

Original Research Article

Endocrine and metabolic effects of an oral contraceptive containing estetrol and drospirenone

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ARTICLE INFO

Article history:

Received 11 October 2020

Received in revised form 18 December 2020

Accepted 1 January 2021

Keywords:

Combined oral contraception

Drospirenone

Endocrine

Estetrol

Ethinylestradiol

Metabolic

ABSTRACT

Objectives: To evaluate the effect on endocrine and metabolic parameters of a new combined oral contraceptive (COC) containing estetrol (E4) and drospirenone (DRSP).**Study design:** Randomized, open-label, controlled, 3-arm, parallel study. Healthy subjects received either E4 15 mg/DRSP 3 mg (E4/DRSP) ($n = 38$), or ethinylestradiol (EE) 30 µg/levonorgestrel (LNG) 150 µg ($n = 29$), or EE 20 µg/DRSP 3 mg ($n = 31$) for 6 treatment cycles. Median percentage change from baseline to cycle 3 and to cycle 6 were evaluated for endocrine parameters, liver proteins, lipid profile, and carbohydrate metabolism.**Results:** At cycle 6, E4/DRSP treatment had less effect on gonadotropins (follicle stimulating hormone [FSH] +30.5%, luteinizing hormone [LH] −7.5%) compared to EE/LNG (FSH −84.0%, LH −92.0%) and EE/DRSP (FSH −64.0%, LH −90.0%). With E4/DRSP increases in total cortisol (+26.0%) and cortisol binding globulin ([CBG] (+40.0%)) were less compared to EE/LNG (cortisol +109.0%, CBG +152.0%) and EE/DRSP (cortisol +107.0%, CBG +140.0%). Liver proteins, except CRP, increased, but the effect was less pronounced with E4/DRSP for angiotensinogen (+75.0%) compared to EE/LNG (+170.0%) and EE/DRSP (+206.5%) and for sex hormone binding globulin ([SHBG] +55.0%), compared to EE/LNG (+74.0%) and EE/DRSP (+251.0%). E4/DRSP had minimal impact on lipid parameters; the largest effect was observed for triglycerides (+24.0%), which was less compared to EE/LNG (+28.0%) and EE/DRSP (+65.5%). E4/DRSP had no effect on carbohydrate metabolism.**Conclusions:** E4/DRSP treatment has limited effects on endocrine and metabolic parameters. The effects on gonadotropins, cortisol, CBG, angiotensinogen, SHBG and triglycerides were less pronounced compared to EE-containing products.**Implications statement:** Combining E4 15 mg with DRSP 3 mg resulted in a COC with a different metabolic profile in comparison to EE-containing products. The clinical relevance of these findings needs to be further assessed, using clinical endpoints to establish the safety profile of this new COC.

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1. Introduction

Most oral contraceptives contain ethinylestradiol (EE) as the estrogenic component. The lower doses of EE in combined oral contraceptives (COCs) have been shown to be safe. However, EE can cause serious cardiovascular side effects such as venous thromboembolism, especially in women with risk factors. In addition, EE

increases the synthesis of various liver proteins, and affects lipid and carbohydrate metabolism [1].

Compared to EE, the effect of the natural human hormone estradiol (E2) on hepatic metabolism is reduced [2,3]. Therefore, replacing EE with E2 in a COC is associated with fewer metabolic effects, an improved safety profile [4,5] and a similar or even lower cardiovascular risk compared to other COCs [6]. The type of progestin used in COCs also determines their endocrine and metabolic effects. The newer progestins such as drospirenone (DRSP) bind more specifically to the progesterone receptor. This results in a reduction in androgenic, estrogenic, and glucocorticoid-related side

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effects, and a more neutral effect on metabolic parameters [7], while maintaining contraceptive efficacy.

Estetrol (E4) is a human-specific native estrogen produced in the fetal liver during pregnancy [8]. Chemically synthesized E4 is identical to the natural hormone and has been studied in contraception, menopause, osteoporosis, and breast cancer [9–11]. E4 in combination with DRSP inhibits ovulation and is associated with a favorable vaginal bleeding, safety and tolerability profile, and with high user satisfaction [9,12,13]. E4 (alone or in combination with DRSP) has limited effects on liver function and metabolic and endocrine parameters when used in doses up to 10 mg and for less than 3 months [14,15]. The objective of this study was to assess the effect of E4 15 mg/DRSP 3 mg (E4/DRSP), the target dose for pregnancy prevention, on endocrine and metabolic parameters after 6 treatment cycles. This study included two frequently used EE-containing COCs as comparators, one with levonorgestrel (LNG), considered to be one of the safest COCs, and one with DRSP, to validate changes related to the estrogen source.

2. Materials and methods

2.1. Study design

This was a single-center, randomized, open-label, controlled, 3-arm, parallel, exploratory study conducted from September 2016 through October 2017 at Dinoox BV, Groningen, the Netherlands (EudraCT 2016-001316-37, Clinicaltrials.gov NCT02957630). An independent ethics committee approved the study, which was conducted in accordance with Declaration of Helsinki and the ICH GCP guidelines. All participants provided written informed consent before study entry. The study consisted of a pretreatment cycle (baseline), followed by 6 treatment cycles of 28 days, and 5 visits: a screening visit, a pretreatment/randomization visit, 2 treatment visits (at cycles 3 and 6), and an end-of-study visit. Target sample size was 100 (40 in the investigational group and 30 per comparator group).

2.2. Study population

Participants included were healthy females aged 18 to 50 years with a body mass index between 18.0 and 30.0 kg/m², and a natural menstrual cycle of maximum 35 days. Excluded were subjects with contraindications for the use of oral contraceptives, with dyslipoproteinemia, or those using antilipidemic agents. The use of hormonal contraceptives and concomitant medications that interact with COCs was not allowed from 2 cycles before treatment initiation and during the study.

2.3. Study treatment

Subjects were stratified by previous hormonal contraceptive use (2 menstrual cycles or >2 menstrual cycles without use before study treatment initiation) and by age (≤ 35 years or >35 years of age). Subjects were randomly assigned, using a computerized, open-label, allocation sequence, to one of the following treatments in a 4:3:3 ratio: E4 15 mg (as monohydrate, equivalent to 14.2 mg anhydrous) combined with DRSP 3 mg (E4/DRSP), EE 30 μ g combined with LNG 150 μ g (EE/LNG), or EE 20 μ g combined with DRSP 3 mg (EE/DRSP). Women took 1 tablet daily for 6 consecutive cycles of 28 days. The E4/DRSP and EE/DRSP treatments were provided in a 24-day active/4-day placebo regimen, and EE/LNG in a 21-day active/7-day placebo regimen. E4/DRSP was manufactured by Haupt Pharma, Germany and provided by Estetra SPRL, Belgium. EE/LNG (Melleva 150/30, Leon Farma, Spain) and EE/DRSP (Yaz, Bayer Healthcare, Germany) were obtained from a local pharmacy. Study treatment started on the first day of menses follow-

ing the pretreatment cycle. Treatment compliance verification was based on a diary and check of returned packages.

