Clinical Article

Hemostatic and metabolic effects of lowering the ethinyl-estradiol dose from 30 mcg to 20 mcg in oral contraceptives containing desogestrel

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The metabolic and hemostatic effects of two oral contraceptives containing 150 mcg desogestrel and 20 mcg ethinyl-estradiol (EE) (MERCILON) or 30 mcg EE (MARVELON) were compared in order to examine the effect of reducing the EE dose in contraceptive pills. Forty-nine women participated in this randomized study during 6 cycles. In both groups, there was a significant increase in triglycerides, HDL-cholesterol and apoprotein A1; the same increase was observed for SBP and CBG. Slight and transient variations of fasting blood glucose levels were seen in the 30 mcg EE group and in the two groups for fasting insulin levels. The increase in renin substrate was significantly higher with the 30 mcg EE than with the 20 mcg EE pill. In both groups, plasminogen increased significantly, but antithrombin III, total and free protein S and fibrinogen decreased significantly only in women taking the 30 mcg EE pill, whereas there was no significant change in the 20 mcg EE group. Reducing the dose of EE in oral contraceptives from 30 mcg to 20

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mcg minimizes their impact on renin substrate and hemostatic parameters.

Keywords: Ethinyl-estradiol; progestogen; lipoproteins; renin substrate; antithrombin; sex steroid binding protein; oral contraceptives.

Introduction

Oral contraceptive agents (OC) can induce substantial changes in plasma lipoprotein levels, glucose tolerance, blood pressure and hemostatic parameters (1-5). These effects may contribute to an increased risk of cardiovascular events in pill users (6,7).

In order to limit these potential hazardous side effects, the estrogen content of the pills has been reduced from 100 to 30 mcg of ethinyl-estradiol (EE) and, more recently, new progestogens have been proposed. These third generation progestogens (i.e., desogestrel, gestodene, norgestimate) are characterized by a potent negative feed-back activity on the hypothalamus, a high affinity for endometrial progesterone receptors and a very weak affinity for the androgen receptors (8,9). The properties of desogestrel allowed a further reduction in the estrogenic content (20 mcg of EE) of the pill in order to improve the clinical and biological tolerance.

The aim of this prospective study was to examine whether the reduction of EE from 30 to 20 mcg per day in low-dose monophasic combinations, containing the same dose of progestogen (desogestrel, DG, 150 mcg), results in a decrease in the metabolic and hemostatic impact of OC.

Material and methods

Fifty-eight healthy women gave their informed consent to participate in the study. These regularly menstruating women were at least three months post-partum or post-abortion, were not lactating and had not received any steroid treatment during the previous three months. Exclusion criteria were: symptoms or history of venous and arterial disease, diabetes (according to WHO criteria), hyperlipidemia (cholesterol >6.4 mmol/l and triglycerides >2.5 mmol/l), obesity (body mass index over 27), eating disorders, consumption of more than 10 cigarettes per day, hypertension (blood pressure over 140/90 mm Hg), benign or malignant gynecological tumours, known or suspected cancer and treatment with antibiotics, barbiturates or other drugs interfering with hepatic metabolism.

The subjects were allocated at random into two groups. In the group Marvelon, women received a monophasic combination of 30 mcg EE plus 150 mcg DG and in the group Mercilon, a combination of 20 mcg EE plus

150 mcg DG. Both preparations were administered in a cyclical manner for 21 days followed by 7 days free of medication during six consecutive cycles.

Women were investigated during the last week of the control cycle and between days 15-21 of the third and sixth treatment cycles. On each occasion, a clinical control was performed including gynecological examination, blood pressure and body weight measurements. Body mass index (BMI = weight/(height)^2 – kg/m^2) was determined for each subject. Blood pressure was determined by oscillometric method (Dinamap^R) in patients resting in the supine position for 15 minutes. Fasting blood samples were collected for determination of plasma lipids, apolipoprotein, blood glucose and insulin, hemostatic parameters (antithrombin III, plasminogen, fibrinogen, protein C, protein S), sex steroid binding protein (SBP), cortisol binding globulin (CBG), renin substrate (RS).

Total cholesterol (TC) and triglycerides (TG) were measured by enzymatic methods (10). High density lipoprotein-cholesterol (HDL-cholesterol) was determined after precipitation of apolipoprotein B-containing lipoproteins with sodium phosphotungstate in the presence of magnesium chloride and HDL was measured enzymatically in the supernatant (10). Low density lipoprotein-cholesterol was calculated according to the Friedewald estimation (11). Apolipoprotein A1 and B were determined by a nephelometric assay (10).

