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Effects of a contraceptive containing drospirenone and ethinylestradiol on blood pressure, metabolic profile and neurohumoral axis in hypertensive women at reproductive age

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ABSTRACT

The use of combined oral contraceptives is widespread among hypertensive women despite being associated with increased cardiovascular risk. Contraceptives containing drospirenone, which has antimineralocorticoid properties, may have a positive or neutral effect on neurohumoral activation and metabolic homeostasis of hypertensive women at reproductive age.

Objectives: To evaluate the effect of combined oral contraceptive containing drospirenone + ethinylestradiol on the systemic blood pressure, metabolic variables and neurohumoral axis in hypertensive women in reproductive age.

Design: Prospective controlled trial with 56 hypertensive women allocated in two groups: 30 volunteers under oral combined contraceptive use and 26 volunteers using 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 and, for the biochemical and hormonal analyses two blood samples were obtained. Student's t test was used to determine differences between groups and moments and $p < 0.05$ was considered statistically significant.

Results: Comparing antropometric and blood pressure measurements, cardiac sympatho-vagal modulation, baroreceptor sensitivity, metabolic and neurohumoral axis variables between baseline and after 6 months, no significant difference was detected in each group or between groups. Except serum triglyceride levels which increased in the group of women using EE + DRSP after 6 months of use.

Conclusion: A contraceptive containing 20 mcg of ethinyl estradiol and 3 mg of drospirenone causes no significant changes in clinical and autonomic parameters, metabolic variables and neurohumoral axis of hypertensive women.

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Introduction

Hypertension in women of reproductive age presents important clinical implications and challenges, not only because of its role as a risk factor for cardiovascular disease, but also because of the issues associated with pregnancy and contraception [1]. Hypertension is a major source of maternal and fetal morbidity and some methods of contraception may further increase the risk of cardiovascular events [2].

Combined oral contraceptive (OC) is one of the most commonly prescribed birth control methods, used by millions of women in many countries [3]. OCs induce mild increase of arterial blood pressure in the general population, but in about 5% of the female users it is likely to get higher results. Adverse effects on blood pressure increase with age, duration of the use of OCs and the presence of other risk factors such as smoking, obesity and prior diagnosis of hypertension. Moreover, OCs may impose additional

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adverse outcomes in women by stimulating the renin angiotensin aldosterone system (RAAS) and also by causing metabolic disarrangements and pro-thrombotic effects [4–6].

Even considering that contraception guidelines point to an indication against the use of OC by uncontrolled hypertensive women or with other cardiovascular risk factors, epidemiological studies have shown that a high rate of hypertensive women are in regular use of OC [1,7]. Furthermore, hypertensive women may develop adverse effects related to the interaction of antihypertensive drugs and OCs.

The types and doses of estrogens have been associated with the adverse effects related to OCs [5,8].

Recent meta-analysis has shown that even OCs with low hormone levels (ethinylestradiol, estradiol (EE)), associated or not with new progestogens may still lead to thromboembolic events causing increased cardiovascular risk in women in general [9–12].

Drospirenone (DRSP) is the most similar synthetic progestin to the natural progesterone, and is structurally similar to spironolactone, acting as an antagonist of aldosterone receptors with clinically recognized antimineralocorticoid activity [13–15]. DRSP molecule in combination with EE, initially studied as hormone replacement therapy in hypertensive postmenopausal women [16,17], demonstrated a high capability to neutralize the estrogen-induced RAAS activation [18,19]. Moreover, OCs containing EE + DRSP did not increase blood pressure and had little impact on metabolic profile in both normotensive young women [20] and postmenopausal hypertensive women [21–23]. There are few informations in the literature regarding to the effects of OCs containing EE + DRSP used as a contraceptive method in the population of hypertensive women. Therefore, the aim of this study was to prospectively evaluate the impact of OC containing EE + DRSP coadministered with antihypertensive drugs on arterial blood pressure, metabolic homeostasis and neurohumoral axis in hypertensive women.