2.4. Study assessments and primary outcome parameters

Primary outcome parameters:

- 1 Endocrine function: prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P), thyroid stimulating hormone (TSH), free thyroxine (fT3)/free triiodothyronine (fT4), dehydroepiandrosterone sulfate (DHEAS), androstenedione, total testosterone (T), free T, dihydrotestosterone (DHT), total cortisol, free cortisol, free cortisol index, and aldosterone;
- 2 Liver proteins: C-reactive protein (CRP), cortisol binding globulin (CBG), sex hormone binding globulin (SHBG), thyroxine binding globulin (TBG) and angiotensinogen;
- 3 Lipid profile: high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, ratio HDL-C/LDL-C, lipoprotein A, apolipoprotein A1, apolipoprotein B and triglycerides;
- 4 Carbohydrate metabolism: insulin, glucose, C-peptide, glycated hemoglobin (HbA1c), oral glucose tolerance test (OGTT) and calculation of Homeostasis Model Assessment-Insulin Resistance (HOMA-IR). For the OGTT test, the following parameters were calculated for glucose and insulin:
 - pre-OGTT concentration (Cpre);
 - maximum change from Cpre (Emax);
 - area under the serum concentration-time curve post OGTT (AUC);
 - area under the Cpre subtracted serum concentration-time curve post OGTT (rAUC).

Blood was sampled between days 18 and 21 at baseline and during cycles 3 and 6. Samples were analyzed by BARC laboratories, Gent, Belgium and samples for E2 were analyzed by ABL, Assen, the Netherlands. For the OGTT, subjects consumed a solution containing 75 g of glucose. Blood glucose and insulin concentrations were measured before ($t = 0$) and 0.5, 1, 1.5, 2 and 3 hours after intake of the glucose solution. Analytical methods, including reference ranges, are provided in Supplementary Table 1.

2.5. Statistical analysis

Statistical analyses were performed using SAS for Windows. All randomized subjects who had at least one post-treatment endocrine or metabolic assessment, and no major protocol deviations (Per Protocol Set [PPS] population) were included in the analysis. Parameters were summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, maximum and coefficient of variation [CV]). No formal sample size calculation was performed. The number of subjects included in this study (i.e., 40 in the E4/DRSP group and 30 subjects in each of the reference groups) is commonly used for studies investigating metabolic effects of contraceptives. Hence, the sample size was deemed sufficient to characterize the effect of E4/DRSP on the endocrine and metabolic parameters and make a descriptive comparison with the 2 EE-containing reference products. No formal statistical analysis was planned for this exploratory study; however, post hoc non-parametric analysis was performed on the absolute change from baseline for all endocrine, liver protein, and lipid profile parameters. A signed-rank test explored the difference between cycle 3 and baseline, and cycle 6 and baseline. The Kruskal-Wallis test explored treatment differences in the change from baseline at cycle 3 and at cycle 6; a significant overall treatment difference was followed by pairwise treatment comparisons using the Dwass-Steel-Critchlow-Fligner procedure. Alpha was set at 0.05.

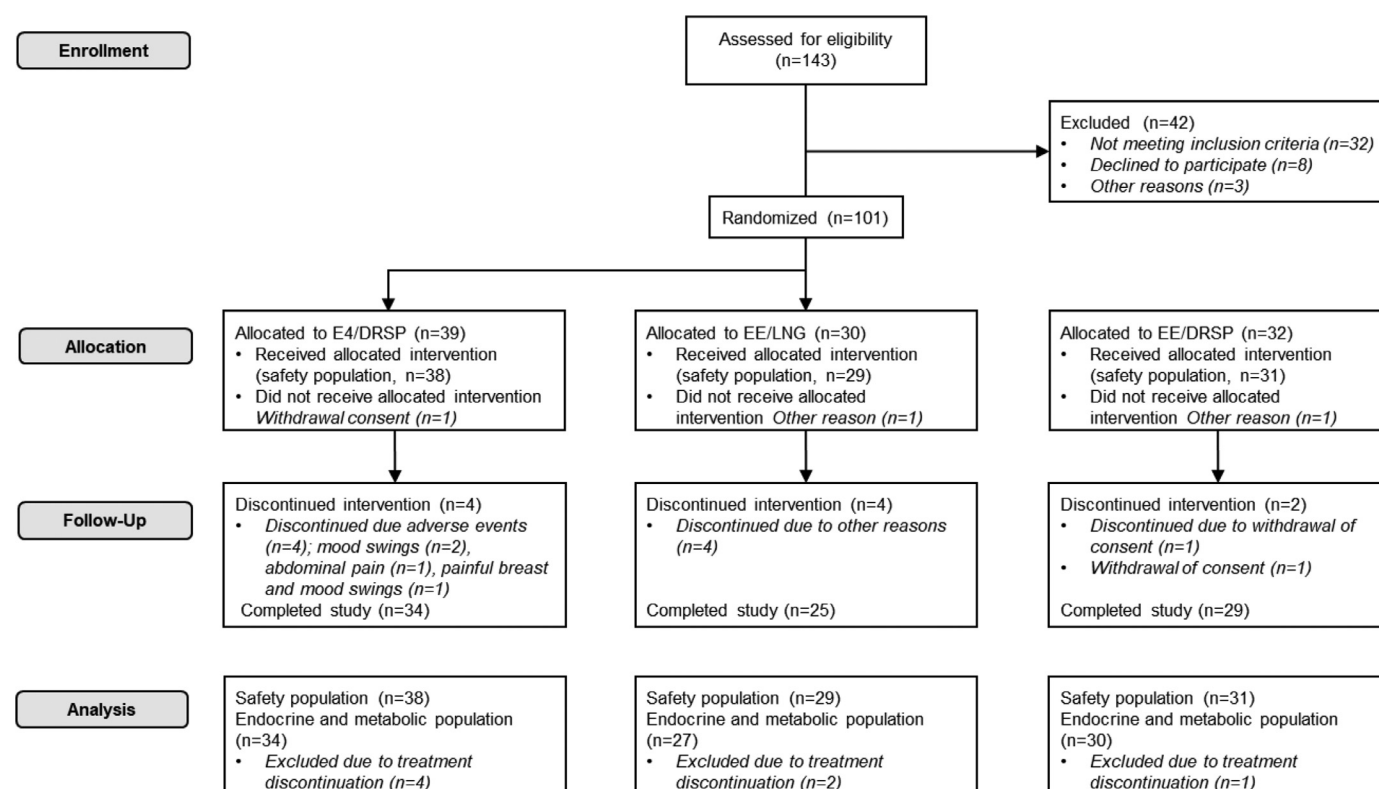


Fig. 1. Disposition of subjects.