Blood glucose was measured by an enzymatic procedure (glucose oxidase). Insulin levels were determined by radioimmunoassay. Antithrombin III (AT III) determinations were done by two methods: a nephelometric method (BNA Behring) and an amidolytic technique using ACA-SX (Dupont de Nemours, Wilmington, Delaware, USA). Fibrinogen was measured according to Clauss (12) and plasminogen by a amidolytic method (ACA-SX Dupont). Protein C and protein S (total and free) antigen were assayed by ELISA method using commercially available kits (Diagnostica Stago, Asnières, France).

Renin substrate (RS) concentrations were measured by a method based on angiotensin I generation and expressed as ng of angiotensin I liberated per ml of plasma by an excess of renin (13). Sex steroid binding protein (SBP) and cortisol binding globulin (CBG) were measured by electro-immunoassay on ready-to-use immunoplates (14).

Statistical analysis

Results are expressed as mean ± standard deviation. Data obtained during the 3rd and the 6th cycle were compared to the values at baseline in each group (intra-group comparison) by a Wilcoxon test, and the evolution of the different parameters during treatment was compared between groups (inter-group comparison) by a Mann-Whitney U-test.

Results

Four subjects (2 in each group) who gave their informed consent dropped out of the study before baseline examination. Three subjects involved in the study (1 in the Mercilon group and 2 in the Marvelon group) left the study during the first trimester for personal reasons. One subject in each group complained of nausea and left the study. Finally, 49 subjects completed the study: 29 in the group Mercilon and 20 in the group Marvelon. The difference in the number of subjects between groups is related to the procedure of randomization which was equilibrated, 6 patients for each clinician, but all the forecast patients could not be included.

At baseline, there were no significant differences between groups in terms of age, body mass index, tobacco consumption, blood pressure, characteristics of menstrual cycle and mean values for all laboratory parameters.

Data on plasma lipids are shown in Table 1. In each group, there was a significant increase in triglycerides, HDL-cholesterol and Apo A1 concentration from baseline to the third and sixth cycle. There was no significant variation in total cholesterol and Apo B. The evolution of plasma lipids during treatment was not significantly different between the two groups.

There was a transient (3rd cycle) but significant ($p < 0.05$) increase in

TABLE 1. Plasma lipids and apoproteins in Mercilon (n = 29) or Marvelon (n = 20) users (Values are mean ± SD)

			Control cycle	3rd cycle	6th cycle
	Triglycerides	mmol/l	0.81 ± 0.27	0.99 ± 0.28***	1.05 ± 0.28**
20 mcg EE	Total-cholesterol	mmol/l	4.98 ± 0.93	4.90 ± 0.70	5.03 ± 0.75
+	HDL-cholesterol	mmol/l	1.13 ± 0.21	1.29 ± 0.21**	1.26 ± 0.26*
150 mcg DG	LDL-cholesterol	mmol/l	3.48 ± 0.88	3.17 ± 0.67	3.22 ± 0.64
(Mercilon)	Apo A1	g/l	1.52 ± 0.27	1.71 ± 0.28**	1.72 ± 0.35*
	Apo B	g/l	0.95 ± 0.23	0.98 ± 0.23	1.00 ± 0.20
			Control cycle	3rd cycle	6th cycle
	Triglycerides	mmol/l	0.81 ± 0.26	1.17 ± 0.40**	1.06 ± 0.41**
30 mcg EE	Total-cholesterol	mmol/l	4.93 ± 0.90	4.98 ± 0.77	5.10 ± 1.11
+	HDL-cholesterol	mmol/l	1.11 ± 0.21	1.26 ± 0.21**	1.31 ± 0.21**
150 mcg DG	LDL-cholesterol	mmol/l	3.46 ± 0.82	3.20 ± 0.77*	3.33 ± 1.03
(Marvelon)	Apo A1	g/l	1.50 ± 0.27	1.74 ± 0.26**	1.80 ± 0.34**
	Apo B	g/l	0.95 ± 0.21	1.01 ± 0.23	1.03 ± 0.28

*p <0.05 versus control cycle. **p <0.01 versus control cycle. ***p <0.001 versus control cycle.

fasting blood glucose in the Marvelon group (control cycle: 4.6 mmol/l ± 0.3, 3rd cycle: 4.9 ± 0.4; 6th cycle: 4.7 ± 0.3) whereas no significant variation appeared in the Mercilon group (control cycle: 4.6 mmol/l ± 0.5; 3rd cycle: 4.6 ± 0.3; 6th cycle: 4.7 ± 0.5). At a third cycle, there was a significant difference between the two groups in the evolution of the blood glucose levels; there was a significant ($p < 0.05$) increase in the Marvelon group compared to the Mercilon group. At the 6th cycle, blood glucose was not significantly different between groups. Fasting insulin levels increased significantly ($p < 0.05$) during the 6th cycle in the Mercilon group (control cycle: 9.5 ± 3.6 mcU/ml; 3rd cycle: 10.2 ± 2.9; 6th cycle: 12.5 ± 6.5) and during the 3rd cycle in the Marvelon group (control cycle: 10.1 ± 3.9 mcU/ml; 3rd cycle: 12.5 ± 4.1; 6th cycle: 12.2 ± 3) as compared with basal values. There were no significant inter-group differences in insulin levels.

