Pharmaceutica Analytica Acta
ISSN: 2153-2435

Stocco et al., Pharmaceut Anal Acta 2013, 4:1
DOI: 10.4172/2153-2435.1000208

Research Article Open Access

The Effect of Different Contraceptive Drugs on the Lipid Profile of Brazilian Women

Bianca Stocco[1]*, Helen F. Fumagalli[1], Silvio Antônio Franceschini[2], Cleni Mara Marzocchi Machado[1] and Maria Regina Torqueti Toloi[1]

[1]*Department of Clinical, Toxicological and Bromatological Analysis, Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo,14040-903, Ribeirão Preto, Brazil*
[2]*Department of Obstetrics and Gynecology, Faculty of Medicine of Ribeirão Preto, University of São Paulo, 14049-900, Ribeirão Preto, Brazil*

Abstract

Purpose: Evaluating the concentration of the lipoproteins HDL, LDL, VLDL, triglycerides and total cholesterol in the serum of women who use oral combined contraceptives containing anti-androgenic progestogen in comparison to control group.

Method: Cross-sectional study developed with 47 women (18 to 30 years), distributed into two groups of patients who used oral contraceptive drugs containing 20 or 30 µg de Ethinylestradiol (EE) combined to Drospirenone (DRSP), compared to a control group. The serum levels of lipids (Total cholesterol, Triglycerides and HDL) were quantified through Trinder's method. The levels of LDL and VLDL were obtained through mathematical formulas.

Results: In the users of DRSP/30EE there was an increase in the levels of total cholesterol, triglycerides, HDL and VLDL in relation to control group. In the users of DRSP/20EE, there was an increase in the levels of total cholesterol and HDL.

Conclusion: The anti-androgenic progestogen drospirenone was not effective to counterbalance the beneficial effect of the estrogen on the levels of the lipoprotein HDL.

Introduction

Under physiological conditions, endothelial cells are responsible for the maintenance of vascular integrity. Thus, these cells prevent the activation and aggregation of inflammatory cells and platelets, promote fibrinolysis and control vascular tonus. These anti-atherogenic properties of the endothelial cells are controlled by the enzyme nitric oxide synthase (eNOS), which is responsible for the synthesis and release of nitric oxide (NO). The release of this molecule inhibits the expression of inflammatory cytokines and adhesion molecules (ICAM and VCAM), prevents the activation of platelets and promotes vasodilation [1]. Nevertheless, the continuous exposure of the endothelium to risk factors such as smoking, hypertension, obesity, inflammation, insulin resistance and hyperlipidemia, may lead to endothelial dysfunction, which contributes to the formation of atherosclerotic plaque and cardiovascular diseases [2].

Many studies have observed a greater incidence of atherosclerosis and cardiovascular diseases in men in comparison to women of the same age. However, the same result is not observed for women in menopause, due to the cardio protective effect of estrogen [3,4]. *In vitro* studies have demonstrated that estrogen exerts favorable actions on the endothelium, for instance, stimulating the production of nitric oxide [5] and reducing the expression of adhesion molecules [6]. Moreover, estrogen is capable of promoting *in vivo* protective actions, such as the decrease of soluble adhesion molecules [7] and reduction of hepatic triglyceride lipase, which degrades HDL (High Density Lipoprotein), stimulating, thus, the production of HDL cholesterol and reducing the production of LDL (Low Density Lipoprotein) cholesterol [8]. Epidemiological studies developed in the last five decades demonstrated that the levels of HDL cholesterol are inversely related to the clinical events that predispose atherosclerosis and cardiovascular diseases, whereas the levels of LDL cholesterol are directly related to these events [9,10]. HDL protects against cardiovascular diseases through the regulation of the efflux of cholesterol from tissue and modulation of the inflammation. It may also remove cholesterol from macrophages, which are believed to be one of the mechanisms through which this molecule may protect against atherosclerosis [11]. Other properties include antioxidant and vasoprotective effects [12].