Table 1
Mean demographic data at study entry—Safety population

	E4/DRSP n = 38	EE/LNG n = 29	EE/DRSP n = 31	All n = 98
Age, y. (range)	26.7 (19–47)	26.2 (18–44)	25.6 (18–40)	26.2 (18–47)
Weight, kg (range)	68.1 (53.1–97.8)	65.6 (50.4–79.2)	63.2 (50.3–80.7)	65.8 (50.3–97.8)
Height, cm (range)	170.8 (159–188)	169.6 (160–181)	168.4 (155–183)	169.7 (155–188)
BMI, kg/m ² (range)	23.33 (19.2–30.0)	22.83 (18.3–29.8)	22.27 (18.6–26.7)	22.85 (18.3–30.0)

BMI, body mass index. n = number of patients randomized and who started treatment (Safety population).

3. Results

3.1. Study population

Of 101 subjects allocated to treatment, 98 received study treatment and 88 completed the study (Fig. 1). The analysis of the primary endpoints was performed on data from 91 subjects in the PPS population. Demographics were similar between groups (Table 1).

Cycle 3 results were similar to those of cycle 6 and are therefore only provided in the tables and figures.

3.2. Endocrine parameters

E2 and progesterone were both suppressed with no obvious differences between treatment groups (Table 2). E4/DRSP slightly increased FSH (30.5%) and had hardly any effect on LH (−7.5%). FSH and LH were decreased with both EE/LNG (−84.0% and −92.0%, respectively) and EE/DRSP (−64.0% and −90.0%); Androstenedione and free T decreased in a similar way in all 3 treatment groups (Androstenedione: −31.0%, −49.0%, −40.0%; free T: −50.0%, −50.0%, −71.0%, respectively). Total cortisol increased by more than 100%

during treatment with EE/LNG (109.0%) and EE/DRSP (107.0%), while E4/DRSP only slightly increased total cortisol (26.0%). Calculated free cortisol decreased (−4.5%, −8.6%, and −11.7% for E4/DRSP, EE/LNG and EE/DRSP, respectively) and free cortisol index showed a similar decrease (−8.4%, −10.7%, and −14.7%, respectively). Aldosterone increased with E4/DRSP (103.0%) and EE/DRSP (179.5%) and decreased for EE/LNG (−40.0%). Other endocrine parameters prolactin, DHEAS, DHT, total T, fT3, and fT4 changed from baseline in one or more treatment groups. TSH remained relatively stable in all treatment groups.

All median endocrine parameters remained within reference ranges, except for the prolactin increase for E4/DRSP and EE/LNG, the free T decrease for EE/DRSP, and the cortisol increase with all treatments.

3.3. Liver proteins

Liver parameters, except CRP, increased from baseline in all 3 treatment groups (Table 3). Median values were within reference ranges except for SHBG in the EE/DRSP. Angiotensinogen increased by 170.0% and 206.5% for EE/LNG and EE/DRSP, respectively, and by 75.0% for E4/DRSP. SHBG increased substantially for EE/DRSP

Table 2

Endocrine parameters at baseline, cycle 3 and cycle 6 and change from baseline after treatment with E4/DRSP, EE/LNG, or EE/DRSP for 6 cycles in healthy females

