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Effects of extended regimens of the contraceptive vaginal ring on carbohydrate metabolism

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Abstract

Background: There are few publications on the metabolic effects of extended regimens of the contraceptive vaginal ring. The aim of this study was to assess changes in fasting plasma glucose levels and insulin concentration of women using the contraceptive vaginal ring continuously over a 1-year period.

Study Design: This prospective cohort enrolled 75 women (ages 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. Fasting glucose and insulin levels were measured, and homeostatic model assessment was calculated at baseline and every 3 months during the 1-year study period. The repeated-measures analysis of variance test was used to analyze differences in the results of these exams over time.

Results: None of the 75 participants had results outside the normal range in any of the assessments. There were no pregnancies during the 1-year period, and a total of 62 participants completed the study. There were no significant changes in mean fasting glucose levels (79.3 and 78.9 mg/dL at baseline and after 12 months, respectively), mean fasting insulin concentration (9.6 and 10.1 μU/mL) or mean homeostatic model assessment results (1.88% and 1.97%).

Conclusion: Fasting plasma glucose concentration, insulin levels and homeostatic model assessment values of women using the vaginal ring on an extended regimen did not change significantly over a 1-year period.

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

1. Introduction

Combined oral contraceptives (COCs), one of the most popular and effective birth control methods in the world, offer several benefits but may affect lipid and carbohydrate metabolism. The metabolic effects of combined hormonal contraceptives have been extensively investigated. However, most of these studies have included a heterogeneous group of participants of various ages and anthropometric parameters, using different doses and types of hormones. Although some studies suggest that combined hormonal contraception may increase insulin resistance in healthy women, these metabolic effects do not have clinical repercussions [1–6].

Recent reports suggest that new COCs containing lower doses and new, less androgenic progestins (desogestrel and drospirenone) may have less effect on carbohydrate metabolism. However, these findings are still controversial, with some reports indicating that even these less androgenic progestins may cause altered insulin response in COC users [2–4].

The introduction of novel forms of hormonal contraceptives using different routes of administration has led to the investigation of the metabolic effects of these new methods [7–10].

The present study aimed to assess the effects of extended regimens of the contraceptive vaginal ring in fasting plasma glucose levels and insulin concentration of women.

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2. Patients and methods

Between April 2004 and March 2005, all women who attended an educational session on pregnancy prevention at the gynecological 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 and height measurements, cardiac and pulmonary auscultation, and abdominal palpation. The following information was collected at enrollment: age, parity, age at menarche and first sexual intercourse, marital status, education and previous use of contraceptives. Exclusion criteria followed the World Health Organization recommendations and included pregnancy and contraindications for estrogen use, such as lactation, active liver disease, active thromboembolic disease, severe hypertension (blood pressure >140/100 mmHg) and diabetes mellitus. 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 [11].

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. On their first visit, all participants received two rings, and at each monthly visit, they received a new ring. Each patient received instructions to leave the ring in place during 21 continuous days and then replace it with a new ring and repeat this procedure for a total of four rings. After this period of 84 days of continuous ring use, the patient was instructed to remove the ring and wait 7 days before introducing a new vaginal ring and repeating the sequence.

Participants were evaluated prospectively during 12 months. At baseline and every 3 months, the participants had a complete physical examination, and blood was collected for laboratory exams that included fasting plasma glucose, insulin concentration and homeostatic model assessment (HOMA) test. They were invited to return to the clinic each 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 their monthly follow-up visit. All the patients' addresses and telephone numbers were recorded at the clinic, and if they missed one monthly follow-up visit, they were contacted through the telephone or by mail. Participants were informed that if they missed more than one appointment, they would automatically be excluded from the study.

Blood samples were collected after a 12-h fasting period. Blood was collected in nonheparinized tubes containing Sarstedt® (Nümbrecht Germany), delicately homogenized and immediately centrifuged at 2500 rpm for 10 min, After automatic incubation, plasma glucose levels were measured by spectrophotometry using the colorimetric method and reagents provided by the Vitros Chemistry®, Glicose Ortho Clinical Diagnostic, a Johnson & Johnson Company (NJ, USA) [12–15].

Plasma glucose concentration <100 mg/dL (<5.6 mmol/L) was considered normal. Patients with glucose levels of 100–125 mg/dL (5.6–6.9 mmol/L) were labeled as having impaired fasting glucose, and those with values ≥126 mg/dL (≥7.0 mmol/L) were diagnosed as diabetics. These cutoffs have an analytical imprecision of up to 3% and a total error of less than 7.9% [12–15].

Fasting plasma insulin concentration was assessed by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA). Values were interpreted according to body mass index (BMI) and considered normal if 2–13 μU/mL for women with BMI <25, 2–19 μU/mL for those with BMI 25–30 and 2–23 μU/mL for those with BMI >30. The intratest variation coefficient is 9% for high values and 9.8% for low values [12–15].

The HOMA was used to measure insulin resistance. It was calculated using fasting plasma glucose and insulin values (in millimoles) and the following formula: (insulin × glucose)/22.5. Results >2.71 indicate insulin resistance in our population and were considered abnormal [12].

The results were analyzed descriptively according to intent to treat, and the repeated-measures analysis of variance test was used to compare differences in laboratory results between the four study periods. Significance was set at $p<.05$. Sample size was calculated as a minimum of 50 patients followed during 1 year with a 95% power to detect 1 standard deviation between five annual means.

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 were 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. Most of the women had used birth control methods in the past: 62.7% reported previous use of oral or injectable contraceptives, 12% had used condoms, 9.3% had used periodic abstinence, 1.3% had used intrauterine devices and 14.7% had never used any form of contraception. 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 differences in this distribution at the end of the 12-month period (41.9%, 45.2% and 12.9%, respectively, p=.41) [16].

All participants had fasting glucose values <100 mg/dL throughout the study period, and mean fasting plasma