Materials and methods

This study enrolled 60 hypertensive female volunteers recruited from the outpatient clinics of the Gynecology Department and Hypertension Unit of the General Hospital, School of Medicine, University of São Paulo, Brazil. The Research Ethics Committee of the University of São Paulo reviewed and approved the study. All patients were submitted to a clinical examination by both a cardiologist and a gynecologist.

The inclusion criteria were women aged between 20 and 40 years old, with previous diagnosis of essential arterial hypertension under antihypertensive medications, and regular menstrual cycles without the use of hormonal contraceptives for at least 6 months prior to the study. The exclusion criteria were women with uncontrolled hypertension, detected target organ damage, positive pregnancy tests, current smoking, previous episode of thromboembolism, autoimmune disease, morbid obesity, diabetes mellitus and women who were taking any chronic medication, except antihypertensive drugs [5].

Sample size

The minimum size of the sample was determined from a pilot sample and a previous publication [20]. Two hemodynamic variables and four autonomic tone parameters were used. Considering that a type I error of 0.05 and a power of 0.8 would be necessary to detect a difference between the two groups of 20% on average, the minimum necessary sample size per group for the study of each of these six variables was 30 patients.

Experimental design

All selected women were eligible for both the contraceptive methods, i.e., OCs or non-hormonal methods. However, after being counseled regarding the advantages, disadvantages and side effects of each contraceptive method, the volunteers were free to choose the type of contraception they wanted to use. Therefore, women who agreed to participate in the study were allocated into two groups, users and nonusers: **(1) EE + DRSP group:** women who chose to use an OC containing 20 mcg EE + 3 mg DRSP, with 24 days of active pills and a 4 day pill-free interval (n = 30), **(2) non-OC group:** women who chose to use a non-hormonal method of contraception (condoms or copper IUD) (n = 30).

All volunteers were evaluated during the same menstrual cycle phase: follicular phase at baseline for both groups; follicular phase in the follow-up period for the control group; high hormonal phase in the contraceptive group. All examinations were performed during the same time of the day, and were conducted in a temperature-controlled room. All patients were instructed to abstain from exercise, caffeine and alcohol for 12 h before testing.

Evaluation methods for body mass index and office blood pressure.

Body mass index (BMI) was obtained by using measures of weight and height of each subject (weight/height^2) acquired during the basal evaluation and at the end of the study (6 months).

Blood pressure measurement (BP) in the office was obtained using the auscultatory method with a calibrated mercury sphygmomanometer following the recent guideline technique recommendations. Hemodynamic parameters obtained during rest in supine position, with the Finometer® device (FMS, Finapres Medical System, Anhem, The Netherlands) [24,25].

Heart rate variability and autonomic nervous system parameters

The blood 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 into 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. Forms of acquisition and analysis of variability was performed as previously published protocol [20,26].

Biochemical and hormonal variables

Two blood samples (initial phase and with 6 months of COC use) were obtained for biochemical and hormonal measurements according to the routine standard protocols.

Statistical analysis

The variables of interest in both groups were assessed at baseline and after 6 months of use of the chosen contraceptive method. An intergroup comparison was performed of the mean of each clinical parameter variable at baseline using Student's *t* test or the Mann–Whitney test, depending on the characteristics of each variable. The mean of each variable was analyzed as a function of time and group using the scores from the tests of generalized

Table 1
Anthropometric and clinical variables in women using EE + DRSP and nonusers (non OC) at baseline and after 6   months of follow-up.

	Non OC (n = 26)			EE + DRSP (n = 30)		
	Baseline	6 months	p	Baseline	6 months	p
Weight (kg)	74.4 ± 3.3	73.8 ± 3.4	0.08	77.5 ± 2.6	76.4 ± 2.6	0.04[*]
AC (cm)	95.9 ± 2.6	94.8 ± 2.6	0.76	97.9 ± 2.0	97.2 ± 2.0	0.66
BMI (kg/m2)	29.0 ± 1.1	28.7 ± 1.2	0.20	30.3 ± 0.9	29.8 ± 0.9	0.04[*]
SBP (mmHg)	129.0 ± 2.5	130.3 ± 2.4	0.70	127.8 ± 2.1	126.6 ± 2.5	0.57
DBP (mmHg)	87.6 ± 1.9	87.0 ± 1.4	0.57	83.9 ± 1.3	83.7 ± 1.8	0.93

Mean values standard error.
AC = abdominal circumference; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.
[*] $p < 0.05$ baseline vs 6 months.

estimating equation models or nonparametric tests (Mann–Whitney test and Wilcoxon rank sum test).

