A double-blind comparative study of the effects of a 23-day oral contraceptive regimen with 20 μg ethinyl estradiol and 75 μg gestodene and a 21-day regimen with 30 μg ethinyl estradiol and 75 μg gestodene on hemostatic variables, lipids, and carbohydrate metabolism

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Abstract

In this double-blind study we compared the influence of two oral contraceptives, a 23-day regimen with 20 μg ethinyl estradiol and 75 μg gestodene (23-day 20/75) and a 21-day regimen with 30 μg ethinyl estradiol and 75 μg gestodene (21-day 30/75), on hemostatic variables, lipids, and carbohydrate metabolism. The volunteers received the preparations daily for six 28-day cycles. Hemostatic variables and lipids were measured at baseline and after six treatment cycles. Carbohydrate metabolism was assessed by determination of the area under the curve (AUC) of carbohydrate parameters after oral glucose tolerance tests performed at baseline and after three treatment cycles.

Data from 33 volunteers in each group were obtained. No significant differences between the effects of both treatments on the hemostatic system were detected. Neither the overall change of all hemostatic variables from baseline to treatment Cycle 6 [defined as primary target variable in the study] nor the change of any of the individual hemostatic parameters differed significantly between the treatment groups. Likewise, no significant nor clinically relevant differences in the effects of both treatments on the volunteers’ lipid profiles were detected. The data on carbohydrate variables suggested a slightly more favorable influence of the 23-day 20/75 regimen. The increase of the glucose AUCs after three cycles tended to be stronger with the 21-day 30/75 regimen than with the 23-day 20/75 regimen. In addition, the AUCs for insulin and C-peptide were slightly reduced after three cycles with the 23-day 20/75 regimen but slightly increased with the 21-day 30/75 regimen.

Both study treatments were safe and well tolerated by the volunteers as shown by the nature and frequency of adverse events, the routine laboratory examinations, and the physical and gynecological examinations. Both preparations provided adequate contraceptive reliability. The only pregnancy during treatment was attributable to intake errors.

In conclusion, the prolongation of the treatment phase of an oral contraceptive with 20 μg ethinyl estradiol does not evoke more pronounced metabolic effects than a conventional 21-day regimen with 30 μg ethinyl estradiol. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Oral contraceptives; Ethinyl estradiol; Gestodene; Hemostasis; Lipids; Carbohydrate metabolism; 23-day regimen

1. Introduction

In the past few years a considerable amount of clinical data on low-dose oral contraceptives (OCs) containing 20 μg ethinyl estradiol, particularly in combination with gestodene, has been collected [1–4]. It has been shown that a low ethinyl estradiol dose of 20 μg, in combination with gestodene, desogestrel, or levonorgestrel, provides reliable contraceptive protection [1–3,5–6]. Regarding cycle control, clinical experience suggests that despite initial doubts, the low estrogen dose preparations are acceptable for most and are completely satisfactory for many users. However,
any further improvement of cycle control would be beneficial for the users.

A possible approach to further reduce the frequency of intermenstrual bleeding and adverse events is the modification of the application regimen. The regimen investigated in this study is characterized by a longer treatment interval of 23 instead of 21 days per cycle and a shorter hormone-free interval of 5 instead of 7 days per cycle. As shown in a previous study, the prolongation of the hormone intake improved ovarian suppression [7] and had a favorable influence on cycle control. Additionally, the modification of the regimen has the potential to reduce hormone surges caused by ovarian recovery during the hormone-free interval, which have been described for some 21-day low-dose OCs.

In the present study, we investigated the influence of the new regimen on hemostatic variables, lipids, and carbohydrate metabolism. Therefore, we compared a new preparation containing 20 μg ethinyl estradiol and 75 μg gestodene in a 23-day regimen (23-day 20/75) to a marketed OC containing 30 μg ethinyl estradiol and 75 μg gestodene in a 21-day regimen (21-day 30/75). The latter was chosen as a reference because it was considered unacceptable for the new preparation to induce more pronounced metabolic changes than a preparation containing 30 μg ethinyl estradiol. The study was a phase III, multicenter, double-blind, randomized study. It was conducted in The Netherlands, and the treatment period lasted for six 28-day treatment cycles.

