Evaluation of lipid profile, high-sensitivity C-reactive protein and D-dimer in users of oral contraceptives of different types

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

João Victor M. Guedes; Natália R. Nunes; Letícia G. R. Ferreira; Thais G. Vilar; Melina B. Pinheiro; Caroline P. Domingueti

Universidade Federal de São João del-Rei (UFSJ), Minas Gerais, Brazil.

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) contraceptives. They can also be classified in first-, second-, third- and fourth-generation, according to the type of progestogen.

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. 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 and the chronic subclinical inflammation. In addition, they act like...
procoagulant agents, favoring a hypercoagulability state, and then raising the risk of thromboembolic diseases(15).

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(16). 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(13, 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 115 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/m²) | 21 (19-23) | 21 (20-25) | 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* |
| TC (mg/dl) | 150 ± 25 | 174 ± 32 | 165 ± 29 | 172 ± 24 | 0.001* |
| HDL-C (mg/dl) | 54 ± 10 | 62 ± 14 | 63 ± 16 | 65 ± 14 | 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* |
| 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) | 0.006* |
| 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*** |
| 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, 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 control; ***p < 0.05 for fourth-generation users compared to control; †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).

**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 nonusers, 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 (22, 25, 35-38), 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
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: Cem 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 imunotezimento fluorescente. Resultados: As usuárias de anticoncepcionais orais apresentaram níveis de PCRus e D-dimer menores do que as não usuárias. Usuárias de quarta geração de baixa dose apresentaram níveis menores de dímero D do que as usuárias de terceira geração de baixa dose. Triglicerídeos, PCRus e D-dimer apresentaram correlação positiva entre si. 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.
References

