Reduced hemostatic effects with drospirenone-based oral contraceptives containing estetrol vs. ethinyl estradiol☆☆,★☆☆,★

Cornelis Klufta,⁎, Yvette Zimmermnb, Marie Mawetc, Christine Klippingd, Ingrid J.M. Duijkersec,1, Jacoline Neuteboomoa, Jean-Michel Foidartc,1, Herjan Coelingh Benninkb,1

aGood Biomarker Sciences, Zernikedreef 8, 2333CL, Leiden, the Netherlands
bPantarhei Bioscience, P.O. Box 464, 3700, AL, Zeist, the Netherlands
cEstetra SPRL, Rue Saint Exupery, 4460 Grace-Hollogne, Belgium
dDinox BV, Hanzeplein 1, 9713GZ, Groningen, the Netherlands

Received 4 April 2016; revised 28 August 2016; accepted 29 August 2016

Summary

Objective: The effects of estetrol (E4), a natural fetal estrogen, combined with drospirenone (DRSP) were evaluated on plasma levels of sex hormone-binding globulin (SHBG), angiotensinogen and 12 hemostasis markers.

Study design: Combinations of 3 mg DRSP with 5 or 10 mg E4 were compared with YAZ® (20 mcg ethinyl estradiol and 3 mg DRSP; EE/DRSP) in parallel groups of 15–18 healthy young women. Main outcome was the relative change from pretreatment to the end (day 24±1) of the third treatment cycle.

Results: All E4 combinations showed low estrogen impact compared to EE/DRSP. Effects on SHBG and angiotensinogen of 10 mg E4 combined with DRSP were 15%–20% that of EE/DRSP.

Both E4/DRSP combinations reduced D-dimer level and the 5 mg E4/DRSP combination also decreased fragment 1+2.

Conclusions: The reduction in coagulation markers suggests an anticoagulant effect from DRSP.

The indications of a low thrombosis risk for E4 preparations should be validated in larger studies.

Keywords: Estetrol; Ethinyl estradiol; Drospirenone; Hemostasis; SHBG; Estrogenicity

1. Introduction

Current hormonal contraceptive preparations contain ethinyl estradiol (EE) predominantly, and more recently also the natural 17β-estradiol (E2) [1]. Hagen et al. [2] discovered the natural fetal estrogen, estetrol (E4). It is produced by the fetus and detected in the maternal circulation during pregnancy from 9 weeks of gestation until only shortly after birth [3]. Estrogenic potency is lower than that of EE and E2, but at dosages of 5–20 mg, E4 was...
successfully evaluated for contraception and vaginal bleeding patterns with either levonorgestrel (LNG) or drospirenone (DRSP) as progesterin [4–6].

Interestingly, E4 neither binds to sex hormone-binding globulin (SHBG) nor induces its synthesis in vitro by hepatocytes [7]. E4 shows selective estrogen receptor (ERα and ERβ) receptor binding with a preference for ERα [8]. E4 selectively activates the nuclear ER (ERα) but blocks the membrane ERα [9]. Transgenic mice lacking this membrane ERα do not ovulate, demonstrating that this receptor is essential for ovulation and fertility [10]. The selective blockade of the membrane ERα by E4 could therefore contribute to the blockade of ovulation.

Thus, E4 is an option for addition to the repertoire of estrogenic components of oral combined contraceptives (COCs) [6]. Whether oral E4 exerts effects on the liver and endothelium similar to oral EE, and oral E2, resulting in increases in estrogenic markers such as SHBG, angiotensinogen and changes in hemostasis variables is an important question.

These liver estrogenicity markers and hemostasis variables are also sensitive to the progestin used in COC. Markers and variables are notably less modified with LNG compared to desogestrel, gestodene and DRSP [11–17].

Hepatic estrogenicity and hemostasis markers are in the list of the European Medicines Agency (EMA) [18] advised to evaluate potential risk for thrombotic side effects of hormonal contraceptives. Accordingly, we checked the behavior of these safety markers in combinations of E4 dosages with DRSP.

Our aim was to document the effects on hemostasis variables and liver estrogenicity markers of combinations of E4 (5 and 10 mg) with DRSP (3 mg) in comparison with YAZ® (20 mcg EE with 3 mg DRSP; EE/DRSP). We administered all combinations according to a 24- to 4-day regimen.

