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Influence of oral contraceptive use on lipid levels and cardiorespiratory responses among healthy sedentary women

Influência do uso de contraceptivos orais nos níveis lipídicos e nas respostas cardiorrespiratórias de mulheres saudáveis e sedentárias

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Abstract

Objective: To evaluate the influence of oral contraceptive use on lipid levels, heart rate (HR) variability and aerobic capacity among sedentary young women. **Methods:** The subjects were 20 healthy women (23.55±1.88 years): ten used oral contraceptives (TG) and ten did not (CG). Ergospirometric test on a cycle ergometer was used to determine the aerobic capacity at the anaerobic threshold and at the exercise peak. In addition, recordings of HR and R-R (iRR) intervals in the supine and seated positions, for 15 minutes, and biochemical blood analysis were performed. The iRR (ms) indices were analyzed in the time domain (TD) for RMSSD, RMSM and pNN50 (%), and in the frequency domain (FD) using fast Fourier transforms from low (LF) and high (HF) frequency bands in normalized units, obtaining the LF/HF ratio. Mann-Whitney and Kruskal-Wallis, with α=5%, were used for statistical analyses. **Results:** The triglyceride and cholesterol levels in the TG were greater than those in the CG ($p<0.05$). At the anaerobic threshold and at the exercise peak, the power (W), oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), ($\dot{V}O_2/\dot{V}CO_2$) ratio, pulmonary ventilation and HR were not significantly different between the groups. The indices for HR variability in the TD and FD for the two groups in the supine and seated positions were also not different. **Conclusions:** The use of oral contraceptives did not influence the aerobic capacity or the autonomic modulation of the HR. However, it influenced the total cholesterol and triglyceride levels. These assessments are important for determining protocols for physical training for cardiovascular disease prevention.

Key words: contraceptive therapy; heart rate; aerobic capacity.

Resumo

Objetivo: Avaliar a influência do uso de contraceptivos orais (CO) sobre os níveis lipídicos, a variabilidade da freqüência cardíaca (VFC) e a capacidade aeróbia em mulheres jovens sedentárias. **Materiais e métodos:** Vinte mulheres saudáveis (23,55±1,88 anos), sendo dez que utilizam CO (GT) e dez que não utilizam CO (GC). **Protocolos:** teste ergoespirométrico (TE), em cicloergômetro para determinar a capacidade aeróbia no limiar de anaerobiose (LA) e no pico do exercício; captação da FC e dos intervalos R-R (iRR) nas posições supina e sentada durante 15 minutos; análise bioquímica de sangue. Os índices dos iRR(ms) foram analisados no domínio do tempo (DT), RMSSD, RMSM e pNN50(%) e no domínio da freqüência (DF), usando a transformada rápida de Fourier a partir das bandas de baixa freqüência (BF) e alta freqüência (AF), em unidades normalizadas (un), e a razão a BF/AF. **Estatística:** Mann-Whitney e Kruskal-Wallis, α=5%. **Resultados:** Os níveis de triglicérides e de colesterol do GT foram superiores aos do GC ($p<0,05$). No LA e no pico do exercício, a potência (W), o consumo de oxigênio, a produção de dióxido de carbono, a razão $\dot{V}O_2/\dot{V}CO_2$, a ventilação pulmonar e a freqüência cardíaca (FC) foram semelhantes ($p>0,05$) entre os grupos. Os índices da VFC no DT e no DF da posição supina e sentada intergrupos foram semelhantes. **Conclusões:** O uso de CO não influenciou na capacidade aeróbia e na modulação autonômica da FC, mas influenciou nos níveis de colesterol total e triglicérides. Estas avaliações são importantes para a determinação de protocolos de treinamento físico na prevenção de doenças cardiovasculares.

Palavras-chave: terapia contraceptiva; freqüência cardíaca; capacidade aeróbia.