Parameter	Treatment	Baseline	Cycle 3		Cycle 6 ^a	
		Median (min-max)	Median (min-max)	Median %CFB (min-max)	Median (min-max)	Median %CFB (min-max)
Prolactin (ng/mL)	E4/DRSP	19.60 (6.6, 45.4)	23.50 (5.8, 58.2)	17.5 ^c (−44.0, 171.0)	25.10 (9.9, 83.8)	19.5 ^c (−33.0, 201.0)
	EE/LNG	18.90 (10.3, 29.3)	27.50 (6.5, 48.8)	23.0 ^c (−58.0, 317.0)	23.80 (7.6, 51.3)	22.0 ^c (−52.0, 230.0)
	EE/DRSP	22.00 (9.9, 48.8)	22.15 (7.3, 74.1)	8.0 (−81.0, 181.0)	18.60 (6.8, 65.6)	−3.0 (−43.0, 148.0)
FSH (mIU/mL)	E4/DRSP	4.50 (1.6, 13.0)	4.70 (0.4, 8.9)	20.0 (−92.0, 200.0)	4.55 (0.5, 9.6)	30.5 (−90.0, 169.0)
	EE/LNG	4.50 (1.8, 24.1)	0.60 (0.1, 4.0)	−87.0 ^{c,d} (−100, 65.0)	1.00 (0.1, 4.2)	−84.0 ^{c,d} (−100, 110.0)
	EE/DRSP	5.10 (1.6, 14.3)	1.20 (0.1, 9.2)	−79.0 ^{c,d} (−99.0, 254.0)	0.70 (0.1, 7.8)	−64.0 ^{c,d} (−99.0, 256.0)
LH (mIU/mL)	E4/DRSP	7.25 (1.3, 36.3)	6.10 (0.5, 13.3)	−17.0 (−95.0, 538.0)	6.10 (0.2, 13.0)	−7.5 (−98.0, 392.0)
	EE/LNG	8.40 (2.8, 136.7)	0.10 (0.1, 8.2)	−97.0 ^{c,d} (−100, −46.0)	0.70 (0.1, 6.8)	−92.0 ^{c,d} (−100, 61.0)
	EE/DRSP	9.35 (1.7, 75.2)	1.40 (0.1, 10.3)	−87.5 ^{c,d} (−100, 182.0)	0.60 (0.1, 8.4)	−90.0 ^{c,d} (−100, 212.0)
E2 ^b (pg/mL)	E4/DRSP	113.5 (31.0, 346.0)	12.0 (12.0, 34.0)	−87.0 ^c (−97.0, −54.0)	13.5 (12.0, 66.0)	−86.5 ^c (−97.0, −8.0)
	EE/LNG	148.0 (48.0, 516.0)	12.0 (12.0, 20.0)	−92.0 ^c (−98.0, −75.0)	12.0 (12.0, 28.0)	−92.0 ^c (−98.0, −75.0)
	EE/DRSP	114.5 (23.0, 579.0)	12.0 (12.0, 61.0)	−86.0 ^c (−98.0, −48.0)	12.0 (12.0, 82.0)	−87.0 ^c (−98.0, −40.0)
Progesterone (ng/mL)	E4/DRSP	5.75 (0.2, 22.3)	0.25 (0.2, 0.6)	−93.5 ^c (−99.0, 150.0)	0.30 (0.2, 0.7)	−96.0 ^c (−99.0, 100.0)
	EE/LNG	6.70 (0.2, 20.6)	0.30 (0.2, 0.6)	−94.0 ^c (−99.0, 100.0)	0.20 (0.2, 0.6)	−95.0 ^c (−99.0, 150.0)
	EE/DRSP	1.15 (0.2, 13.2)	0.30 (0.2, 0.9)	−70.5 ^c (−98.0, 100.0)	0.40 (0.2, 0.7)	−60.0 ^c (−98.0, 100.0)
TSH (mU/L)	E4/DRSP	2.05 (1.24, 4.93)	2.26 (0.83, 8.19)	4.0 (−44.0, 153.0)	2.28 (0.15, 5.17)	6.0 (−90.0, 109.0)
	EE/LNG	2.07 (0.61, 4.84)	2.40 (0.81, 5.93)	28.0 ^c (−62.0, 211.0)	2.07 (1.07, 6.86)	12.0 (−41.0, 428.0)
	EE/DRSP	2.44 (0.89, 5.45)	2.66 (0.88, 10.10)	18.0 (−47.0, 211.0)	2.69 (0.84, 6.10)	7.0 (−49.0, 76.0)
fT3 (pg/dL)	E4/DRSP	3.26 (2.70, 4.01)	3.25 (2.43, 3.84)	−2.0 (−28.0, 26.0)	3.28 (2.64, 4.06)	−4.5 (−23.0, 25.0)
	EE/LNG	3.38 (2.31, 3.94)	3.47 (2.73, 5.45)	4.0 (−14.0, 46.0)	3.40 (2.74, 4.48)	6.0 ^{c,d} (−26.0, 39.0)
	EE/DRSP	3.23 (2.61, 4.67)	3.49 (2.68, 4.53)	3.0 (−20.0, 36.0)	3.43 (2.41, 4.16)	2.0 (−36.0, 35.0)
fT4 (ng/dL)	E4/DRSP	1.14 (0.87, 1.50)	1.21 (0.86, 1.50)	7.5 ^c (−15.0, 25.0)	1.21 (0.90, 1.49)	4.0 ^c (−12.0, 25.0)
	EE/LNG	1.15 (0.86, 1.36)	1.22 (1.00, 1.71)	10.0 ^c (−10.0, 29.0)	1.24 (0.91, 1.53)	6.0 ^c (−14.0, 36.0)
	EE/DRSP	1.23 (0.91, 1.62)	1.26 (0.97, 1.56)	4.0 ^c (−16.0, 20.0)	1.23 (0.96, 1.62)	2.0 ^c (−21.0, 20.0)
DHEAS (μg/dL)	E4/DRSP	273.5 (94, 535)	241.5 (86, 587)	−14.5 ^c (−35.0, 31.0)	251.5 (92, 538)	−10.5 ^c (−41.0, 32.0)
	EE/LNG	265.0 (71, 773)	211.0 (78, 623)	−20.0 ^c (−37.0, 15.0)	208.0 (74, 350)	16.0 ^c (−41.0, 21.0)
	EE/DRSP	239.0 (115, 535)	178.5 (62, 412)	−23.5 ^c (−59.0, −3.0)	179.0 (62, 314)	−27.0 ^{c,d} (−60.0, 13.0)
Androstene-dione (nmol/L)	E4/DRSP	9.90 (6.4, 22.6)	6.70 (1.8, 11.8)	−32.0 ^c (−92.0, 48.0)	7.5 (3.6, 12.1)	−31.0 ^c (−72.0, 44.0)
	EE/LNG	10.70 (2.4, 21.9)	5.90 (2.3, 12.0)	−44.0 ^c (−83.0, 108.0)	5.40 (2.6, 10.6)	−49.0 ^c (−80.0, 75.0)
	EE/DRSP	10.05 (4.2, 16.2)	6.35 (1.8, 13.4)	−40.0 ^c (−80.0, 50.0)	5.90 (2.1, 13.1)	−40.0 ^c (−70.0, 26.0)
Total T (ng/dL)	E4/DRSP	38.0 (12, 71)	26.5 (12, 47)	−35.0 ^c (−68.0, 2.0)	24.5 (12, 47)	−31.0 ^c (−63.0, 10.0)
	EE/LNG	41.0 (12, 76)	21.0 (12, 43)	−40.5 ^c (−71.0, 14.0)	19.0 (12, 41)	−37.5 ^c (−70.0, 41.0)
	EE/DRSP	34.0 (18, 79)	20.5 (12, 69)	−41.0 ^c (−77.0, 15.0)	21.0 (12, 67)	−33.0 ^c (−79.0, 15.0)
Free T (ng/dL)	E4/DRSP	0.50 (0.100, 1.00)	0.20 (0.10, 0.70)	−50.0 ^c (−80.0, 0.0)	0.20 (0.09, 0.60)	−50.0 ^c (−80.0, 0.0)
	EE/LNG	0.50 (0.10, 1.20)	0.20 (0.09, 0.50)	−60.0 ^c (−80.0, 0.0)	0.20 (0.09, 0.30)	−50.0 ^c (−83.0, 0.0)
	EE/DRSP	0.35 (0.20, 0.80)	0.086 (0.09, 0.20)	−75.0 ^c (−89.0, −50.0)	0.09 (0.09, 0.20)	−71.0 ^c (−89.0, −50.0)

(continued on next page)

Table 2 (continued)

