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Original research article

Drospirenone and levonorgestrel in combination with either 30 or 20 mcg ethinylestradiol reduce soluble adhesion molecules in Brazilian women; cross-sectional study

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Abstract

Background: The objective of this study was to evaluate the effect of three contraceptive pills containing ethinylestradiol (EE) (20 or 30 mcg) in combination with drospirenone (DRSP) and levonorgestrel (LNG) on plasma concentration of adhesion molecules vascular cell adhesion molecule -1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin.

Study Design: A cross-sectional study was conducted with 72 participants (18–30 years old) distributed into three groups that used oral contraceptives containing EE 20 or 30 mcg combined with DRSP 3 mg or EE 30 mcg/LNG 150 mcg for at least 6 months. The control group was comprised of nonusers of contraceptives. Soluble VCAM-1, soluble ICAM-1 and soluble E-selectin were evaluated by enzyme-linked immunosorbent assay.

Results: Compared to the control group, a significant decrease was found in VCAM-1 and ICAM-1 concentrations with use of DRSP/20 EE and LNG/30 EE.

Conclusions: DRSP/20 EE and LNG/30 EE induce favorable changes in endothelial function.

Keywords: Combined oral contraceptives; Adhesion molecules; Drospirenone; Atherosclerosis

1. Introduction

Endothelial damage and activation contribute to the development of cardiovascular diseases since they are involved in the progression of atherosclerosis [1,2]. Cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin are considered markers of endothelial activation and inflammation [3]. The expression of these molecules attracts inflammatory cells, which contribute to the formation of the atherosclerotic plaque, obstructing the vessel and causing lesions to the endothelium, ending in cardiovascular diseases including angina and myocardial infarction [4].

The levels of these adhesion molecules present in the serum and in the plasma are considered markers for atherosclerosis and cardiovascular disease [5,6].

The estrogen present in hormonal contraceptives promote beneficial effects to the vascular system such as intense vasodilatation induced by the synthesis and the activity of nitric oxide [7], modulation of the vascular tonus through the production of prostaglandin I_2, the expression of nitric oxide synthase and endothelin-1 (ET-1) [8], inhibition of the vasoconstriction induced by ET-1 [9], inhibition of the activity of the sympathetic nervous system [10] and reduction of the expression of adhesion molecules involved in the endothelium–leukocyte interaction. This set of actions promoted by the estrogen in the endothelium contributes to

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decrease the risk of arterial thrombosis by regulating the functions of the endothelial cells [11].

Despite these beneficial effects caused by the estrogen, the progestagen present in oral combined contraceptives may compromise this vascular protection since it may increase the levels of adhesion molecules [12].

Studies demonstrate a reduction in the levels of cell adhesion molecules (ICAM-1, VCAM-1, E- and P- selectin) in women in menopause treated with hormone replacement therapy (HRT) [13–15]. Despite these studies, few studies report the impact of oral contraceptives on the levels of adhesion molecules in women in fertile age [3,16]. The effect of oral contraceptives containing the progestin drospirenone (DRSP) combined with ethinylestradiol (EE) on the levels of these adhesion molecules has not yet been assessed.

Therefore, the study objective was to evaluate the impact of oral contraceptives containing the progestagen levonorgestrel (LNG) and DRSP and different doses of EE on the plasma concentration of adhesion molecules in fertile Brazilian women.

2. Material and methods

2.1. Study design

A cross-sectional study was performed involving 72 women distributed into four groups: women taking oral contraceptives containing EE 20 or 30 mcg combined with DRSP 3 mg 21/7 or 24/4 and EE 30 mcg combined with LNG 0.15 mg 21/7. The control group was comprised of nonusers of steroid contraceptive methods (Fig. 1). This study was carried out from August 2009 to June 2010 in the Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, São Paulo, Brazil.

Sample size calculations were performed by using Proc Power in SAS 9.1 (SAS Institute, Cary, NC, USA). Considering comparisons between population means of the soluble ICAM-1 (sICAM-1) by a one-way analysis of variance (ANOVA), it was found that a sample size of 20 individuals at each group is sufficient for detecting a minimum difference of 40 ng/mL between two of four groups at a significance level of .05, power of .80 and a standard deviation of 40 ng/mL.

The protocol was approved by the committee of ethics in research of the Faculty of Pharmaceutical Sciences of Ribeirão Preto. All women were informed with respect to the nature of the study and voluntarily agreed to participate by signing an informed consent form.

2.2. Participants

The participants were healthy Brazilian female students who used the services of the Gynecology and Obstetrics Department offered by the Integrated Health System of the University of São Paulo, campus Ribeirão Preto, and students who used the services of the Gynecology and Obstetrics Department of the Basic Health Unit of Cuiabá-School Hospital of the Faculty of Medicine of Ribeirão Preto.

The inclusion criteria adopted were as follows: age between 18 and 30 years old, body mass index 19–30 kg/m^2, user or nonuser (control group) of the contraceptive for a minimum period of 6 months and a maximum period of 24 months. Women were not admitted to the study if they were pregnant; if they were using cigarettes or anti-inflammatory drugs; and if they had a personal history of cardiovascular disease, hypertension, thromboembolism, chronic and acute hepatopathies, diabetes and autoimmune disease. A questionnaire was completed in order to obtain information such as the frequency of physical exercise and family history of thrombosis, which were statistically analyzed.

A single sample of venous blood was collected in standardized conditions from each subject between 8:00

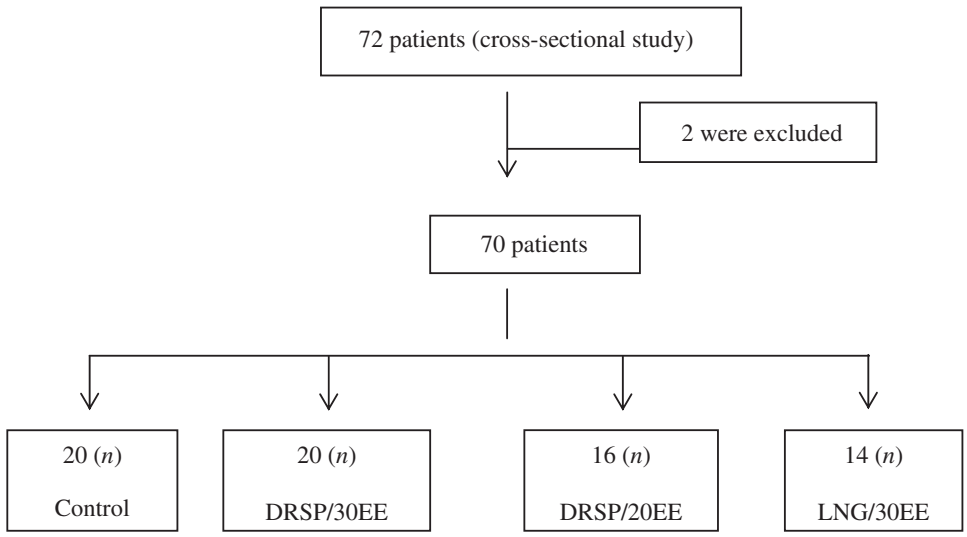

Fig. 1. Study design. *n*, number of patients.