2. Materials and methods

2.1. Study design

This was an open-label, parallel, dose-finding, single-center (Dinox BV, Groningen, the Netherlands) study with young, healthy female volunteers of reproductive age. The study was performed from November 2009 through November 2010 and was registered as TC2102 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2102).

The local ethics committee approved the study protocol and the protocol was conducted in accordance with the tenets of the Declaration of Helsinki and the International Conference on Harmonization and Good Clinical Practice. From all participants, written informed consent was obtained prior to entry into the study.

2.2. Study population

Healthy women 18–35 years of age with a body mass index (BMI) of 18–30 kg/m² were eligible for inclusion. Subjects who were using a hormonal contraceptive at the time of screening had at least one washout cycle prior to the start of the study. Spontaneous ovulation between day 9 (±1) and day 24 (±1) was verified in the pretreatment cycle by a progesterone concentration ≥16 nM (5 ng/mL) and a luteal phase duration of ≥6 days. We applied the following exclusion criteria: failure to ovulate before day 24 in the observational pretreatment cycle, contraindications for the use of contraceptive steroids, clinically relevant abnormal laboratory findings, duration of the washout cycle after stopping hormonal contraceptives >42 days, pregnancy or lactation, prior pregnancy despite accurate hormonal contraceptive use, history of breast cancer, uterine and/or ovarian abnormalities, at least one abnormal cervical smear in the 3 years prior to screening, renal insufficiency, hepatic dysfunction, adrenal insufficiency, use of drugs that affect CYP3A4 activity, use of antihypertensive drugs, use of an injectable hormonal contraceptive within 6 months of screening, delivery or abortion in the past 2 months, use of investigational drugs in the past 2 months, and a recent history (i.e., within 12 months) of alcohol and/or drug abuse. Cigarette smoking (up to 10 per day) was permitted in participants up to 30 years of age; participants >30 years of age were required to be nonsmokers. The use of additional sex steroids was prohibited throughout the study.

The study utilized a parallel design (Fig. 1).

2.3. Study treatment

The study included the following three treatment groups: 20 mcg EE combined with 3 mg DRSP (EE/DRSP), 5 mg E4 combined with 3 mg DRSP (5 mg E4/DRSP), and 10 mg E4 combined with 3 mg DRSP (10 mg E4/DRSP). All subjects were stratified according to the day of ovulation in the pretreatment cycle and then assigned to a treatment group. E4 was supplied as 5 or 10 mg tablets. DRSP was supplied as 3 mg tablets. EE/DRSP was supplied as tablets in their original package. The participants in the two E4/DRSP groups were blinded with respect to the E4 dose; blinding of the EE/DRSP group was not possible.

E4 was synthesized by Cambridge Major Laboratories Europe (Weert, the Netherlands). The study medication was produced, packaged, labeled and released in accordance with Good Manufacturing Practice guidelines (Haupt Pharma, Munster, Germany).

Oral treatment was started on the first day of menstruation following the pretreatment cycle and continued daily for 24 days followed by a 4-day break; treatment compliance was verified by the use of a diary. The percentages of previous users were 40%, 20% and 28% in the 5 mg E4/DRSP, 10 mg/DRSP and EE/DRSP groups, respectively. The treatment period (which included three treatment cycles) was followed by a posttreatment cycle with no hormonal treatment.

2.4. Study measurements

Blood samples for the present analysis were collected at four time points during the study (i.e., Samples 1–4 in Fig. 1).
The blood samples contained either 0.11 mM citrate or CTAD (0.11 mM citrate plus theophylline, adenosine and dipyriramol); ETP-based APCr, APTT-based APC global and prothrombin fragment 1+2 (F1+2) were measured in the CTAD samples.

Sample 1 was taken on day 3 (±1 day) in the pretreatment cycle (Sample 1). Samples 2 and 3 were taken on day 24 (±1 day) in the first and third treatment cycles, respectively. Sample 4 was taken on day 3 (±1 day) in the first cycle following the posttreatment cycle (“Follow-up” in Fig. 1). For primary analysis, the measured values were compared between Sample 1 and Sample 3 for each participant.

Specimens were collected after the participants fasted and abstained from alcohol overnight and at least 1 h after smoking. Subjects were instructed to rest comfortably in a sitting position for at least 15 min prior to blood collection. Venipuncture using minimal stasis (≤ 15 mmHg pressure) was used for blood collection. In accordance with the study design, the first tube was not used for hemostasis analysis. Plasma samples were stored below −60 °C until analysis at the end of the study.

