Oral Contraceptives Highlight the Genotype-Specific Association Between Serum Phospholipids and Activated Factor VII


Abstract—The present analysis was undertaken to study the effect of oral contraceptive (OC) use on activated factor VII (FVIIa) in subjects characterized by FVII genotypes, with the further aim of evaluating the role of lipids in this pharmacological interaction. In OC users (n = 42) and nonusers (n = 130) of comparable age, we examined the FVII phenotypic variables (FVII coagulant activity [FVIIc], FVII antigen, and FVIIa), FVII genotypes (the 353R/Q and 5’F7 polymorphisms analyzed in combination; alleles M1/M2 and A1/A2, respectively), and a number of lipid and lipoprotein parameters: serum concentrations of total cholesterol (chol), low density lipoprotein and high density lipoprotein-chol, triglycerides, phospholipids (PhLs), apolipoprotein A1, and lipoprotein(a). PhLs, triglycerides, apolipoprotein A1, chol, FVII antigen, FVIIc, and high density lipoprotein-chol levels were shown to be statistically higher in users than nonusers. FVII levels, particularly those of FVIIa and FVIIc, were much higher in homozygotes for the A1 and M1 alleles (A11 M11), especially in OC users. A strong association was found between PhL and FVIIa: in the multiple regression analysis, women taking OCs who had elevated PhL concentrations also had very high levels of FVIIa, but only if their genotype was A11 M11. These results indicate that the increased FVII levels in OC users depend on the FVII genotype and that high PhL concentrations predict very high levels of FVIIa and FVIIc. (Arterioscler Thromb Vasc Biol. 1999;19:2024-2028.)

Key Words: factor VII ■ activated factor VII ■ phospholipids ■ factor VII genotype

Since the introduction of oral contraceptives (OCs) in the 1960s, epidemiological studies have revealed an association between their use and an increase in the risk of cardiovascular disease (CVD).1–6 The most important cardiovascular complications noted were venous thromboembolism, myocardial infarction, and thrombotic stroke.6–11 with higher risk and susceptibility in female smokers in the 35+ age range.12 The increased CVD risk has been attributed to the estrogenic component:7,13 in fact, it was found to be reduced after the introduction of OCs containing a lower estrogen dose,13–18 but recently venous thromboembolism was found to be higher in women using contraceptives containing third-generation progestogens.19–22

The effect of OCs on hemostasis is an increase in the levels of some coagulation factors (factors II, VII [FVII], IX, X, XI, and VIII; von Willebrand factor; and fibrinogen), of protein C, and of protein complexes and fragments related to the activation of coagulation (thrombin-antithrombin complexes and D-dimer); these enhance fibrinolysis and decrease the levels of antithrombin III, protein S, and C4b-binding protein.23–31

Concerning FVII, a relationship between FVII levels, the dose of estrogen,23–28,31 and progestogen (norethisterone but not norgestrel32) was consistently found. It is difficult, though, to pinpoint whether these changes are due to the estrogen or the progestative compound, and it is still a matter of debate whether the excess CVD risk after the use of OCs is related to the resulting dyslipidemia, the hemostasis changes, or both. Recently, a meta-analysis33 pointed out the absence of an association between the duration of OC administration and CVD risk; the same analysis showed that the increased risk was limited to the period of OC administration.

Because FVII has attracted attention owing to its association with lipids (namely triglycerides [TGs] and cholesterol...
We thought it appropriate to analyze, in a group of women on OCs, the interaction between lipids on the one hand and FVII phenotype and genotype on the other. In fact, recent data published by our group indicate that there is a close relationship between FVII, particularly the activated form (FVIIa), and certain FVII genotypes,

\[ \text{[chol]} \]

and is considered a risk factor for CVD.\(^{45,47} \) Some writers have suggested a relationship between OC use and FVIIa.\(^{34} \) Furthermore, certain FVII genotypes,\(^{48,49} \) and that high phospholipid (PhL) concentrations predict high FVIIa levels.\(^{50} \)