2. Materials and methods

The study was performed as a double-blind, randomized, prospective study at two centers in The Netherlands (Dinox B.V., Groenewoudseweg 317, NL-6525 TX Nijmegen and Stichting Octomed, Wassenaarseweg 56, NL-2333 CK Leiden) from October 1996 to August 1997. We compared two OCs: one, 23-day 20/75, and the other, 21-day 30/75. The study protocol was approved by the appropriate ethics committees before the study started.

The investigators recruited a total of 70 healthy women aged 18–35 years for the study. Of these, 66 volunteers were included in the efficacy analysis (two did not take the study medication, two prematurely discontinued the study). The women’s wish for contraception for at least six 28-day cycles was a prerequisite for their participation in the study. New OC users as well as women who wanted to change their OC (switchers) were included in the study. Switchers had to have at least two OC-free cycles, one wash-out cycle and one pretreatment cycle, before they started to take the study medication. The exclusion criteria were similar to the known contraindications for OC use. Further exclusion criteria were the use of parenteral depot-contraceptives during the last 6 months before the study, specified concomitant pathology, diagnostically unclassified genital bleeding, and a history of migraine accompanying menstruation. All volunteers gave informed consent prior to their participation.

The volunteers were randomized to either of two treatment groups. Neither the investigator nor the volunteers knew which volunteer was assigned to which treatment. The volunteers had to take the first tablet on the first day of withdrawal bleeding. In the 23-day 20/75 group, the volunteers took 23 tablets containing 20 μg ethinyl estradiol and 75 μg gestodene on the first 23 days of a 28-day cycle followed by 5 placebo tablets for the last 5 days. In the 21-day 30/75 regimen, the volunteers took 21 tablets containing 30 μg ethinyl estradiol and 75 μg gestodene on the first 21 days of a cycle followed by 7 placebo tablets for the last 7 days of the cycle. The treatment period consisted of six consecutive 28-day cycles, all of which started on the same week day as the initial cycle. The study medications were supplied in calendar packs. If a woman missed the scheduled intake time, she was instructed to take the tablet until up to 12 h after the scheduled time and to record the delay in her diary. All deviations from the scheduled tablet intakes had to be recorded in a diary.

Each subject had a thorough medical and gynecological examination that included a cervical cytology examination by the Papanicolau smear method and a pregnancy test before treatment start. Routine laboratory examinations (liver enzymes, hematologic variables, lipids, creatinine, bilirubin, alkaline phosphatase, total protein, and electrolytes) were carried out by two local laboratories in The Netherlands (Institute for Prevention and Diagnosis, Leiden, for the volunteers at Stichting Octomed, and Canissius-Wilhelmina Ziekenhuis, Klinisch Chemisch Laboratorium, Nijmegen, for the volunteers at Dinox B.V.).

Blood samples for the hemostatic and lipid variables were taken during the pretreatment cycle, treatment Cycles 3 and 6 (on cycle days 17–21), and the follow-up cycle (on cycle days 14–18). Because the data obtained for treatment Cycles 3 and 6 were not suggestive of different trends, we only report the data obtained for treatment Cycle 6 at the present time.

In a subgroup of 27 volunteers, oral glucose tolerance tests (OGTTs) were done in the pretreatment cycle and in treatment Cycle 3 (on cycle days 17–21). Glucose was administered as dextrose solution in a fruit-flavored beverage at a dose of 1 g/kg body weight. The influence of the study treatments on carbohydrate metabolism was assessed by measurements of plasma glucose, insulin, and C-peptide levels. Blood samples were taken at a fasting state before glucose administration (together with the samples required for general clinical chemistry variables, screening variables, hemostatic profile, and lipid profile) and at 30 min intervals until 3 h thereafter.

The laboratory samples for hemostasis, lipid, and carbohydrate variables were analyzed by one central laboratory for all volunteers (IPD, Institute for Prevention and Diagnosis, Leiden, The Netherlands). This laboratory worked according to the Principles of Good Laboratory Practice and
regularly participated in quality assurance procedures. Only widely accepted test kits were applied. The hemostatic variables were determined by using Enzygnost D-Dimer micro, Enzygnost F1+2 micro, Coatest APC resistance test (Intrinsic Pathway), Bioclot Protein C/S (Biopool), StaClot-rTF (Factor VIIa), Coamaic Antithrombin kit, Clauss method for fibrinogen, Thrombonostika Active PAI-1 kit, Imulyse t-PA kit (Biopool).

