CHAPTER 7

Metabolic profile of a continuous versus a cyclic low-dose combined oral contraceptive after one year of use

Eur J Contracept Reprod Health Care 2011 Apr;16(2):85-94

J. Burggraaf[1], M Rad[1], ML de Kam[1], SO Skouby[2], J Jespersen[3], U Winkler[4], AF Cohen[1], C Kluft[1,5]

1 Centre for Human Drug Research, Leiden
2 TNO Quality of Life, Gaubius Laboratory, Leiden
3 Pfizer Inc., Collegeville, PA, USA

ABSTRACT

OBJECTIVES: To compare the effects of a combined oral contraceptive (COC) taken continuously with those of one of similar composition taken cyclically on 30 variables related to haemostasis, lipids, carbohydrates, bone metabolism, and sex-hormone binding globulin (SHBG).
Methods: This randomised, open-label, multicentre, comparative substudy of a larger phase 3 trial was performed involving 147 healthy women (age 18–49 years). Participants received either the COC containing levonorgestrel (LNG) 90 µg and ethinylestradiol (EE) 20 µg continuously or the one containing LNG 100 µg and EE 20 µg cyclically, in a 21-days-on / 7-days-off pattern.
Results: After 13 pill packs, changes in total cholesterol (0.23 vs. −0.06 mmol/l), low-density lipoprotein (0.25 vs. −0.12 mmol/l), and high-density lipoprotein (−0.06 vs. −0.15 mmol/l) differed significantly ($p<.05$) between the continuous and cyclic regimens, respectively. Increases were significantly greater ($p<.05$) for protein C antigen (11.8% vs. 6.1%) and SHBG (791 vs. 565 nmol/l), and significantly smaller ($p<.05$, ranks) for D-dimer (19 vs. 37 µg FE/l).
CONCLUSIONS: Overall, the continuous and cyclic regimens affected metabolic variables similarly. The larger increase in SHBG with the continuous COC is consistent with a higher net oestrogenic effect due to a lower daily dose of LNG. Prospective studies are required to determine the long-term effects of this first continuous COC regimen.

INTRODUCTION

Extended regimens of intake of combined oral contraceptives (COCs) have become increasingly popular over the years because of their alleviation of cycle-related conditions such as premenstrual syndrome, headache during the pill-free week, excessive menstrual bleeding, and dysmenorrhoea. The most common extended pattern of intake skips the pill-free week of the usual 21-days-on, 7-days-off monophasic COC regimen for up to six cycles.

The long-term metabolic effects of such a regimen are largely unknown. The continuous use of a COC implies uninterrupted exposure to an oestrogen and a progestin, and may result in effects different from those of the cyclic regimen. Of particular interest are the metabolic changes that are associated with the risk of arterial disease and venous thromboembolism (VTE). The former could be affected through induction of more profound effects on lipid and carbohydrate metabolism, and the latter through induction of a greater imbalance in procoagulant and anticoagulant activity, possibly due to extended steroid exposure. The continuous regimen may decrease the risk of VTE by preventing the up- and down-regulation of the levels of procoagulant and anticoagulant factors during the pill-free week and the first week of pill intake, since such fluctuations might cause an imbalance in these levels. However, there is no epidemiologic proof available that such a cyclic risk alteration is associated with an increased VTE risk.

Prior to this report, two 6-month studies that evaluated continuous ethinylestradiol (EE) 30 µg with gestodene 75 µg [1], or compared EE 30 µg with drospirenone 3 mg taken continuously versus cyclically [2], were published. The authors of these trials concluded that metabolic changes with continuous regimens were similar to those with cyclic regimens. This study compares a COC taken continuously with one containing the same amount of EE, and a slightly higher progestin dose, used cyclically. This low-dose continuous COC called Lybrel™ was approved by the Food and Drug Administration and marketed in the United States of America and contains 90 µg LNG and 20 µg EE. It was derived from the already established cyclic low-dose COC containing 100 µg LNG and 20 µg EE (Alesse™ in the United States; Loette™ in Europe). This report describes a multicentre substudy comparing the effects of the above-mentioned COCs on haemostatic variables and on lipid, carbohydrate, and bone metabolism, investigating the effects of extended steroid exposure and of different oestrogen/progestin ratios.

MATERIALS AND METHODS

Study design

This was an open-label, randomised, multicentre substudy (two sites in The Netherlands and two sites in Poland) conducted in 2003-2004. The substudy compared the metabolic effects of a continuous regimen of a COC containing 90 µg LNG and 20 µg EE (LNG/EE 90/20) with those of a cyclic regimen (21 days on, 7 days off) of a COC containing 100 µg LNG and 20 µg EE (LNG/EE 100/20). Both treatments were taken for a full year, the former without interruption.

The substudy was part of a larger main study of the two treatments that demonstrated their full safety and contraceptive efficacy (Pearl Index for continuous 0.00, 95% confidence interval (CI) 0.00-1.56 and for cyclic 1.19, 95% CI 0.25-3.48) in 641 women aged 18 to 49 years of age over 13 cycles [3]. The main study was conducted according to the Declaration of Helsinki and its amendments and in accordance with the Guidelines for Good Clinical Practice. The study protocol received Medical Ethics Committee approval prior to its start.