### Methods

#### Study Population

Of the 501 volunteer subjects enrolled in the “Clotart” study in 5 European countries (France, Italy, the Netherlands, Norway, and Spain),\(^{19,21}\) 219 (47.7%) were females; of these, 42 were taking OCs. All participants declared themselves to be in good health and free from CVD, diabetes, and cancer. General enrollment criteria were as previously reported.\(^{49,50} \) Women on OCs were compared with a control group of 130 women not taking OCs of comparable age range: 21.3 to 50.8 years (median, 32.5) for the women on the OC pill and 19.1 to 50.5 years (median, 33.8) for the controls (in the tables and in the statistical analysis, data were adjusted for age). All the subjects gave their informed consent.

#### Blood Sampling

Blood for coagulation studies was taken in 5-mL Vacutainer tubes (Becton Dickinson Vacutainer Systems Europe) containing 0.129 mol/L buffered sodium citrate. For the lipid assays, tubes without anticoagulant were used; serum was prepared by incubation of blood for \( \geq 2 \) hours at \( 37^\circ \text{C} \). All samples were centrifuged at 2000g for 15 minutes. Sera and plasma were harvested and divided into aliquots in plastic tubes (Sorenson BiScience). Samples were frozen at \(-80^\circ \text{C} \) in cryotubes and boxes (CryoStore Systems, Nunc Inc) and subsequently sent on dry ice to the central repository at the coordinating institution (Thrombosis Center, University of Rome) for redistribution. For the genetic evaluation, pellets from the citrated blood samples were harvested in plastic tubes and frozen at \(-10^\circ \text{C} \).

#### Assay Procedures

FVII coagulation activity (FVIIc) and FVII antigen (FVIIAg) assays were carried out as previously reported.\(^{48–50} \) In detail, FVIIc was assayed by an automated 1-stage assay with a recombinant thromboplastin preparation with an international sensitivity index close to 1 (Innovin, Dade). FVII was assayed with a commercial kit (Staclot boplastin preparation with an international sensitivity index close to 1 (Innovin, Dade)). FVIIa was assayed by an automated 1-stage assay with a recombinant thrombin preparation (Staclot VIIa-rTF, Diagnostica Stago).\(^{51,48–50} \) Values were expressed in mU/mL, with 30 mU being equivalent to 1 ng of FVIIa. For FVIIa the standard was a locally prepared, pooled plasma (20 males and 20 females). Protein FVIIc was determined by an F7-dependent clotting assay (Enzymost F7 assay, Dade-Behring). FVII genetic markers were evaluated as previously reported.\(^{48–50} \) Comparisons were made between the most frequent FVII genotypes. The alleles of the polymorphism in the promoter region (5’F7) were denominated A2 (single decamer insertion) and A1 (absence of the decamer), and the alleles of the 353 RQ polymorphism, characterized by a mutation in the second position of the 353 codon, were denominated M1 (codon for arginine) and M2 (codon for glutamine). Tight linkage disequilibrium between the A1 and M1 as well as between the A2 and M2 alleles was found (\( \Delta \) values ranging from 0.85 to 0.93), regardless of the population studied.\(^{48} \)

Total cholesterol was determined using a commercial kit (Cholesterol, Du Pont) based on the production of stoichiometric amounts of \( \text{H}_2\text{O} \) generated by cholesterol esterase and cholesterol oxidase.\(^{52} \) HDL-cholesterol was determined by using the same procedure after precipitation of the other cholesterol-containing lipoprotein fractions by a phosphotungstate solution buffered to pH 5.73 (HDL-CHOL Du Pont). LDL-cholesterol was evaluated by the indirect procedure as proposed by Friedewald et al.\(^{54} \) TGs were assayed by a kinetic NAD-coupled procedure (Triglycerides, Du Pont). Choline-containing PhLs were evaluated by a choline oxidase determination of the amount of choline liberated by phospholipase D\(^{56} \) (Phospholipids, SGM Italia).