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Introduction

Women share several risk factors in the development of cardiovascular disease, such as family history, obesity, smoking habits, unfavorable lipid profiles, high levels of homocistein and fibrinogen, physical inactivity (sedentary habits), use of oral contraceptives (OC), *diabetes mellitus*, hypertension, and genetic factors[1]. Among these factors, physical inactivity associated to the use of low-dose, single-phase combined OC, have been considered to be an important risk factor for dyslipidemia, contributing to the development of atherogenesis and coronary arterial disease (CAD)[2,3]. Furthermore, studies reveal negative influences on the aerobic functional capacity with the use of contraceptive therapy[4,5].

Large clinical assays show that the extended use of estrogen associated with progesterone cannot be beneficial[6] and may, also, compromise the efficiency of the autonomic modulation of the heart rate (HR). These authors report that, in women who are not users of oral contraceptives, no evidence was shown of changes in autonomic HR modulation during the follicular phase of the menstrual cycle, in comparison with oral contraceptive users[7].

Some studies show no evidence of unfavorable effects due to estrogenic therapy on autonomic HR control with women who practice regular physical training, in the rest condition[8,9]. Studies report that there are alterations of the metabolism of plasmatic lipids of young, females using oral contraceptives, and that the estrogen and progesterone dosages are related[7,8]. Such alterations are associated with the increase of risks in CAD[10,11]. However, other authors report that low-dose, combined contraceptives reduce the adverse effects of the increases of the total triglyceride and cholesterol serum levels[12].

Furthermore, there is still the need of greater knowledge about the single-phase combined estrogen/progesterone therapy over the cardiorespiratory and metabolic variables in young sedentary women. Thus, from the analyses of cardiorespiratory and metabolic variables, as an integral part of physical therapy evaluations, valuable information about the physiological conditions of the subjects may be obtained. This may help identify possible alterations that will contribute to the development of cardiovascular diseases.

Therefore, considering the current doubts of oral contraceptive use on the development of cardiovascular disease, the aim of this study was to investigate the lipid levels, HR autonomic modulation, and aerobic capacity of young sedentary women who were users and non-users of low-dose, combined estrogen/progesterone OC.

Materials and methods

Subjects

Sampling calculus obtained from the analysis using the GraphPad StatMate 2.0 for Windows software program, with 80% power and α=5%, was for eight volunteer subjects for each group. All subjects were pre-selected from a clinical evaluation, resting electrocardiogram (ECG) of 12 derivations, blood and urine biochemical assays, and a physical therapy examination. This was a cross-sectional study, performed with 20 healthy, sedentary volunteer subjects (23.55±1.88 years old) with a weak aerobic level, according to the American Heart Association. They were divided into two groups of ten, considering the ones that used combined oral contraceptives, or the therapy group (TG), and the ones who did not, or the control group (CG). Each participant demonstrated normal ECGs in 12 resting derivations, corporal mass index of 21.22±2.01kg/m^2, systolic and diastolic arterial pressure during rest of 110 and 70mmHg on average, respectively. The CG females showed regular menstrual cycles of between 28 and 30 days, and the ones from the TG had used OC for 15.22±12.77 months. A minimal time of six months of OC use was established. The subjects did not show any evidence of cardiovascular changes, as observed through clinical examination.

The subjects were oriented about the relevance of the research, the experimental procedures, and after agreeing, signed informed consent form, according to rule nº 196 of the National Health Council (NHC). The Research Ethics Committee of the Universidade Metodista de Piracicaba (Unimep) approved the research, for the the protocol of nº 43/06.

Tests were always performed during the afternoon, in order to avoid interferences of the circadian variations. The laboratory was air-conditioned, with an average temperature of 22ºC, a relative air humidity of around 50%, and a barometric pressure of approximately 710mmHg. The volunteers were oriented not to consume stimulating beverages (tea, coffee, alcohol), not to perform physical activities within 24 hours before the experiment, to have a good sleep (at least eight hours), and to have light meals on the day of the test.

Experimental protocols

Total cholesterol levels were evaluated by using the automatic chloromimetric enzymatic method, and the triglycerides using the automatic enzymatic method, performed between the seventh and tenth day of the menstrual cycle. All volunteers fasted for between 12 and 15 hours, in order to perform the sampling for the blood biochemical examinations.