We measured the following hemostasis and hepatic estrogenicity markers: antithrombin (Coamatic LR Antithrombin, Instrumentation Laboratory, Bedford, MA, USA; CV: <10%, reference range: 75%–130%); ETP-based APC resistance (ratio of thrombin generation with and without APC (Activated Protein C: APE 1660 PAL, Erl); tissue factor (Innovin, Dade Behring, Miami, FL, USA), phospholipid micelles 15 μM, DOPC/DOPE/DOPS 3:1:1 (Avanti Polar Lipids, Alabaster, AL, USA), Substrate S2238 (Instrumentation Laboratory); defibrination of plasma with Reptilase (Pentapharm, Basel, Switzerland; reference range <2.4; CV: <20%); APC-APTT global (Coamatic APC resistance, Chromogenix, Instrumentation Laboratory; CV: <15%; ratio reference range: 2.1–3.7); protein S activity (STA Protein S Clotting, Diagnostica Stago, Gennevilliers, France; CV: <10%; reference range: 70%–140%); protein C activity (Coamatic Protein C, Chromogenix, Instrumentation Laboratory; CV: <10%; reference values: 70%–140%); fibrinogen (STA Fibrinogen, Diagnostica Stago; CV: <10%; reference range: 1.7%–4.5 g/L); prothrombin fragment 1+2 [Enzygnost F1+2 (monoclonal) kit; Siemens Healthcare Diagnostics Products GmbH, The Hague, the Netherlands; CV: <15%; reference range: 69–229 pM]; prothrombin antigen (FII-EIA; Affinity Biologics Inc., Ancaster, Ontario, Canada; CV: <10%; reference range: 75%–130%); D-dimer (GBS-EIA, GBS monoclonal 14: 7/8; 7, Conjugate DD13/PO; CV: <10%; reference range: <310 ng FE/mL); free TFPI (Aserachrom Free TFPI=Tissue Factor Pathway Inhibitor), Diagnostica Stago; CV: <10%, reference range: 0.6–8.9 ng/mL); E-selectin (Quantikine Human sE-Selectin kit; R&D Systems, Minneapolis, MN, USA; CV: <10%, reference range: 23–80 ng/mL); t-PA antigen (Trinilize tPA antigen kit; Trinity Biotech, Jamestown, NY, USA; CV: <10%, reference range: 1.2–12.5 ng/mL); SHBG (Cobas ECLIA assay; Roche Diagnostics, Almere, the Netherlands; CV%: <10%, reference range: 26–130 nM); and angiotensinogen (Human Total Angiotensinogen assay kit; IBL, Gunma, Japan; CV: <10%, reference range: 430–1040 pM).

2.5. Safety

We recorded adverse events throughout the study period. In addition, general physical and gynecological examinations (including vital signs, breast palpation and transvaginal ultrasonography) were performed at screening and within 2 weeks after discontinuation of the study treatment [19].

2.6. Statistics

For each target variable, the percent change relative to Sample 1 was calculated, and the median value and interquartile range (Q1–Q3) was calculated for each treatment group. The relative change was tested using the Wilcoxon signed rank test; differences were considered significant at p<.05.

3. Results

3.1. Subjects

The demographics and baseline characteristics were similar between treatment groups. The mean age was 23.8 years (range: 18 to 33 years), and the majority of subjects...
were of Caucasian descent. The mean height was 170.9 cm (range: 152–188 cm), the mean weight was 67.16 kg (range: 44.3 to 90.3 kg), and the mean BMI was 22.92 kg/m² (range: 18.3 to 30.0 kg/m²).

In total, 48 women provided blood samples through Sample 4. The 5 mg E4/DRSP and 10 mg E4/DRSP groups contained 15 participants each, and the EE/DRSP group contained 18 participants. Based on the subjects’ diary records, treatment compliance was generally good (>91%) in all treatment groups. Overall, 14 subject’s committed 18 protocol violations, all of which were considered minor. With respect to the hemostasis baseline characteristics, the values measured in Sample 1 (on day 3 of the pretreatment cycle) were all within their respective normal range (see Materials and methods).

### 3.2. Hepatic estrogenicity markers

In the EE/DRSP group, both SHBG and angiotensinogen increased significantly in the third cycle (to 381% and 256% of baseline, respectively) (Fig. 2). In contrast, SHBG and angiotensinogen were 100% (i.e., no change) and 125% of baseline in the 5 mg E4/DRSP group and 143% and 131% of baseline in the 10 mg E4/DRSP group. Thus, compared to 20 mcg EE, both 5 mg E4 and 10 mg E4 had nearly no effect on SHBG and minor on angiotensinogen.