ApoA1 was determined by a turbidimetric endpoint measurement using 10 mmol/L PEG and a specific polyclonal antibody\(^{57} \) (Apo A1, Du Pont). Lp(a) was determined by an enzyme immunoassay using a monoclonal anti–kringle IV antibody and a polyclonal anti-Lp(a) antibody conjugated with horseradish peroxidase\(^{58} \) (Macro Lp(a), Strategic Diagnostic). Each participating laboratory carried out 1 or more analyses on the entire study population.

### Statistical Analysis

The procedures used were from the BMDP software package. The distribution of variables was assessed for deviation from normality, and the appropriate normalizing (logarithmic) transformation was used to analyze the data by parametric methods. Tables were computed on the untransformed data. Parametric ANOVAs (1-way, 2-way) and ANCOVAs (with age as a covariate) were used, including the main effects and interactions in the models. Pearson’s linear correlation coefficients were used to detect any association between variables. A fixed multiple linear regression model was fitted to the data to estimate the effect (after adjustment for the effects of age, sex, and country) of high concentrations in each independent lipid variable on the dependent one (FVII parameters). Problems due to collinearity were checked and ruled out during the analysis. The appropriate Student’s \( t \) tests were performed to assess the significance of correlation and regression coefficients and of differences in coefficients between subgroups.

### Results

#### General Description of the Subject Sample in the “Users” and “Nonusers” Subgroups

In Table 1, the levels of the variables and the statistical evaluation concerning the data for OC users and nonusers are set out. The following variables were significantly different between users and nonusers: PhLs, TGs, ApoA1, chol, FVIIAg, FVIIc, and HDL-cholesterol.

#### Influence of FVII Genotypes on FVII Levels in Users and Nonusers

A highly significant difference in FVII levels was noted between the genotypes studied and between OC users and nonusers (Table 2): women with the A11 M11 genotype had significantly higher values than did those with other genotypes, more so for FVIIa and FVIIc than for FVIIAg. OC users had significantly higher levels of FVII than nonusers. This trend was more apparent with regard to FVIIc and FVIIAg than to FVIIa. F1 + 2 levels were significantly higher in the subjects with the A11 M11 genotype who were on OCs in comparison with those not taking OCs (1.21 versus 1.10 mmol/L, \( F=7.4, P=0.008 \)).

#### Multiple Regression Analysis of the Effect of High Lipid Concentrations on FVII Levels

High PhL concentrations were associated with very high and significant FVIIa and FVIIc levels in OC users (Table 3). The difference between users and nonusers was more significant for FVIIa and FVIIc than for FVIIAg. OC users had significantly higher levels of FVII than nonusers. High concentrations of TGs and chol, on the other hand, were found to be consistently associated with insignificant changes of FVII in both users and nonusers.

#### Multiple Regression Analysis Regarding the Influence of FVII Genotypes on the Interaction Between FVII and PhL

In the A11 M11 genotype, high PhL levels were associated with markedly elevated FVIIa levels in OC users (Table 4). The differences between users and nonusers were highly
significant. Comparisons with the other genotypes could not be performed because of the small number of subjects in this category.

Discussion
This cross-sectional study was carried out using samples taken from healthy subjects enrolled through the use of a questionnaire focusing on the presence of risk factors for CVD. It is worth mentioning that this investigation did not take into account the details of OC use, such as the brand of OC and the duration of OC intake. If this approach is seen as a bias for comparative evaluations concerning the effects of OC and the duration of OC intake. If this approach is seen as a bias for comparative evaluations concerning the effects of OCs,14,25–31 as does that of chol, TGs, HDL-chol, and apoA1 levels.32,59–62