Heart rate data measurements were obtained from the ECG, recorded on a cardiac monitor of a channel (Miniscope II, Instramed, Porto Alegre, RS, Brazil), with the DII derivation with activated carbon electrodes (R28 Carbo Cone, Implemed, São Paulo, SP, Brazil). The negative electrode was placed at the manubrio-sternal joint, the positive one at the fifth space on the left anterior axillary line, and the neutral electrode at the fifth right intercostals space. A Lab-PC+ (National Instruments Co., Austin, TX, USA) analogical-digital converter was used in order to process the ECG signals, which represented an interface between the cardiac monitor and a Pentium III PC. Signal recording was performed in real time, after the A/D conversion, with a sampling rate of 500 Hz. The calculation of HR and R-R intervals was performed, beat-to-beat, by using a specific software program[13]. Recording of the R-R intervals took place for a period of 15 minutes during rest, with the volunteers in both the supine and seated positions, respectively, and breathing spontaneously.

For the CG volunteers, experiments were conducted between the fifth and the tenth day of the menstrual cycle, considering the slightest hormonal fluctuations, while for the TG, they always took place on the 21st day of medication (active phase), and on the 28th day, without medication (inactive phase)[14].

Performance of the ergospirometric test (ET) aimed at assessing the aerobic functional capability of the volunteers at the anaerobiosis threshold (AT) level, and at the peak of physical exercise, from the cardiorespiratory variables. The ET took place on an electromagnetic brake cycle ergometer (Corival 400 model, Quinton, Seattle, WA, USA) with the seat height regulated in order to allow knee flexion of about 5º. The ET protocol was made up of a 60 seconds pre-test rest, with the volunteer seated on the cycle ergometer, starting exercise with a freeload during 240 seconds, followed by an increase of resistance of 15watts (W) for 60 seconds, until physical exhaustion, that is, when the volunteer could not keep the speed at 60rpm. During ET, breathing and metabolic variables were obtained, breath-by-breath, by using a system of measuring of exhaled gases (CPX/D MedGraphics, Breeze, St. Paul, MN, USA). These variables were later processed and calculated in mobile averages, every eight breathing cycles, in order to better observe the kinetics of their answers during exercise. Aerobic capacities at the test peak and AT were evaluated from the oxygen consumption data (VO_2) in $1/min^{-1}$ (Table 3).

Visual analysis of the answers of the breathing and metabolic variables was made by three duly trained observers in order to determine AT. The criterion adopted was lost of parallelism, that is, a disproportionate increase of carbon dioxide (VCO_2) production in relation to the oxygen consume (VO_2)[15].

Heart rate variation was analyzed in the domain of time (DT) and frequency (DF). The region with greatest stability of the iRR series of data was used for these analyses, as long as it included, at least, five minutes or 256 consecutive beats. Analysis at the DT was performed from the indexes RMSSD (square root of the adding of the square of the differences between the recorded iR-R, divided by the nº of iR-R of the selected data series minus one); RMSM (square root of the adding of the square of the differences of the individual values in relation to the average value, divided by the number of iR-R of the selected data series); and pNN50 (percentage of the adjacent iR-R with differences larger than 50 ms)[16].

For the frequency domain analysis, the procedure of linear tendency removal was used, and the fast Fourier transform was applied in a single window, on the previously selected sequence of the R-R interval values. The potency range components were computed on the low (LF: 0.04-0.15Hz) and high (HF: 0.15-0.4Hz) frequency bands, in absolute units (ms^2) and in normalized units (un), which corresponded to the percentage of the total range, subtracted from the component of the very low frequency (VLF: 0.003-0.04Hz). Since both divisions of the autonomic nervous system, sympathetic, and parasympathetic, modulated the LF band, and the HF band is correlated to vagal control, the LF/HF ratio was calculated, in order to evaluate the sympathetic-vagal balance[16].

The analysis of data distribution of all studied variables in the different conditions have shown that the data did not have a normal distribution, as analyzed by the Kolmogorov-Smirnov test. In this manner, non-parametric statistical tests were selected in order to compare the data. From the Mann-Whitney and Kruskal-Wallis tests, the statistical analysis of significance was performed for non-paired samples, with the significance level established at 5%.

