml)	109.1 ± 30.0	89.8 ± 26.3*	88.4 ± 21.3*
Nordin's index[b] (Ca/Creatinine 1:1)	5.6 ± 3.0	5.5 ± 2.2	5.5 ± 1.8
Calcitonin[c] (pg/ml)	22.8 ± 10.1	26.5 ± 13.1	24.2 ± 9.9
Parathormone[c] (ng/ml)	30.1 ± 8.9	28.0 ± 10.9	28.8 ± 9.2

[a] serum; [b] urine; [c] plasma; * = $P < .05$

Bleeding pattern

Withdrawal bleeding was present in all 348 therapeutic cycles. In 31 of them (8.9%), breakthrough spotting was also reported and 20 of these episodes occurred in the first three months of the treatment.

Side effects

The most frequent side effect was breast tenderness which tended to occur in the first three months of treatment (30.8%); headache (11.5%) and depression (7.7%) were also reported.

Discussion

The study results indicate that a pill containing 20 mcg of ethinyl estradiol and 150 mcg of desogestrel is well tolerated, provides good contraception and has a good effect on premenopausal symptoms.

We found a slight increase in serum triglycerides; as already shown in literature, triglycerides increase in the first months of therapy and then reach a steady state. In our opinion such a small increase is of questionable clinical significance. Only one patient was excluded from the study owing to an alteration in clotting parameters, as documented by laboratory data. The occurrence of a venous thrombosis in a patient smoking less than 5 cigarettes per day who had a leg fracture immobilized in plaster shows that risk factors for venous thromboembolism should not be ignored.

Our formulation appeared to have a beneficial effect on bone metabolism.

In our opinion, the use of a contraceptive pill containing low doses of estrogen and a progestogen with little androgenic activity is appropriate up to the menopause in healthy non-smoking women without cardiovascular risk factors; their clotting parameters should be measured periodically.

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