### 3.3. Hemostasis variables

The percent change in hemostasis variables measured at the end of treatment cycle 3 (Sample 3) relative to baseline is summarized in Table 1. In addition, the values for the three most relevant coagulation inhibitors (free TFPI, protein S activity, and antithrombin) and for the global coagulation inhibition (ETP-based APCr) test are shown graphically in Fig. 3.

Importantly, both concentrations of E4 had no effect on antithrombin (Fig. 3B), protein S activity (Fig. 3C) or APCr (Fig. 3D), and had only a relatively minor effect on free TFPI (Fig. 3A); in contrast, as expected EE had a significant negative effect on all four markers of coagulation inhibition, thereby promoting coagulation.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>YAZ®</th>
<th>5 mg E4-DRSP</th>
<th>10 mg E4-DRSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>n=17</td>
<td>n=15</td>
<td>n=15</td>
</tr>
<tr>
<td>Estrogenicity markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHBG antigen</td>
<td>381 (313–462)</td>
<td>100 (90–125)</td>
<td>143 (129–176)</td>
</tr>
<tr>
<td>p[0.001]</td>
<td></td>
<td>p[0.05]</td>
<td>p[0.01]</td>
</tr>
<tr>
<td>Angiotensinogen antigen</td>
<td>256 (229–344)</td>
<td>125 (92–146)</td>
<td>131 (113–145)</td>
</tr>
<tr>
<td>p[0.001]</td>
<td></td>
<td>p[0.05]</td>
<td>p[0.01]</td>
</tr>
<tr>
<td>Global assays, markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APTT-based</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APC global</td>
<td>92 (83–97)</td>
<td>103 (90–106)</td>
<td>100 (90–105)</td>
</tr>
<tr>
<td>p[0.05]</td>
<td></td>
<td>p[0.05]</td>
<td>p[0.05]</td>
</tr>
<tr>
<td>ETP-based APCr</td>
<td>275 (196–348)</td>
<td>105 (93–129)</td>
<td>99 (87–154)</td>
</tr>
<tr>
<td>p[0.05]</td>
<td></td>
<td>p[0.05]</td>
<td>p[0.05]</td>
</tr>
<tr>
<td>D-dimer</td>
<td>127 (101–154)</td>
<td>74 (48–92)</td>
<td>74 (57–94)</td>
</tr>
<tr>
<td>p[0.01]</td>
<td></td>
<td>p[0.01]</td>
<td>p[0.05]</td>
</tr>
<tr>
<td>F 1+2 antigen</td>
<td>163 (131–193)</td>
<td>77 (68–83)</td>
<td>97 (76–114)</td>
</tr>
<tr>
<td>p[0.001]</td>
<td></td>
<td>p[0.001]</td>
<td>p[0.05]</td>
</tr>
<tr>
<td>Levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen activity</td>
<td>119 (113–126)</td>
<td>107 (97–116)</td>
<td>99 (93–107)</td>
</tr>
<tr>
<td>p[0.001]</td>
<td></td>
<td>p[0.05]</td>
<td>p[0.05]</td>
</tr>
<tr>
<td>Prothrombin antigen</td>
<td>113 (96–134)</td>
<td>110 (88–123)</td>
<td>118 (108–141)</td>
</tr>
<tr>
<td>p[0.05]</td>
<td></td>
<td>p[0.01]</td>
<td>p[0.05]</td>
</tr>
<tr>
<td>Protein C activity</td>
<td>111 (107–125)</td>
<td>99 (88–102)</td>
<td>99 (91–106)</td>
</tr>
<tr>
<td>p[0.001]</td>
<td></td>
<td>p[0.05]</td>
<td>p[0.05]</td>
</tr>
<tr>
<td>Protein S activity</td>
<td>73 (67–80)</td>
<td>107 (101–116)</td>
<td>103 (96–117)</td>
</tr>
<tr>
<td>p[0.001]</td>
<td></td>
<td>p[0.05]</td>
<td>p[0.05]</td>
</tr>
<tr>
<td>Free TFPI antigen</td>
<td>55 (46–58)</td>
<td>85 (77–101)</td>
<td>83 (80–92)</td>
</tr>
<tr>
<td>p[0.001]</td>
<td></td>
<td>p[0.01]</td>
<td>p[0.001]</td>
</tr>
<tr>
<td>Antithrombin activity</td>
<td>95 (90–99)</td>
<td>99 (94–110)</td>
<td>102 (95–107)</td>
</tr>
<tr>
<td>p[0.01]</td>
<td></td>
<td>p[0.05]</td>
<td>p[0.05]</td>
</tr>
<tr>
<td>t-PA antigen</td>
<td>52 (43–68)</td>
<td>92 (75–104)</td>
<td>90 (60–104)</td>
</tr>
<tr>
<td>p[0.001]</td>
<td></td>
<td>p[0.05]</td>
<td>p[0.05]</td>
</tr>
<tr>
<td>s-E-Selectin antigen</td>
<td>80 (74–88)</td>
<td>101 (96–114)</td>
<td>92 (82–105)</td>
</tr>
<tr>
<td>p[0.001]</td>
<td></td>
<td>p[0.05]</td>
<td>p[0.05]</td>
</tr>
</tbody>
</table>