Results

As is shown, in Table 1, that the average values of the blood biochemical exams regarding the plasmatic concentrations of total cholesterol and triglycerides showed statistically significant differences ($p<0.05$) and were higher for the TG, and the average values of progesterone for the CG.

It is shown, in Table 2, the ethinylestradiol and prostagen dosages of the OC used by the TG. Prostagens varied between gestoden, or cyproterone acetate, or drospirenone.

The values for potency (Watts), oxygen consumption ($\dot{V}O_2$) in $mL.kg^{-1}.min^{-1}$, carbon dioxide production ($\dot{V}CO_2$) in L/min, $\dot{V}O_2/\dot{V}CO_2$ ratio (RER), pulmonary ventilation (PV) in L/min, and HR in bpm, obtained during ET at exercise peak and at anaerobiosis threshold (AT) are shown at Table 3. It is observable that the variables values were similar ($p>0.05$) in both situations analyzed between the CG and TG.

It is observed, in Table 4 that the average values for the time domain indices (RMSSD (ms), RMSM (ms), pNN50 (%)), and frequency domain indices (BF (un), AF (un) and BF/AF ratio) of the HRV, did not demonstrate statistically significant differences (p>0.05) in the supine and seated positions, between the CG and the TG on the active (TG-AP) and inactive (TG-IP) phases.

Discussion

Many studies discuss the risks of combined OC regarding the development of cardiovascular diseases, however, there is still much debate about this subject. The estrogen/progesterone dosages contained in oral contraceptives is an important factor, since before the 1980s, these hormones

Table 1. Median values obtained by biochemical analysis of the blood control group and therapy group subjects.

Variables	CG (N = 10)	TG (N = 10)
Glycose (mg/dL)	84 (76; 89)	81.5 (75; 99)
Uric Acid (mg/dL)	4 (2.7; 4.7)	4 (2.6; 4.5)
Creatinine (mg/dL)	0.6 (0.5; 0.84)	0.7 (0.6; 0.9)
Total Cholesterol (mg/dL)	156 (156; 195)	219 (169; 250)*
Triglycerides (mg/dL)	74 (45; 127)	148 (100;180)*
Stradiol (pg/mL)	73.1 (7; 452)	25 (7; 60)
Progesterone (ng/mL)	1 (0.5;16.2)	2.8 (0.9; 8.1)*
LH (mUI/mL)	2.45 (0.5; 15.1)	1 (0.8; 9.5)
FSH (mUI/mL)	2.83 (1; 6.4)	0.43 (1; 2.8)

Data are reported as medians (minimum; maximum). CG=control group; GT=therapy group; N=number of volunteers; mg/dL=milligrams per deciliters; pg/mL=picograms per milliliter; ng/mL=nanograms per milliliter; mUI/mL=international milliunits per milliliters; *p<0.05. Level of α=5%.

Table 2. Values of low-dose oral contraceptive (OC) obtained by the therapy group subjects.

N	Comercial Name	Ethinil-estradiol (mg)	Gestoden (Desogestrel) (mg)	Cyproterone acetate (mg)	Drospirenone (mg)
3	Femiane	0.02	0.075	-	-
1	Harmonet	0.02	0.075	-	-
2	Tâmisa 20	0.02	0.075	-	-
1	Selena	0.035	-	2.0	-
2	Diane 35	0.035	-	2.0	-
1	Yasmin	0.03	-	-	3.0

N=number of oral contraceptive users; mg=milligrams.

Table 3. Values of variables for anaerobic threshold (AT) and at the exercise peak in ergospirometric test (ET) obtained by the control groups (CG) and therapy groups (TG).

