Effects of two contraceptives containing drospirenone on blood pressure in normotensive women: a randomized-controlled trial

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Objective Drospirenone (DRSP) is a progestogen derived from spironolactone with antimineralocorticoid action that seems to exert a favorable effect on blood pressure (BP); however, when associated with ethinylestradiol (EE), this effect does not seem to occur. This study aimed to assess possible differences in BP associated with the use of combined oral contraceptives containing DRSP with different doses of EE.

Materials and methods This open-label parallel-group randomized clinical trial involved women randomized to use either 30 mcg of EE + DRSP (n = 22) or 20 mcg of EE + DRSP (n = 22). Daytime, nighttime, and 24-h BP were evaluated by ambulatory blood pressure monitoring at the beginning of the trial and 6 months after drug therapy.

Results The groups were similar in terms of demographic characteristics. The mean 24-h systolic blood pressure and diastolic blood pressure (DBP) were similar between the groups before and after treatment (P > 0.05). With respect to day and nighttime systolic blood pressure and DBP, no statistically significant difference was observed in BP values between the two groups either before or after treatment, except for the daytime DBP in the 30EE + DRSP group. In this group, a decrease of 2 mmHg (3%) in daytime DBP was observed after 6 months of drug therapy (P = 0.04).

Conclusion There was no difference in BP associated with the use of combined oral contraceptives containing DRSP irrespective of the EE dose used. Blood Press Monit 20:310–315 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Keywords: ambulatory blood pressure monitoring, blood pressure, contraception, drospirenone

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Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality among women in both developed and developing countries, including Brazil [1,2]. Although combined oral contraceptives (COCs) represent the contraceptive method of choice worldwide, used by \textasciitilde 20% of women of reproductive age [3], COCs have been associated with the increased occurrence of cardiovascular and thromboembolic events, particularly when associated with higher estrogen doses [4,5].

Despite attempts to reduce the adverse effects of COC, some side effects remain. Increased blood pressure (BP) is one of these side effects [6], and systemic arterial hypertension is a contraindication to the use of COCs [7]. In normotensive patients, COCs can increase BP [8–12]. In addition, increases in BP levels of 4–5 mmHg have been documented with the use of COCs containing low doses of ethinylestradiol (EE) [10,13,14], and these results were confirmed by other studies using ambulatory blood pressure monitoring (ABPM) [11]. Small reductions in systolic blood pressure (SBP) (10 mmHg) and diastolic blood pressure (BP) (5 mmHg) are associated with one- to two-fifths reduction in future cardiovascular disease [15].

Initially, this effect on BP was only attributed to the use of estrogen. However, recent evidence suggests that progestogens may also exert an important effect on BP [13,16]. Most progestogens used are ineffective in antagonizing the effects of estrogen, particularly on BP [17]. However, drospirenone (DRSP), a derivative of spironolactone with an antimineralocorticoid action, can counteract the increase in BP associated with the use of estrogen in COCs [12,18].

When combined with estradiol in hormone replacement therapy (HRT), DRSP decreased BP in postmenopausal women with mild to moderate hypertension [19,20]. Studies assessing BP during the use of contraceptives containing DRSP are limited [12,21–24] and, most of them are limited to casual measurement of BP during study follow-up [3,22–25]. Therefore, considering the absence of randomized clinical trials assessing the effect of COCs containing DRSP on BP measured by ABPM, there is a need for studies assessing the effect of DRSP on BP in women taking COCs.
the primary objective of this study was to compare the effect of two COCs with different EE doses (30 mcg EE + DRSP and 20 mcg EE + DRSP) on BP assessed by ABPM after 6 months of treatment. In addition, as a secondary objective, we compared the period before COC use with the period after COC use.

**Materials and methods**

**Trial design**

This study was an open-label, parallel-group, and randomized clinical trial.

**Participants**

The inclusion criteria were as follows: sexually active women who did not wish to become pregnant, age between 18 and 35 years, with menstrual cycles lasting between 24 and 32 days, and BMI between 18.0 and 29.9 kg/m². The exclusion criteria were as follows: smoking, use of drugs and/or alcohol, clinical and/or laboratory signs of hyperandrogenism, use of hormonal contraception within 6 months before the initiation of the study, presence of chronic and/or acute inflammatory processes, use of medications with endothelial effects (e.g. statins), breastfeeding or having stopped breastfeeding within 2 months before the initiation of the study, and medical conditions classified as category 3 or 4 according to the WHO medical eligibility criteria for contraceptive prescription [7].