1. Brito MB, Nobre F, Vieira CS. Hormonal contraception and cardiovascular system. Arq Bras Cardiol. 2011; 96(4): 81-9.
2. Wannamacher L. Anticoncepcionais orais: o que há de novo. Uso racional de medicamentos: temas selecionados. 2003; 1(1): 1-4.
3. Fazio G, Ferrara F, Alessandro GBC, Ferro F, Novo G, Novo S. Prothrombotic effects of contraceptives. Current Pharmaceutical Design. 2010; 16(1): 5490-6.
4. Petto J, Pereira LS, Santos ACN, Gieta BA, Melo TA, Ladeia AMT. Inflamação subclínica em mulheres que utilizam contraceptivo oral. Revista Brasileira de Cardiologia. 2013; 26(6): 465-71.
5. Ferreira ACP, Montes MBA, Franceschini AS, Toloi MRT. Efeitos do contraceptivo oral contendo 20 μg de etinilestradiol e 150 μg de desogestrel sobre os sistemas de coagulação e fibrinólise. Rev Bras Hemol Hemoter. 2010; 22(2): 77-87.
6. Pearson TA, Mensah GA, Alexander RW, et al; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003; 107(5): 499-511.
7. Liao JK. Beyond lipid lowering: the role of statins in vascular protection. Int J Cardiol. 2002; 86(1): 5-18.
8. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003; 111(1): 1805-12.
9. Santos SCM, Canashiro JA, Gebara OCE, et al. Efeitos agudos dos estrogênios associados a progestogênicos sobre a trigliceridemia e reatividade vascular pós-prandial. Arq Bras Cardiol. 2004; 83(5): 385-90.
10. Alipour A, Elte JW, Van Zaanen HC, Rietveld AP, Cabezas MC. Prothrombotic effects of contraceptives. Current Pharmaceutical Design. 2010; 16(1): 5490-6.
11. Roche HM, Gibney MJ. Effect of long-chain n-3 polyunsaturated fatty acids on fasting and postprandial triacylglycerol metabolism. Am J Clin Nutr. 2000; 71(l): 232-7.
12. Issa JS, Diamant J, Forti N. Lipemia pós-prandial. Influência do envelhecimento. Arq Bras Cardiol. 2007; 85(1): 15-9.
13. Harrison M, O’Gorman DJ, McCaffrey N, et al. Influence of acute exercise with and without carbohydrate replacement on postprandial lipid metabolism. J Appl Physiol. 2009; 106(3): 943-9.
14. Sorensen C, Pedersen OB, Petersen MS, et al. Combined oral contraception and obesity are strong predictors of low-grade inflammation in healthy individuals: results from the Danish Blood Donor Study (DBDS). PLoS One. 2014; 9(1): 1-8.
15. Langer B, Wolosker M. Coagulação e fibrinólise: ideias atuais e suas aplicações clínicas. Rev Med (São Paulo). 2006; 85(4): 157-64.
16. Kluf C, Meijer P, Laguardia KD, Fisher AC. Comparison of a transdermal contraceptive patch vs. oral contraceptives on hemostasis variables. Elsevier Contraception. 2008; 77(1): 77-83.
17. Sitruk-Ware R, Nath A. Characteristics and metabolic effects of estrogen and progestins contained in oral contraceptive pills. Best Pract Res Clin Endocrinol Metab. 2013; 27(1): 13-24.
18. Tricotel A, Raguideau F, Collin C, Zureik M. Estimate of venous thromboembolism and related deaths attributable to the use of combined oral contraceptives in France. PLoS One. 2014; 9(4): 1-9.
19. Robinson GE, Burren T, Mackie IJ, et al. Changes in haemostasis after stopping the combined contraceptive pill: implications for major surgery. BMJ. 1991; 302(6771): 269-71.
20. Organización Panamericana de la Salud. Protocolo y directrices: conjunto de ações para a redução multifatorial de enfermidades não transmisíveis (CARMEN/CINDI). OPAS. 1997.
21. Cagnacci A, Piacenti I, Zanin R, Xholli A, Tirelli, A. Influence of an oral contraceptive containing drospirenone on insulin sensitivity of healthy women. Eur J Obstet Gynecol Reprod Biol. 2014; 178(1): 48-50.
22. Duvillard L, Dautin G, Florentin E, Petit JM, Gambert P, Vergès B. Changes in apolipoprotein B100-containing lipoprotein metabolism due to an estrogen plus progestin oral contraceptive: a stable isotope kinetic study. J Clin Endocrinol Metab. 2010; 95(5): 2140-6.
23. Giribela CRG, Colombo FMC, Nisenbaum MG, et al. Effects of a combined oral contraceptive containing 20 mcg of ethinylestradiol and 3 mg of drospirenone on the blood pressure, renin-angiotensin-aldosterone system, insulin resistance, and androgenic profile of healthy young women. Gynecol Endocrinol. 2015; 31(11): 912-5.
24. Grandi G, Piacenti I, Volpe A, Cagnacci A. Modification of body composition and metabolism during oral contraceptives containing non-androgenic progestins in association with estradiol or ethinyl estradiol. Gynecol Endocrinol. 2014; 30(9): 676-80.
25. Kripiani A, Periyasamy AJ, Agarwal N, Kulshretha V, Kumar A, Ammini AC. Effect of oral contraceptive containing ethinyl estradiol combined with drospirenone vs. desogestrel on clinical and biochemical parameters in patients with polycystic ovary syndrome. Contraception. 2010; 82(1): 139-46.
26. Markantes G, Saltanavros AD, Vervita V, et al. Increased plasma viscosity in young women with polycystic ovary syndrome using an oral contraceptive containing 35 lg ethinyl estradiol and 2 mg cyproterone acetate. Gynecol Endocrinol. 2011; 27(12): 971-7.
27. Morais TL, Giribela C, Nisenbaum MG, Guerra G, Mello N, Baracat E, Colombo FMC. Effects of a contraceptive containing drospirenone and ethinylestradiol on blood pressure, metabolic profile and neurohumoral axis in hypertensive women at reproductive age. Eur J Obstet Gynecol Reprod Biol. 2014; 182(1): 113-7.
28. Naka KK, Kalantaridou SN, Bechioulis A, et al. Effect of ethinylestradiol/cyproterone acetate on endothelial function in young non-obese women with polycystic ovary syndrome: a pilot study. Gynecol Endocrinol. 2011; 27(9): 615-21.
29. Petersen KR, Skouby SO, Dreisler A, Kuhl C, Svenstrup B. Comparative trial of the effects on glucose tolerance and lipoprotein metabolism of two new oral contraceptives containing gestodene and desogestrel. Acta Obstet Gynecol Scand. 1988; 67(1): 37-41.
30. Winkler UH, Sudik R. The effects of two monophasic oral contraceptives containing 30 mcg of ethinyl estradiol and either 2 mg of chlormadinone acetate or 0.15 mg of desogestrel on lipid, hormone and metabolic parameters. Contraception. 2009; 79(1): 15-23.
31. Dashni N, Kelley JL, Thayer RH, Onkot JA. Concurrent inductions of avian hepatic lipogenesis, plasma lipids, and plasma apolipoprotein B by estrogen. J Lipid Res. 1983; 24(1): 368-80.
32. Homma H, Kurachi H, Nishio Y, et al. Estrogen suppresses transcription of lipoprotein lipase gene: existence of a unique estrogen response element on the lipoprotein lipase promoter. J Biol Chem. 2000; 275(15): 11404-11.

