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Extended regimens of the combined contraceptive vaginal ring containing etonogestrel and ethinyl estradiol: effects on lipid metabolism

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Abstract

Background: Oral contraceptives used for extended periods of time have been studied because of their potential benefits; however, there have been few publications on extended regimens of vaginal contraceptive rings. The aim of this study was to evaluate modifications in the lipid profile of women using the vaginal ring continuously over a 1-year period.

Study Design: This prospective cohort enrolled 75 women (18–37 years) who used a contraceptive vaginal ring releasing 120 mcg of etonogestrel and 15 mcg of ethinyl estradiol daily continuously for 84 days, followed by a 7-day ring-free interval, during 1 year. At baseline and every 3 months during the 1-year study period, blood was collected to assess cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides and apolipoproteins A-I and B. The ANOVA test was used to analyze differences in the results of these exams over time.

Results: After 1 year of continuous contraceptive use, there was a significant increase in triglycerides as well as in total and HDL-C levels. There was a nonsignificant decrease in the mean concentration of LDL-C during the study period. Apolipoprotein A-I increased and apolipoprotein B decreased, but the apolipoprotein A-I/apolipoprotein B ratio did not change significantly.

Conclusion: The combined contraceptive vaginal ring used on an extended regimen causes changes in the lipid profile metabolism of users. Despite the vaginal route of administration, the steroids released by the ring caused significant changes in lipids and lipoproteins, which were typical of those seen with ethinyl estradiol given either orally or parenterally.

Keywords: Metabolic change; Vaginal hormonal contraception; Continuous; Contraceptive vaginal ring; Extended cycle; Combined contraceptives

1. Introduction

Combined oral contraceptives are one of the most popular forms of birth control worldwide and are used by women of all ages. The atherogenic effects of steroid contraceptives have been investigated ever since these agents became commercially available, with conflicting results [1–5]. Progestogen dose and type can produce changes in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels [6,7]. Progestogens with androgenic effects used in combined hormonal contraceptives can reduce HDL-C and after years of use could increase cardiovascular risks [6–8].

Cardiovascular diseases have reached epidemic proportions and are the main cause of mortality and morbidity in developed countries [9]. The main risk factors for cardiovascular events are age, family history, tobacco use, sedentary lifestyle, obesity, high cholesterol levels, hypertension and diabetes [9–12].

Over the years, new contraceptives with consistently lower doses of estrogens and progestogens have become available, as well as less androgenic progestogens. Besides the traditional oral route, women now have the possibility of using hormonal contraception through alternative routes, in various regimens [13,14]. The main focus of most studies on hormonal contraceptives used for extended regimens is vaginal bleeding, since the main reason why women chose this regimen is to avoid periodic bleeding. Up to the present, there have been few studies on clinical and metabolic effects of extended regimens of hormonal contraceptives.

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Motivated by the paucity of information in this field, the objective of this study was to assess changes in the lipid profile of women using contraceptive vaginal rings on extended regimens during a 1-year period.

2. Patients and methods

Between April 2004 and March 2005, all women who attended an educative session on pregnancy prevention at the Gynecology Clinic of the Western Paulista University (Presidente Prudente, state of São Paulo, Brazil) and who voluntarily opted for extended regimens of the contraceptive vaginal ring (84 days with the ring and 7 ring-free days) were invited to participate in the study. After giving their informed consent, all patients had a complete physical and pelvic examination, including blood pressure, weight, height, cardiac and pulmonary auscultation and abdominal palpation. Additional information included age, parity, age at menarche and first sexual intercourse, marital status, education and previous use of contraceptives.

Exclusion criteria followed the WHO recommendations and included pregnancy and contraindications for estrogen use, such as lactation, active liver disease, active thromboembolic disease, severe hypertension (BP >140/100 mmHg) and diabetes mellitus, among others [15]. Women who reported the use of oral or monthly injectable hormonal contraceptives during the last 3 months were also excluded, as well as those who had been using depot-medroxyprogesterone acetate injections in the 6 months prior to enrollment.

Eligible women received a vaginal ring manufactured by Organon, Brazil, that released daily doses of etonogestrel (120 mcg) and ethinyl estradiol (15 mcg). The vaginal ring was provided free of charge at the clinic, and each woman was told to place the ring in her vagina within 5 days of the onset of menses. Each patient received instructions to leave the ring in place during 21 continuous days and then replace it with a new ring and continue consecutively, for a total of 4 rings. After this period of 84 days, the patient was instructed to remove the ring and wait 7 days before introducing a new vaginal ring.