Parameter	Treatment	Baseline	Cycle 3		Cycle 6 ^a	
		Median (min-max)	Median (min-max)	Median %CFB (min-max)	Median (min-max)	Median %CFB (min-max)
DHT (nmol/L)	E4/DRSP	0.35 (0.19, 1.43)	0.35 (0.15, 5.82)	−4.0 (−78.0, 854.0)	0.40 (0.15, 0.85)	−13.0 (−56.0, 80.0)
	EE/LNG	0.35 (0.15, 0.92)	0.20 (0.15, 0.47)	−35.0 ^c (−71.0, 73.0)	0.28 (0.15, 0.54)	−25.0 ^c (−72.0, 120.0)
	EE/DRSP	0.39 (0.15, 6.59)	0.27 (0.15, 4.10)	−17.0 (−93.0, 832.0)	0.36 (0.15, 1.02)	−3.5 (−60.0, 106.0)
Cortisol (μg/dL)	E4/DRSP	16.5 (9.6, 25.9)	21.05 (11.3, 34.8)	30.0 ^c (−16.0, 143.0)	20.6 (11.2, 32.7)	26.0 ^c (−25.0, 129.0)
	EE/LNG	15.2 (9.8, 23.5)	34.70 (22.5, 48.1)	117.0^{c,d} (19.0, 274.0)	32.7 (20.7, 39.6)	109.0^{c,d} (13.0, 248.0)
	EE/DRSP	17.7 (8.8, 23.2)	35.15 (20.0, 62.8)	104.0^{c,d} (−12.0, 380.0)	37.7 (22.3, 62.7)	107.0^{c,d} (13.0, 326.0)
Free cortisol (μmol/L)	E4/DRSP	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	8.3 (−56.89, 192.35)	0.02 (0.01, 0.03)	−4.5 (−60.00, 90.15)
	EE/LNG	0.02 (0.01, 0.04)	0.02 (0.01, 0.03)	6.5 (−68.36, 56.15)	0.01 (0.01, 0.02)	−8.6 (−65.08, 63.66)
	EE/DRSP	0.02 (0.01, 0.04)	0.02 (0.00, 0.03)	−14.6 (−67.25, 120.76)	0.01 (0.01, 0.04)	−11.7 (−68.27, 154.52)
Free cortisol Index (nmol/mg)	E4/DRSP	7.31 (4.12, 11.96)	7.75 (3.58, 10.76)	1.06 (−47.08, 116.82)	6.99 (3.29, 9.74)	−8.4 (−51.09, 52.05)
	EE/LNG	6.87 (4.52, 13.52)	6.57 (3.25, 9.29)	−0.94 (−59.95, 29.39)	6.19 (3.44, 8.05)	−10.7 ^c (−56.58, 37.91)
	EE/DRSP	7.73 (4.26, 11.84)	6.47 (2.43, 9.45)	−16.62 ^c (−60.63, 59.68)	6.09 (3.76, 10.91)	−14.7 ^c (−58.96, 81.26)
Aldosterone (pmol/L)	E4/DRSP	610.0 (90, 4106)	1171 (299, 3333)	103.0 ^c (−70.0, 542.0)	1398 (146, 4343)	103.0 ^c (−80.0, 627.0)
	EE/LNG	617.0 (179, 2368)	497.0 (156, 1726)	−11.0 ^d (−85.0, 148.0)	473.0 (69, 1289)	−40.0 ^{c,d} (−89.0, 288.0)
	EE/DRSP	614.5 (141, 1632)	1366 (175, 5959)	172.5 ^c (−64.0, 1384)	1396 (219, 6930)	179.5 ^c (−30.0, 617.0)

CFB, change from baseline; DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; E2, estradiol; FSH, follicle stimulating hormone; free T, free testosterone; fT3, free triiodothyronine; fT4, free thyroxine; LH, luteinizing hormone; total T, total testosterone; TSH, thyroid stimulating hormone.

Statistically significant differences from treatment with E4/DRSP are shown in bold. The significance level alpha of 5% was not adjusted for multiple testing as appropriate for exploratory analyses.

^a Data at cycle 6 or end of treatment.^b Limited E2 data available in serum show a similar trend.

^b Limited E2 data available in serum show a similar trend.

^c Difference vs baseline, $p < 0.05$.

^d Different from treatment with E4/DRSP, $p < 0.05$.

(251.0%); levels were 74.0% and 55.0% for EE/LNG and E4/DRSP, respectively. The cortisol carrier CBG increased with EE/LNG (152.0%) and EE/DRSP (140.0%); whereas an increase of only 40.0% was found for E4/DRSP (Table 3). TBG levels increased for EE/DRSP (70.0%), EE/LNG (37.0%) and E4/DRSP (17.0%).

3.4. Lipid profile

Overall, lipid parameters changed slightly. Differences were minor between treatment groups and median values remained within reference ranges (Table 4). Triglycerides changed to a lesser extent for E4/DRSP (24.0%) compared with EE/DRSP (65.5%); EE/LNG increased triglycerides levels by 28.0%. Apolipoprotein A1 increased for EE/DRSP (19.5%) and E4/DRSP (5.0%), and decreased for EE/LNG (−3.0%). Apolipoprotein B increased for E4/DRSP (4.0%), EE/LNG (23.0%), and EE/DRSP (11.5%). HDL-C slightly increased for EE/DRSP (8.5%) and E4/DRSP (4.0%), and decreased for EE/LNG (−16.0%). With E4/DRSP no significant changes from baseline were observed for LDL-C, total cholesterol, ratio HDL-C/LDL-C and lipoprotein A.

3.5. Carbohydrate metabolism

Carbohydrate parameters, including fasting insulin and glucose, C-peptide and HbA1c remained relatively stable in all treatment groups. Insulin resistance, calculated using HOMA-IR, increased for all treatments. However, variation in these data was large (Supplementary Table 2). At baseline, median (min-max) HOMA-IR val-

ues were 1.6 (0.6–3.8), 1.6 (0.3–4.4), and 1.4 (0.4–4.6) for E4/DRSP, EE/LNG, and EE/DRSP, respectively. At cycle 6, HOMA-IR increased to 2.2 (0.9–5.6), 2.0 (1.0–15.3), and 2.0 (1.2–5.7), respectively.

Baseline OGTT glucose concentrations increased with a peak after approximately 30 minutes and decreased thereafter, reaching baseline values after 90 minutes (Fig. 2). Insulin levels increased with a peak at 30 minutes, almost reaching baseline values after 180 minutes. OGTT glucose and insulin concentrations varied substantially with no remarkable treatment differences (Supplementary Table 2).

