Effect of a Combined Oral Contraceptive Containing 30 mg Ethinylestradiol and 75 mg Gestodene on Haemostatic Mechanisms in a Group of Albanian Women

Eliana Ibrahimi, Mynyr Koni, and Jurida Ademi

Abstract—The aim of the study was to determine the effect of combined oral contraceptive (COC) on the coagulation system in healthy Albanian women. The study included 28 women between ages 23 and 47. The subjects had no history of thromboembolic disease. Laboratory assessments were performed before and after 2 months of treatment with ethinylestradiol 30 µg and gestodene 75 µg. Plasma levels of PT, APTT, factor V, factor VIII, fibrinogen, Protein C, D-dimer and AT III were evaluated. Comparison of the values of these parameters before and after treatment, showed that concentrations of fibrinogen, Protein C, Factor VIII and D-dimer were significantly higher after 2 month of treatment compared to the baseline. The level of AT III was significantly lower after treatment. There was no significant difference in the level of factor V, PT and APTT. Changes in haemostatic system during COC use might increase the risk for thrombotic situations.

Keywords—Combined oral contraceptives, hemostasis parameters, prothrombotic risk.

I. INTRODUCTION

It is well known that the use of combined oral contraceptives (COCs) is associated with an increased risk of venous thromboembolic events (VTEs), including deep vein thrombosis (DVT) and pulmonary embolism (PE), and may be associated with an increased risk of the arterial thromboembolic events, including acute myocardial infarction (AMI) and ischemic stroke (IS), which are principally a consequence of the estrogen component of the COCs [1]-[2]-[3]. When the estrogen dose of the first contraceptive formulations was decreased from 75–100 µg of mestranol to 50 µg of ethinyl estradiol (EE), this resulted in a 25% decrease in deep VTE events. [2]-[4]-[5]. Studies performed at the beginning of the 1990s showed that users of low-dose COCs had a lower risk of developing VTE because they presented an adequate hemostatic balance, i.e., an increase in fibrinolytic activity as well as an increase in prothrombotic activity [6]-[7]-[8]. Jung-Hoffmann and Kuhl [9] succeeded in explaining the higher thrombogenic risk in users of COCs containing desogestrel or gestodene, compared with users of COCs containing levonorgestrel, by demonstrating that GSD could inhibit cytochrome P-450 at the hepatic microsome and reduce the metabolism of EE that provoked increased estrogen serum concentrations.

The increased risk of VTE associated with an oral contraceptive containing DSG or GSD is still controversial, particularly since no plausible biological explanation for the result can be found. An important step in the understanding of the biological mechanisms of the VT development was made in the 1990s when a large number of hereditary risk factors were discovered. Presently, a few strong and many weak genetic risk factors are known. Deficiencies of the natural coagulation inhibitors, antithrombin, protein C and protein S are considered to be strong risk factors [25], and cause 5- to 10-fold increase of the VT risk [26]. Factor V Leiden, prothrombin 20210A, non-O blood group and fibrinogen 10034 T increase the risk 2 to 5 times and are regarded as moderately strong risk factors [27]-[28]-[29]-30]. There are also many weak genetic risk factors identified, with relative risks between 1 and 1.5 [25].

Many studies have evaluated the influence of the progestin and estrogenic components of COCs on several coagulation and fibrinolytic parameters [10]-[11]. Therefore, the aim of the this study was to evaluate the effect of COCs containing 30 µg EE and 75 µg GSD on the hemostatic parameters: procoagulation factors [activated partial thromboplastin time (APTT), prothrombin time (PT), factor V, factor VIII and fibrinogen], coagulation inhibitors (antithrombin III and protein C) and fibrinolytic system activation (D-dimer).

II. MATERIAL AND METHODS

A. Study design

The study was conducted at “Ana Diagnostic Center” gynecologic clinic in Tirana, Albania. All participants signed an informed consent form. Twenty-eight healthy women requesting contraception were included and followed up for 2 months. Smokers and women with contraindication to COCs were excluded from the study.

All participants were instructed to use COC with 30 µg EE and 75 µg GSD, initiating pill intake on the first day of the cycle. Clinical and laboratory assessments were carried out prior to initiation of medication (pretreatment) and after 2 months of COC use. All participants were submitted to a
blood collection to perform the following laboratory tests: APTT, PT, fibrinogen, factor V, factor VIII, AT III, protein C and D-dimer.

B. Laboratory methods

Blood samples were centrifuged at 1500 rev/min for 15 min to extract plasma. APTT, PT, fibrinogen, factor V, factor VIII were measured using coagulometry (BF II Siemens analyzer and Siemens kits). AT III was measured by nephelometry (BN prospec analyzers, Siemens). Protein C and D-dimer were evaluated using Vidas kits (Biomerieux).

C. Statistical analyses

The student test for paired samples was used for numerical variables to compare values of the coagulation factors at two time intervals (pretreatment and after 2 months of COC use). Significance was established at p < 0.05. SPSS 20 was the statistical package used for all the analysis.