Paired statistics: Wilcoxon signed rank test.

* Evaluated number of individuals with data from all sampling points.
At visit 4 (about 5 weeks after treatment discontinuation), participants who had received the 20 mcg EE/DRSP combination had values of SHBG, angiotensinogen, protein S activity, free TFPI and ETP-APC resistance that remained elevated compared to their pretreatment values (Figs. 2A and B, and 3A, B, and D). The residual change from baseline was compared to the peak value at visit 3 and calculated to be 10%–15% of that peak value.

The effects of E4 and EE on D-dimer and F1+2 (two molecular markers of coagulation activity) are illustrated in Fig. 4A and B, respectively. As reported previously, EE-containing COCs increased both markers, indicating activation of coagulation. Strikingly, however, E4-containing COCs did not increase either marker, but rather decreased both markers.

The effects of E4 and EE on D-dimer and F1+2 (two molecular markers of coagulation activity) are illustrated in Fig. 4A and B, respectively. As reported previously, EE-containing COCs increased both markers, indicating activation of coagulation. Strikingly, however, E4-containing COCs did not increase either marker, but rather decreased both markers.

4. Discussion

Here, we report that E4-containing COCs have considerably reduced effects with respect to hemostasis. None of the studied levels except free TFPI showed a significant change (Table 1). Specifically, with the exception of the modest decrease in free TFPI, E4/DRSP had no effect on coagulation inhibition which is in striking contrast to the well-documented significant negative effects of EE on multiple factors involved in coagulation inhibition [11,12,14,15].

E4 has estrogenic effects on reproductive tissues and organs. The estrogenic effect of 10 and 20 mg E4 alone, administered during 28 days, was previously shown in a study in premenopausal women. Ovulation in the 10 and 20 mg E4 groups was inhibited in one-third and two-thirds of the cycles, respectively [6]. In postmenopausal women, E4 alone in a dose range of 2–40 mg per day dose-dependently showed estrogenic effects on vaginal cytology and hot flushes [20].

The current study provides evidence that COCs containing 5 or 10 mg E4 have some hepatic and endothelial estrogenicity, although the estrogenic effects are much less than the effects of an EE-containing COC. The estrogenicity as indicated by the liver variables SHBG and angiotensinogen is 15%–20% compared to EE/DRSP (Table 1), and the free TFPI reduction is 33%–38% of that of EE/DRSP (Table 1).

Previously, the pharmacodynamic effects of E4/DRSP and EE/DRSP on a broad range of biochemical liver parameters, including carrier proteins, lipids, liver function

---

**Fig. 3.** (A) Median levels (interquartile range up or down) of free TFPI relative to the pretreatment value (=100%). Data for 5 mg E4, 10 mg E4 and 20 mcg EE combinations with 3 mg DRSP. For sample identification, see Fig. 1. Paired statistics: Wilcoxon signed rank test. (B) Median levels (interquartile range up or down) of protein S activity relative to the pretreatment value (=100%). Data for 5 mg E4, 10 mg E4 and 20 mcg EE combinations with 3 mg DRSP. For sample identification, see Fig. 1. Paired statistics: Wilcoxon signed rank test. (C) Median levels (interquartile range up or down) of antithrombin activity relative to the pretreatment value (=100%). Data for 5 mg E4, 10 mg E4 and 20 mcg EE combinations with 3 mg DRSP. For sample identification, see Fig. 1. Paired statistics: Wilcoxon signed rank test. (D) Median levels (interquartile range up or down) of ETP-based APC resistance relative to the pretreatment value (=100%). Data for 5 mg E4, 10 mg E4 and 20 mcg EE combinations with 3 mg DRSP. For sample identification, see Fig. 1. Paired statistics: Wilcoxon signed rank test.
parameters and markers of bone metabolism, have been reported and are consistent with the current data [19].