Women willing to use COC after fulfilling the inclusion/exclusion criteria were included consecutively. Women were selected consecutively from a basic healthcare unit in Ribeirão Preto and the contraception clinic at the Clinics Hospital of the Ribeirão Preto Medical School, University of São Paulo, Brazil (Hospital das Clínicas da Faculdade de Medicina de Ribeirão, Universidade de São Paulo–HCRP-USP), before receiving a COC prescription. Recruitment was carried out between January 2011 and July 2013 through written and spoken media, such as local newspapers, and advertisements (spoken or written) in hospital waiting rooms. The research ethics committee of HCRP-USP approved the study, and all patients were required to fill out a logbook with information on the day and nighttime, eating habits, and any symptoms, activities, and important events. The 24-h BP monitoring was considered statistically acceptable in the presence of more than 80% successful measurements. Twenty-four-hour BP, day, and nighttime SBP and DBP were calculated. Normal BP values were considered to be less than 135/85 mmHg for daytime, less than 120/70 mmHg for nighttime, and less than 130/80 mmHg for 24 h [28]. The day and nighttime heart rate were also analyzed in the ABPM device.

**Interventions**

Each volunteer was assigned randomly to one of the following intervention groups: (a) use of COC containing 30 mcg of EE + 3 mg of DRSP (Yasmin; Schering do Brasil Química e Farmacêutica Ltda, São Paulo, Brazil) or (b) use of COC containing 20 mcg of EE + 3 mg DRSP (20EE + DRSP) (Yaz; Schering do Brasil Química e Farmacêutica Ltda). The volunteers were instructed to initiate COC use until the fifth day of the menstrual cycle and to continue treatment according to the manufacturer’s guidelines.

**Outcomes**

The primary objective was to compare the effect of two COCs with different EE doses (30EE + DRSP and 20EE + DRSP) on BP assessed by ABPM after 6 months of treatment. The variables analyzed were age, parity, baseline BP, weight, and BMI. Twenty-four-hour mean SBP, 24-h mean DBP, and day and nighttime SBP and DBP were measured by ABPM. The variables obtained by ABPM were assessed over two time periods: at the early follicular phase (up to the fifth day of the menstrual cycle) before the onset of COC treatment on the second or the third week of use of the sixth blister pack of COC. On the day of evaluation, the patient showed up for consultation in the morning. The medical follow-up involved an assessment of complete medical history, measurement of BP by auscultation using a mercury sphygmomanometer – according to the guidelines of the American Heart Association [26] – and anthropometric measurements (weight and height). Weight was measured with the patient wearing light clothing and height was measured with the patient barefoot. BMI was calculated using the formula BMI = weight (kg)/height (m)². Immediately after medical consultation, the patient was referred to the cardiology sector for placement of the measuring device for ABPM. On the return visit, in addition to anthropometric measurements and ABPM, the compliance of the patient to the prescribed medications and the reported side effects were also assessed. The ABPM device was programmed to measure BP every 15 min during wakefulness and every 30 min during sleep [27,28]. After 24 h, the patient was allowed to remove the device. During the monitoring period, patients were required to fill out a logbook with information on the day and nighttime, eating habits, and any symptoms, activities, and important events. The 24-h BP monitoring was considered statistically acceptable in the presence of more than 80% successful measurements. Twenty-four-hour BP, day, and nighttime SBP and DBP were calculated. Normal BP values were considered to be less than 135/85 mmHg for daytime, less than 120/70 mmHg for nighttime, and less than 130/80 mmHg for 24 h [28]. The day and nighttime heart rate were also analyzed in the ABPM device.

**Sample size**

The main variable chosen for sample calculation was the 24-h mean DBP because this variable is the most likely to be altered by COC. Considering the 24-h mean DBP values among women of reproductive age before beginning the use of COCs [12], 16 women would be required per group with an α value of 5% and power of 80% to achieve a difference of at least 10% in daytime 24-h mean DBP between the groups. This difference was chosen because lower values would not be clinically relevant. We included 22 women in each group because of the possibility of sample loss during the study.
Randomization, allocation, and implementation
The patients included in the study design were randomized into blocks of four using a computer program (https://www.sealedenvelope.com/simple-randomiser/v1/lists) for assignment into the 30EE + DRSP or the 20EE + DRSP groups. Randomization was performed by one researcher (C.S.V.), and the randomization results were placed in sealed envelopes, which were opened by another researcher (M.N.N.) only after the participants had signed the informed consent form.

Statistical analysis
The clinical variables (BMI, weight, and parity) were compared between the two groups using the $\chi^2$-test (for qualitative variables) or the $t$-test (for quantitative variables with a normal distribution). To analyze the variables assessed by ABPM, a linear mixed-effects regression model was used. This method was appropriate because of the multiple analyses involved in the study (multiple variables, two treatment groups, and several time points). SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) was used for the calculations. The variables were evaluated using the intention-to-treat analysis, and missing data were imputed using the last-observation carried forward technique. A significance level of 5% was used. The statistician was blinded to the COC groups.

Results
A total of 60 women were selected to participate in the study. Of these, 44 women were included. Of the 16 women excluded, two were diagnosed with polycystic ovary syndrome, two reported migraine with aura, four were smokers, and eight could not attend the follow-up visit. Of the women included, 22 were randomized to the 30EE + DRSP group and 22 were randomized to the 20EE + DRSP group. In the 30EE + DRSP group, one patient was excluded because of worsening of migraine without aura, and therefore, 21 volunteers completed the follow-up. In the 20EE + DRSP group, four patients were excluded (three because they were lost to follow-up and one because of worsening of migraine without aura), and therefore, 18 participants completed the follow-up. Figure 1 shows the flow chart of the study.