Most of the studies14,28,61–63 and a recent review31 have described an increase in FVIIc and FVIIAg levels that was roughly related to the estrogen dose. In a recent report,30 FVIIa was also assayed, and it was found to be increased. In fact, the increase noted in FVII levels represents a well-documented effect of OCs,14,25–31 as does that of chol, TGs, HDL-chol, and apoA1 levels.32,59–62

The levels of FVII and the concentrations of lipids in this study are consistent with those described in other reports of women on low-dose or sequential OC pills. In fact, the study are consistent with those described in other reports of subjects observed in outpatient or inpatient clinics. Between Genotype Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit of Measure</th>
<th>OC Use</th>
<th>Yes</th>
<th>No</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIIc</td>
<td>%PNP</td>
<td></td>
<td>134.95 (37.56)</td>
<td>118.28 (27.37)</td>
<td>7.50</td>
<td>0.0068</td>
</tr>
<tr>
<td>FVIIAg</td>
<td>%PNP</td>
<td></td>
<td>111.07 (16.27)</td>
<td>102.21 (18.29)</td>
<td>7.95</td>
<td>0.0054</td>
</tr>
<tr>
<td>FVIIa</td>
<td>mU/ml</td>
<td></td>
<td>84.72 (41.0)</td>
<td>68.94 (26.05)</td>
<td>3.09</td>
<td>NS</td>
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<tr>
<td>Chol</td>
<td>mmol/L</td>
<td></td>
<td>5.53 (1.02)</td>
<td>5.03 (0.84)</td>
<td>8.41</td>
<td>0.0043</td>
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<tr>
<td>HDL-chol</td>
<td>mmol/L</td>
<td></td>
<td>1.63 (0.37)</td>
<td>1.47 (0.39)</td>
<td>4.72</td>
<td>0.0314</td>
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<tr>
<td>LDL-chol</td>
<td>mmol/L</td>
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<td>3.44 (1.04)</td>
<td>3.21 (0.76)</td>
<td>1.67</td>
<td>NS</td>
</tr>
<tr>
<td>TGS</td>
<td>mmol/L</td>
<td></td>
<td>0.99 (0.36)</td>
<td>0.73 (0.42)</td>
<td>19.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PhLs</td>
<td>mmol/L</td>
<td></td>
<td>3.25 (0.44)</td>
<td>2.84 (0.39)</td>
<td>27.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ApoA1</td>
<td>μmol/L</td>
<td></td>
<td>56.18 (11.11)</td>
<td>48.54 (9.18)</td>
<td>16.99</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>μmol/L</td>
<td></td>
<td>0.66 (0.70)</td>
<td>0.61 (0.55)</td>
<td>0.04</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean and (SD).

Between Genotype Groups

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>OC Use</th>
<th>n</th>
<th>FVIIc (%)</th>
<th>FVIIAg (%)</th>
<th>FVIIa (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A11 M11</td>
<td>Yes</td>
<td>30</td>
<td>145.9 (36.0)</td>
<td>113.8 (15.5)</td>
<td>96.9 (40.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>98</td>
<td>124.5 (24.7)</td>
<td>105.0 (18.0)</td>
<td>73.3 (25.1)</td>
</tr>
<tr>
<td>A12 M12+</td>
<td>Yes</td>
<td>8</td>
<td>111.5 (27.2)</td>
<td>106.9 (19.0)</td>
<td>57.4 (28.3)</td>
</tr>
<tr>
<td>A22 M22</td>
<td>No</td>
<td>26</td>
<td>97.4 (25.7)</td>
<td>93.4 (16.5)</td>
<td>50.9 (19.2)</td>
</tr>
</tbody>
</table>

Comparisons

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OC</th>
<th>F</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIIc</td>
<td>F=27.78, P&lt;0.0001</td>
<td>F=8.23, P=0.0047</td>
<td></td>
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<tr>
<td>FVIIAg</td>
<td>F=5.80, P=0.0172</td>
<td>F=7.91, P=0.0055</td>
<td></td>
</tr>
<tr>
<td>FVIIa</td>
<td>F=31.91, P&lt;0.0001</td>
<td>F=1.74, P=NS</td>
<td></td>
</tr>
</tbody>
</table>

Slope was significantly different from 0 at *P<0.01; †P<0.05. Comparisons were made between OC users and nonusers. The values of the standardized regression coefficient are shown, together with the effect produced on FVII parameters by a hypothetical 50% increase of the lipid variables.

