

Comparison of Postprandial Lipemia between Women who are on **Oral Contraceptive Methods and Those who are not**

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Abstract

Background: Postprandial Lipemia (PPL) is a physiological process that reflects the ability of the body to metabolize lipids. Even though the influence of oral contraceptives (OC) on PPL is not known, it is a known fact that their use increases fasting lipid values.

Objective: To compare the PPL between women who are on OC and those who are not.

Methods: A prospective analytical study which assessed eutrophic women, aged between 18 and 28 years old, who were irregularly active and with fasting triglycerides ≤150 mg/dL. They were divided into two groups: oral contraceptive group (COG) and non-oral contraceptive group (NCOG). Volunteers were submitted to the PPL test, in which blood samples were collected in time 0 (12-hour fasting) and after the intake of lipids in times 180 and 240 minutes. In order to compare the triglyceride deltas, which reflect PPL, the two-tailed Mann-Whitney test was used for independent samples between fasting collections and 180 minutes ($\Delta 1$) and between fasting and 240 minutes ($\Delta 2$).

Results: Forty women were assessed and equally divided between groups. In the fasting lipid profile, it was observed that HDL did not present significant differences and that triglycerides in COG were twice as high in comparison to NCOG. Medians of $\Delta 1$ and $\Delta 2$ presented significant differences in both comparisons (p ≤ 0.05).

Conclusion: The results point out that women who are irregularly active and use OC present more PPL in relation to those who do not use OC, which suggests that in this population, its chronic use increases the risk of heart conditions. (Arq Bras Cardiol. 2014; 103(3):245-250)

Keywords: Contraceptives, Oral; Women; Metabolism; Insulin; Triglycerides; Cholesterol.

Introduction

Postprandial lipemia (PPL) is a physiological process defined as the increased plasma triglyceride and esterified lipoprotein concentration after the intake of fats1. It reflects the ability of the body to metabolize lipids, being also known as postprandial clearance. In healthy adults, its peak is reached in the third or fourth hour after the intake of fats, and its cycle is completed between the sixth and the eighth hour^{2,3}.

It began to be studied in the 1950s, however, it was first described in 1979, by Zilversmit, who reported the existence of a strong connection between PPL and the atherosclerotic process4. Currently, this relationship is well established, and the atherosclerotic disease is defined as a postprandial event^{5,6}.

usually being prolonged for men⁷, showing increasing

tendency with age8, in carbohydrate-rich diets9, among smokers¹⁰ and obese people¹¹. It is less common in physically active individuals¹² and more present among diabetic^{13,14} and dyslipidemic patients¹⁵.

Even though up until now the influence of oral contraceptives (OC) on PPL is not known, some studies16-21 show that its use causes triglycerides to increase, as well as total cholesterol and low density lipoprotein, even at low-doses¹⁷. Therefore, this study aimed at comparing PPL of women who use OC and those who do not use it.

The magnitude and the amplitude of PPL are multifactorial,

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Methods

A prospective analytical study which assessed eutrophic women aged from 18 to 28 years old, classified as being irregularly active by the long version of the International Physical Activity Questionnaire²², with fasting triglycerides \leq 150 mg/dL.

Diabetic women, those who are dyslipidemic on drug treatment, with renal disease, with diagnosed hypo/ hyperthyroidism, history of drunkenness or smoking, in a hypo/hypercaloric diet and on corticosteroids, diuretics or beta blockers were excluded. Sample calculation was conducted by considering alpha = 0.05 (bidirectional) and beta = 0.80, adopting a significant difference of 20% for

PPL between groups. Considering that the coefficient of variation of the triglyceride dose in the laboratory is 5%, and that a difference four times higher than the expected one invalidates this analytical coefficient of variation, 36 volunteers were necessary, that is, 18 volunteers in each group. Sample calculation was performed with GraphPad StatMate 2.0 for Windows.

The sample was composed in accordance with the pre-established criteria, being divided into two groups: oral contraceptive group (COG), formed by volunteers who had been on low-dose estradiol OC (15-30 mcg) for at least one year, and the non-oral contraceptive group (NCOG), composed by women who had not been on any type of hormone-based contraceptives for at least six months.

Data collection

The selected volunteers answered a standard questionnaire and were submitted to physical examinations, both aiming at collecting general information about the sample characteristics. The physical examination was comprised of measurements of heart rate and blood pressure at rest, as well as total body mass, height and waist circumference.

