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Avaliação de perfil lipídico, proteína C reativa ultrassensível e dímero D de usuárias de diferentes tipos de contraceptivos orais

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ABSTRACT

Introduction: The use of oral contraceptives increases women's risk of developing cardiovascular and thromboembolic diseases, due to alterations in hemostatic and lipid profile. **Objectives:** Analyze the association between the use of different types of oral contraceptives with lipid profile and levels of serum high-sensitivity C-reactive protein (hsCRP) and plasma D-dimer. **Methods:** One hundred fifty-four participants were divided into the following groups: control nonusers ($n = 41$), medium-dose users ($n = 32$), third-generation low-dose users ($n = 40$), and fourth-generation low-dose users ($n = 41$). Triglycerides and total cholesterol serum levels were determined by colorimetric enzymatic method; high-density lipoprotein (HDL) cholesterol levels, by precipitation method; low-density lipoprotein (LDL) cholesterol levels, by Friedewald equation; hsCRP levels, by immunoturbidimetric method; and D-dimer levels, by fluorescence immunoassay. **Results:** Oral contraceptive users had higher serum levels of triglycerides, total cholesterol, HDL cholesterol (HDL-C), HDL/LDL index and hsCRP compared to controls. Medium-dose users had higher D-dimer plasma levels than controls and higher triglycerides serum levels than low-dose users. Triglycerides, hsCRP and D-dimer were positively correlated to each other. **Conclusion:** The use of combined oral contraceptives was associated with an unfavorable lipid profile and a chronic subclinical inflammation, with atherogenic potential. Furthermore, medium-dose contraceptives induced a higher thrombogenic potential, since they were associated with increased D-dimer levels in comparison to low-dose ones.

Key words: oral combined contraceptives; inflammation; lipids; thrombophilia.

INTRODUCTION

Oral contraceptives were a major breakthrough in contraception, promoting significant emancipation of women. According to composition, they are classified as combined (composed of estrogens and progestogens) and not combined (composed only of progestogens). According to the dose of ethinylestradiol, they are classified as low-dose (≤ 30 µg), medium-dose (> 30 and < 50 µg) and high-dose (≥ 50 µg)[1, 2] contraceptives. They can also be classified in first-, second-, third- and fourth-generation, according to the type of progestogen[3].

The prolonged use of these contraceptives has advantages that contribute to adherence to treatment, such as reduction of premenstrual tension, relief of menstrual cramps, and improvement in hirsutism and acne[2]. However, they are associated with a higher risk of cardiovascular and thromboembolic diseases in women, such as acute myocardial infarction, ischemic stroke and deep venous thrombosis. The higher risk of cardiovascular events has been associated with changes in lipid metabolism through the modification of low-density lipoprotein (LDL) and high-density lipoprotein cholesterol (HDL-C) levels[3] and the chronic subclinical inflammation[4]. In addition, they act like

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procoagulant agents, favoring a hypercoagulability state, and then raising the risk of thromboembolic diseases[5].

Inflammation is an uninterrupted effect of the atherosclerotic process, which promotes the formation of the lipid stria, and even the movement and rupture of the atherosclerotic plaque[6, 7]. Thus, it is known that the atherosclerotic process is chronic and has a long subclinical phase[4]. High-sensitivity C-reactive protein (hsCRP) is the best biomarker of chronic subclinical inflammation and is associated with the risk of cardiovascular diseases[8-13]. It has been demonstrated that the use of oral contraceptives may increase hsCRP levels, contributing to a higher cardiovascular risk[4, 14].

Coagulation and fibrinolysis occur together for the hemostatic balance in the organism, and thus, blood can flow normally through arteries and veins. In order to avoid exaggerated blood clotting, the fibrin clot is degraded by plasmin, resulting in fibrin degradation products[15], such as D-dimer. Use of oral contraceptives has been associated with a high risk of thromboembolic events. Therefore, the D-dimer can be evaluated, since it reflects human fibrinolytic activity and is considered an important biomarker of hypercoagulability[16].

However, it is known that the combination of different substances in contraceptives may have different effects on lipid profile, subclinical inflammation process and hypercoagulability state, so that contraceptives from different generations may have different effects on the risk of atherosclerotic and thromboembolic events[3, 17]. Besides, the dose of ethinylestradiol is also associated with an increased risk of these adverse outcomes[1].