Participants were evaluated prospectively during 12 months. Before initiating the use of the contraceptive ring, all patients had a full physical examination and 20 mL blood was collected after a 12-h fasting period for the following exams: total cholesterol (TC), HDL-C, LDL-C, apolipoprotein A-1 (apo A-I), apolipoprotein B (apo-B) and triglycerides (TG). The women were invited to return to the clinic every month, to receive a new ring free of charge. At the beginning of the study, all participants also received a prescription for the vaginal rings, so they could purchase them at a local pharmacy in case they missed a follow-up visit. All the patients' addresses and telephone numbers were recorded at the clinic and if they missed one follow-up visit, they were contacted through telephone or by mail. Participants were informed that if they missed more than one appointment, they would automatically be excluded from the study.

After entering the study, all participants repeated their physical evaluation and had new blood samples taken every 3 months during 1 year, totaling four examinations. All exams were performed at the same laboratory.

Venous blood samples were centrifuged at 2500 rpm for 10 min at room temperature to separate the serum. TC and TG concentrations were assessed by enzymatic colorimetric assay using Randox® Cholesterol CHOD-PAP (County Antrim, UK) and Randox® Triglycerides GPO-PAP (County Antrim, UK) reagents, respectively, Friedewald's equation was used to estimate LDL-C concentration [16]. HDL-C concentration was determined using the homogeneous enzymatic method with Randox® HDL Cholesterol Direct (County Antrim, UK) reagent.

Apo B and A-I concentrations were determined by turbidometry using Biotécnica® Apolipoproteína B Turbidimetria (Varginha, Brazil) and Biotécnica® Apolipoproteína A-I Turbidimetria (Varginha, Brazil) reagents, respectively. All assays were performed in a Cobas Mira Plus® (Roche Diagnostic Systems, Welwyn Garden City, UK) equipment using a standard control serum to ensure accuracy of measurements.

The results were analyzed descriptively and the ANOVA test was used to compare differences in laboratory results between the four study periods. If differences were detected, pairwise comparisons were performed between the values obtained at 0–3, 0–6, 0–9 and 0–12 months. Significance was set at $p<.05$.

The university's ethics committee approved the study, and all participants signed an informed consent at enrollment.

3. Results

Between April 2004 and March 2005, a total of 75 women enrolled and 62 completed the study leading to a discontinuation rate of 17.3% (Fig. 1). There were no cases of pregnancy during the study period.

Table 1 presents the main characteristics of the participants. The median age was 24.4 years (ranging from 18 to 37 years), mean age at menarche was 10.3 years (±0.6 years SD) and median age at first intercourse was 16.7 years (±2.1 years). Half of the participants (50.7%) had at least one previous pregnancy. Approximately two thirds (62.7%) had previously used oral or injectable contraceptives, 12% had used condoms, 9.3% had used periodic abstinence, 1.3% had used intrauterine devices and 14.7% reported never having used any form of birth control.

At baseline, 46.8% of the participants had normal weight (BMI 18.5–24.9 kg/m^2), 45.2% were overweight (BMI 25–29.9) and 8% were obese (BMI 30 or more). There were no significant differences in this distribution at the end of the 12-month period (41.9%, 45.2% and 12.9%, respectively, p=.41) [17].

As presented in Table 2, mean TC levels increased from 156.7 mg/dL at the beginning of the study to 168.4 mg/dL at