4. Discussion

Previous studies, of shorter duration and with a lower E4 dose, indicated that E4 alone and E4 in combination with DRSP have limited effects on serum lipids, and liver and carbohydrate metabolism [14,16]. The results of the present 6-cycle study, conducted with E4 15 mg/DRSP 3 mg, provide additional insight to these previous observations. E4/DRSP had a different and potentially favorable metabolic profile compared to the 2 EE-based COC reference treatments, EE/LNG and EE/DRSP.

As expected, all treatments decreased E2 and progesterone levels, indicative for the contraceptive efficacy of all combinations. E4/DRSP had less effect on LH and FSH compared to the EE-containing products. This observation was confirmed in a study on ovarian function, which showed that E4/DRSP (E4 15 mg/DRSP 3

Table 3

Liver proteins at baseline, cycle 3 and cycle 6 and change from baseline after treatment with E4/DRSP, EE/LNG, or EE/DRSP for 6 cycles in healthy females

Parameter	Treatment	Baseline	Cycle 3	Median %CFB (min-max)	Cycle 6 ^a	Median %CFB (min-max)
		Median (min-max)	Median (min-max)		Median (min-max)	
CRP (mg/dL)	E4/DRSP	0.10 (0.10, 0.88)	0.13 (0.10, 2.88)	0.0 (−63.0, 2780)	0.15 (0.10, 1.77)	0.0 ^b (−52.0, 1670)
	EE/LNG	0.10 (0.10, 4.72)	0.17 (0.10, 2.89)	20.0 (−83.0, 2790)	0.20 (0.10, 1.51)	30.0 (−97.0, 1410)
	EE/DRSP	0.10 (0.10, 0.70)	0.22 (0.10, 1.62)	70.0 ^b (−79.0, 1520)	0.17 (0.10, 1.09)	30.0 ^b (−86.0, 607.0)
CBG (μg/mL)	E4/DRSP	61.0 (45, 99)	80.0 (56, 127)	36.0 ^b (−40.0, 95.0)	82.5 (62, 144)	40.0 ^b (−27.0, 122.0)
	EE/LNG	61.0 (30, 90)	150.0 (101, 352)	152.0^{b,c} (55.0, 376.0)	152.0 (109, 318)	152.0^{b,c} (65.0, 354.0)
	EE/DRSP	58.5 (45, 101)	153.0 (102, 300)	149.5^{b,c} (58.0, 345.0)	152.5 (90, 303)	140.0^{b,c} (65.0, 448.0)
SHBG (nmol/L)	E4/DRSP	64.75 (25.3, 117.9)	97.0 (45.5, 185.7)	51.5 ^b (−23.0, 132.0)	87.15 (52.7, 196.0)	55.0 ^b (−22.0, 171.0)
	EE/LNG	67.30 (27.1, 144.4)	118.6 (58.5, 187.6)	67.0 ^b (−10.0, 313.0)	119.80 (65.2, 191.4)	74.0 ^b (−17.0, 261.0)
	EE/DRSP	70.55 (36.2, 125.6)	245.9 (164.0, 382.0)	239.5^{b,c} (128.0, 608.0)	264.30 (162.3, 447.4)	251.0^{b,c} (122.0, 637.0)
TBG (mg/L)	E4/DRSP	18.30 (12.5, 33.9)	22.5 (15.1, 30.5)	27.0 ^b (−15.0, 55.0)	22.00 (16.2, 39.9)	17.0 ^b (−27.0, 67.0)
	EE/LNG	18.10 (12.0, 31.9)	25.4 (19.6, 34.0)	47.0^{b,c} (1.0, 89.0)	23.70 (18.2, 37.9)	37.0^{b,c} (6.0, 99.0)
	EE/DRSP	17.55 (13.0, 27.5)	31.8 (20.5, 39.7)	79.5^{b,c} (9.0, 153.0)	28.05 (20.6, 43.2)	70.0^{b,c} (12.0, 108.0)
Angiotensinogen (μg/mL)	E4/DRSP	76.75 (47.0, 140.3)	113.9 (62.0, 186.5)	50.0 ^b (−17.0, 205.0)	138.00 (58.7, 231.1)	75.0 ^b (−26.0, 198.0)
	EE/LNG	81.50 (41.9, 135.8)	200.4 (146.2, 368.1)	181.0^{b,c} (38.0, 779.0)	222.90 (137.3, 399.5)	170.0^{b,c} (39.0, 853.0)
	EE/DRSP	74.85 (43.4, 147.0)	229.9 (97.0, 430.4)	214.5^{b,c} (36.0, 508.0)	262.50 (110.6, 453.9)	206.5^{b,c} (103.0, 413.0)

CBG, cortisol binding globulin; CFB, change from baseline; CRP, C-reactive protein; SHBG, sex hormone binding globulin; TBG, thyroxine binding globulin.

Statistically significant differences from treatment with E4/DRSP are shown in bold. The significance level alpha of 5% was not adjusted for multiple testing as appropriate for exploratory analyses.

^a Data at cycle 6 or end of treatment.^b Difference vs baseline, $p < 0.05$.^c Different from treatment with E4/DRSP, $p < 0.05$.

mg), despite the lower suppression of LH and FSH, results in adequate ovulation inhibition and ovarian function suppression [17]. Moreover, 2 recently completed phase 3 clinical trials showed that treatment with E4/DRSP at the dose studied here provides good contraceptive efficacy [18,19].

All 3 COCs increased the levels of liver proteins. The increases for angiotensinogen, CBG and TBG were significantly lower for E4/DRSP compared to EE/LNG and EE/DRSP. EE/DRSP increased SHBG substantially; EE/LNG and E4/DRSP had a limited effect on SHBG. Previous observations have shown that E4 slightly increases SHBG. These data suggest that E4 in combination with DRSP has a low estrogenic effect, in particular on the liver [15,20]. The milder effect of E4/DRSP on CBG, angiotensinogen, and gonadotropins compared to EE/DRSP and EE/LNG, also points toward lower total estrogenicity compared to EE/LNG and EE/DRSP, which could potentially be beneficial for the safety profile of E4/DRSP. The lower estrogenic effect of E4/DRSP was also reflected by the low impact of E4/DRSP on hemostatic activation [15,16,21].