33. Chen MJ, Yang WS, Chen HE, et al. Increased follistatin levels after oral contraceptive treatment in obese and non-obese women with polycystic ovary syndrome. Hum Reprod. 2010; 25(3): 779-85.

34. Machado RB, Fabrini P, Cruz AM, Maia E, Bastos AC. Clinical and metabolic aspects of the continuous use of a contraceptive association of ethinyl estradiol (30 µg) and gestodene (75 µg). Contraception. 2004; 70(1): 365-70.

35. Romualdi D, Cicco SD, Bussaca M, Gagliano D, Lanzone A, Guido M. Clinical efficacy and metabolic impact of two different dosages of ethinyl-estradiol in association with drospirenone in normal-weight women with polycystic ovary syndrome: a randomized study. J Endocrinol. 2013; 36(1): 636-41.

36. Whal P, Walden C, Knopp R, et al. Effect of estrogen/progestin potency on lipid/lipoprotein cholesterol. New Engl J Med. 1983; 308(15): 862-7.

37. Winkler UH, Rohm P, Hoschen K. An open-label, comparative study of the effects of a dose-reduced oral contraceptive containing 0.02 mg ethinylestradiol/2 mg chlormadinone acetate on hemostatic parameters and lipid and carbohydrate metabolism variables. Contraception. 2010; 81(1): 391-400.

38. Yildizhan R, Yildizhan B, Adali E, Yoruk P, Birol F, Suer N. Effects of two combined oral contraceptives containing ethinyl estradiol 30 µg combined with either gestodene or drospirenone on hemostatic parameters, lipid profiles and blood pressure. Arch Gynecol Obstet. 2009; 280(1): 255-61.

39. Döring A, Fröhlich M, Löwel H, Koenig W. Third generation oral contraceptive use and cardiovascular risk factors. Atherosclerosis. 2004; 172(1): 281-6.

40. Javidan NA, Haghollahi F, Ramezanazadeh F, et al. Effects of ethinyl estradiol plus desogestrel on premenstrual symptoms in Iranian women. Acta Med Iran. 2014; 52(11): 857-43.

41. Foulon T, Payen N, Laporte F, et al. Effects of two low-dose oral contraceptives containing ethinylestradiol and either desogestrel or levonorgestrel on serum lipids and lipoproteins with particular regard to LDL size. Contraception. 2001; 64(1): 11-6.

42. Mammen EE. Oral contraceptive pills and hormonal replacement therapy and thromboembolic disease. Hematol Oncol Clin North Am. 2000; 14(5): 1045-59.

43. Wiegartz I, Lee JH, Kutschera E, Winkler UH, Kuhl H. Effect of four oral contraceptives on hemostatic parameters. Contraception. 2004; 70(1): 97-106.

44. Piltonen T, Puurunen J, Hedberg P, et al. Oral, transdermal and vaginal combined contraceptives induce an increase in markers of chronic inflammation and impair insulin sensitivity in young healthy normal-weight women: a randomizes study. Hum Reprod. 2012; 27(10): 3046-56.

45. Pirkola J, Vaarasnaksi M, Ala-Korpela M, et al. Low-grade, systemic inflammation in adolescents: association with early-life factors, gender, and lifestyle. Am J Epidemiol. 2010; 171(1): 72-82.

46. Margetic S. Inflammation and haemostasis. Biochem Med. 2012; 22(1): 49-62.

47. Adeniji AA, Essah PA, Nesler JE, Cheang KI. Metabolic effects of a commonly used combined hormonal oral contraceptive in women with and without polycystic ovary syndrome. J Women’s Health. 2016; 1(1): 1-7.

48. Bhattacharya MS, Jha A. Comparative study of the therapeutic effects of oral contraceptive pills containing desogestrel, cyproterone acetate, and drospirenone in patients with polycystic ovary syndrome. Fertil Steril. 2012; 98(4): 1053-9.

49. Uras R, Etzi R, et al. Evidence that in healthy young women, a six-cycle treatment with oral contraceptive containing 30 mcg of ethinylestradiol plus 2 mg of chlormadinone acetate reduces fat mass. Contraception. 2009; 79(1): 117-21.

CORRESPONDING AUTHOR

Caroline Pereira Domingueti
Universidade Federal de São João del-Rei, campus Centro Oeste Dona Lindu; Rua Sebastião Gonçalves Coelho, 400; Chanadour; CEP: 35501-296; Divinópolis-MG, Brasil; Phone: +55 (37) 99957-2442; e-mail: caroldomingueti@ufsj.edu.br.

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