A pulse heart meter from Polar was used to measure heart rate. Blood pressure measurement was in accordance with the guidelines of the Brazilian Society of Hypertension²³, and the instrument used was a tensiometer for mid-sized adult, calibrated by the National Institute of Metrology, Standardization and Industrial Quality (Inmetro), and a duo-sonic stethoscope, both from BD.

Height was measured by a Sanny professional stadiometer, 0.1 cm accuracy. Participants were barefoot, with gluteus and shoulders leaning on a vertical support. Total body mass was measured by a digital Filizola scale, with maximum capacity of 150 kg, verified by Inmetro, certified to establish the margin of error of ± 100 g.

Waist circumference was obtained by a metallic and non-elastic measuring tape from Starrett, with measurement definition of 0.1 cm. The smallest curvature located between the last rib and the iliac crest was measured, without compressing the tissues²⁴.

Body mass index (BMI) was calculated with measurements of mass and height, according to Quetelet's equation: BMI = mass (kg)/height² (m). The adopted cutoff points were the ones recommended by the IV Brazilian Guideline for Dyslipidemia and Atherosclerosis prevention, by the Department of Atherosclerosis of Brazilian Society of Cardiology²⁵, that is, low weight (BMI <18.5), eutrophic (18.5 < BMI < 24.9), overweight (25 < BMI < 29.9) and obesity (BMI \geq 30).

Postprandial lipemia test

All volunteers were submitted to a PPL test. After the cannulation of the antecubital vein, blood samples were collected to measure triglycerides in time 0 (12-hour fasting) and after the intake of a substance containing 25 g of fat and of

a diet cereal bar, in times 180 and 240 minutes. Lipoprotein, glutamic pyruvic transaminase, glycemia and total cholesterol were measured only in the fasting period. All collections were performed by a trained professional in a laboratory adapted for this type of procedure.

The lipid compound was provided by Tecnovida and, from the 25 g of lipids, 15 g were monounsaturated, 8 g were poly-unsaturated and 2 g were saturated, which corresponds to 45% of the daily recommended intake of fats for a 2,000 kcal diet. The cereal bar had 0 g of carbohydrates, 1.2 g of proteins and 0.8 g of lipids. The bar was administered so that the intake of the lipid compound would be more palatable and so it would not cause gastric discomfort.

In the PPL test, volunteers were advised not to change their diet in the week of the test and not to practice any unusual physical effort, and also not to consume alcohol in the 24 hours prior to the test. The test was conducted between the fifth and the tenth day of the menstrual cycle, considering the lower hormone flows, and/or on the 28th day without medication (inactive phase), as recommended by Casazza et al²⁶.

The values of triglycerides, total cholesterol and highdensity lipoprotein were obtained by the enzymatic method. Values of low-density and very-low density lipoproteins were calculated by the Friedewald equation. Glutamic pyruvic transaminase was measured by the colorimetric method (Reitman-Frankel).

Ethical criteria

During the study, the guidelines concerning the research on human beings in the Declaration of Helsinki and in Resolution 196/96 of the National Health Council were observed. This study was submitted to and approved by the Research Ethics Committee of the Science and Technology School of Salvador (protocol 3390).

All of the participants received detailed information about the objectives of the study, as well as about the risks and benefits involved in the procedures. They signed the informed consent form.

Statistical analysis

In order to verify data distribution, the symmetry and the kurtosis tests were conducted, as well as Shapiro-Wilk. Deltas (Δ) that reflect PPL, that is, the variation of triglycerides between collection in the fasting period and at 180 min (Δ 1) and 240 min (Δ 2), did not present normal distribution, and were described as median and quartile interval. Therefore, in order to compare Δ 1 and Δ 2, the two-tailed Mann-Whitney test was used for independent samples.

The other variables and the peak points of PPL in 180 and 240 minutes presented normal distribution, being described as mean and standard-deviation. The two-tailed unpaired Student's t-test was applied to compare these variables.

All of the analyses were conducted with the statistical package BioEstat 5.0, with a 5% significance level.

Results

Forty-six women were assessed, out of whom six were excluded for presenting fasting triglycerides higher than 150 mg/dL; two of them were in NCOG and four were in COG, so there were forty women who were equally divided in both groups.