Body mass index and blood pressure (systolic and diastolic) were not significantly modified by treatment in either group.

Data on hemostatic parameters are shown in Table 2. AT III activity ($p < 0.01$) and antigen ($P < 0.05$) decreased significantly during the 3rd and 6th cycle in the Marvelon group and were not significantly modified in the Mercilon group. There was no significant inter-group difference in AT III activity and antigen.

TABLE 2. Hemostatic parameters in Mercilon (n = 29) or Marvelon (n = 20) users (Values are mean ± SD)

			Control cycle	3rd cycle	6th cycle
20 mcg EE + 150 mcg DG (Mercilon)	AT III activity	%	94 ± 8	93 ± 10	92 ± 7
	AT III antigen	%	95 ± 7	94 ± 9	92 ± 6
	Plasminogen	%	97 ± 16	123 ± 20**	114 ± 14**
	Protein C	%	99 ± 21	106 ± 24	109 ± 13
	Total protein S	%	98 ± 15	93 ± 14	98 ± 12
	Free protein S	%	93 ± 12	88 ± 11	91 ± 10
	Fibrinogen	g/l	3.62 ± 0.83	3.81 ± 0.73	3.61 ± 0.80
			Control cycle	3rd cycle	6th cycle
30 mcg EE + 150 mcg DG (Marvelon)	AT III activity	%	95 ± 8	89 ± 10**	90 ± 11**
	AT III antigen	%	97 ± 7	93 ± 7*	92 ± 9*
	Plasminogen	%	101 ± 20	127 ± 20**	123 ± 20**
	Protein C	%	105 ± 17	109 ± 21	113 ± 22
	Total protein S	%	97 ± 16	93 ± 17*	90 ± 17*
	Free protein S	%	93 ± 15	90 ± 14	83 ± 16**
	Fibrinogen	g/l	3.66 ± 0.63	3.61 ± 0.64	3.45 ± 0.46*

*$p < 0.05$ versus control cycle. **$p < 0.01$ versus control cycle.

Plasminogen increased significantly ($p < 0.01$) during the 3rd and 6th cycle as compared with basal values in both groups and there was no difference between groups.

There were no significant variations in protein C during the study. There was a significant decrease in total protein S during the 3rd ($p < 0.05$) and 6th ($p < 0.01$) cycle and of free protein S during the 6th cycle ($p < 0.01$) in the Marvelon group, whereas non-significant changes in these parameters were found in the Mercilon group. Fibrinogen decreased significantly ($p < 0.05$) during the 6th cycle in the Marvelon group.

Plasma levels of sex steroid binding protein and renin substrate increased significantly ($p < 0.01$) during the 3rd and the 6th cycle as compared with basal values in each group (Figures 1 and 2). There was no significant inter-group difference in the sex steroid binding protein evolution during treatment.

By contrast, the increase in renin substrate between the control and the 6th cycle was significantly ($p < 0.05$) higher in the Marvelon group as compared with the Mercilon group.