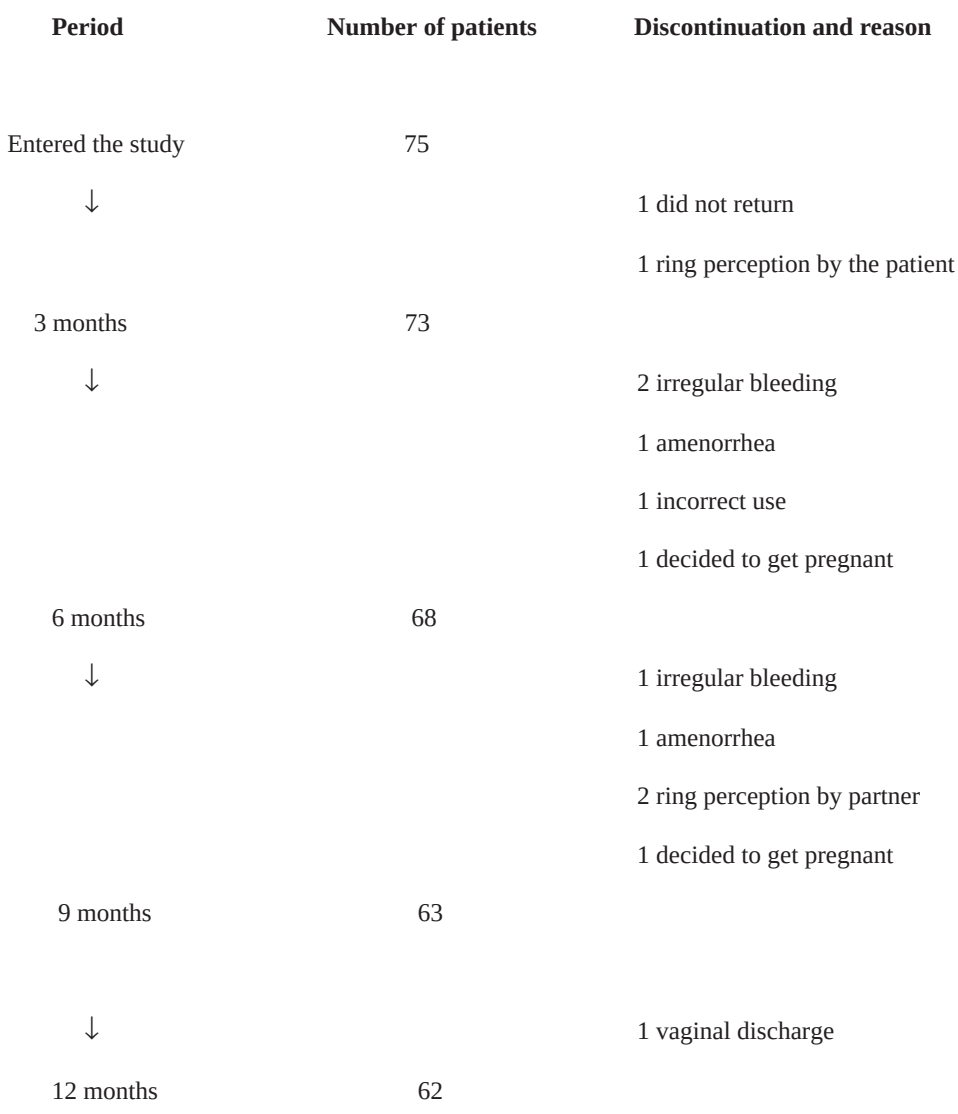

Fig. 1. Flowchart of 75 patients starting extended regimen of the contraceptive vaginal ring.

Table 1
Main baseline characteristics of 75 participants on extended regimens of the contraceptive vaginal ring

Characteristics	
Age (years)	
· Range	18–37
· Mean (SD)	24.4 (6.4)
Body mass index (m/kg^2)	
· Range	19–35
· Mean (SD)	25.1 (1.6)
Age at menarche, mean (SD)	10.3 (0.6)
Age at first intercourse, median	16.7±2.1
Multiparous	50.7%
Previous contraception[a]	85.3%

[a] Use of any birth control method.

the end of the 1-year period of continuous vaginal ring use, a significant increase ($p<.01$). Mean HDL-C concentrations rose from 50.2 at baseline to 57.3 mg/dL at 12 months ($p<.01$), and TG levels increased from 76.5 to 107.5 mg/dL after 1 year ($p<.001$).

The mean concentration of LDL-C declined from 91.3 mg/dL at the beginning of the study to 89.7 mg/dL during the study period, a nonsignificant decrease. Serum apo B levels followed the same pattern and also declined slightly from 87.8 to 85.2 mg/dL ($p=.09$), while apo A-I increased from 112.2 mg/dL at baseline to 126.8 mg/dL ($p<.001$), after 1 year of continuous contraceptive vaginal ring use. Despite these changes in individual apolipoprotein levels, the ratio remained normal throughout the study period and did not change significantly (Table 2).