Results

A total of 60 hypertensive women was included, 30 in each group. However, four women of the non-OC group did not remain in the study, due to the following reasons: they neither attended the visits, nor collected tests or experienced adverse effects with intra uterine disposable (IUD) and chose to start OC. None of the women in this trial became pregnant during the study period. In addition, the patients included in the protocol were not performing regular exercise, and maintained the same diet during the follow-up.

Table 1 shows the clinical data and office blood pressure of the non-OC and EE + DRSP groups who completed the study. Both groups were comparable in age, BMI and blood pressure. The groups have class I obesity and blood pressure at a controlled level. These results show that women using EE + DRSP after 6 months have a small reduction in weight and BMI. The same event could not be observed in the control group. There were no significant changes in the systolic and diastolic blood pressure after 6 months in either group.

Prescription of antihypertensive drugs was guided by the current guidelines and was maintained unchanged during all protocol. There were no differences regarding number and classes of drugs used by both the groups. Monotherapy was used by 30% and 36% of patients of non-OC and EE + DRSP groups, respectively. Diuretics were the most prescribed drug (approximately 70% of patients in both groups) and were used as monotherapy (21% and 20% of patients in non-OC and EE + DRSP groups, respectively) or in association with other classes of antihypertensive drugs. Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers were used as monotherapy or in association with other classes, in 52% and 57% of patients of non-OC and EE + DRSP groups, respectively. Calcium channel inhibitors were prescribed for few patients, around 7% in both groups.

The autonomic variables at baseline and after 6 months referring to the two groups of female users and non-users of OC

are presented in Table 2. The sympathetic–vagal modulation and baroreflex sensitivity have shown no statistically significant differences when comparing the time (baseline vs after 6 months) of hypertensive women using EE + DRSP with nonusers.

Table 3 shows that women who did not use OCs had no changes in the components of RAAS or in the concentrations of electrolytes in the metabolism of lipids and glucose. However, it was possible to see a significant increase in the levels of triglycerides in the subjects using EE + DRSP. There was also a trend towards increased aldosterone and A/R ratio after 6 months of using OC, but no changes in electrolytes were observed.

Comments

The main findings of this study can be summarized as the following: hypertensive women using EE + DRSP have shown a mild, but statistically significant reduction in weight and BMI, associated with a neutral profile in the activation of the RAAS, and the maintenance of the sympathetic–vagal balance and baroreflex sensitivity. No changes were found in the blood pressure measured in the office or analyzed in a beat-to-beat basis for a short period of time. Nevertheless, a negative impact of the use of EE + DRSP could be observeded in hypertensive individuals: there was an increase in triglycerides, approximately 41% after 6 months of use, compared to baseline. All variables remained similar in the non-OC group during the 6-months of follow-up period.

Drospirenone is an analog of spironolactone, with biochemical and pharmacological profiles that are similar to those of endogenous progesterone, with an antimineralocorticoid property and a mild anti-androgenic activity. It was initially developed in combination with EE (17-β estradiol) for the treatment of hormone replacement in hypertensive postmenopausal women [23]. It has the capacity not only to neutralize the induced RAAS stimulation by estrogen, but also to block testosterone receptors, decreasing the androgenic effects [18,19]. The use of EE in low doses associated with DRSP has been used as contraceptives for more than a decade. This combination, compared to the previous generations of contraceptives, has a better androgen profile [5,8]; however, it keeps an increased risk of pro-thrombogenic effects [9–12].

