Is lipid profile determination necessary in women wishing to use oral contraceptives?

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Abstract

Introduction: Although coronary heart disease in users of combined oral contraceptives (COCs) is rare, one of the principal risk factors for its occurrence is dyslipidemia.

Objective: To evaluate the prevalence of dyslipidemia in women wishing to use COCs, and its association with known clinical risk factors in order to evaluate the need to determine the lipid profile in this population.

Study Design: Cross-sectional study involving 516 women aged 18–40 years, 54% nulligravid, who wished to use COCs and presented no contraindications. Dyslipidemia was classified according to the National Cholesterol Educational Project Adult Treatment Panel III guidelines, which define levels of total cholesterol ≥200 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides >150 mg/dL, and low-density lipoprotein cholesterol ≥160 mg/dL as an abnormal lipid profile. The lipid profile was determined, and the association between clinical risk factors and the presence of dyslipidemia was evaluated by the chi-squared test and logistic regression. The receiver operating characteristic curve was constructed to compare body mass index (BMI) and smoking relevance for dyslipidemia.

Results: The prevalence of dyslipidemia was 33.9%. Smoking and BMI were significantly associated with the presence of dyslipidemia, with sensitivity of 31.3–54% and specificity of 41.9–67.7% for diagnosis of dyslipidemia, respectively.

Conclusion: The high prevalence of dyslipidemia could justify lipid profile evaluation before prescribing a COC. BMI and smoking represent modest predictive markers for the presence of dyslipidemia in candidates for the use of combined oral contraceptives.

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Keywords: Cardiovascular risk; Combined oral contraceptive; Dyslipidemia; Hypercholesterolemia; Lipid profile

1. Introduction

The first report of coronary artery thrombosis associated with the use of a combined oral contraceptive (COC) was published in 1963 [1]. Later studies established the use of oral contraceptives as a risk factor for venous as well as arterial thrombosis, which led to substantial modifications in the formulations in order to reduce the cardiovascular risk among users of this contraceptive modality [2–7]. Nevertheless, the COCs currently available are still associated with risk of venous and arterial thromboembolic events [8–12]. In a rigorous meta-analysis, Baillargeon et al [11] demonstrated a significant risk of myocardial infarction and cerebrovascular accident among users of low-dose COCs compared to non-users, irrespective of the type of progestogen used.

Although rare in users of contraceptive pills, the occurrence of myocardial infarction is also associated with known risk factors such as obesity, hypertension, smoking and dyslipidemias [11]. Tanis et al. [10] showed that hypercholesterolemia was the most important risk factor for myocardial infarction in women using COCs, followed by diabetes, smoking and arterial hypertension. Although international organizations suggest performing a laboratory assessment of lipid profile in all adults older than 20 years [13], the World Health Organization (WHO) medical eligibility criteria for contraceptive use do not recommend routine lipid profile testing prior to the initiation of contraceptive methods, including COCs [14]. In this
document, known hyperlipidaemias are recognized as a condition affecting eligibility for COC use. However, the WHO classifies known hyperlipidaemia as Category 2 (advantages of using the method generally outweigh the theoretical or proven risks) and 3 (theoretical or proven risks usually outweigh the advantages of using the method) for initiation and continuation of COC use, respectively. Adaptation of the WHO eligibility criteria in other countries, such as the United States, maintained the Categories 2 and 3 for COC use in presence of known hyperlipidaemias [15].

Although COCs could exert favorable effects on the lipid profile, such as reduction in low-density lipoprotein (LDL) and increase in high-density lipoprotein (HDL) levels, their frequent use is indicated in women who are at higher risk of dyslipidemia and consequent cardiovascular events, for example, women with polycystic ovary syndrome [16]. Despite the presence of other clinically identifiable risk factors, the prescription of COCs is not necessarily followed by lipid profile screening nor do candidates for contraceptive use report data regarding lipid levels [14,15].

The objective of the present study was to evaluate the prevalence of dyslipidemias in healthy women who wished to use COCs, and to correlate laboratory lipid alterations with clinically identifiable risk factors in an attempt to demonstrate the need or not for routine assessment of lipid profile before the use of COCs.