Table 1 presents the general data of the sample. It is possible to observe that groups were homogeneous, so there were no differences concerning age, BMI, waist circumference and glycemia. Out of the OC used by the volunteers, 100% had ethinyl estradiol; 50% had gestoden; 33.3%, levonorgestrel; 5.6%, chlormadinone acetate; 5.6%, drospirenone; and 5.6%, desogestrel.

Table 2 presents the comparison of the fasting lipid profile between groups. It is possible to observe that only HDL had no significant differences. Fasting triglycerides in COG were approximately twice as high as those in the NCOG.

The values of mean and standard-deviation of triglycerides in times 180 and 240 minutes, respectively for NCOG and COG, were $85 \pm 24.4 \times 156 \pm 41.1$ and $82 \pm 21.0 \times 147 \pm 36.5$, which can be observed in Graphic 1, with significant difference between points (p = 0.0001). As with fasting, the difference between mean values of triglycerides in collection points was approximately 100% higher in COG. It is also possible to observe, in Graphic 1, that the amplitude of PPL was similar in both groups. The peak occurred in the third hour, and the plateau remained until the fourth hour.

The median and the quartile interval of deltas 1 and 2 are described in Table 3, in which is possible to observe a significant difference ($p \le 0.05$) for both comparisons.

Discussion

Even though it is not possible to establish an independent causality relation between the use of OC and PPL, based on the results of this study, it was verified that PPL is more present among women who are on OC in comparison to those who are not. This information is reinforced by the homogeneity of the sample, whose factors that interfere directly on PPL were minimized at the time of group formation. The limitation of homogeneity focuses on the lack of control concerning dietary habits and the social

status of the studied women. The influence of regionalism is also discussed. Since all of the volunteers were from the same region, it was not possible to establish the influence of local culture on the found results, which would have been possible if women from other regions had been evaluated.

It is important to mention that millions of women in the world use OC^{27} , and new formulas have been developed in order to reduce its adverse effects, especially those related to lipid metabolism²⁸. In Brazil, the most prevalent contraceptive method until the age of 30 is the hormone pill²⁹. Even at low doses, the use of OC increases the values of total cholesterol, low-density lipoproteins and fasting triglycerides among healthy women at reproductive age¹⁶. The longer the time of use, the stronger its effect on lipid profile^{17,30}. Some studies report that three months are sufficient to cause changes in lipid metabolism^{21,28}.

The mean time of OC use among the volunteers in this study was higher in comparison to other investigations^{17,19-21}. This possibly had reflections on the fasting lipid profile, which was higher in comparison to previous studies¹⁹⁻²¹. The higher value of triglycerides can be one of the explanations for PPL to be more frequent in COG than in NCOG, once it is directly related to serum values of fasting triglycerides^{3,31}.

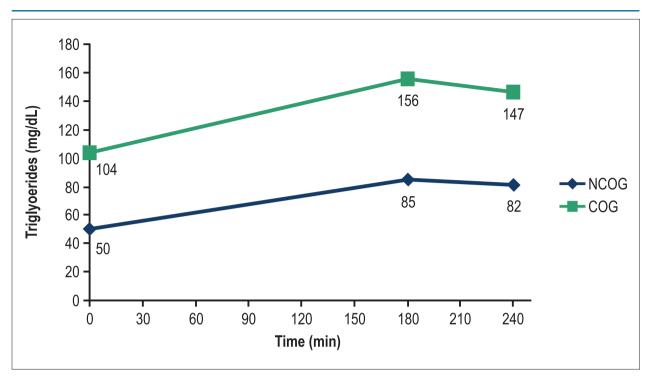
The conventional modifiable risk factors for the atherosclerostic disease include smoking, dyslipidemia, diabetes, systemic arterial hypertension, obesity and sedentary lifestyle²⁵. Even though PPL is not considered to be a conventional risk factor, studies show that less than half of the cardiovascular events are associated with conventional factors³². Since the 1990s, PPL has stood out as the best predictor of cardiovascular risk³³⁻³⁶, once it is correlated to several factors that triggering factors for cardiovascular diseases, even in normotriglyceridemic individuals^{3,25}.

The decreasing lipid clearance leads to the increasing exposure of endothelial cells to esterified lipoproteins, and such an exposure causes changes in vascular reactivity associated with the progression of atherosclerosis and cardiovascular events. In the postprandial state, the increasing elevation of triglycerides can cause not only endothelial dysfunction, but also the lower availability of nitric oxide and the increasing oxidative stress, and such changes are strongly involved in the genesis of atherosclerosis¹³.