Estrogen, the cardio protective hormone, is also present in medications with contraceptive action, such as oral combined contraceptives, containing synthetic progesterone and estrogen in their formulation, which are responsible for the inhibition of the natural production of these hormones by the ovaries [13]. Despite of the protective effect developed by the estrogen, progesterone may exert adverse influence on the metabolism of the lipids [14].

Progesterone administered solely or combined with estrogen may reduce the plasma concentration of triglycerides and HDL cholesterol in women in pre and post menopause [15].

Androgenic progestogens, derived from testosterone, have greater interference in the beneficial alterations of estrogen over the lipid profile, since they promote a reversion in the increase of HDL due to an increase in the activity of hepatic lipases [16].

In this sense, the purpose of this study was to evaluate the effect of two formulations of contraceptive medications, containing different

***Corresponding author:** Bianca Stocco, Avenida do Cafe, S/N, Bloco M, Sala 52, Ribeirao Preto, Sao Paulo, ZIP 14040-903, Brazil, Tel: + 55-16-3602-4220/4208; Fax: + 55-16-3602-4725; E-mail: bianca.sto@hotmail.com

Received December 18, 2012; **Accepted** January 23, 2013; **Published** January 28, 2013

Citation: Stocco B, Fumagalli HF, Franceschini SA, Marzocchi Machado CM, Torqueti Toloi MR (2013) The Effect of Different Contraceptive Drugs on the Lipid Profile of Brazilian Women. Pharmaceut Anal Acta 4: 208. doi:10.4172/2153-2435.1000208

doses of estrogen and drospirenone progestogen, spironolactone-derived progesterone, with anti-androgenic and diuretic effects [17] on the lipid profile of Brazilian women.

Material and Methods

Clinical protocol

This study had the voluntary participation of 47 healthy women, who were students at the University of São Paulo, Campus of Ribeirão Preto, and users of the Gynecology and Obstetrics Department of the Basic Health Unit at the University Hospital of Ribeirão Preto School of Medicine (FMRP-USP). The volunteers were distributed into three groups, namely: a control group, consisting of women who do not use a hormonal contraceptive method; and two groups made of women who use contraceptives containing 3 mg of drospirenone (DRSP) combined with 30 or 20 mcg of ethinylestradiol (EE), as indicated by the following diagram (Figure 1).

Patients were selected according to the inclusion and exclusion criteria adopted. Inclusion criteria were: age between 18 and 30 years, body mass index (BMI) ≤ 30 Kg/m^2, user or non-user (control group) of contraceptive for a minimum period of six months and a maximum period of 24 months. Pregnant patients, smokers, patients under the prescription of anti-inflammatory medication or with personal history of cardiovascular disease, hypertension, thrombosis, hepatopathies, diabetes or autoimmune diseases were excluded from the study. The volunteers answered a questionnaire that aimed at obtaining information such as age, body mass index (BMI), frequency in the practice of physical exercise and family history of thromboembolic disease (Table 1). Blood samples were collected in the morning with a butterfly needle and, after collection, centrifuged to obtain serum, whose aliquots were placed in polyethylene tubes and stored at -70°C for the maximum period of six months. After this period, serum samples were thawed in bain-marie at 37°C for the development of laboratorial assays.

Laboratorial variables

The biochemical variables total cholesterol, HDL cholesterol and triglycerides were quantified in the serum of the patients with the assistance of the automated device BT 3000 plus Wiener Lab®, through the enzymatic reaction of Trinder's colorimetric method, using the Kit Wiener lab (Rosario-Argentina). Levels of LDL cholesterol were calculated through the formula of Friedewald: [LDL-cholesterol]=[total cholesterol]-[HDL cholesterol]- [triglycerides]/5. Levels of VLDL-cholesterol were calculated through the formula: [VLDL]=[triglycerides]/5 [18].