The characteristics of the study participants are shown in Table 1. No significant differences were observed in age, BMI, weight, and parity.

The 24-h mean SBP and DBP values were similar between the 30EE + DRSP and the 20EE + DRSP groups before and after treatment ($P > 0.05$) (Figs 2 and 3). With respect to day and nighttime SBP, DBP, and heart rate values, no difference was observed between the 30EE + DRSP and the 20EE + DRSP groups either before or after treatment, except for daytime DBP in the 30EE + DRSP group; in this group, a decrease of 2 mmHg (3%) in DBP was observed after 6 months of COC use ($P = 0.04$) (Table 2).

No cases of pregnancy or thromboembolic events were observed in any of the patients during the study period. Two patients in the 30EE + DRSP group reported breast tenderness and another patient reported headache without migraine features. In the 20EE + DRSP group, only one patient reported breast tenderness and there were no complaints of other adverse effects.

Discussion
The main finding of our study was that 24-h BP was similar between the groups either before or after treatment. In the 30EE + DRSP group, a decrease of 2 mmHg (3%) in daytime DBP was observed after 6 months of COC use. The formulation with 20 mcg of EE did not yield better performance in BP compared with the 30-mcg dose.
The comparison of our results with the results of other studies indicates that only one study, which evaluated BP during treatment with COC and DRSP, reported an increase in BP [21]. However, the volunteers presented with polycystic ovary syndrome and consequently may have had outcomes distinct from those of women without the syndrome. Our data indicate no changes in BP, which is consistent with most other studies that evaluated DRSP as the progestogen combined with EE [3,12,22,24,25]. Of these studies, only two were randomized clinical trials, and they used casual measurements rather than ABPM to assess BP. Casual evaluations of BP may not detect changes in BP that would be less important in normotensive patients, but valuable in hypertensive patients. However, even in normotensive women, small and sustained changes in BP can alter future cardiovascular risk [15]. In our study, a 3% decrease in DBP (2 mmHg) was observed in the 30EE + DRSP group.

Previous studies that evaluated COCs and progestogens other than DRSP reported increased BP [13,29,30], even when contraception was provided by the nonoral route [31]. Therefore, the presence of DRSP may have contributed toward a lack of change in BP in the groups and prevented its increase, as reported by other authors [3,12,22,24,25].

Previous studies have shown that hypertension is twice as common among postmenopausal women, irrespective of...
weight or BMI [32]. In addition, DRSP-containing compounds used in HRT by postmenopausal women with hypertension showed a significant effect in decreasing BP [33]. DRSP with its selective aldosterone-blocking properties can lead to a reduction of BP [34]. White et al. [19] reported that combined HRT containing DRSP in its formulation significantly decreased SBP among postmenopausal women with mild hypertension, measured both by causal measurements and by ABPM. However, studies that evaluated BP among users of COC containing DRSP did not observe this decrease [12,21,22,25]. Therefore, we hypothesize that this difference is because of the type of estrogen combined with DRSP (EE in contraceptives or natural estrogen in the case of HRT). Because of its high biological potency compared with estradiol, EE exacerbates the hepatic production of angiotensinogen, which in turn leads to increased BP through the renin–angiotensin–aldosterone system [35].

One of the limitations of this study was that the 6-month follow-up period might not accurately represent the behavior of BP with chronic use of COCs. In addition, the lack of changes in BP does not indicate that these formulations are not associated with an increased risk of vascular complications. Therefore, new controlled-randomized studies using this same contraceptive formulation in patients with increased cardiovascular risk, including mild hypertension, are needed to justify its use among hypertensive women.

Many studies have evaluated BP among COC users using only casual measurements during medical consultations [3,8,10,22,25], but few studies have used ABPM for this purpose [11,12,21,31,36]. Because ABPM is considered one of the most reliable methods for assessing BP, our study provides more reliable and reproducible results than if we used casual BP measurements. Williamson et al. [37] reported that the SBP levels of normotensive women undergoing COC treatment increased by 10 mmHg, and this change can be diagnosed only by ABPM and not by casual measurements; this result is important when assessing the risk of stroke among women [15].

In addition to the advantages of using ABPM for measuring BP, another strength of our study is that it is the first randomized study to assess BP among women who used contraceptive formulations containing DRSP and two different doses of EE.

Therefore, we conclude that there was no difference in BP associated with the use of COCs containing DRSP irrespective of the EE dose used among healthy women, but these findings cannot be extrapolated to hypertensive patients. Although our results did not indicate any increase in BP among patients using the drugs in question, further studies are required to confirm the safety of use of these contraceptive formulations among hypertensive women.

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### Conflicts of interest

Carolina S. Vieira and Rui A. Ferriani give occasional lectures for Bayer Healthcare. For the remaining authors there are no conflicts of interest.

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Drospirenone and blood pressure de Nadai et al. 315


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