Table 1 – General characteristics of the studied groups

Variable	NCOG (mean ± SD)	COG (mean ± SD)	p value*
Age (years)	23 ± 2.9	24 ± 2.9	0.5421
Body mass index (kg/m²)	21 ± 0.8	22 ± 0.9	0.2575
Waist circumference (cm)	71 ± 3.2	71 ± 2.7	0.9705
Systolic arterial pressure (mmHg)	103 ± 10.2	107 ± 10.7	0.7364
Diastolic arterial pressure (mmHg)	67 ± 10.2	70 ± 8.0	0.2466
Glycemia (mg/dL)	82 ± 5.9	84 ± 4.2	0.4622
Glutamic pyruvic transaminase (U/L)	14 ± 5.2	16 ± 4.4	0.1462
Time of oral contraceptive (years)	-	4.8 ± 2.2	-

SD: standard-deviation; COG: oral contraceptive group; NCOG: non-oral contraceptive group. * two-tailed unpaired Student's t-test.



Graph 1 - Postprandial lipemia in the contraceptive group and in the non-contraceptive group.

Table 2 - Comparison of fasting lipid profile (mg/dL) of the studied groups

Variable	COG (mean ± SD)	NCOG (mean ± SD)	p value*
Triglycerides	106 ± 22.7	53 ± 15.8	0.0001
Total cholesterol	208 ± 43.6	157 ± 37.7	0.0001
HDL	55 ± 9.9	50 ± 11.9	0.1872
LDL	131 ± 10.7	106 ± 33.6	0.0153
VLDL	21 ± 9.7	11 ± 5.1	0.0001

COG: oral contraceptive group; NCOG: non-oral contraceptive group; SD: standard-deviation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein. * two-tailed unpaired Student's t test.

Table 3 - Comparison of postprandial lipemia between NCOG and COG

Variable*	NCOG	COG	p value**
Delta 1 of TG	35 (21 – 45)	47 (40 – 55)	0.0152
Delta 2 of TG	28 (20 – 38)	45 (20 – 70)	0.0417

Delta 1: difference of serum triglycerides between time 0 and 180 min; delta 2: difference of serum triglycerides between time 0 and 240 min; COG: oral contraceptive group; NCOG: non-oral contraceptive group; TG: triglycerides. *Described in median and quartile interval. **Two-tailed Mann-Whitney test for independent samples.

In this study, even though the amplitude of PLL in both groups is similar (Graph 1), the highest value of PPL in COG (Table 3) suggests that, chronically, these women have a potentially more atherogenic postprandial lipid curve, and, consequently, they present with higher risks of developing

cardiovascular diseases. To strengthen this idea, it is observed that even though both groups present triglyceride values within normality levels, COG presented higher values of fasting lipid profile (Table 2) and peak PPL (Graph 1) in comparison to NCOG.

In this context, the meta-analysis conducted by Hokanson and Austin in 1996 showed that the magnitude of PPL in women is associated with an increase of 76% in the risk of developing a coronary disease, while among men this risk was of 32%³⁷. Some studies point out that approximately 40% of individuals with premature coronary artery disease present with normal fasting lipid profile, but with delayed clearance during PPL^{35,38}.

Also based on the results of this study, it is plausible to infer that women in COG are more prone to forming arterial and venous thrombi. OC and the increased PPL, independently, increase the activation of the blood-coagulation factor VII and inhibit the action of plasminogen, and these factors are proven to favor the formation of venous and arterial thrombi^{28,39}.

Facing the exposed, it is recommended to assess the risks and benefits related to the prescription of this contraceptive method, as well as to conduct a strict clinical follow-up, especially concerning cardiovascular risks in this population. In order for the results in this study to be elucidated, some prospective cohort studies that measure the clinical outcomes and other variables of inflammatory response should be conducted.

Conclusion

Results indicate that, among young, healthy and physically inactive women, PPL is more present for those who are on oral contraceptives than for those who are not, which suggests that, in this population, the chronic use of oral contraceptives, even at low dosages, increases the risk of developing cardiovascular diseases.

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Author contributions

Conception and design of the research: Petto J, Ladeia AMT; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Petto J, Vasques LMR, Pinheiro RL, Giesta BA, Santos ACN, Gomes Neto M, Ladeia AMT; Statistical analysis and Critical revision of the manuscript for intellectual content: Petto J, Gomes Neto M, Ladeia AMT.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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