Statistical analyses

After verifying the normal distribution of the samples involved in this study, the population means of the quantitative variables age, BMI, total cholesterol, LDL, VLDL, HDL and triglycerides in the three groups of volunteers were compared through the analysis of variance (ANOVA). Bonferroni's posttest was used in order to compare the quantitative variables among the groups. The Chi test 2 was used to compare the mean of the qualitative variables frequency in the practice of physical exercise and family history of thrombosis among the three groups. In all analyses the program SPSS version 17 (PASW Statistics) was used, and the significance level adopted was of 5% (α= 0.05). The confidence interval of the mean was calculated with a significance level of 95%.

Results

The characteristics of all 47 women, who participated in this study and were divided into three groups, are presented in table 1.

Regarding the age of the participants, it is possible to identify that older patients are found in the control group, whereas younger patients are in group III. The age difference between these two groups was found significant (p=0.01). Group III has patients with lower BMI, frequency in the practice of physical exercise and personal or family history of thrombosis. Group II has patients with higher frequency in the practice of physical exercise and control group comprises patients with higher personal or family incidence of thrombosis.

The results obtained through the analyses of the biochemical variables are described in table 2.

In the results obtained with the analyses of the biochemical

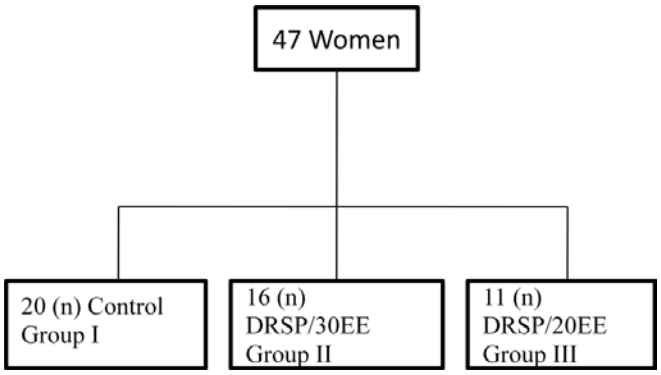

Figure 1: Study design. DRSP, Drospirenone; EE, ethinylestradiol; (n), number of participants.

Variable	Control (n=20)	Group II (n=16)	Group III (n=11)	p value
Age (years) Mean (SD)	26.3(2.4)	24.7(2.4)	23.2(3)	0.01
BMI (Kg/m^2) Mean (SD)	22.4(2.9)	22.9(2.7)	21.3(2.8)	<0.05
Exercise % (*n*)	37.5(6)	43.8(7)	18.8(3)	<0.05
Thrombosis % (*n*)	46.7(7)	33.3(5)	20(3)	<0.05

Values expressed as mean and standard deviation (SD)

Table 1: Characteristics of the women involved in the study.

Variable	Control (n=20)	Group II (n=16)	Group III (n=11)	p value
HDL Mean (SD) (CI)	48.8(9) (44.5-53)	62.8(6.5) (59.2-66.3)	64.2(2.7) (55.6-72.7)	0.0
LDL Mean (SD) (CI)	98.5(19) (89.5-107.4)	101.8(26) (87.7-115.8)	104.9(22) (89.8-120)	<0.05
VLDL Mean (SD) (CI)	15.08(11.8) (9.5-20.6)	25.7(8.5) (21.2-30.3)	22.7(9.4) (16.4-29.1)	0.01
Total Chol. Mean (SD) (CI)	162.4(24) (151.1-173.7)	190.3(31.1) (173.7-207)	192(23.4) (176.3-207.8)	0.01
Triglycerides Mean (SD) (CI)	75.4(79) (47.8-103)	128.8(48) (106-151.6)	114(47) (82.3-145.5)	0.01

Values expressed as mean, standard deviation (SD) and confidence interval of the mean of 95% (CI)

Table 2: Biochemical variables analyzed in this study.

variables, it is possible to identify that the control group has lower levels of HDL cholesterol in comparison to the groups that use DRSP/30EE and DRSP/20EE (p=0.0). For the variable LDL cholesterol, no significant differences were found in the levels of this lipoprotein among the studied groups. Regarding VLDL cholesterol, it is possible to observe that the group using DRSP/30EE presents higher levels of this lipoprotein in relation to control group (p=0.01). In the quantification of total cholesterol, control group presents lower levels in comparison to the other groups, made of contraceptive users (p=0.01). As for triglycerides, it is observed that control group has lower levels in relation to the group using DRSP/30EE (p=0.01).