2. Material and methods

A cross-sectional study was conducted on 516 women who wished to use contraceptive methods. The women were seen at the Gynecological Specialties Outpatient Center, University Hospital of the Jundiai Medicine School. The study protocol was approved by the ethics committee of the Jundiai Medicine School. After they had received detailed information about the study, all patients voluntarily agreed to participate by signing the free informed consent form. Sexually active women aged 18–40 years, who had not used contraceptive methods in the last 6 months and who wished to start or restart a contraceptive method were included in the study. All women were potential candidates for any COC. Excluded were women with a contraindication for COCs, which is characterized by the presence of any clinical condition included in Category 3 or 4 of the WHO medical eligibility criteria for the use of COCs [14]. The woman’s medical history was recorded and a complete physical and gynecological exam was carried out. Clinical data such as age, body mass index (BMI), blood pressure and personal and family histories of cardiovascular diseases were obtained. Total cholesterol, HDL, LDL and triglycerides were measured for the assessment of lipid profile. Fasting blood glucose was also determined. Cholesterol, HDL and triglycerides were measured using a colorimetric method (reagents from Randox, UK, and Diasys, Germany). LDL was calculated according to the Lipid Research Clinics method. Fasting glucose levels were determined by the UV endpoint method (Randox, UK).

Dyslipidemia was classified according to the National Cholesterol Education Program (NCEP) III Guidelines, which define levels of total cholesterol ≥ 200 mg/dL, HDL < 40 mg/dL, triglycerides > 150 mg/dL, and LDL ≥ 160 mg/dL as an abnormal lipid profile [13].

The following clinically identifiable risk factors were analyzed: smoking, pre-hypertension, obesity, personal history of diabetes mellitus and family history of early coronary heart disease (< 55 years), and/or dyslipidemia. Pre-hypertension was defined as a blood pressure of 120–139/80–89 mmHg upon initial assessment [17]. Overweight/obesity was defined based on a minimum BMI of more than 27.3 kg/m² [18]. Diabetes was defined as fasting blood glucose ≥ 126 mg/dL [19].

Descriptive analysis and frequency distribution tables were used for all variables. Quantitative variables are reported as the mean and standard deviation. The association between risk factors and dyslipidemia was evaluated using the chi-squared test. Significant variables were first entered into a simple logistic regression model and then into a multiple logistic regression model. The receiver operating characteristic (ROC) curve was constructed to compare BMI and smoking to discriminate dyslipidemia. Cut-off point for BMI was determined to maximize sensitivity and specificity for a diagnosis of dyslipidemia. Area under the curve, positive predictive value (PPV) and negative predictive value (NPV) were also calculated. Significance level was defined at 5% and the software use throughout the analysis was the SAS statistical software package, version 9.1.

3. Results

Table 1 shows the clinical and laboratory characteristics of the 516 women studied. The mean age of the patients was 28 years and the mean BMI was 23.5 kg/m². Blood pressure and mean levels of total cholesterol, HDL, LDL and triglycerides were within the normal range. None of the women had diabetes. Among the clinically identifiable risk

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<tr>
<th>Table 1</th>
<th>Clinical and laboratory characteristics of the patients studied</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>28.00 ± 6.17</td>
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<tr>
<td>Body weight (kg)</td>
<td>60.39 ± 10.80</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.60 ± 0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.54 ± 4.11</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>116.42 ± 9.41</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74.35 ± 7.60</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>166.03 ± 34.33</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>51.02 ± 13.89</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>95.26 ± 31.47</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>93.87 ± 66.24</td>
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<tr>
<td>Blood glucose (mg/dL)</td>
<td>87.62 ± 11.33</td>
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SBP, systolic blood pressure; DBP, diastolic blood pressure.
factors for cardiovascular disease, 13.6% of the women presented a BMI \( \geq 27.3 \) kg/m\(^2\), 23.8% had pre-hypertension, 12.6% were smokers and 20.7% reported a family history of myocardial infarction before age 55 (Table 2).

Alterations in the lipid profile are shown in Table 3. The most frequent alteration was low HDL (16.3%), followed by hypercholesterolemia (13.8%), hypertriglyceridemia (11.8%), and elevated LDL (4.1%). The prevalence of dyslipidemias was 33.9% (Table 4).

A BMI \( \geq 27.3 \) kg/m\(^2\) and smoking were significantly associated with the presence of dyslipidemia, whereas blood pressure levels or a family history of coronary heart disease were not correlated with lipid alterations (Table 5). Simple logistic regression showed a significant association between BMI and dyslipidemia and between smoking and dyslipidemia (OR=2.729; 95% CI: 1.611–4.621 and OR=2.021; 95% CI: 1.182–3.455, respectively). A significant association between BMI, smoking and dyslipidemia was also demonstrated by multiple logistic regression (Table 6).

The association between BMI and dyslipidemia, calculated using the ROC curve, showed a cut-off value for BMI of 23.9 kg/m\(^2\), with sensitivity of 54% and specificity of 67.7% for diagnosis of dyslipidemia (Fig. 1). The association between smoking and dyslipidemia showed sensitivity of 31.3%, specificity of 41.9% (AUC=0.63, p=.0322), PPV and NPV of 35.7% and 37.1%, respectively.