Few studies were conducted involving young university populations to evaluate this question. Since most women who use oral contraceptives are young, the association with cardiovascular and thromboembolic diseases becomes worrisome. The risk associated with the use of different types of contraceptives is still not understood by users and neglected by health professionals[18]. Therefore, there is a clear need to develop further studies that evaluate these parameters, considering the associated risks. Thus, this study aimed to analyze the association between the use of different types of oral contraceptives and lipid profile, levels of serum hsCRP and plasma D-dimer.

METHODS

The study was approved by the Research Ethics Committee of Universidade Federal São João del-Rei (UFSJ) (CAAE: 38854914.8.0000.5545). All participants were informed about the research objectives and signed the consent form.

They were 113 women aged between 18 and 30 years, students of Pharmacy, Biochemistry, Nursing and Medicine courses of UFSJ, who used combined monophasic oral contraceptives containing cyproterone and ethinylestradiol (medium dose), desogestrel or gestodene and ethinylestradiol (third-generation low dose), drospirenone or chlormadinone and ethinylestradiol (fourth-generation low dose) for a minimum period of one year. There were also 41 controls, aged between 18 and 30 years, who were not using contraceptives for a minimum period of one year, since it was demonstrated that homeostatic parameters normalize after four months of interruption of combined oral contraceptive use[19]. The study participants were divided into the following groups: controls ($n = 41$), medium-dose users ($n = 32$), third-generation low-dose users ($n = 40$), and fourth-generation low-dose users ($n = 41$).

Women who presented any of the following conditions were not included: liver disease, alcoholism, coagulation disorder, cancer, developing infectious or inflammatory process, kidney disease, autoimmune disease, diabetes mellitus, high blood pressure, pregnancy and smoking.

Information, such as age, use of contraceptives, use of medications and others, was obtained through an interview with the students and filling out the clinical form. After the interview, weight, height and blood pressure were measured, and the body mass index (BMI) was calculated. The practice of physical activity was evaluated through a standardized questionnaire[20].

Serum triglyceride levels were determined by the colorimetric enzymatic method using the Triglycerides Liquiform kit (Labtest®); total cholesterol (TC) levels, by the colorimetric enzymatic method using the Cholesterol Liquiform kit (Labtest®); HDL-C levels, by the precipitation method using the HDL cholesterol kit (Labtest®); and the LDL-C levels, by the Friedewald indirect method: LDL-C = TC − (HDLc + TG/5). D-dimer plasma levels were determined by the fluorescence immunoassay method using the Alere Triage® D-dimer test; and hsCRP, by turbidimetry method using the Ultrasensitive Reactive Protein C kit (Bioclin®).

Statistical analysis was performed using the software SPSS 20.0. Shapiro-Wilk normality test was performed for continuous variables. Mean and standard deviation were calculated for normal distribution variables. The Anova method was used to compare the four groups; and Student's *t*-test, for comparison between two groups. The median and 25% and 75% percentiles were calculated for not normal distribution variables. The Kruskal-Wallis H method was used for comparison between the four groups; and the Mann-Whitney *U* test, for comparison between two groups. Categorical variables were presented as absolute and relative frequencies, and the chi-square test was used to compare these variables. D-dimer levels

were categorized into two groups: ≤ 100 ng/ml and > 100 ng/ml, and analyzed by Student's *t*-test. Spearman's correlation was used to verify the correlation between variables. For all the statistical tests performed, p value < 0.05 was considered significant.

RESULTS

The clinical and laboratory characteristics of the 154 women participating in the study are presented in the **Table**. Oral contraceptive users had higher levels of triglycerides, TC, HDL-C, HDL/LDL index and hsCRP than nonusers. The users of third- and fourth-generation low-dose oral contraceptives had lower triglycerides levels than the users of medium-dose oral contraceptives ($p < 0.001$ and $p = 0.006$, respectively). The users of medium-dose oral contraceptives had higher levels of D-dimer than nonusers ($p = 0.005$).

No significant differences were observed between groups with respect to age; body mass index (BMI); systolic and diastolic blood pressure; LDL-C; HDL/TC index; family history of thrombosis, breast cancer and cardiovascular disease; physical activity; and time of contraceptive use.