At all study visits, blood pressure and body weight were measured. Adverse events, concomitant medication usage, and treatment compliance, including a record of intake errors and cycle control patterns, were recorded by using the volunteers’ diaries and through general questioning by the investigators. In the follow-up period, the volunteers were again asked about their general health during the treatment period. Furthermore, medical and gynecological examinations, including cervical cytology and routine laboratory examinations, were repeated.

The volunteers documented bleeding pattern before and during the study in their diaries. The definition of intracyclic bleeding used for the assessment of the bleeding diary was dependent on the treatment cycle number and the treatment group. In the first treatment cycle, intracyclic bleeding was defined as any vaginal bleeding between cycle days 8 and 21 for the 21-day 30/75 regimen and between cycle days 8 and 23 for the 23-day 20/75 regimen. In treatment Cycles 2–6 and in the follow-up cycle, it was any vaginal bleeding between cycle days 4 and 21 for the 21-day 30/75 regimen and between days 6 and 23 for the 23-day 20/75 regimen. Thus, in the first treatment cycle, the length of the period in which intracyclic bleeding could occur was 16 days for the 21-day 30/75 regimen and 16 days for the 23-day 20/75 regimen. In all subsequent cycles, it was 17 days for both regimens.

2.1. Statistical methods

Statistical analyses were performed for both the “intention-to-treat” (ITT) and the “valid case analysis” (VCA) populations. All randomized volunteers who took at least one tablet of the study medication were included in the ITT population. Volunteers with major protocol deviations that affected the primary target variable were excluded from the VCA population.

The primary target variable (C_i) was the overall individual change (Ci) of all hemostasis variables between the pretreatment cycle and treatment Cycle 6. It was calculated for each individual volunteer i using the following distance function [8]:

\[
C_i = \sqrt{\sum_{j=1}^{p} D_{ij}^2}
\]

where

\[
D_{ij} = \begin{cases} 
(X_{ij} - Y_{ij}) & \text{if } X_{ij} \neq 0 \text{ or } Y_{ij} \neq 0 \\
(X_{ij} + Y_{ij}) & \text{if } X_{ij} = 0 \text{ and } Y_{ij} = 0 \\
\text{Undefined} & \text{if } X_{ij} \text{ is missing or } Y_{ij} \text{ is missing}
\end{cases}
\]

The secondary target variables included the relative changes of each individual hemostasis and lipid variable and the absolute change of the area under the curve (AUC) for glucose, insulin, and C-peptide. The relative change of a variable was defined as the difference of the value measured in treatment Cycle 6 minus the value measured in the pretreatment cycle divided by the value measured in the pretreatment cycle times 100%. The absolute changes of the AUCs were calculated as the difference of the value measured in Cycle 3 minus the value measured in the pretreatment cycle.

To show the superiority of the 23-day 20/75 regimen to the 21-day 30/75 regimen, the null hypothesis, which stated that the C_i is not generally smaller for the 23-day 20/75 regimen than for the 21-day 30/75 regimen, was tested against the alternative hypothesis, which stated that the C_i is generally smaller for the 23-day 20/75 regimen than for the 21-day 30/75 regimen. For each secondary target variable, the null hypothesis, which stated that the mean values are equal in both treatment groups, was tested against its alternative, which stated that the mean values in both treatment groups were not equal.

The distribution of the C_i was assumed to be skewed because of its lower bound 0. Therefore, a nonparametric test was planned, and the null hypothesis for the C_i was tested by using the one-sided Wilcoxon rank sum test at a significance level \( \alpha \) of 5%. For each secondary target variable, the null hypothesis was tested by using the two-sided t test for independent samples with the assumption of equal variances. The significance level \( \alpha \) of 5% for these tests was not adjusted for multiple testing as appropriate for exploratory analyses.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics at baseline</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>(n = 35)</td>
</tr>
<tr>
<td>Mean age (years)</td>
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<tr>
<td>[range]</td>
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<tr>
<td>Mean weight (kg)</td>
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<td>[range]</td>
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<tr>
<td>Mean height (cm)</td>
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<tr>
<td>[range]</td>
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<tr>
<td>Prevalence of smoking (%)</td>
</tr>
<tr>
<td>Prior use of OCs (%)</td>
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<tr>
<td>Volunteers with regular cycles (%)</td>
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<tr>
<td>Mean menstrual duration (days)</td>
</tr>
<tr>
<td>[range]</td>
</tr>
</tbody>
</table>

