European Journal of Obstetrics & Gynecology and Reproductive Biology 175 (2014) 62–66

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Effects of a contraceptive containing drospirenone and ethinyl estradiol on blood pressure and autonomic tone: a prospective controlled clinical trial

Marcelo Gil Nisenbaum [a,*], Nilson Roberto de Melo [a], Cassiana Rosa Galvão Giribela [a], Tércio Lemos de Morais [c], Grazia Maria Guerra [b], Katia de Angelis [c], Cristiano Mostarda [b], Edmund Chada Baracat [a], Fernanda Marciano Consolim-Colombo [b,c]

[a] Gynecology Department, Clinics Hospital, University of São Paulo Medical School, São Paulo 05403-000, Brazil
[b] Hypertension Unit, Heart Institute (InCor), University of São Paulo, São Paulo 05403-000, Brazil
[c] Universidade Nove de Julho, (UNINOVE), São Paulo 01504-000, Brazil

ARTICLE INFO

Article history:
Received 21 July 2013
Received in revised form 17 December 2013
Accepted 5 January 2014

Keywords:
Oral contraceptive
Blood pressure
Autonomic nervous system
Cardiovascular risk

ABSTRACT

Background: The use of combined oral contraceptives has been associated with an increased risk of adverse cardiovascular events. Whether these drugs alter cardiac autonomic nervous system control is not completely determined.
Objective: To evaluate the effect of a contraceptive containing 20 mcg of ethinyl estradiol and 3 mg of drospirenone on the heart rate variability, baroreflex sensitivity and blood pressure of healthy women.
Study design: Prospective controlled trial with 69 healthy women allocated in two groups: 36 volunteers under oral combined contraceptive use and 33 volunteers using of non-hormonal contraceptive methods. Subjects were tested before the introduction of the contraceptive method and 6 months after its use. For data acquisition, we used continuous non-invasive beat-to-beat blood pressure curve recordings. Multiple ANOVA was used to determine differences between groups and moments and $p < 0.05$ was considered statistically significant.
Results: At baseline, there were no differences in demographic and autonomic parameters between groups. Comparing cardiac sympatho-vagal modulation, baroreceptor sensitivity and blood pressure measurements between baseline and after 6 months, no significant difference was detected in each group or between groups.
Conclusion: A contraceptive containing 20 mcg of ethinyl estradiol and 3 mg of drospirenone causes no significant changes in clinical, hemodynamic and autonomic parameters of normal women.

1. Introduction

Since their introduction in the 1960s, the use of combined hormonal oral contraceptives (COCs) has been related to an increased risk of cardiovascular disease [1]. The exact mechanism by which COCs may increase cardiovascular risk is still unclear, although it is most likely multifactorial and complex. The understanding of this mechanism is extremely important considering the large number of women taking COCs: it is estimated that nearly 20% of women of reproductive age are currently prescribed oral contraceptives [2].

Many studies have demonstrated increases in blood pressure in women after chronic use of COCs [2,3]. In addition to the changes in blood pressure, other factors have been proposed and investigated to explain the COC-associated increase in cardiovascular risk, such as changes in insulin resistance, lipid profile and endothelial function, as well as the development of coagulation disorders and, more recently, changes in the functioning of the autonomic nervous system [2,4]. The latter change is considered one of the most important mechanisms underlying the pathogenesis of hypertension and cardiovascular disease [5,6].

Few studies have been conducted to examine the impact of hormonal contraception on heart rate variability and on the autonomic nervous system, and no prospective, controlled study has been published to date [7–10].

When evaluating the different types of contraceptives, attention has been drawn to a formulation containing drospirenone (DRSP), a progestin derived from spironolactone with

* Corresponding author at: Avenida Dr. Enéas Carvalho de Aguiar, 255, 10 andar ICHC, Cerqueira César, São Paulo, CEP-05403-000.
Tel.: +55 1126616647/+55 1126617209.
E-mail addresses: mgnisen@hotmail.com, mgnisen@terra.com.br (M.G. Nisenbaum).

0301-2115/$ – see front matter © 2014 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejogrb.2014.01.006

anti-mineralocorticoid and anti-androgenic actions [11]. Studies in normotensive women show that the use of DRSP was associated with favorable effects on the cardiovascular system [11,12]. Additionally, a possible mechanism by which COCs could increase blood pressure is via activation of the renin-angiotensin system, and itis known that DRSP, like endogenous progesterone, attenuates the vascular effects of estrogen and can therefore block this effect [13]. Furthermore, a recent study has shown an anti-inflammatory action of DRSP with potential cardiovascular protective effect [14]. On the other hand, recent studies also suggest the possibility of DRSP having greater thrombotic risk, while other studies show a similar risk to other contraceptive pills [15,16].

Therefore, the objective of this study was to evaluate the effect of a contraceptive consisting of ethinyl estradiol (EE) and DRSP on heart rate variability and the autonomic nervous system, which is important for evaluating the safety of these drugs.