In a double-blind randomized study, it was evaluated the effect of DRSP + EE in hypertensive postmenopausal women already receiving enalapril [21]. An assessment of the plasma renin activity and serum aldosterone was measured before the treatment and at the end of treatment (day 14). The authors have demonstrated that the plasma renin activity and aldosterone levels showed no statistically significant difference between the groups. However, a small and non significant increase in aldosterone levels in patients that received DRSP + EE which was consistent with an antimineralocorticoid effect due to DRSP, could be observed in previous studies [18,21]. It is important to show that the OC used in this study did not increase the serum aldosterone levels, as these, independent of angiotensin II, have serious implications in the pathogenesis of the progressive renal and cardiovascular disease

Table 2
Assessment of autonomic hypertensive women using EE + DRSP and non-users (control) of COHCs: baseline and after 6 months of follow-up.

	Non OC n = 26		p	EE + DRSP n = 30		p
	Baseline	6 months		Baseline	6 months	
VAR (RR)	2109.2 ± 337.8	3023.6 ± 715.4	0.16	3031.8 ± 595.3	2387.9 ± 286.1	0.30
% LF	51.5 ± 3.69	49.0 ± 3.63	0.57	50.2 ± 3.0	50.9 ± 3.1	0.82
% HF	48.5 ± 3.69	51.0 ± 3.63	0.57	49.8 ± 3.0	49.1 ± 3.1	0.82
LF/HF	1.5 ± 0.3	1.3 ± 0.3	0.40	1.3 ± 0.2	1.3 ± 0.2	0.99
Alfa index (mmhg/ms)	7.0 ± 0.7	7.6 ± 0.8	0.52	8.1 ± 0.8	8.0 ± 0.5	0.88

Mean values standard error.
[*] $p < 0.05$ baseline vs 6 months.

Table 3

Metabolic assessment of hypertensive women using EE + DRSP and nonusers (control) using COHC: baseline and after 6 months of follow-up.

	Non OC (n = 26)		p	EE + DRSP (n = 30)		p
	Baseline	6 months		Baseline	6 months	
Renin (ng/mL/h)	4.8 ± 1.3	4.0 ± 1.1	0.70	4.9 ± 0.8	4.6 ± 0.9	0.87
Aldosterone (ng/dL)	12.3 ± 1.6	11.0 ± 1.7	0.82	9.8 ± 1.0	13.9 ± 1.7	0.13
Aldosterone/renin ratio	2.65 ± 1.5	2.57 ± 1.54	0.88	2.1 ± 1.0	3.0 ± 1.5	0.78
Potassium (mEq/L)	4.1 ± 0.1	4.2 ± 0.1	0.26	4.1 ± 0.0	4.1 ± 0.1	0.56
Sodium (mEq/L)	139.4 ± 0.7	141.2 ± 0.7	0.05	139.9 ± 0.7	138.1 ± 0.7	0.54
Creatinine (mg/dL)	0.8 ± 0.0	0.7 ± 0.0	0.41	0.8 ± 0.0	0.7 ± 0.0	0.33
Urea (mg/dL)	32.1 ± 1.6	29.4 ± 1.7	0.33	28.1 ± 1.2	27.0 ± 1.3	0.79
Glucose (mg/dL)	94.7 ± 2.1	96.3 ± 3.2	0.31	96.7 ± 1.8	94.1 ± 2.5	0.27
Insulin (UI) [a]	14.4 ± 3.2	12.3 ± 1.4	0.55	13.7 ± 2.2	13.3 ± 2.1	0.86
HOMA1 (IR) [a]	3.2 ± 0.5	3.0 ± 0.4	0.59	3.1 ± 0.5	2.9 ± 0.4	0.59
Cholesterol (mg/dL)	188.1 ± 7.9	186.3 ± 6.9	0.74	197.6 ± 8.6	195.9 ± 10.9	0.73
LDL-col. (mg/dL)	109.8 ± 7.9	110.5 ± 6.7	0.88	118.1 ± 9.3	102.7 ± 11.6	0.27
HDL-col. (mg/dL)	58.2 ± 2.7	55.6 ± 2.5	0.46	54.6 ± 2.0	60.2 ± 2.3	0.06
Triglycerides (mg/dL)	100.2 ± 9.1	100.6 ± 10.5	0.98	124.3 ± 12.1	174.7 ± 14.7	0.01 [*]
Hemoglobin (g/dL)	13.3 ± 0.2	13.1 ± 0.3	0.81	13.5 ± 0.2	12.9 ± 0.1	0.08
Platelet (mil/mm3)	268.6 ± 16.5	268.9 ± 15.8	0.67	286.2 ± 15.3	296.4 ± 13.2	0.42

Mean values standard error.