p denotes the number of defined values D_{ij}, X_{ij}, and Y_{ij} are the values of the hemostasis variable j for volunteer i, measured in the pretreatment cycle and in treatment Cycle 6, respectively.
Table 2
Hemostatic parameters (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Unit</th>
<th>Baseline</th>
<th>Cycle 6</th>
<th>% change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>23-day 20/75</td>
<td>21-day 30/75</td>
<td>23-day 20/75</td>
<td>21-day 30/75</td>
</tr>
<tr>
<td>Act. Factor VII</td>
<td>mU/mL</td>
<td>46.2 ± 16.6</td>
<td>55.4 ± 18.2</td>
<td>62.5 ± 21.9</td>
<td>77.5 ± 38.1</td>
</tr>
<tr>
<td>Total Factor VII</td>
<td>%</td>
<td>120.7 ± 21.0</td>
<td>124.7 ± 19.4</td>
<td>163.2 ± 35.5</td>
<td>173.9 ± 35.4</td>
</tr>
<tr>
<td>Factor X</td>
<td>%</td>
<td>84.6 ± 16.2</td>
<td>88.8 ± 18.7</td>
<td>102.5 ± 15.9</td>
<td>107.5 ± 16.9</td>
</tr>
<tr>
<td>AT III</td>
<td>%</td>
<td>94.2 ± 11.3</td>
<td>93.7 ± 8.6</td>
<td>90.5 ± 11.8</td>
<td>89.7 ± 7.5</td>
</tr>
<tr>
<td>Protein C activity</td>
<td>%</td>
<td>96.7 ± 35.5</td>
<td>110.2 ± 38.6</td>
<td>96.0 ± 32.6</td>
<td>109.4 ± 30.4</td>
</tr>
<tr>
<td>Protein S activity</td>
<td>%</td>
<td>87.5 ± 11.2</td>
<td>87.4 ± 17.7</td>
<td>81.4 ± 10.6</td>
<td>79.0 ± 7.8</td>
</tr>
<tr>
<td>APC resistance</td>
<td>Ratio</td>
<td>4.22 ± 0.67</td>
<td>4.29 ± 0.96</td>
<td>4.23 ± 0.99</td>
<td>4.08 ± 0.68</td>
</tr>
<tr>
<td>PAI-1 activity</td>
<td>IU/L</td>
<td>18.8 ± 21.1</td>
<td>16.1 ± 15.8</td>
<td>2.53 ± 4.23</td>
<td>2.78 ± 4.38</td>
</tr>
<tr>
<td>PAI-1 antigen ng/mL</td>
<td>39.8 ± 21.3</td>
<td>41.8 ± 33.8</td>
<td>11.42 ± 11.14</td>
<td>11.70 ± 10.94</td>
<td>-68.72 ± 21.36</td>
</tr>
<tr>
<td>D-dimer</td>
<td>g/L</td>
<td>2.0 ± 0.4</td>
<td>2.8 ± 0.3</td>
<td>3.5 ± 0.6</td>
<td>3.4 ± 0.4</td>
</tr>
<tr>
<td>Prothrombin fragments F1+2</td>
<td>mmol/L</td>
<td>0.63 ± 0.21</td>
<td>0.73 ± 0.32</td>
<td>1.21 ± 1.12</td>
<td>1.02 ± 0.69</td>
</tr>
<tr>
<td>D-dimer (µg/L)</td>
<td></td>
<td>14.3 ± 8.8</td>
<td>18.7 ± 15.1</td>
<td>32.2 ± 26.1</td>
<td>31.6 ± 19.9</td>
</tr>
</tbody>
</table>

3. Results

Of 70 randomized volunteers, 69 received treatment: 35 took the 23-day 20/75 regimen and 34 took the 21-day 30/75 regimen. A total of 66 volunteers, 33 in each group, were included in the VCA population. The demographic characteristics of the two groups at baseline were well matched (Table 1).

