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Route of administration of contraceptives containing desogestrel/etonorgestrel and insulin sensitivity: a prospective randomized study☆

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Abstract

Background: The study was conducted to investigate whether hormonal contraceptives administered via the oral and vaginal route exert a similar effect on insulin sensitivity (SI).

Study Design: This is a prospective, randomized study performed in the University Hospital. Subjects were healthy lean young women, needing a hormonal contraceptive, randomly allocated to receive for 6 months (a) an oral contraceptive (OC) containing 30 mcg ethinylestradiol (EE)/150 mcg desogestrel (DSG) (high-estrogen group; n=12), (b) an OC containing 20 mcg EE/150 mcg DSG (low-estrogen group; n=12) and (c) a vaginal ring contraceptive releasing, per day, 15 mcg EE/120 mcg etonorgestrel, the active DSG metabolite (n=12). SI and glucose utilization independent of insulin (Sg) were evaluated by the minimal model method. Modifications of total, high-density lipoprotein (HDL) and low-density lipoprotein cholesterol and triglycerides were also evaluated.

Results: Sg did not vary with any treatment. SI decreased during OCs (5.74±0.49 vs. 3.86±0.44; p=.0005), independently of the high/low-estrogen dose. SI did not decrease during vaginal ring use (4.64±1.03 vs. 5.25±1.36; p=.57; p=.019 vs. oral). Total cholesterol and HDL cholesterol increased (p=.02) during OCs, independently of the dose. Triglycerides increased during both oral (p=.01) and vaginal (p=.032) contraceptive use.

Conclusions: The present data indicate that in contrast to OC use, vaginal contraception with the ring does not deteriorate SI. The vaginal ring may represent an appropriate choice for long-term contraception in women at risk for developing diabetes mellitus or metabolic syndrome.

Keywords: Contraception; Insulin; Pharmacokinetics; Vagina; Desogestrel; Ring

1. Introduction

Contraception should be effective, easy to use, devoid of side effects and safe. Safety is still an issue for hormonal contraception, particularly when its metabolic impact and the long-term consequences upon the cardiovascular system are considered. Cardiovascular risk is increased in women having metabolic syndrome, whose underlying alteration is represented by reduced insulin sensitivity (SI) [1–3]. SI is decreased by currently used hormonal contraceptives. Insulin receptors [4] and subclinical metabolic abnormalities, including reduced SI [5–7], are induced by hormonal contraceptives containing levonorgestrel. Oral contraceptives (OCs) containing gestodene or desogestrel (DSG) are considered more neutral [8], but still, gestodene-containing pills decrease SI [7,9,10]. The recent introduction of combined hormonal contraceptives by nonoral routes has enhanced contraceptive choice [11–13]. The vaginal route of contraceptive administration (i.e., vaginal ring) appears to offer some pharmacokinetic advantages [14,15]. Ethinylestradiol (EE) and etonorgestrel (the active form of DSG) are released in a constant manner with peak levels 30% and 40%, respectively, lower than those that occur with a 30-mcg EE/150-mcg DSG oral pill and with systemic exposure to EE 50% lower than, and to progestin similar to, that of the oral pill [14,15]. Whether this formulation produces a better metabolic profile, particularly in SI, is still unknown.

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In the present study, we investigated modification of SI induced by the association of EE and DSG or its active form etonorgestrel, administered via the oral or vaginal route, respectively.

2. Materials and methods

Between January 2005 and January 2007, lean healthy women [body mass index (BMI)=20–25 kg/m^2], 18 to 35 years of age, attending the outpatient service for contraception were invited by a physician to participate in our study. Inclusion criteria were women with normal menstrual cycles in the previous 12 months with a cycle length ranging between 28 and 31 days, nonuse of OCs or medicines possibly influencing glucose and lipid metabolism for the 6 months preceding the study and willingness to use either oral or vaginal hormonal contraception. Among 65 screened women, 45 were eligible and 36 gave their informed consent to participate in the study, which had been previously approved by our local ethics committee and Institutional Review Board. The primary outcome of the study was modification in SI. Secondary outcomes were modifications in glucose utilization independent of insulin (Sg), β-cell response to glucose (C-peptide), insulin clearance (C-peptide/insulin) and modifications in lipoproteins and liver enzymes.