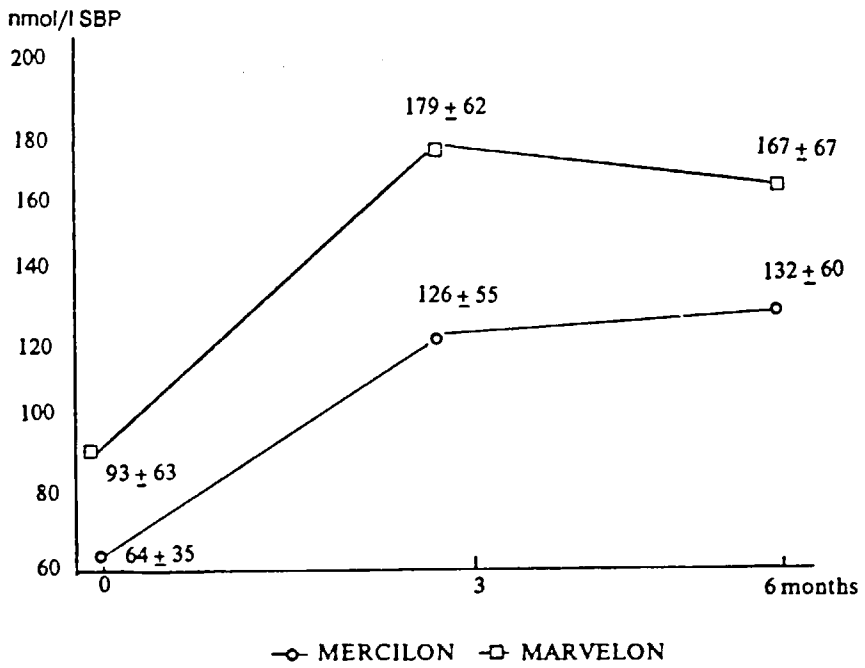

FIGURE 1. Sex steroid binding before and after 3 and 6 cycles of contraception.
MARVELON: 30 mcg ethinyl-estradiol + 150 mcg desogestrel (N=20).
MERCILON: 20 mcg ethinyl-estradiol + 150 mcg desogestrel (n=29).

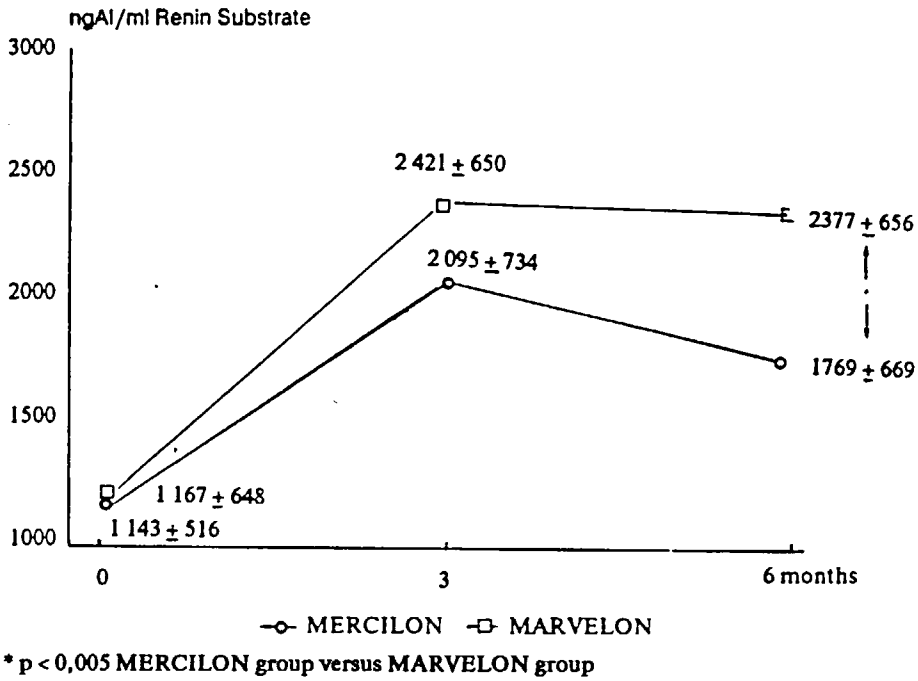

FIGURE 2. Renin substrate before and after 3 and 6 cycles of contraception. MARVELON: 30 mcg ethinyl-estradiol + 150 mcg desogestrel (N=20). MERCILON: 20 mcg ethinyl-estradiol + 150 mcg desogestrel (n=29).

As far as CBG is concerned, there was a significant increase in the Marvelon group (control cycle: 0.99 mcmol/l ± 0.47; 3rd cycle: 1.56 ± 0.52 – $p < 0.01$; 6th cycle: 1.42 ± 0.44 – $p < 0.05$) and the Mercilon group (control cycle: 0.78 mcmol/l ± 0.28; 3rd cycle: 1.25 ± 0.33 – $p < 0.001$; 6th cycle: 1.32 ± 0.41 – $p < 0.01$) as compared with basal values.

Discussion

Many pharmacodynamic studies have compared the metabolic impact of OCs differing in their progestogen content. It was shown that third generation progestogens resulted in lesser adverse effects on lipoprotein metabolism and glucose tolerance than androgenic progestogens such as levonorgestrel (7,15-17). In contrast, similar coagulation abnormalities have been reported with new progestogens (18-20). Few studies are available that compare the metabolic impact of OCs containing the same progestogen and differing in the EE content.