2. Methods

The volunteers in this study were 80 healthy women recruited from primary and secondary health care facilities. Each participant underwent medical screening by a physician and provided written and oral consent. This study was approved by the Research Ethics Committee, General Hospital, School of Medicine, University of São Paulo. To be included, subjects were normotensive healthy women, without any chronic disease, age between 20 and 40 years, with regular menstrual cycles and having used no hormonal contraceptives for at least 6 months prior to the start of the study. Exclusion criteria were a positive pregnancy test, a category 3 or 4 classification according to WHO's Medical Eligibility Criteria for contraceptive use [17], current smoking, obesity, fasting glucose above 100 mg/dL, insulin resistance or lipid profile abnormalities.

2.1. Sample size calculation

The minimum size of the sample was determined from a pilot sample containing ten observations for each group. Six variables were used to determine the sample size: four variables that concerned autonomic tone and two hemodynamic variables. Considering that a type I error of 0.05 and a power of 0.8 was necessary to detect a difference between the two groups of 20% on average, the minimum sample size per group necessary for the study of each of these six variables was 32 patients. The calculations were based on the equation of Diggle et al. [18].

2.2. Experimental design

All women selected were eligible for both contraceptive methods. However, after being counseled regarding the advantages, disadvantages and side effects of each contraceptive method, the volunteers were allowed to freely choose the type of contraception they wanted to use: COCs or non-hormonal methods. Therefore, women who agreed to participate in the study were allocated into two groups: (1) users–women who chose to use a COC containing 20 mcg EE and 3 mg DRSP, with 24 days of active pills and a 4 day pill-free interval ($n = 40$), and (2) nonusers–women who chose to use a non-hormonal method of contraception (condoms or copper IUD) ($n = 40$).

All volunteers were evaluated during the same menstrual cycle phase: follicular phase at baseline for both groups; follicular phase in the follow-up of the control group; high hormonal phase in the contraceptive group. All studies were conducted in a temperature-controlled room, and the subjects were instructed to abstain from exercise, caffeine, and alcohol for 12 h before testing. All examinations were performed during the same time of day for both trials. Data acquisition was performed with the volunteer in the supine position for 15 min. The analysis was performed using the final 5 min of each acquisition period.

2.3. Evaluation methods for body mass index, blood pressure and hemodynamic variables

2.3.1. Body mass index (BMI)

BMI was obtained using measures of weight and height of each subject acquired during basal evaluation and at the end of the study.

2.3.2. Office blood pressure measurement

Blood pressure was obtained using the auscultatory method with a calibrated mercury sphygmomanometer following the American Heart Association technique recommendations. Three measurements were made and the value considered was the average of the measurements [19].

2.3.3. Hemodynamic variables

The pressure curves were obtained on a beat-to-beat basis, continuously and noninvasively, with the Finometer® device (FMS, Finapres Medical System, Anhem, The Netherlands). This device was equipped with BeatScope software, which generated data on the systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP); heart rate (HR); cardiac output (CO); and total peripheral resistance (TPR), based on values derived from the arterial pressure curve and information on patient age, gender, weight and height. Studies in the literature regarding the validation of this method using direct and invasive measurements have demonstrated its accuracy and that the values obtained can be superimposed onto the curve of brachial artery pressure [20–22].

2.4. Heart rate variability and autonomic nervous system parameters

The pressure curves obtained with the Finometer® device were simultaneously recorded in another computer equipped with biological signal acquisition and signal conversion software (AT/MCA-CODAS; DATAC Instruments Inc., Akron, Ohio, USA). The sampling frequency of the signals was 1000 Hz. The stored signals were subsequently subjected to an analysis routine that provided values for HR variability, blood pressure, and spontaneous baroreflex sensitivity. After these signals were pre-amplified (General Purpose Amplifier; Stemtech, Inc., 4-GPA), they were converted from analog to digital and then stored for later analysis. Each heart beat was identified by the use of a specialized algorithm implemented in Matlab MT (MATLAB 6.0, Mathworks) that automatically detects systolic and diastolic pressure waves. The pulse interval or *R-R* interval was calculated as the difference between the beginning and end points of the cycle ($t_1 - t_0$).The power spectral density of the *R–R* interval was obtained by fast Fourier transformation using Welch's method over 16,384 points with a Hanning window and 50% overlap. The spectral bands for humans were defined according to references from the literature; specifically, the spectral bands used were 0.0–0.04 Hz (very low frequency, VLF), 0.04–0.15 Hz (low frequency, LF), and 0.15–0.4 Hz (high frequency, HF) [20–22].

2.5. Statistical analysis

The variables of interest in both groups were assessed at baseline and after 6 months of use of the chosen contraceptive method. Statistical analysis of the data was carried out with R 2.9 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.1 (SAS Institute, Cary, NC) softwares.