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The effects of 2 mg chlormadinone acetate/30 mcg ethinylestradiol, alone or combined with spironolactone, on cardiovascular risk markers in women with polycystic ovary syndrome☆,☆☆

Carolina Sales Vieira[a,b,*], Wellington P. Martins[a,b,c], Janaína Boldrini França Fernandes[a], Gustavo Mafaldo Soares[d], Rosana Maria dos Reis[a,b], Marcos Felipe Silva de Sá[a,b], Rui Alberto Ferriani[a,b]

[a]*Department of Gynecology and Obstetrics, Medical School of Ribeirão Preto, University of São Paulo, Brazil, Avenida Bandeirantes, 3900 - Campus Universitário, Monte Alegre, Ribeirão Preto, SP, CEP-14049-900, Brazil*

[b]*National Institute of Hormones and Women's Health, Ribeirão Preto, SP, CEP-14049-900, Brazil*

[c]*Escola de Ultrassonografia e Reciclagem Médica de Ribeirão Preto (EURP), Rua Casemiro de Abreu 660, Ribeirão Preto, SP, CEP-14020-060, Brazil*

[d]*Department of Obstetrics and Gynecology, Federal University of Rio Grande do Norte, Brazil, Caixa Postal 1524, Campus Universitário Lagoa Nova, Natal, RN, CEP-59072-970, Brazil*

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Abstract

Background: Polycystic ovary syndrome (PCOS) is an endocrine disorder associated with metabolic dysfunction and changes in cardiovascular risk markers, and using oral contraceptives (OCs) may exert a further negative effect on these alterations in patients with PCOS. Thus, the primary objective of this study was to assess the effects on arterial function and structure of an OC containing chlormadinone acetate (2 mg) and ethinylestradiol (30 mcg), alone or combined with spironolactone (OC+SPL), in patients with PCOS.
Study Design: This was a randomized, controlled clinical trial. Fifty women with PCOS between 18 and 35 years of age were randomized by a computer program to use OC or OC+SPL. Brachial artery flow-mediated vasodilation, carotid intima-media thickness and the carotid artery stiffness index were evaluated at baseline and after 6 and 12 months. Serum markers for cardiovascular disease were also analyzed. The intragroup data were analyzed using analysis of variance with Tukey's post hoc test. A multivariate linear regression model was used to analyze the intergroup data.
Results: At 12 months, the increase in mean total cholesterol levels was greater in the OC+SPL group than in the OC group (27% vs. 13%, respectively; p=.02). The increase in mean sex hormone-binding globulin levels was greater in the OC group than in the OC+SPL group (424% vs. 364%, respectively; p=.01). No statistically significant differences between the groups were found for any of the other variables.
Conclusion: The addition of spironolactone to an OC containing chlormadinone acetate and ethinylestradiol conferred no cardiovascular risk-marker advantages in young women with PCOS.

Keywords: Contraceptives; Oral; Hormonal; Cardiovascular diseases; Polycystic ovary syndrome; Spironolactone

1. Introduction

The reconfiguration of polycystic ovary syndrome (PCOS) from an endocrinopathy with exclusively reproductive effects to a metabolic syndrome with reproductive implications [1] has altered the therapeutic management of patients with this disorder. PCOS is associated with metabolic disorders (such as hypertension, diabetes and dyslipidemia) that, in and of themselves, are risk factors for cardiovascular disease (CVD) and have clinical implications

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* Corresponding author. Departamento de Ginecologia e Obstetrícia da Faculdade de Medicina de Ribeirão Preto/USP, Av. Bandeirantes 3900, Campus Universitário, Ribeirão Preto, SP, CEP-14049-900, Brazil. Tel.: +55 16 3602 2804; fax: +55 16 3633 0946.

E-mail addresses: carol.sales@uol.com.br, carol.sales@usp.br (C.S. Vieira).

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for women's health [2]. To reduce the risk CVD, which is elevated in these patients, lifestyle modification should always precede and/or accompany any intervention in women with PCOS [3]. Nevertheless, for women with PCOS who do not wish to conceive, oral contraceptives (OCs) are still the treatment of choice for regulating the menstrual cycle and the clinical manifestations of excess androgens [4,5].

In a previous study, our group reported increased arterial stiffness, an independent CVD risk factor, in young, nonobese women with PCOS compared to ovulating controls paired for weight and age [5]. In addition, we also reported imbalanced circulating matrix metalloproteinases in these women [6], which can contribute to the future development of atherosclerosis. These alterations are associated with the hyperandrogenism present in women with PCOS.