[*] $p < 0.05$ baseline vs 6 months.

[a] HOMA1 = < 2.8 normal cut-off value, according to Geloneze et al. [31].

(CVD) [21]. Studies have demonstrated that the blocking of aldosterone receptors with spironolactone may significantly reduce the risk of morbidity and mortality in patients with severe heart failure [27]. It has become of great interest to research on the antagonism of aldosterone receptors in combination with the antagonists of angiotensin receptors or ACE inhibitors [21,27,28].

In hypertensive women using anti-hypertensive drugs, which per se can already alter potassium levels, the concomitant use of a drug with spironolactone-like activity could lead to a stronger electrolyte disturbance [22,28]. In a previous study with hypertensive postmenopausal women using RAAS inhibitors it was shown that only 7% of women had at least one value that was equal to or greater than 5.5 mEq/L during the treatment with DRSP, regarded as transient hyperkalemia; the values returned to baseline levels at the end of the observation period [22,23]. Potassium levels, commonly elevated in hypertensive women, did not increase at the end of this study. This may be associated with the use of diuretics by most hypertensive patients included in the trial, separately, or associated with the RAAS inhibitors. The other presecribed antihypertensives do not show, as a characteristic, an increase in potassium. The importance of studying the serum potassium levels is due to their relation with the development of severe cardiac arrhythmias during hyperkalemia [28]. It was emphasized that the presence of hyperkalemia would limit the use of COHC with drospirenone [23]. It has been reported that DRSP could change the concentration of plasmatic sodium [13]; however, this fact could not be observed in the patients in this study, either.

We must take in account that the conclusions regarding the effects of drosperinone on RAAS axis of hypertensive women were obtained when drosperinone was administered on top of usual antihypertensive drugs. Therefore, drosperinone in combination with antihypertensive drugs, including diuretics or RAAS inhibitors, is well tolerated by hypertensive women, without significant deleterious effects on RAAS axis.

Hypertension is characterized by changes in the autonomic control, particularly in the sympathetic–vagal modulation to the heart and baroreflex sensitivity, which can be improved with the use of antihypertensive drugs and BP control [29]. DRSP could have a positive impact on the autonomic parameters; however, no influence of this drug on autonomic variables could be observed. Hypertensive postmenopausal women using DRSP have shown slight, but significant reductions in BP detected by ambulatory BP monitoring [21,23].

Through the ways of BP measurement used in this study (pressure measurement in the office and in short time rest records), it was not possible to show an impact in reducing BP. It is likely that by using long-term monitoring, such an effect might be shown. The demonstration that OC containing EE + DRSP used by hypertensive women causes neither increased blood pressure nor modifications in hemodynamic and autonomic parameters is clinically relevant, since the autonomous system is considered one of the most important mechanisms underlying the pathogenesis of hypertension and cardiovascular disease [29,30]. Since the present study lacks power to identify small but clinically relevant blood pressure changes, more studies addressing this point are desired.

In conclusion, the use of the third-generation OC containing EE + DRSP by young hypertensive women using anti-hypertensive drugs has not been associated with neither neurohumoral activation, nor electrolyte or metabolic abnormalities except for an increase in triglycerides. Thus, DRSP seems to have a good safety profile regarding this female population, and its indication or not depends on other adverse drug effects, particularly, the risk of thromboembolic events.

Condensation

Drospirenone and ethinyl estradiol use for young hypertensive women using anti-hypertensive drugs has not been associated with neither neurohumoral activation, nor electrolyte or metabolic.

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