Summary of the study:
In a recent report by our group, it was observed that high PhL concentrations were associated with high FVIIa levels. To test the strength of this association in the context of OC use, we noted, however, great variation in the FVIIa levels, which could explain the lack of statistical difference between users and nonusers. This prompted us to evaluate the impact of FVII genotypes, the importance of which has been demonstrated in determining the genetic analysis demonstrated that FVIIc and FVIIa levels were much higher in the A11 M11 genotype than in the others. The use of OCs displayed only an interaction between OC use and genotype was ruled out parameters by a hypothetical 50% increase of the lipid variables.

Table 2: FVII Levels in OC Users and Nonusers: Comparisons Between Genotype Groups

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>OC Use</th>
<th>n</th>
<th>FVIIc (%)</th>
<th>FVIIAg (%)</th>
<th>FVIIa (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A11 M11</td>
<td>Yes</td>
<td>30</td>
<td>145.9 (36.0)</td>
<td>113.8 (15.5)</td>
<td>96.9 (40.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>98</td>
<td>124.5 (24.7)</td>
<td>105.0 (18.0)</td>
<td>73.3 (25.1)</td>
</tr>
<tr>
<td>A12 M12+</td>
<td>Yes</td>
<td>8</td>
<td>111.5 (27.2)</td>
<td>106.9 (19.0)</td>
<td>57.4 (28.3)</td>
</tr>
<tr>
<td>A22 M22</td>
<td>No</td>
<td>26</td>
<td>97.4 (25.7)</td>
<td>93.4 (16.5)</td>
<td>50.9 (19.2)</td>
</tr>
</tbody>
</table>

Comparisons

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OC</th>
<th>F</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIIc</td>
<td>F=27.78, P&lt;0.0001</td>
<td>F=8.23, P=0.0047</td>
<td></td>
</tr>
<tr>
<td>FVIIAg</td>
<td>F=5.80, P=0.0172</td>
<td>F=7.91, P=0.0055</td>
<td></td>
</tr>
<tr>
<td>FVIIa</td>
<td>F=31.91, P&lt;0.0001</td>
<td>F=1.74, P=NS</td>
<td></td>
</tr>
</tbody>
</table>

Slope was significantly different from 0 at *P<0.01; †P<0.05. Comparisons were made between OC users and nonusers. The values of the standardized regression coefficient are shown, together with the effect produced on FVII parameters by a hypothetical 50% increase of the lipid variables.

Table 3: Multiple Regression Analysis Concerning the Effect of PhLs, TGs, and Concentrations on FVII Levels as the Dependent Variable (Age, Sex, and Center Included in the Regression Model)

<table>
<thead>
<tr>
<th>PhL (+50%)</th>
<th>OC</th>
<th>FVIIa</th>
<th>FVIIc</th>
<th>FVIIAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>+0.62*</td>
<td>+0.73†</td>
<td>+0.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+211.5%†</td>
<td>+66.6%*</td>
<td>+33.0%</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>+0.32†</td>
<td>+0.32†</td>
<td>+0.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+46.8%*</td>
<td>+26.2%*</td>
<td>+9.9%</td>
<td></td>
</tr>
</tbody>
</table>

Slope was significantly different from 0 at *P<0.01; †P<0.05. Comparisons were made between OC users and nonusers. The values of the standardized regression coefficient are shown, together with the effect produced on FVII parameters by a hypothetical 50% increase of the lipid variables.