### 4. Discussion

In the present series, only potential candidates for COC use were evaluated. In fact, the sample studied here corresponds to women who would receive prescription of COCs, irrespective of their lipid profile. In this respect, the risk factors for coronary heart disease identified in the initial assessment would not necessarily prevent the use of COCs. Overweight/obesity, defined in the present study as a BMI\( \geq 27.3 \) kg/m\(^2\), is not a contraindication to COC use, nor is smoking in women \(< 35\) years or a family history of early coronary heart disease. Since a blood pressure \( \geq 140/90 \) mmHg is classified by the WHO as Category 3 for COC use [14], we defined a blood pressure \( > 120/80 \) mmHg and \(< 140/
90 mmHg as pre-hypertension, with no contraindication to COC use. This would therefore represent in clinical practice the possibility to use a COC based on clinical criteria including medical history and physical examination without the need for complementary laboratory investigation. On this basis, we made an attempt to determine the occult prevalence of dyslipidemias in healthy women of fertile age and to demonstrate their association with some clinical marker that would indicate the need for laboratory investigation of lipid alterations. The latest edition of the WHO Medical Eligibility Criteria (2009) includes known dyslipidemias as Category 2 or 3 for the initiation or continuation of COC use, respectively [14]. According to these criteria, routine lipid profile testing is not cost effective because of the rarity of the condition and the high cost of the tests. In contrast, organizations such as the NCEP recommend the measurement of lipid levels in adults older than 20 years [13]. Since lipid alterations are not rare in the young population, the prevalence of dyslipidemia (33.9%) observed in the present study was not surprising. Goff et al [20] demonstrated an overall prevalence of dyslipidemias of 25.9% among women aged 45 to 84 years from different ethnic groups in the United States, with this rate reaching 38.7% after 75 years of age. Higher rates were observed among German women, ranging from 39.8 to 59.7% in women aged 18 to 40 years [21]. In Brazil, an estimated 40% of women develop dyslipidemias after 20 years of age and higher rates are observed after 50 years [22].

According to the eligibility criteria of the WHO, the use of COCs would not be contraindicated in the women diagnosed with dyslipidemia in the present study. However, the clinical parameters that were significantly associated with dyslipidemia, i.e., smoking and BMI, which alone are not a contraindication to COC use, indicate greater caution in the prescription of these drugs, classified now as Category 2 or 3 [14].

Despite the favorable effect of COCs on lipid metabolism and the low incidence of arterial events in users of different formulations, the association of contraceptive steroids with other risk factors may lead to changes in the cardiovascular risk profile. In fact, studies investigating arterial events in users of contraceptive pills have shown a definite relationship with clinically identifiable risk factors such as obesity, smoking and hypertension [10,11].

We believe that the evaluation of the prevalence of dyslipidemia among young healthy women and the demonstration of its association with clinically identifiable risk factor in a real-life scenario were strengths of this study. In addition, in clinical practice, the diagnosis of dyslipidemia permits early interventions to change lifestyle habits and to adapt the contraceptive method. On the other hand, the main limitations of the present study were its cross-sectional design, which may lead to memory bias when recalling family and personal histories, and the lack of follow-up and confirmation of the presence of dyslipidemia after lifestyle changes as recommended based on the lipid alterations seen in the initial assessment, particularly for young women [13].

Although a significant association between overweight/obesity or smoking and dyslipidemia was observed, these intermediate markers were not sufficiently able to discriminate the group of women most suitable for the lipid profile determination, based on analysis of sensitivity, specificity, positive predictive value and negative predictive value found. In fact, non-obese women and nonsmokers could also have dyslipidemia, and if these women were excluded from the assessment of lipid profile, this diagnosis of dyslipidemia would be underestimated. The impact of the administration of COCs in women with no previous diagnosis of dyslipidemia is debatable. There is an association between lipid abnormalities and increased risk of arterial disease among users of this therapeutic modality.

<table>
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<tr>
<th>Table 6</th>
<th>Multiple logistic regression between body mass index, smoking and dyslipidemia</th>
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<tr>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Body mass index ≥ 27.3</td>
<td>2.768</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.082</td>
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OR, odds ratio; 95% CI, 95% confidence interval.
In conclusion, the high prevalence of dyslipidemia could justify measurement of the lipid profile evaluation before prescribing a COC, regardless of the presence of clinically identifiable risk factors. Body mass index and smoking represent modest predictive markers for the presence of dyslipidemia in candidates for oral contraceptive use.

References