Atherosclerosis has a long latent phase before the symptoms are manifested. Therefore, the ability to evaluate arterial function prior to developing an angiographically measurable atherosclerotic plaque is an important aspect of early detection [7,8]. Several noninvasive measures of arterial structure and function have been shown to be clinically useful, including measuring the carotid intima-media thickness (IMT), endothelial function and arterial stiffness [9,10].

Given that OCs can reduce the hyperandrogenism associated with PCOS, there are questions about whether attempts to increase the anti-androgenic effect of OCs are associated with metabolic benefits. To our knowledge, no studies have evaluated the effects of chlormadinone acetate (2 mg) and ethinylestradiol (30 mcg), either by itself or combined with an anti-androgenic drug, on clinical and subclinical CVD markers in women with PCOS. Therefore, the primary objective of the present study was to compare the effects of this OC, alone or in combination with spironolactone (SPL), on the arterial function and structure of young women with PCOS over a 12-month period. The rationale for adding SPL to OC therapy in PCOS was to augment the anti-androgenic effects of the OC.

2. Methods

2.1. Participants

An open-label, controlled, randomized clinical trial was conducted at the University Hospital of the Ribeirão Preto School of Medicine, University of São Paulo (HC-FMRP-USP), Brazil, between January 2007 and July 2009. The study was registered with ClinicalTrials.gov (http://clinicaltrials.gov/; NCT00842140).

The following inclusion criteria were used: female, 18 to 35 years of age, a PCOS diagnosis, no desire to conceive, and wishing to use an OC. The PCOS diagnosis was confirmed by the Rotterdam consensus criteria [11]. The following exclusion criteria were used at screening: patients with a body mass index (BMI) $\geq$40 kg/m^2; any clinical conditions corresponding to Categories 3 or 4 of the World Health Organization Medical Eligibility Criteria for OC use [12]; smoking; alcoholism; illicit drug use; any systemic disease (systemic arterial hypertension, diabetes mellitus, immune system diseases or thyroid diseases) except PCOS; current or previous (up to 2 months before the study) use of oral, vaginal, monthly injectable or transdermal combined hormonal contraceptives; current or previous use (up to 6 months before the study) of a long-acting hormonal contraceptive method (injectable, implant or intrauterine device); 12 or fewer weeks since childbirth; currently breastfeeding or had stopped breastfeeding within 2 months of the screening visit; chronic and/or acute inflammatory processes; and the use of medications known to interfere with inflammatory markers or CVD risk factors (hypoglycemic drugs, anti-inflammatory drugs or statins). All the volunteers gave written informed consent, and the study was approved by the institutional review board.

The principal variable used to calculate the sample size was the carotid artery stiffness index because a previous study had found that this variable is higher in women with PCOS than in ovulating controls [5]. Given a standard deviation (SD) of .96 in the arterial stiffness for women with PCOS [5], at least 16 patients in each group at the end of the study were required to achieve a minimum detectable difference of 1 SD between the pre- and post-treatment periods with an alpha of .05 and 80% power.

Of the 100 women with a PCOS diagnosis at the university hospital during the recruitment period of the study, 60 met the inclusion criteria. However, 10 of these women were excluded (one was being prescribed topiramate, three refused to undergo a hormonal contraceptive washout and six were smokers). Ultimately, 50 women with PCOS were enrolled in the study. Immediately following their PCOS diagnoses, these women were randomized to one of the two treatment arms in a 1:1 proportion using a randomizer program (http://www.randomizer.org). The following treatment arms were used: Group 1 received cyclic use of an OC containing 2 mg chlormadinone acetate/30 mcg ethinylestradiol (EE) (Belara®, Janssen Cilag, Grünenthal, Germany); and Group 2 received the same OC combined with SPL (100 mg/day) (EMS, São Bernardo do Campo, SP, Brazil). Participation could be discontinued during the study for the following reasons: the subject's request, pregnancy, smoking beginning during the study, failure to comply with the protocol, and experiencing a serious adverse effect. The study subjects were followed up at 12 months, and nine subjects discontinued the study (seven had adverse gastric reactions, one moved to another city and one wanted to become pregnant) (Fig. 1).

2.2. Data collection and evaluation of variables

The participants received five medical assessments during the study: prior to initiating the medication (baseline), and at 3, 6, 9 and 12 months. At these visits, patient compliance