	ET - Pico	Power (W)	$\dot{V}O_2$ (mL.kg^{-1}.min^{-1})	$\dot{V}CO_2$ (L/min)	RER	VE (L/min)	FC (bpm)
GC	Median	131	25.80	1.78	1.22	56.60	179
	Min	108	17.80	1.48	1.10	42.10	168
	Max	156	30.40	1.78	1.34	81.10	193
TG	Median	115.5	24.20	1.51	1.23	62.20	183
	Min	84	18.30	1.13	1.10	41.70	161
	Max	167	27.00	2.37	1.34	92.10	198
	AT						
	Median	65.5	12.1	0.67	0.92	19.85	127
CG	Min	54	8.6	0.44	0.91	13.00	104
	Max	97	18	0.89	0.97	21.90	139
	Median	64.5	12.3	0.65	0.94	21.90	133
GT	Min	49	8.7	0.39	0.89	13.2	107
	Max	86	19	0.97	0.98	31.7	160

Data are reported as medians (minimum; maximum). CG=control group; TG=therapy group; W=Watts; VO_2=oxygen uptake; VCO_2=carbon dioxide production; RER=ratio of gas exchange VO_2/VCO_2; PV=pulmonary ventilation; mL.kg^{-1}.min^{-1}= milliliter per kilogram per minute; HR=heart rate; bpm=beat per minutes; min=minutes; ET=ergospyrometric test; Level of significance α=5%.

Table 4. Indices values obtained analyses heart rate variability for the control groups (CG) and therapy groups (TG) in the active (TG-AP) and inactive phases (TG-IP) in the supine and sitting positions.

Test Condition Indices	CG	TG-AP	GT-FI	p
Supine				
RMSSD (ms)	43.9 (19; 71.4)	46.1 (25.9; 66.4)	46 (19.4; 90.1)	0.84
RMSM (ms)	45.1 (22.4; 66.5)	53.3 (28.8; 82.2)	52.2 (24.7; 137.3)	0.56
PNN50 (%)	74 (1; 152)	26.4 (2.6; 43.8)	29.7 (1; 52)	0.96
BF (un)	0.3 (0.6; 0.2)	0.3 (0.2; 0.7)	0.37 (16; 78)	0.60
AF (un)	0.6 (0.7; 0.3)	0.6 (0.2; 0.7)	0.62 (22; 84)	0.60
BF/AF	0.5 (0.2; 2.2)	0.5 (0.3; 2.9)	0.6 (0.1; 3.4)	0.61
Sitting				
RMSSD (ms)	24.35 (11.2; 38.8)	30.3 (13.8; 49.3)	24.3 (16;74)	0.47
RMSM (ms)	41.22 (18.9; 68)	43.5 (25.2; 91.5)	40.8 (27; 130)	0.72
PNN50 (%)	4.15 (1; 59)	36 (2; 69)	3.1 (56; 1)	0.34
LF (nu)	0.68 (0.4; 0.8)	0.6 (0.16; 0.82)	0.62 (0.3; 0.8)	0.85
HF (nu)	0.32 (0.1; 0.5)	0.3 (0.1; 0.8)	0.38 (0.1; 0.6)	0.85
LF/HF	2.08 (0.8; 4.6)	1.79 (0.1; 4.7)	1.64 (0.5; 8.2)	0.85

Data are reported as medians (minimum; maximum).ms=milliseconds; %=percent; nu=normalized units; LF=low frequency; HF=high frequency; LF/HF. Level of significance α=5%.

containing high doses, caused collateral effects such as liquid retention, nauseas, headaches, body weight changes, and increased risks of thrombo-lythic and ischemic diseases[17]. With the reduction of the estradiol and progesterone dosages contained in the OC, these collateral effects were only observed in women aged more than 35 years old, or when associated to smoking habits[18,19].

The combined single-phase OC utilized by the subjects varied between: ethinilestradiol/gestoden (desogestrel), ethinilestradiol/cyproterone acetate or ethinilestradiol/drospirenone. These medications have an excellent safety profile, for they belong to the class of modern contraceptives, with less than 35 micrograms of estrogen (low doses) and the progestogenes belong to the "second and third generation" of OC with similar efficiency and collateral effects among young women[20,21].

In the present study, the results from the biochemical exams for total cholesterol and triglycerides of the contraceptive therapy for young users, showed higher values in relation to the young women from the CG, which reached the threshold limits regarding the normal band. This occurrence may be attributed to the fact that cholesterol is the elementary block in steroidgenesis[22]. These data are in accordance with the ones by Sheriff[2] and by Foulon et al.[3], which report that the use of combined OC (estrogen/progesterone) increases the total cholesterol plasmatic levels, which may increase or leave unaltered the triglyceride levels. Foulon et al.[3] report also that this triglyceride increase is found in women who are users of ethinilestradiol/desogestrel combined single-phase OC, similar to the data in this study.