3.1. Hemostatic parameters

The individual change (Ci) of all hemostatic variables between the pretreatment cycle and treatment Cycle 6, which was defined as the primary target variable, was almost the same in both treatment groups, with 0.33 in the 23-day 20/75 group and 0.32 in the 21-day 30/75 group. The superiority of the 23-day 20/75 regimen to the 21-day 30/75 regimen with respect to the primary target variable could not be shown (p = 0.24). The results suggested no difference between the 23-day 20/75 regimen and the 21-day 30/75 regimen regarding the influence on the hemostatic profile.

The relative changes of each individual hemostatic variable from pretreatment to treatment Cycle 6 were secondary target variables. The effects of both treatments on each hemostatic variable were similar. The most pronounced changes from baseline were observed for the concentration of prothrombin fragments F1+2 and D-dimer. These variables also showed the largest differences between the effects of the two study treatments. The concentration of the prothrombin fragments F1+2 was increased from baseline to treatment Cycle 6 by an average of 103% in the 23-day 20/75 group and by 48% in the 21-day 30/75 group. The concentration of D-dimer was increased by an average of 194% in the 23-day 20/75 group and by 117% in the 21-day 30/75 group. However, for none of the hemostatic variables were the differences in the relative changes from baseline to treatment Cycle 6 significant between the treatments (Table 2).

3.2. Lipids

The relative changes of each lipid variable from the pretreatment cycle to treatment Cycle 6 were secondary target variables. The changes from baseline to treatment Cycle 6 were similar in both treatment groups for all measured lipid variables (Table 3). Both treatments had the strongest effect on the triglycerides concentrations, which were increased by an average of 41% in the 23-day 20/75 group compared to 46% in the 21-day 30/75. All other parameters changed by less than 20%. The increase in total HDL-cholesterol was larger in the 21-day 30/75 group (7.8%) than in the 23-day 20/75 group (3.3%); this difference was, however, not significant. For HDL2-cholesterol, constant levels (0.77%) in the 21-day 30/75 group were seen, whereas a slight decrease (13.5%) was seen in 23-day 20/75 group. LDL-cholesterol was almost unaffected by both treatments. The increase of apolipoprotein A1 was stronger in the 21-day 30/75 group than in the 23-day 20/75, whereas apolipoproteins A2 and B were equally affected by both treatments (Table 3). For none of the measured lipid variables were the relative changes from baseline to treatment Cycle 6 significantly different between the two treatment groups (Table 3).

3.3. Carbohydrate metabolism

A subpopulation of 27 volunteers of the VCA population, 12 in the 23-day 20/75 group and 15 in the 21-day 30/75 group, took part in the OGTT. The absolute changes from the pretreatment cycle to treatment Cycle 3 in the 3-h AUC of glucose, insulin, and C-peptide were secondary target variables. As shown in Table 4, the increase of the
mean AUC for glucose was stronger in the 21-day 30/75 group (by 1634 mg/dL/min) than in the 23-day 20/75 group (by 344 mg/dL/min). However, this difference was not significant. The AUC of insulin was decreased by 777 μIU/mL × min in the 23-day 20/75 group and increased by 1913 μIU/mL × min in the 21-day 30/75 group. This difference between the two treatments was significant (p = 0.033). The concentration of C-peptide was also slightly decreased in the 23-day 20/75 group and increased in the 21-day 30/75 group, a difference that was not significant.

### 3.4. Tolerability

The number of volunteers who had adverse events was 30 (85.7%) in the 23-day 20/75 group and 27 (79.4%) in the 21-day 30/75 group. The number of events was 127 in the 23-day 20/75 group and 120 in the 21-day 30/75 group. The most frequent adverse events were headache (61 adverse events in 17, 24.6%, volunteers) and dysmenorrhea (30 adverse events in 23-day 20/75 group and 120 in the 21-day 30/75 group. The number of events was 127 in the 23-day 20/75 group and 27 (79.4%) in the 21-day 30/75 group. The number of events was 127 in the 23-day 20/75 group and 27 (79.4%) in the 21-day 30/75 group. No serious adverse events occurred.

Physical and gynecological examinations showed only few abnormal findings, all of which were medically irrelevant. The pre- and post-treatment condition of the volunteers was the same overall. No appreciable influence of the treatments on body weight and blood pressure was detected.

No intracyclic bleeding at all was recorded in the 23-day 20/75 group, whereas in the 21-day 30/75 group all but one volunteer (97%) had intracyclic bleeding in the first treatment cycle and eight volunteers (24%) had intracyclic bleeding in at least one additional cycle.