III. RESULTS

Comparison of the values of these parameters before and after treatment with COC, showed the following results: Concentrations of fibrinogen, Protein C, Factor VIII and D-dimer were significantly higher after 2 month of treatment compared to the baseline. The level of AT III was significantly lower after treatment. There was no significant difference in the level of factor V, PT and APTT (Table I).

IV. DISCUSSIONS

Several studies have reported changes in hemostatic balance in COC users [19]-[20]-[21]-[22]. It is well documented that the risk of VTE associated with combined OC use is an estrogen dose-related association with fewer circulatory adverse events in women using a 20 µg EE pill than in women using higher dosed OCs [39]-[48]. Further, the estrogen dose has been related to the extent of changes in the hemostatic system; OCs containing 50 µg EE have been shown to have more impact on the various hemostatic variables than OCs containing 30 µg EE [41]-[45]-[46]-[47]-[48], while the 20 µg EE dose OC in combination with GSD has been found to show a less pronounced effect on hemostatic variables than pills containing 30 µg EE [41]-[42]-[43]-[44]-[45]. However, a critical analysis of these trials showed methodological limitations such as heterogeneity of the populations studied, the laboratory examinations used in the evaluation, the type of COC evaluated, and frequent association with other risk factors such as smoking [21]-[22]-[23].

The estrogen components of COCs are the main ones responsible for the thromboembolic phenomena found in users of this kind of hormonal contraceptive, although, recently, progestins have also been implicated. Actually, both GSD and DSG can act synergically with EE to precipitate changes in hemostasis and coagulation [24], thereby justifying the interest in studying hemostatic variables in users of COCs containing associations of 30 µg EE with these progestins. Studies on COCs containing DSG have shown an adequate hemostatic balance, i.e. any increases in procoagulation parameters are counteracted by high fibrinolytic activity [7]-[14]-[25]-[26]. Studies on COCs containing GSD plus 30 µg EE are few and their results are not in agreement with those obtained in this study, i.e. our results also showed no significant reduction in APTT and PT during treatment, suggesting no tendency towards coagulation activation. In agreement with previous studies fibrinogen values increased during the study period. [8]-[12]-[14]-[15].

Fibrinogen increased values, and changes of two important natural anticoagulants, ATIII and protein C, reduce hemostatic stability. The similar behavior of D-dimer, whose stability characterizes fibrinolytic system action in lysis of fibrin clots, reinforces the risk for VTE. In a global analysis of the results of this study, it was observed that all parameters evaluated have changed. Significant changes were observed in procoagulation factor (fibrinogen), the principal natural anticoagulants (ATIII and protein C) or in fibrinolytic activity (D-dimer). Our findings were obtained from young, healthy, non-smoking women who had no family history of VTE, thereby characterizing a high-risk for VTE. Moreover, a COC containing a low dose of EE was used [7]-[23]-[37]. It is interesting to note that the hemostatic effects of DSG are similar to those found with GSD in some studies [36] and significantly more evident than results found with GSD in other studies [35]. The present study allowed us to demonstrate that GSD showed synergism with EE on hemostasis and coagulation variables that could increase thrombogenic risk, in agreement to the findings of Shoupe [37] in which GSD increased factors VII and X and decreased AT III, acting as an element of synergic action to EE in stimulating procoagulation phenomena. However, it is important to note that the changes observed in coagulation and fibrinolysis parameters during the use of COCs by healthy women cannot explain the increased risk of thromboembolic disease; hence caution should be exercised in considering results from this kind of clinical trial. In conclusion, the use of a COC containing 30 µg EE and 75 µg GSD for a period of 2 months in healthy women with no associated risk factors caused significant changes in hemostatic parameters suggestive of a higher prothrombotic risk. The clinical significance of these findings should be evaluated in a larger

<table>
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<th>Parameters</th>
<th>Baseline</th>
<th>After treatment</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>PT (sec)</td>
<td>11.3 ± 0.23</td>
<td>11.5 ± 0.34</td>
<td>0.66 &quot;</td>
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<tr>
<td>APTT (sec)</td>
<td>28.5 ± 0.46</td>
<td>28.7 ± 0.49</td>
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<td>Fibrinogen (g/l)</td>
<td>2.67 ± 0.18</td>
<td>3.20 ± 0.15</td>
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<td>Factor V (%)</td>
<td>86.2 ± 2.4</td>
<td>87.4 ± 2.2</td>
<td>0.59 &quot;</td>
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<tr>
<td>Factor VIII (%)</td>
<td>89.1 ± 2.55</td>
<td>10.6 ± 2.49</td>
<td>0.001</td>
</tr>
<tr>
<td>Protein C (%)</td>
<td>119.12 ± 3.36</td>
<td>132.5 ± 6.67</td>
<td>0.038</td>
</tr>
<tr>
<td>AT III (%)</td>
<td>0.24 ± 0.0061</td>
<td>0.20 ± 0.0065</td>
<td>0.001</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>140.24 ± 8.29</td>
<td>342.44 ± 14.08</td>
<td>0.001</td>
</tr>
</tbody>
</table>

TABLE I

DIFFERENT PARAMETERS STUDIED BEFORE AND AFTER COCS USE
cohort of women with associated risk factors such as smoking and over a longer period of COC use.

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REFERENCES