The influences of the combined OC over the plasmatic lipids will depend on the balance between the estrogen/progesterone dosages. Koh et al.[23], observed in their study that low estrogen/progesterone dosages of combined contraceptives reduce the adverse effects of the plasmatic lipids and lipoproteins. On the other hand, Martins, Gomes and Pasini[24], report that oral contraceptive therapy contributes to the increases of the plasmatic cholesterol levels, with the most evident effects at the age of 30 to 39 years. However, these authors also report that in women at the age of 20 to 29, there seems to be no relationships between the cholesterol levels and the use of OC. However, Godsland et al.[25] have observed in users of low-dose combined OC an increase of 13 to 75% at the triglyceride levels.

This study's limitations are related to the fact that the experimental design is of a transversal type, and that only the minimal time use was considered, resulting in a considerable dispersal in total oral contraceptive time use. Thus, the performance of lipid profile exams prior to the use of OC is considered relevant. It is also important that more detailed exams of the lipid fractions are made both before and during the use of contraceptives, since dyslipidemia is an important risk factor for coronary artery disease.

In the autonomic modulation of the HR from the TD indices (RMSSD, RMSM, and pNN50) and FD (BF,AF and BF/AF), the use of contraceptives was verified and did not influence the results, since no differences were observed between the two groups. Such a fact can be attributed to the pharmacological properties of low doses of estrogen/progesterone, as well as the maintenance of the integrity of the autonomic modulation of the HR, since the values found were within the normality range[26]. These findings corroborated the study by Schueller et al.[7], which verified that in young females, 27 belonging to the CG, and 31 who made use of single-phase OC, no differences in the autonomic modulation of the HR were observed. This fact was attributed to the duration and the pharmacological properties utilized in the contraceptives. However, the authors report that post-menopause women are more susceptible to the effects of the hormonal repositioning therapy, and demonstrate changes in the autonomic nervous system activity.

Other studies that assessed women before and after OC therapy have observed decreases in aerobic capacity during therapy[24]. Authors assert that this fact may be related to the decreases of the autonomic nervous system activity induced by the exogenous estradiol administration, thus increasing the levels of nitric oxide, which is a potent vasodilator. This mechanism hinders the redistribution of the blood flow to the active musculature, thus limiting its development at peak exercise levels. However, the effects of the contraceptive in the present results during physical exercise (potency (W), VO_2 in $mL.kg.min^{-1}$, VCO_2 (L/min), RER, VE (L/min) and HR (bpm)) obtained at the peak exercise level during ET, did not demonstrate significant statistical differences ($p>0.05$) between the CG and TG, suggesting the OC did not influence the aerobic capacity of sedentary young women.

Although the average potency and HR values did not shown any significant differences, a higher reached potency value for a lower HR at the peak exercise levels was observed in the CG, in relation to the TG, which suggested a greater cardiorespiratory aptitude. These findings were in accordance to the ones by Giacomoni and Falgairette[27], who found a lower cardiorespiratory aptitude in OC users. It is worth pointing out that the average values obtained for the VO_2 during exercise peak (25.80mL/kg/min), are in accordance to Neves et al.[28], who observed average values of peak VO_2=22.6±3.1mL/kg/min in sedentary young women.

The breathing and metabolic variables found in the present study, at the AT level, did not result in statistically significant differences in the comparisons between the CG and TG. These data agreed with the study by Redman et al.[29], who did not observe any influences by the combined single-phase OC in the aerobic capacity at the AT level. Such occurrences in the present study may be due to the fact that the volunteers were using the low dosage OC. Thus, more studies regarding this topic are needed, with the inclusion of other ages, and risk factors associated with the use of OC.

Conclusions

The present results suggest that low doses of estrogen/ progesterone did not affect the aerobic capacity and autonomic modulation in this selected age range. However, it does contribute to modifications of the lipoprotein metabolism related to increases of the total cholesterol and triglycerides levels. These are important risk factors in the development of CAD in sedentary women.

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