The overall levels of the routine laboratory values before and after treatment did not suggest an influence of the study preparations. The incidence of laboratory abnormalities was low and not appreciably different in the pre- and the post-treatment examinations. Individual deviations from normal laboratory ranges were transient and mostly small and not clinically relevant.

### 4. Discussion

Our results indicate that both preparations have similar effects on hemostatic variables, lipids, and carbohydrate metabolism. After six treatment cycles, the measured hemostatic variables, which included pro- and anti-coagulatory as well as pro- and anti-fibrinolytic variables, formed a new equilibrium at a similar level of turnover in both treatment groups.

The primary target variable, the individual change (Ci) of all hemostatic variables [8] between the pretreatment cycle and treatment Cycle 6 was almost the same in both treatment groups. This parameter was intended to provide a global measure of impact on the hemostatic system. However, the clinical interpretation remains difficult because it summarizes potentially favorable as well as unfavorable changes.

The variables for thrombin and fibrin turnover, prothrombin fragments F1 + 2 and D-dimer, were shifted to a higher level in both treatment groups without significant differences between the treatments. The latter were regarded
as the most relevant indicators for changes in the hemostatic system by the Oral Contraceptive and Hemostasis Study Group in 1999 [9]. The observed changes of all variables remained within normal ranges of variation and were comparable with the effects published for other low-dose OC preparations [10–13].

Regarding the lipid profile, the only substantial influence of both treatments was a relatively strong increase in the triglycerides levels, an effect which is expected after estrogen administration. All other changes were small in both treatment groups. Overall, the impact of the treatments on the lipid profile was minimal. The clinically unfavorable LDL was almost unaffected, and the beneficial total HDL was slightly increased in both treatment groups, suggesting no adverse effects of the preparations on the cardiovascular risk in healthy women [14,15].

The data on carbohydrate variables suggested a slightly more favorable influence of the 23-day 20/75 preparation. Although a significant difference was found for the insulin AUCs, with an increase in the 23-day 20/75 group and an increase in the 21-day 30/75 group, we consider the clinical relevance of this finding as limited. Nonetheless, a chronically reduced insulin sensitivity may be accompanied by adverse metabolic and cardiovascular changes. Therefore, new low-dose OCs should have the least possible impact on carbohydrate metabolism [12].

In conclusion, the data provide evidence that the prolongation of the treatment phase of an OC with 20 μg ethinyl estradiol from 21 days to 23 days does not evoke more pronounced metabolic effects than a conventional 21-day regimen with 30 μg ethinyl estradiol. Interestingly, the difference in the total ethinyl estradiol dose per cycle, 460 μg for the 23-day 20/75 regimen versus 630 μg for the 21-day 30/75 regimen, appears not to have a significant impact on the metabolic variables. According to a study reported by van der Mooren [16], a reduction of the ethinyl estradiol dose from 20 μg to 15 μg also does not decrease the influence on lipid profile, carbohydrate metabolism, and hemostatic balance. Overall, these results support the hypothesis that lowering the hormone content of OCs below a certain threshold may not be accompanied by a decrease in the evoked metabolic changes.

The results of the routine laboratory examinations did not suggest any influence of the study preparations on the laboratory variables. None of the other routine variables examined in the study gave rise to safety concerns. The extent of correlation between the hormone dose of an OC and the incidence of thrombotic diseases is controversial, particularly with low-dose OCs. Gerstman et al. [17] showed in a retrospective analysis of epidemiologic data that vascular diseases were more frequent in users of OCs containing 50 μg ethinyl estradiol than in users of OCs containing 30 μg ethinyl estradiol. Sufficient epidemiologic data for OCs containing 20 μg ethinyl estradiol are currently not available. Moreover, the role of the progestins remains to be clarified. Estrogen and progestins interact at many levels, and in epidemiologic studies of combined OCs, it is difficult to separately assign a risk to either component [18].

The more pronounced ovarian suppression of the 23-day 20/75 regimen [7] and the beneficial effects on the bleeding pattern were investigated in other studies. Our data presented here provide clear evidence that the prolongation of the treatment phase of an OC with 20 μg ethinyl estradiol does not evoke more pronounced metabolic effects than a conventional 21-day regimen with 30 μg ethinyl estradiol.

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