The effects of COCs on lipid metabolism have been extensively studied and appear to be dose-related: COCs with a lower EE dose have a reduced metabolic impact [22]. Estrogens have a positive effect on lipid metabolism, increasing HDL-C and decreasing LDL-C, while progestins, depending on their type and androgenicity, may counteract these positive estrogenic effects [23–25]. COCs with a more androgenic progestin, such as LNG, show a decrease in HDL-C and an increase in LDL-C, while COCs with a newer progestin, such as DRSP, have a more favorable effect on lipids [26,27]. In the present study, there were no large effects on lipid param-

eters, except for triglycerides. High triglyceride serum levels are a contraindication to COC use. The neutrality of E4 on the liver translated into a lower (24.0%) increase in triglyceride serum levels in comparison with EE/DRSP (65.5%). EE/DRSP increased HDL-C slightly and EE/LNG decreased HDL-C, which is in line with previous studies [14,16]. E4/DRSP had no significant effect on HDL-C, indicating that the estrogenic effect of E4 on HDL-C is less than the effect of EE, and corroborates the lower estrogenic impact of E4 on the liver.

COC use has been associated with impaired glucose tolerance and insulin resistance, which are both risk factors for type II diabetes and cardiovascular disease. More recently, marketed COCs appear to be more neutral on carbohydrate metabolism [4]. In our study OGIT parameters for glucose and insulin did not remarkably differ between treatments and observed effects are not considered clinically relevant.

The inclusion of 2 frequently prescribed comparator COCs is a strength of this study, as our study results can be validated based on their well-known effects. The comparator EE/LNG is considered to be one of the safest COCs, and the inclusion of EE/DRSP allows for comparing the effects of different estrogen components. Here, we evaluated the effects of E4/DRSP on parameters that are considered surrogate markers for cardiovascular disease risk factors. These study results are promising but were obtained in a small sample of subjects, with restrictions on body mass index, concomitant medications and other diseases. Further large-scale studies in the full target population, using clinical endpoints, are needed

Table 4
Lipid profile at baseline, cycle 3 and cycle 6 and change from baseline after treatment with E4/DRSP, EE/LNG, or EE/DRSP for 6 cycles in healthy females

Parameter	Treatment	Baseline	Cycle 3		Cycle 6 ^a	
		Median (min-max)	Median (min-max)	Median %CFB (min-max)	Median (min-max)	Median %CFB (min-max)
HDL-C (mg/dL)	E4/DRSP	66.0 (43, 93)	66.5 (50, 90)	0.0 (−26.0, 23.0)	66.0 (52, 91)	4.0 (−24.0, 33.0)
	EE/LNG	69.0 (45, 89)	57.0 (41, 80)	−15.0 ^b (−30.0, 14.0)	59.0 (37, 74)	−16.0 ^{b, c} (−35.0, 11.0)
	EE/DRSP	68.5 (44, 102)	75.5 (55, 110)	8.0 ^b (−19.0, 50.0)	76.0 (49, 107)	8.5 ^b (−17.0, 45)
LDL-C (mg/dL)	E4/DRSP	89.5 (35, 145)	93.0 (34, 150)	2.0 (−33.0, 20.0)	89.0 (41, 146)	−2.0 (−24.0, 32.0)
	EE/LNG	89.0 (43, 163)	88.0 (48, 145)	2.0 (−26.0, 87.0)	98.0 (49, 146)	7.0 (−36.0, 57.0)
	EE/DRSP	92.0 (28, 149)	89.0 (30, 141)	−3.0 (−41.0, 41.0)	85.5 (23, 144)	5.0 (−38.0, 58.0)
Cholesterol (mg/dL)	E4/DRSP	166.5 (103, 217)	163.0 (106, 219)	−0.5 (−15.0, 13.0)	169.0 (116, 244)	4.0 (−20.0, 27.0)
	EE/LNG	166.0 (117, 233)	159.0 (117, 204)	−2.0 (−18.0, 20.0)	175.0 (120, 212)	1.0 (16.0, 25.0)
	EE/DRSP	170.5 (105, 250)	175.5 (107, 226)	4.5 ^{b, c} (−18.0, 22.0)	173.0 (112, 260)	6.5 ^b (−20.0, 39.0)
Ratio HDL-C/LDL-C	E4/DRSP	0.75 (0.4, 1.9)	0.70 (0.4, 1.7)	0.0 (−22.0, 42.0)	0.75 (0.4, 1.5)	0.0 (−25.0, 80.0)
	EE/LNG	0.80 (0.3, 1.7)	0.60 (0.3, 1.5)	−14.0 ^b (−65.0, 40.0)	0.60 (0.3, 1.4)	−17.0 ^{b, c} (−53.0, 40.0)
	EE/DRSP	0.80 (0.4, 2.4)	0.80 (0.5, 2.2)	15.0 (−38.0, 86.0)	0.80 (0.6, 3.4)	17.0 ^b (−46.0, 100.0)
Lipoprotein A (nmol/L)	E4/DRSP	20.00 (20.0, 246.1)	20.00 (20.0, 280.8)	0.0 (−32.0, 38.0)	20.00 (20.0, 276.2)	0.0 (−40.0, 36.0)
	EE/LNG	20.00 (20.0, 361.5)	20.00 (20.0, 236.5)	0.0 ^b (−44.0, 30.0)	20.00 (20.0, 244.7)	0.0 ^b (−55.0, 46.0)
	EE/DRSP	21.95 (20.0, 355.6)	20.00 (20.0, 239.2)	0.0 ^b (−60.0, 83.0)	20.00 (20.0, 262.5)	0.0 ^b (−57.0, 32.0)
Apolipoprotein A1 (mg/dL)	E4/DRSP	161.0 (125, 217)	163.5 (126, 215)	2.0 (−17.0, 20.0)	174.5 (133, 220)	5.0 ^b (−20.0, 23.0)
	EE/LNG	164.0 (123, 202)	155.0 (124, 192)	−4.0 (−20.0, 29.0)	160.0 (120, 194)	−3.0 ^{b, c} (−23.0, 43.0)
	EE/DRSP	162.0 (114, 227)	197.5 (143, 255)	20.5 ^{b, c} (−4.0, 50.0)	190.5 (140, 264)	19.5 ^{b, c} (−5.0, 64.0)
Apolipoprotein B (mg/dL)	E4/DRSP	73.5 (31, 120)	75.0 (30, 137)	4.5 ^b (−15.0, 38.0)	79.0 (35, 139)	4.0 ^b (−20.0, 48.0)
	EE/LNG	73.0 (36, 140)	83.0 (49, 120)	17.0 ^{b, c} (−19.0, 93.0)	90.0 (45, 132)	23.0 ^{b, c} (−12.0, 70.0)
	EE/DRSP	72.0 (28, 104)	78.0 (31, 115)	11.0 ^{b, c} (−30.0, 55.0)	80.0 (31, 135)	11.5 ^b (−17.0, 61.0)
Triglycerides (mg/dL)	E4/DRSP	71.5 (36, 125)	80.0 (48, 169)	10.5 ^b (−43.0, 141.0)	77.5 (50, 228)	24.0 ^b (−28.0, 159.0)
	EE/LNG	65.0 (32, 134)	104.0 (40, 158)	33.0 ^{b, c} (−31.0, 147.0)	88.0 (34, 227)	28.0 ^b (−17.0, 161.0)
	EE/DRSP	62.5 (36, 138)	106.0 (60, 192)	65.0 ^{b, c} (−12.0, 280.0)	103.0 (63, 238)	65.5 ^{b, c} (23.0, 198.0)