TABLE – Clinical and laboratory characteristics of users and nonusers of oral contraceptives

	Controls	Medium-dose	Third-generation	Fourth-generation	*p*-value
Women (*n*)	41	32	40	41	NS
Age (years)	21 (20-23)	22 (20-24)	22 (20-23)	22 (19-24)	NS
BMI (kg/m^2)	21 (19-23)	21 (20-23)	21 (19-22)	23 (20-24)	NS
Systolic blood pressure (mmHg)	110 (100-110)	110 (100-120)	110 (100-110)	110 (100-120)	NS
Diastolic blood pressure (mmHg)	70 (70-80)	70 (60-80)	70 (62-80)	70 (60-80)	NS
Triglycerides (mg/dl)	73 ± 19	148 ± 48	109 ± 26	120 ± 34	< 0.001* < 0.001** < 0.001*** < 0.001† 0.006††
TC (mg/dl)	150 ± 25	174 ± 32	165 ± 29	172 ± 24	0.001* 0.011** < 0.001***
HDL-C (mg/dl)	54 ± 10	62 ± 14	63 ± 16	65 ± 14	0.01* 0.005** < 0.001***
LDL-C (mg/dl)	81 ± 29	81 ± 29	80 ± 24	83 ± 26	NS
HDL/LDL index	0.6 (0.5-0.7)	0.8 (0.6-1)	0.7 (0.5-0.9)	0.7 (0.6-1.1)	0.005* 0.012** 0.001***
HDL/TC index	0.4 (0.3-0.4)	0.4 (0.3-0.4)	0.4 (0.3-0.4)	0.4 (0.3-0.4)	NS
D-dimer > 100 ng/ml [*n* (%)]	8 (16.3)	18 (36.7)	12 (2.5)	11 (22.4)	0.005*
hsCRP (mg/l)	0 (0-1.4)	2.2 (1-4.8)	1.5 (0.5-4.4)	1.8 (0.7-4.2)	< 0.001* < 0.001** < 0.001***
Family history of thrombosis [*n* (%)]	7 (17.1)	4 (12.5)	5 (12.5)	7 (17.1)	NS
Family history of breast cancer [*n* (%)]	9 (22)	6 (18.8)	9 (26)	8 (26.6)	NS
Family history of CVD [*n* (%)]	15 (36.6)	18 (56.2)	22 (55)	17 (41.5)	NS
Physical activity [*n* (%)]	8 (33.3)	5 (18.5)	10 (34.5)	10 (31.2)	NS
Contraceptive use duration (months)	NA	16 (50)	19 (47.5)	24 (58.5)	NS

Variables that showed normal distribution were expressed as mean ± standard deviation and compared by Anova and Student's t-tests. Variables that did not show normal distribution were expressed as median (25%-75% percentiles) and compared using the Kruskal-Wallis H and Mann-Whitney U *tests. Categorical variables were expressed as frequency* n *(%) and compared using the chi-square. Triglycerides, TC, HDL-C, and LDL-C had a normal distribution. HDL/LDL index, HDL/CT index, BMI, systolic blood pressure, diastolic blood pressure, and age, did not present normal distribution.*

BMI: body mass index; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; CVD: cardiovascular disease; NA: not applicable; NS: not significant.

**p < 0.05 for medium-dose users compared to control; **p < 0.05 for third-generation users compared to controls; ***p < 0.05 for fourth-generation users compared to controls; †p < 0.05 for third-generation users compared to medium-dose users; ††p < 0.05 for fourth-generation users compared to medium-dose users; $p < 0.05 for fourth-generation users compared to third-generation users.*

There was a weak positive correlation between hsCRP and triglycerides ($r = 0.39$, $p < 0.001$); D-dimer and triglycerides ($r = 0.303$, $p = 0.006$); hsCRP and D-dimer ($r = 0.395$, $p = 0.001$) (**Figure**). There was no significant correlation of hsCRP and D-dimer with the other lipid variables evaluated (data not shown).