In this study, we analyzed the effect of the reduction of the dose of

ethinyl-estradiol (from 30 to 20 mcg) on the biological effects of OCs containing the same dose (150 mcg) of a third generation progestogen, desogestrel.

In 30 mcg EE + 150 mcg DG users, a significant decrease in antithrombin III and total and free protein S was observed in keeping with previous studies on 30 mcg ethinyl-estradiol-containing pills (19). By contrast, no significant variation in these hemostatic parameters occurred in 20 mcg EE + 150 mcg DG users. Though no significant inter-group differences appeared, these results suggest that lowering ethinyl-estradiol may yield lesser hemostatic alterations than previously reported (4,21). A decrease in AT III and protein S has been observed in the 30 mcg EE pill but levels were not below 70%, as observed in congenital deficiencies associated with thrombosis. However, it might represent a triggering condition in circumstances known to increase the risk of thrombosis and possibly induce a decrease of AT III and/or protein S (surgery for instance). Further study including measurement of markers of coagulation activation such as fragment 1 + 2 could be helpful to determine whether these patients have hemostatic changes associated with prothrombotic state.

This lesser effect on hemostasis with 20 mcg EE-containing OCs has been suggested in a study versus a 30 mcg EE pill (30 mcg EE + 75 mcg gestodene) and a triphasic pill (6 days: 30 mcg EE + 50 mcg levonorgestrel; 5 days: 40 mcg EE + 75 mcg levonorgestrel; 10 days: 30 mcg EE + 125 mcg levonorgestrel). The progestogen was not the same, but there was no significant variation of fibrinopeptide A with the 20 mcg EE pill (6). In other studies with 20 mcg EE + 150 mcg DG, the antithrombin III activity and the fibrinopeptide A remained unchanged (21-23).

The effects on the hemostasis observed with the OCs are mainly due to the estrogen component, some of them being perhaps linked to the nature of the progestogen (3,18,24). This study demonstrated the specific effect of ethinyl-estradiol on the hemostasis factors as the progestogen of the two compared pills was the same and was administered at the same dosage. It is likely that there is a dose-dependent effect of ethinyl-estradiol on coagulation (24).

It was confirmed that, even at a daily dose of 20 mcg, ethinyl-estradiol induced a significant increase in liver-derived proteins such as SBP, CBG and RS (23,25-29). This is not surprising as even very low doses of oral estrogen (i.e., 10 mcg ethinyl-estradiol; 2 mg estradiol) were shown to stimulate the hepatic synthesis of these proteins in post-menopausal women (1). However, in our study, the increase in RS was significantly lower in the Mercilon than in the Marvelon group, indicating that lowering the estrogen content minimizes the impact of OC on this hepatic parameter.

Both OC preparations induced a significant increase in triglycerides as previously reported (30). This is related to the effect of ethinyl-estradiol

on the hepatic production of very low density lipoprotein (1). In our study, there was no significant difference between groups in terms of triglycerides increases. In agreement with previous observations (30-32), HDL-cholesterol and its major apoprotein, Apo Al, also increased significantly with both preparations. This means that the reduction of ethinyl-estradiol to 20 mcg does not suppress the estrogen effect on HDL metabolism. This also indicates that the progestogen component of this OC (i.e., desogestrel) in this dosage exhibits no androgenic effect on HDL-metabolism, in contrast with older progestogens such as levonorgestrel which decrease HDL levels (33-35). In the literature, the results with the 20 mcg pill showed either no effect or an increase of HDL-C and/or apoprotein Al (26,27,30,36). These differences in HDL may also be related to the progestins. In the study by Song et al., HDL-C did not increase significantly in Mercilon users but, in this group, Apo Al increased (32). The effect of OCs on HDL-C is particularly relevant because in the general population the risk of developing cardiovascular disease is inversely correlated to the plasma concentration of HDL-C (10).

In contrast with previous studies (37), we found a transient but significant increase in fasting blood glucose in the subjects using Marvelon, but it was confirmed that blood glucose was not modified by Mercilon (27,38). A transient but significant increase in fasting insulin levels was observed in both groups whereas previous studies showed no significant variation in fasting basal and stimulated insulin levels in Mercilon and Marvelon users (27,32,39). Further studies are needed to precisely determine the effect of the 20 mcg EE-containing pill on glucose tolerance.

Altogether, these results indicate that the reduction of the ethinyl-estradiol content of OCs from 30 to 20 mcg per day does not totally suppress the metabolic effects of OCs but may minimize some of them, particularly the increase of renin substrate. As far as hemostasis is concerned, lesser alterations with the 20 mcg EE pill than with the 30 mcg EE oral contraceptive were observed.

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