Estrogen in COCs serves three primary functions. First, estrogen regulates vaginal bleeding. Second, estrogen inhibits follicle development by inhibiting the secretion of follicle-stimulating hormone, thereby reducing the amount of progesterin needed to effectively inhibit ovulation. Third, the estrogen in COCs serves to replace estradiol that is lost due to the suppression of ovarian function. EE satisfies all three estrogenic functions; however, EE also has a strong estrogenic effect on liver function and vascular endothelium. These hepatic and vascular effects are believed to underlie the increased risk of venous thromboembolism (VTE) in women who use EE-containing COCs. Although this risk can be reduced by some progestins such as LNG, other progestins such as DRSP do not affect the hepatic and vascular estrogenicity of EE.

Interestingly, we observed a reduction in D-dimer and F1+2 in women taking E4-DRSP.

Very recently, Regidor et al. [21] reported the first data on DRSP-only treatment (4 mg) and observed a 19% significant reduction in D-dimer. Our data on reduction of both F1+2 and D-dimer suggest an anticoagulant mechanism for the combination E4 and 3 mg DRSP.

We propose that the effect we observed is due to DRSP.

The study of Regidor et al. [21] showed no appreciable effect of DRSP-only on APC resistance, antithrombin and factor VIII, while protein C was shown to be reduced and factor VII increased by 5%. It indicates low impact of DRSP on these liver hemostatic factors.

Previous mechanistic studies suggest a possible mechanism through which DRSP reduces coagulation activation. DRSP is an antagonist of aldosterone, which induces endothelial inflammation, dysfunction and stiffness [22–25] via mineralocorticoid receptors expressed on the endothelium [26,27]. Both in vivo and in vitro studies have shown that aldosterone activates NF-κB [28], decreases t-PA [29], and increases PAI-1 [29–31], Von Willebrand factor [32], ICAM-1 [33], tissue factor [29], VCAM-1 [34], MCP-1 [34], E-selectin [35], TAT, membrane-bound EPCR [36] and microparticles.

That levels of strong reacting variables for the 20 mcg EE/DRSP combination did not return to pretreatment values in the posttreatment sample being around 5 weeks after discontinuation of treatment, is an observation that may provide on retrospect a limitation to our study only employing a 1-month wash-out. It is not clear whether this is relevant for all COCs used before the study, which concerned 20%–40% of the participants. The residual 10%–15% of the peak value observed in the present study indicates a long-lasting effect that cannot be explained by merely plasma clearance of the factors.

A major weakness of our study is the absence of a treatment arm in which only DRSP was administered. The further limitations concern the small sample sizes, the limited range of BMI and the limited age range (only women of a certain BMI and age were included). Further, we did not identify factor V Leiden in our patient group preventing separate analysis and possibly underlying the largest variation (CV%=69, for sample 3) in effect in ETP-based APC resistance. The selection of biomarkers analysis is based on regulatory guidance as provided by EMA. It is based on expert opinions and includes hemostasis variables known to provide a risk in patients with genetic deviations in these factors and risk factors from epidemiological evaluations. The changes induced by the COCs are generally smaller than those of genetic abnormalities and may indicate an increased risk, when in combination with other risk factors and in relation to the fact that COC induce multiple changes that may cooperate in risk during COC use. The data about the listed factors thus do not necessarily reflect clinical outcome, the more so since unknown factors may play a role.

In conclusion, because E4/DRSP has considerably lower hepatic and vascular estrogenicity than EE/DRSP, we expect that women who take E4-containing COCs may ultimately prove to have a lower risk of VTE compared to women who take EE-containing COCs. Our results using COCs with a given dose of DRSP support this hypothesis, at least with
Acknowledgment

The study was sponsored by ESTETRA Sprl, a joint venture between the MITHRA pharmaceuticals group and Pantarhei Bioscience. The authors thank Petit Ludivine, Maud Jost and Nicole Appels for helpful discussions and help in collecting the data, and Curtis Barrett of English Editing Solutions.

References


Downloaded from ClinicalKey.com at The Royal Society of Medicine January 16, 2017. For personal use only. No other uses without permission. Copyright ©2017. Elsevier Inc. All rights reserved.