Discussion

Hyperlipidemia is among the risk factors that may promote endothelial dysfunction, leading to the development of atherosclerosis and cardiovascular diseases. High concentrations of oxidized LDL may stimulate the production of pro-inflammatory molecules such as VCAM, ICAM and E-selectin, and, therefore, initiate damage to the endothelium [19]. Different from the action of the lipoprotein LDL, HDL protects against cardiovascular diseases through the regulation of the efflux of cholesterol from tissue and modulation of the inflammation [11]. The hormone estrogen, present in oral combined contraceptives, stimulates the production of HDL and reduces the production of LDL cholesterol [8], preventing damage to the endothelium. Despite of this beneficial action of the estrogen to the endothelium, the hormone progesterone, which is also present in oral combined contraceptives, may reduce the plasma concentration of HDL [15].

The literature points out those androgenic progestogens have a greater capability of counterbalancing the beneficial effects of the estrogen on the lipid profile [16]. This study evaluated the levels of lipoproteins, total cholesterol and triglycerides in the serum of women who use oral combined contraceptives containing the progestogen Drospirenone, which has anti-androgenic and diuretic effect [17]. In the study design, the group hypothesized that, due to its anti-androgenic character, the progestogen drospirenone is not effective to change the beneficial actions provided by the estrogen to the lipid profile (Figure 1).

In this study, higher levels of HDL were found in the serum of users of DRSP/20EE and DRSP/30EE, in comparison to control group. This finding agrees to the literature [20] and shows that despite of the presence of the progestogen, the levels of HDL for this group are higher than the levels of this lipoprotein in the control group. Different from this finding, a study developed with 48 women treated with contraceptive containing androgenic progestogen (LNG/20EE and LNG/30EE) observed decrease in the levels of the lipoprotein HDL in comparison to basal analyses [21]. Levels of VLDL, in this study, are higher for patients who use DRSP/30EE in comparison to control group. For users of DRSP/20EE, high levels of VLDL are also observed in relation to control group, but this difference was not considered to be significant. The higher levels of VLDL found in the groups using contraceptives may be also attributed to the hormone estrogen, which can increase the hepatic secretion of this lipoprotein [22]. Levels of triglycerides were also higher in women who use contraceptives when compared to the control group, since VLDL is triglyceride-rich lipoproteins [22]. Nevertheless, the increase in the production of VLDL and, consequently, triglycerides, contributes to increase the clearance of the VLDL particles, since these are rapidly converted into LDL [23]. After being converted into LDL, HDL will promote the efflux of the cholesterol from tissue to the liver, where LDL can be converted into bile acid and secreted through the bile [24]. The levels of total cholesterol were found significantly higher in groups using contraceptives in relation to the control group. Total cholesterol sums the lipoproteins HDL, LDL, and VLDL, and probably presents higher levels in contraceptive users due to the increase observed in the levels of VLDL and HDL.

In face of these findings, the authors conclude that the anti-androgenic progestogen drospirenone was not effective to counterbalance the beneficial effect of the estrogen on the levels of the lipoprotein HDL, which confirms their hypothesis in relation to contraceptives containing androgenic progestogen.