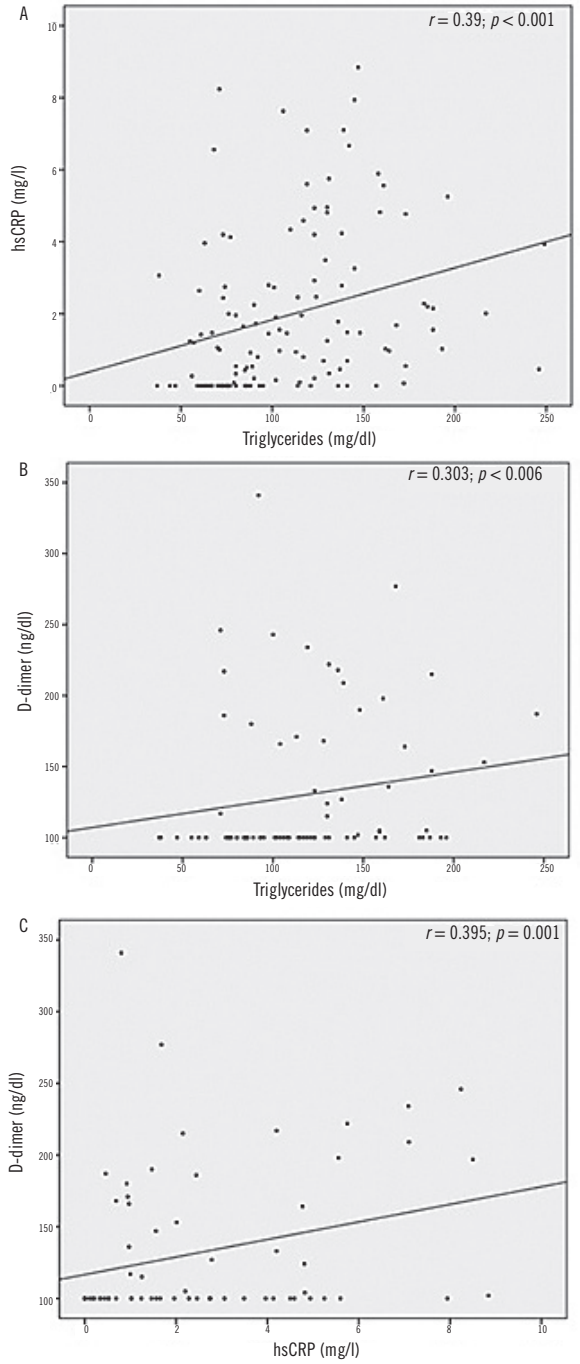

FIGURE – *Correlation between: A) triglycerides and hsCRP; B) triglycerides and D-dimer; C) D-dimer and hsCRP*

hsCRP: high-sensitivity C-reactive protein.

DISCUSSION

Triglyceride levels of oral contraceptive users were higher than those of nonusers, what is in agreement with other studies[21-30]. The use of estrogens is associated with increased hepatic synthesis of triglycerides and suppression of hepatic lipase expression, resulting in increased serum levels of triglycerides[31, 32]. The medium-dose contraceptive users had higher triglyceride levels than low-dose ones, what is probably due to their larger dose of ethinylestradiol, which may stimulate the hepatic synthesis of triglycerides more strongly[31].

The oral contraceptive users had higher total cholesterol levels than nonusers, as a result of increased levels of HDL-C, since a significant difference of LDL-C levels was not observed between users and nonusers. Accordingly, higher HDL/LDL index was observed in oral contraceptive users than in nonursers, but not HDL/TC index, since both HDL-C and TC were increased in oral contraceptive users. Other researchers also described increased HDL-C levels and, consequently, TC levels in oral contraceptives users[24, 25, 28, 33-38], which results from increased hepatic synthesis of HDL lipoprotein[39]. The increase in HDL-C levels provided by oral contraceptive use is beneficial to the organism, since high levels of HDL lipoprotein are associated with an antiatherogenic profile and a reduced cardiovascular risk[39]. Other studies also did not observe significant differences of LDL-C levels between users and nonusers[23, 24, 39, 40], which results from the opposite effects of ethinylestradiol and progestogens on LDL-C levels. While ethinylestradiol reduces LDL-C levels, progestogens raise its levels[41].

Higher D-dimer levels were observed in medium dose users when compared to nonusers, indicating that oral contraception leads to a hypercoagulability state, which depends on the dose of ethinylestradiol. Other studies evidenced the influence of ethinylestradiol dose on D-dimer levels and hypercoagulability state[42, 43].