For each woman, SI and Sg were measured by a frequently sampled intravenous glucose tolerance test (FSIGT) associated with the minimal model method [16–18]. At baseline, the investigation was performed during the early follicular phase (4–7 days after spontaneous menstruation), and then it was repeated during the last 7 days of the last month of hormonal treatment. During the period of contraceptive use, women were requested not to modify their lifestyle or dietary habits. Each woman was allocated to receive for 6 months a hormonal contraceptive containing EE and DSG. One group received a monophasic OC containing 30 mcg EE plus 150 mcg DSG (Practyl 21; Organon, Oss, The Netherlands; *n*=12); this was considered to be the oral, high-estrogen group. A second group received a monophasic OC containing 20 mcg EE plus 150 mcg DSG (Mercilon; Organon; *n*=12); this was considered to be the oral, low-estrogen group. A third group received a monophasic vaginal contraceptive ring releasing, daily, 15 mcg EE and 120 mcg of etonorgestrel, the active DSG metabolite (NuvaRing; Organon; *n*=12); this was considered the vaginal group. Allocation to treatment followed a computer-generated list of randomization. The list was concealed and an independent physician performed the allocation. The three contraceptives were chosen because of the different levels of EE and the different pharmacokinetics of EE and the same active progestin component. The vaginal ring allows lower constant EE levels (50% lower than that of the high OC) and similar exposure to etonorgestrel as both oral administrations, although in a constant (and not in a fluctuating) fashion [13,14].

2.1. FSIGT evaluation

Each woman was hospitalized at 7.00 a.m., following a 12-h overnight fast and a 3-day diet containing at least 200 g/day of carbohydrates. Women were maintained at bed rest. Two polyethylene catheters were placed in two antecubital veins and were kept patent by a slow infusion (1 mL/min) of saline solution. One catheter was used for intravenous glucose or insulin administration and the other for blood collection. At 9.00 a.m., glucose (0.3 g/kg) was injected intravenously over 1 min and was followed 20 min later by an intravenous insulin bolus (0.03 U/kg). Blood arterialization was obtained by placing a heating pad around the forearm, 30 min before blood sampling and for all the period of the test. Consequent vasodilation speeds circulation through capillaries and decreases difference in glucose levels between artery and vein. Samples of arterialized blood were collected at time −5, −1, 2, 4, 8, 20, 22, 30, 40, 60, 70, 100 and 180 min after the glucose load [18]. Undiluted blood was collected after aspiration and elimination of diluted blood contained in the polyethylene catheter. FSIGT with 12 samples, instead of 33, was used because of the high correlation between the results of the two tests and their similar capability of detecting SI variation [18].

2.2. Assays

Blood samples were collected into tubes placed on ice. Blood was immediately centrifuged. An aliquot of serum was immediately tested for glucose levels, whereas another aliquot was immediately frozen at −25°C until assayed. Glucose was determined by the glucose oxidase method. Insulin levels were assayed in all samples, in duplicate, by radioimmunoassay (RIA) methods using commercial kits (Biodata, Guidonia Montecelio, Rome, Italy). Intra-assay and interassay coefficients of variation were 6.2% and 7%, respectively, and sensitivity was 2.1 μU/mL. C-peptide levels were analyzed in the samples collected in the first 20 min of the FSIGT. Assays were performed in duplicate by commercial RIA kits (Biodata, Guidonia Montecelio). Intra-assay and interassay coefficients of variation were 3.2% and 8.5%, respectively, and sensitivity was 0.1 ng/mL. Circulating levels of LH, FSH, estradiol, testosterone and androstenedione were also analyzed in the first sample of FSIGT by RIA. Samples of each subject were analyzed together in the same assay to avoid interassay variability.

Liver function and lipid metabolism were evaluated by the assay of liver enzymes such as glutamic–oxalacetic transaminase (GOT), glutamic–pyravic transaminase (GPT) and γ-glutamine transferase (γGT), and of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, in the first sample of FSIGT. Commonly used laboratory techniques were employed to measure liver enzymes. Plasma total cholesterol and triglycerides were measured by enzymatic methods (Olympus AU 400, Olympus Diagnostic GmbH, Lismeehan, Ireland), while HDL cholesterol was determined