Table 2
Mean lipid concentrations of women using a contraceptive vaginal ring on extended regimens for 1 year

	Months of contraceptive ring use					
	Baseline	3	6	9	12	p*
TC (mg/dL)	156.7 (17.1)	157.6 (16.4)	160 (19.1)*	165.2 (11.1)*	168.4 (18.5)*	<.03
HDL-C (mg/dL)	50.2 (12.8)	53.2 (10.8)	52.6 (9.8)	54.6 (12.5)*	57.3 (19.5)*	<.01
LDL-C (mg/dL)	91.3 (17.2)	88.3 (16.5)	87.7 (8.5)	90.1 (10.1)	89.7 (13.5)	.103
TG (mg/dL)	76.5 (8.4)	80.4 (11.4)	98.6 (9.8)*	102.3 (17.5)*	107.5 (19.1)*	<.002
VLDL-C	15.2 (3.8)	16.1 (4.1)	19.7 (4.3)*	20.5 (4.5)*	21.4 (4.0)*	<.001
Apo A-I (mg/dL)	112.2 (8.7)	118.7 (.9)	116.8 (13.4)	122.4 (11.1)*	126.8 (9.4)*	<.001
Apo B (mg/dL)	87.8 (9.7)	86.8 (8.7)	85.2 (9.1)	86.5 (9.4)	85.2 (6.8)	.092
Ratio[a]	0.78	0.73	0.73	0.71	0.67	.062

Data are presented as mean (SD). ANOVA comparing lipid concentrations obtained in the five periods of the study.
* p<.05, ANOVA, comparing lipid concentration of that period with lipid concentration of the baseline period.
[a] Apo B/apo A-I.

4. Discussion

Women using combined contraceptive vaginal rings (etonogestrel and ethinyl estradiol) for extended regimens had a significant increase of TC levels at the end of 1 year, increased HDL-C, nonsignificant changes in LDL-C concentration and a significant increase in TG concentration. The increase in TC may not have been due only to the increase in HDL cholesterol; the 50% increase in TG was likely associated with an increase in very-low-density lipoprotein cholesterol (VLDL-C). These changes are similar to those reported for women using the ring on traditional regimens (21 days followed by a 7-day pause) [18]. These metabolic changes are probably caused by the combination of ethinyl estradiol associated with etonogestrel. The changes observed are typical of the effects of ethinyl estradiol released by the ring, which was relatively unopposed by etonorgestrel.

Our participants had a significant increase in HDL-C and apo-A1 levels. HDL-C plays an important role in the prevention of atherosclerotic lesions due to its antioxidant and anti-inflammatory actions and because it promotes reverse cholesterol transport, the process of transporting excess cholesterol from foam macrophages in arterial walls to the liver, bile and feces [18,19]. Several epidemiological studies have reported an inverse relation between the concentrations of HDL-C and apo A-I and cardiovascular risk [19,20].

Our participants also had a significant increase in TG starting on the sixth month of ring use. Similar findings have been reported in combined oral contraceptive users and are probably caused by increased hepatic synthesis of TG induced by ethinyl estradiol [21]. Since the TG levels found in women using low-dose contraceptives are mainly caused by increased lipoprotein synthesis and not by changes in lipid catabolism (probably the most significant contributor to atherogenesis), high TG concentrations induced by ethinyl estradiol do not affect the incidence of cardiovascular diseases. Moreover, this effect is also counterbalanced by the estrogen-induced increase in HDL-C. Therefore, increases in TG are not associated with increased cardiovascular risks if HDL-C levels also increase [6].

Studies published in the last 10 years suggest that apolipoprotein concentration reflects the number of atherogenic and nonatherogenic particles [18,20–23]. Despite some controversies, apoproteins A and B are thought to be one of the best predictors for cardiovascular disease at present [19,22,23]. Our patients had an increase in apoprotein A-I concentration and a nonsignificant decrease in apo B, while the ratio between these molecules remained unchanged. It was expected that apo A-I levels would increase, since this apoprotein is the major component of HDL-C [22]. Several previous investigators have reported that increased apo B, changes in the apo B/apo A-I ratio and decreased apo A-I concentration are better predictors of sudden death or myocardial infarction than changes in TG, TC or LDL-C level [19–24].

In the last decades, several studies have assessed the impact of combined hormonal contraceptives on the lipid profile of its users, with conflicting results [25–29]. However, there have been relatively few studies on the effects of extended regimens of combined hormonal contraceptives (either oral or vaginal) on lipid metabolism [30–33].

The main changes in the lipid profile of our users occurred mainly in HDL-C and apo A-I levels and were probably due to the effects of ethinyl estradiol along with effects of etonogestrel. Lipid and lipoprotein changes observed during treatment were small and unrelated to clinical or biochemical risk of atherogenic heart disease. In fact, the pattern of changes indicates a possible beneficial effect on the risk of atherogenic cardiovascular disease.

More studies are needed to confirm the metabolic changes caused by the use of contraceptive vaginal rings used for extended regimens.

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