CFB, change from baseline; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Statistically significant differences from treatment with E4/DRSP are shown in bold. The significance level alpha of 5% was not adjusted for multiple testing as appropriate for exploratory analyses.

^a Data at cycle 6 or end of treatment.

^b Difference vs baseline, $p < 0.05$.

^c Different from treatment with E4/DRSP, $p < 0.05$.

to provide more insight into the cardiovascular safety profile of E4/DRSP.

Overall, the results of this study confirm previous observations that E4/DRSP has limited effects on liver proteins, lipid profile, carbohydrate metabolism, cortisol, and gonadotropins. The effect on other endocrine parameters, including suppression of ovarian steroids, was typical for a COC. In conclusion, combining E4 15 mg with DRSP 3 mg resulted in a different and potentially favorable metabolic profile.

Declaration of competing interest

C. Klipping and I. Duijkers are directors of Dinov BV, a CRO that received funding for the study via PRA Health Sciences. M. Mawet, C. Maillard, A. Bastidas and M. Jost are employees of Mithra. J.M.

Foidart is a member of the board at Mithra and received financial support for the supervision of this study.

Funding

The study was funded by Estetra SRL (an affiliate's company of Mithra Pharmaceuticals).

Acknowledgments

The study was sponsored by Estetra SRL, Liège, Belgium. Medical writing support was provided by Mireille Gerrits, PharmD, at T4C Communications, Hilversum, the Netherlands. Statistical support was provided by Fabrice Nollevaux and Maud Hennion, Phar-

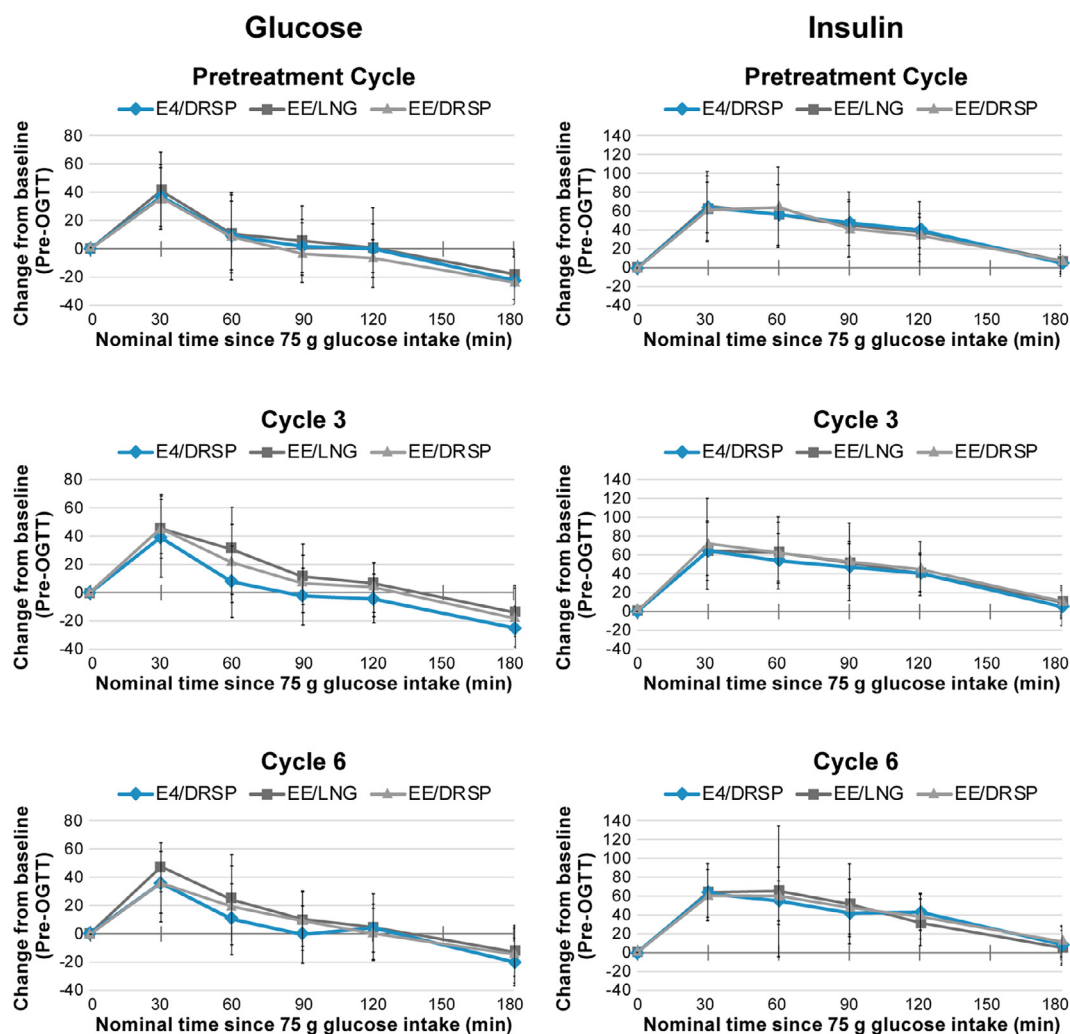


Fig. 2. Mean (\pm SD) glucose (left) and insulin (right) plasma concentrations during OGTT vs time plots at pretreatment, cycle 3 and cycle 6 after treatment with E4/DRSP, EE/LNG, or EE/DRSP for 6 cycles in healthy subjects.

malex, Belgium. PRA Health Sciences was involved as contract research organization for organizing the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.contraception.2021.01.001](https://doi.org/10.1016/j.contraception.2021.01.001).

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