Higher hsCRP levels were observed in oral contraceptive users when compared to nonusers, indicating that oral contraception leads to an increased subclinical inflammatory process, which was also demonstrated by other studies[44, 45]. However, there was no significant difference between groups of different types of oral contraceptives, suggesting that neither the dose of ethinylestradiol nor the type of progestogen are directly associated with the increase in hsCRP levels.

A positive correlation was observed between triglycerides and hsCRP, what is a predictor of cardiovascular risk; and between triglycerides and D-dimer, what is a biomarker of hypercoagulability. These relationships may indicate that the

increase in the levels of triglycerides caused by the use of oral contraceptives may contribute to intensify the subclinical inflammation process and the hypercoagulability state of oral contraceptive users.

A positive correlation between hsCRP and D-dimer was also observed, what suggests an interrelationship between chronic subclinical inflammation and hypercoagulability in oral contraceptive users. Pro-inflammatory mediators can stimulate the expression of coagulant molecules and inhibit the anticoagulant and fibrinolytic pathways, while the components of activated hemostatic system can stimulate the production of pro-inflammatory cytokines[46]. Therefore, this bidirectional relationship between inflammation and hypercoagulability may contribute to intensify the atherogenic and thrombogenic profile of oral contraceptive users.

No significant differences were observed between the groups with respect to blood pressure, age, BMI and physical activity. Other studies also did not find any effect in blood pressure caused by the oral contraceptive use[23, 38, 47-49]. Therefore, it is possible to assume that the sample was very homogeneous in the present study, since all the women included both users and nonusers of oral contraceptives, were young, with normal BMI and blood pressure. However, this study had a limitation since it has a cross-sectional design, so that clinical and biochemical variables were not compared before and after the use of the oral contraceptives.

CONCLUSION

The use of combined oral contraceptives was associated with increased triglycerides, total cholesterol, HDL-C and hsCRP levels. These results together indicate an unfavorable lipid profile and a chronic subclinical inflammation in oral contraceptive users, with atherogenic potential, particularly in medium-dose users. Furthermore, medium-dose contraceptives induced a higher thrombogenic potential, since they were associated with increased D-dimer levels in comparison to low-dose ones. Triglycerides, hsCRP and D-dimer levels were also positively correlated to each other, indicating that there is an interrelationship between hypertriglyceridemia, chronic subclinical inflammation and hypercoagulability in oral contraceptive users, which may contribute to intensify the atherogenic and thrombogenic profile.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

RESUMO

Introdução: *O uso de anticoncepcionais orais aumenta o risco de desenvolvimento de doenças cardiovasculares e tromboembólicas devido a alterações no perfil lipídico e hemostático.* ***Objetivo:*** *Analisar a associação entre o uso de diferentes tipos de anticoncepcionais orais com o perfil lipídico e os níveis da proteína C reativa ultrassensível (PCRus) e do dímero D.* ***Métodos:*** *Cento e quarenta e cinco participantes foram divididas em: não usuárias (*n = *41), usuárias de média dose (*n = *32), usuárias de terceira geração de baixa dose (*n = *40) e usuárias de quarta geração de baixa dose (*n = *41). Níveis de triglicerídeos e colesterol total foram determinados pelo método enzimático colorimétrico; colesterol da lipoproteína de alta densidade (HDL), pelo método de precipitação; colesterol da lipoproteína de baixa densidade (LDL), pela equação de Friedewald; PCRus, por imunoturbidimetria; e dímero D, por imunoensaio fluorescente.* ***Resultados:*** *As usuárias de anticoncepcionais orais apresentaram maiores níveis de triglicerídeos, colesterol total, HDL, índice HDL/LDL e PCRus do que as não usuárias. As usuárias de anticoncepcionais de média dose apresentaram maiores níveis de dímero D do que as não usuárias, e maiores níveis de triglicerídeos do que as usuárias de anticoncepcionais de baixa dose. Triglicerídeos, PCRus e dímero D apresentaram correlação positiva uns com os outros.* ***Conclusão:*** *O uso de anticoncepcionais orais combinados está associado ao perfil lipídico desfavorável e à inflamação crônica subclínica, com potencial aterogênico. Além disso, os anticoncepcionais orais de média dose induziram maior potencial trombogênico, já que foram relacionados com níveis maiores de dímero D em comparação com os de baixa dose.*

Unitermos: *anticoncepcionais orais combinados; inflamação; lipídios; trombofilia.*

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