Discussion
This cross-sectional study was carried out using samples taken from healthy subjects enrolled through the use of a questionnaire focusing on the presence of risk factors for CVD. It is worth mentioning that this investigation did not take into account the details of OC use, such as the brand of OC and the duration of OC intake. If this approach is seen as a bias for comparative evaluations concerning the effects of different generations and brands of OC, it is, in our opinion, useful in providing a general outline of the average impact of OCs on subjects observed in outpatient or inpatient clinics.

The levels of FVII and the concentrations of lipids in this study are consistent with those described in other reports of women on low-dose or sequential OC pills. In fact, the increase noted in FVII levels represents a well-documented effect of OCs,14,25–31 as does that of chol, TGs, HDL-chol, and apoA1 levels.32,59–62

Most of the studies14,28,61–63 and a recent review31 have described an increase in FVIIc and FVIIAg levels that was roughly related to the estrogen dose. In a recent report,30 FVIIa was also assayed, and it was found to be increased. In the present study, while analyzing the total population (Table 1), we were unable to find a statistically significant difference between users and nonusers. We noted, however, great variation in the FVIIa levels, which could explain the lack of statistical difference between users and nonusers. This prompted us to evaluate the impact of FVII genotypes, the importance of which has been demonstrated in determining the genetic analysis demonstrated that FVIIc and FVIIa levels were much higher in the A11 M11 genotype than in the others. The use of OCs displayed only an additional effect on FVII levels, and the presence of an interaction between OC use and genotype was ruled out (Table 2).

In a recent report by our group, it was observed that high PhL concentrations were associated with high FVIIa levels. To test the strength of this association in the context of OC use, we noted, however, great variation in the FVIIa levels, which could explain the lack of statistical difference between users and nonusers. This prompted us to evaluate the impact of FVII genotypes, the importance of which has been demonstrated in determining the genetic analysis demonstrated that FVIIc and FVIIa levels were much higher in the A11 M11 genotype than in the others. The use of OCs displayed only an additional effect on FVII levels, and the presence of an interaction between OC use and genotype was ruled out (Table 2).
increase the risk in women on OCs and eventually precipitate the thrombotic event. In fact, recent studies indicate that there is no evidence that FVII activity, per se, can be considered a risk factor for thrombotic events in women.83,84

Acknowledgments
This work was carried out within the framework of the European Union Concerted Action BMH1-CT94-1202 “The Role of the FVII-Tissue Factor Pathway in Ischemic Heart Disease (Clotar).” The authors wish to thank Michael Briggs for his work in amending the text.

References

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<tr>
<th>Genotypes</th>
<th>OC</th>
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<th>FVIIc</th>
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<tbody>
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<td>Yes</td>
<td>28</td>
<td></td>
<td>0.86*</td>
<td>0.89*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>+221.2%†</td>
<td>+97.8%†</td>
<td>+31.0%</td>
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<tr>
<td><strong>A11 M11</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>92</td>
<td></td>
<td>0.32†</td>
<td>0.43*</td>
<td>0.22</td>
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<tr>
<td></td>
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<td></td>
<td>+36.1*</td>
<td>+29.1%†</td>
<td>+12.1%</td>
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<tr>
<td><strong>A12 M12+</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A22 M22</td>
<td>24</td>
<td></td>
<td>0.71</td>
<td>0.08</td>
<td>0.10</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>+11.4%</td>
<td>+6.4%</td>
<td>+5.4%</td>
</tr>
</tbody>
</table>

NE indicates not evaluated. FVII was the dependent variable; age, sex, and center were included in the regression model. Comparisons were made between OC users and nonusers. The values of the standardized regression coefficient are shown, together with the effect produced by a hypothetical 50% increase of the PhL concentration.

Slope was significantly different from 0 at *P<0.01, †P<0.05.

Differences between values in OC users and nonusers: a, t=4.23, P<0.001; b, t=3.75, P<0.001; c, t=1.89, P=NS.


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