References

1. Loscalzo J (2001) Nitric oxide insufficiency, platelet activation, and arterial thrombosis. Circ Res 88: 756-762.
2. Borissoff JI, Spronk HM, Heeneman S, Tem Cate H (2009) Is thrombin a key player in the 'coagulation atherogenesis' maze? Cardiovasc Res 82: 392-403.
3. Horton TJ, Commerford SR, Pagliassotti MJ, Bessesen DH (2001) Postprandial leg uptake of triglyceride is greater in women than in men. Am J Physiol Endocrinol Metabol 283: 1192-1202.
4. Magkos F, Mittendorfer B (2009) Gender differences in lipid metabolism and the effect of obesity. Obstet Gynecol Clin North Am 36: 245-265, vii.
5. Chow RW, Handelsman DJ, Ng MK (2010) Minireview: rapid actions of sex steroids in the endothelium. Endocrinology 151: 2411-2422.
6. Andrade CM, Sa MF, Toloi MR (2012) Effects of phytoestrogens derived from soy bean on expression of adhesion molecules on HUVEC. Climateric 15: 186-194.
7. Stocco B, Fumagalli HF, Franceschini SA, Martinez EZ, Marzocchi-Machado CM, et al. (2012) Drospirenone and levonorgestrel in combination with either 30 or 20 mcg ethinylestradiol reduce soluble adhesion molecules in Brazilian women; cross-sectional study. Contraception 86: 506-510.
8. Knopp R H, Zhu X, Bonet B (1994) Effects of estrogens on lipoprotein metabolism and cardiovascular disease in women. Atherosclerosis 110: S83-91.
9. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR (1977) High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med 62: 707-714.
10. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al. (2009) Major lipids, apolipoproteins, and risk of vascular disease. JAMA 302: 1993–2000.
11. Yvan-Charvet L, Wang N, Tall AR (2010) Role of HDL, ABCA1, and ABCG1 transporters in cholesterol efflux and immune responses. Arterioscler Thromb Vasc Biol 30: 139-143.
12. Navab M, Reddy ST, Van Lenten BJ, Fogelman AM (2011) HDL and cardiovascular disease: atherogenic and atheroprotective mechanisms. Nat Rev Cardiol 8: 222-232.
13. Frye CA (2006) An overview of oral contraceptives: Mechanism of action and clinical use. Neurology 66: 29-36.
14. Burkman RT (1993) Lipid metabolism effects with desogestrel-containing oral contraceptives. Am J Obstet Gynecol 168: 1033-1340.
15. Duvillard L, Dautin G, Florentin E, Petit JM, Gambert P, et al. (2010) Changes in apolipoprotein B100-containing lipoprotein metabolism due to an estrogen plus progestin oral contraceptive: a stable isotope kinetic study. J Clin Endocrinol Metab 95: 2140-2146.
16. Crook D, Cust MP, Gangar KF, Worthington M, Hillard TC, et al. (1992) Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on serum lipids and lipoproteins. Am J Obstet Gynecol 166: 950-955.
17. Krattenmacher R (2000) Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception 62: 29-38.
18. Bachorik OS, Rifkind BM, Kwiterovich PO (1999) Lipids and dyslipoproteinemias. Clinical diagnosis and treatment methods laboratoriais (ed). São Paulo: Manole Cap 10: 208-236.
19. Colacurci N, Chiàntera A, Fornaro F, de Novellis V, Manzella D, et al. (2005)

Effects of soy isoflavones on endothelial function in healthy postmenopausal women. Menopause 12: 299-307.

20. Machado RB, de Melo NR, Maia H Jr, Cruz AM (2010) Effect of a continuous regimen of contraceptive combination of ethinylestradiol and drospirenone on lipid, carbohydrate and coagulation profiles. Contraception 81: 102-106.

21. Endrikat J, Klipping C, Cronin M, Gerlinger C, Ruebig A, et al. (2002) An open label, comparative study of the effects of a dose-reduced oral contraceptive containing 20 µg ethinyl estradiol and 100 µg levonorgestrel on hemostatic, lipids, and carbohydrate metabolism variables. Contraception 65: 215-221.

22. Soares GM, Vieira CS, de Paula Martins W, Dos Reis RM, et al. (2009) Metabolic and cardiovascular impact of oralcontraceptives in polycystic ovary syndrome. Int J Clin Pract 63: 160-169.

23. Campos H, Walsh BW, Judge H, Sacks FM (1997) Effect of estrogen on very low density lipoprotein and low density lipoprotein subclass metabolism in postmenopausal women. J Clin Endocrinol Metab 82: 3955-3963.

24. Steck TL, Lange Y (2010) Cell cholesterol homeostasis: mediation by active cholesterol. Trends Cell Biol 20: 680-687