Subjects

Subjects were recruited through advertisement with posters and flyers in the university buildings and in the local and national papers and magazines. They were healthy females who were 18–49 years old at the start of treatment and had a body mass index of 16–30 kg/m^2 (inclusive), a regular menstrual cycle of 21–35 days, and no contraindications for use of contraceptive steroids. They were willing to rely on study medication as their only method of contraception. They did not have diabetes, did not smoke more than ten cigarettes daily and did not use anticoagulant drugs, aspirin, lipid-lowering drugs, or drugs that would compromise the contraceptive effect of COCs. Eligibility was determined after a medical screening consisting of medical history, physical and gynaecologic examinations, cervical smear, blood pressure, routine haematology and blood chemistry, urinalysis, and serum pregnancy test. All subjects gave written informed consent for the main study [3] and the metabolic substudy described herein before study initiation.

Blood sampling

Blood sampling for metabolic variables was performed once between days 12 and 26 (depending on the length of the cycle, but always in the luteal phase) of the cycle just before the start of treatment and once during the third week (days 14–21) of pill-intake of treatment pill packs 7 and 13. Subjects all initiated pill intake on cycle days 1, 2, 3, 4, or 5. All samples were taken after a 12-hour fast. Subjects had not been using steroidal contraceptives within two cycles prior to blood sampling at baseline. Prior to each blood sampling, subjects refrained from anti-inflammatory drugs for two weeks and from alcohol for at least 18 hours. Sampling was done after a rest period of 15 minutes in the supine position and by a good clean venepuncture with minimal stasis. Blood was collected in EDTA (lipids and haemoglobin A_{1c} [HbA_{1c}]), citric acid, theophylline, adenosine, dipyridamole (CTAD; F1+2, D-dimer, and plasminogen-activator inhibitor-1 [PAI-1] antigen), Stabylite® (tissue-type plasminogen activator (t-PA) activity), citrate (other haemostatic variables), and serum (bone markers, glucose, and insulin) tubes.

Assays

Metabolic parameters included a carbohydrate and lipid panel, haemostasis variables, bone markers, and sex hormone-binding globulin (SHBG) (Immulyte® SHBG). The carbohydrate panel included fasting glucose (GLU dry chemistry slide for the Vitros 250 Clinical Chemistry analyzer), fasting insulin, and HbA_{1c} (Nycocard® HbA_{1c} kit from Axis Shield). The lipid panel included fasting total cholesterol (TC), high-density lipoprotein (HDL), HDL_2, HDL_3, and very low-density lipoprotein (VLDL) (enzymatic CHOD-PAP, Roche), fasting triglycerides (TG) (GPO-PAP, Roche), low-density lipoprotein (LDL) (calculated according to Friedewald), and lipoprotein a (Lp_a) (Beckman Array rate nephelometer). Samples obtained by ultracentrifugation were characterised for volume by weight and density, and for HDL_2 and HDL_3, TC, VLDL, and TG content. HDL was measured after the apo-B–containing lipoproteins were precipitated with phosphotungstate/Mg^{2+}.

The haemostatic panel included prothrombin and activated partial thromboplastin times (PT and APTT) (Thromborel S from Dade-Behring and STA APTT, respectively), factor VII total (Coa-Set® Factor VII), factor VII activated (Staclot® VIIA-rTF), factor VII clotting (STA Neoplastin® plus), fibrinogen (STA Fibrinogen from Roche on the automated clotting-analyser STA, Diagnostica STAGO/Roche), antithrombin activity against Factor Xa (Coamatic® Antithrombin), protein C antigen (Asserachrom® Protein C kit), protein C activity (STA Protein C Clotting, Diagnostica Stago), protein S total antigen (Asserachrom® Total Protein S), protein S activity (Bioclot™ Protein S kit), t-PA activity (BIA Chromolize™ t-PA kit from Biopool), PAI-1 antigen (Elitest® PAI-1 Antigen, Hyphen Biomed), prothrombin fragment F1+2 (Dade-Behring) and D-dimer (Fibrinostika® FbDP, Organon Teknika / Biomerieux), and factor V Leiden (Coatest® APC™ Resistance-V test, Chromogenix/IL).

The bone marker panel included C-telopeptide (Serum CrossLaps® ELISA, Nordic Bioscience Diagnostics) and osteocalcin (N-MID® osteocalcin ELISA, Nordic Bioscience Diagnostics).

STATISTICAL ANALYSIS

Fifty subjects per group would provide 90% power to detect a difference of 0.458 mmol/l in TC values between treatment groups, assuming a standard deviation of 0.7, using a two-sided test at the 5% level of significance.

The baseline characteristics were compared between groups with either the Fisher exact test or the one-way analysis of variance with treatment as factor. A paired t-test was used to analyse absolute and adjusted mean changes from baseline within treatment groups. An analysis of covariance (ANCOVA) model with treatment as a factor and baseline value as a covariate was used to calculate and compare the adjusted mean changes from baseline between groups. To supplement the use of parametric methods in the presence of some departure from the normality assumption, ANCOVA was also applied to the ranks of the data. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as fasting serum insulin (pmol/l) x fasting serum glucose (mmol/l)/135, per subject per visit [4]. Subsequently, repeated-measures ANCOVA was performed on the log-transformed values, as the absolute values showed a skewed distribution. Outliers were defined as values outside the range of mean ± 3 SD, were identified in a blinded fashion, and were removed from the analysis as indicated in the Results.

In addition, discriminant analysis (DA) was done at $p<.05$ on the log-transformed pill pack 13 change from baseline and on pill pack 13 values, in two

data sets: [1] all data and [2] haemostatic variables. For each variable in the DA, the p-value and the partial R-square value were reported. For variables with a partial R-square ≥.1 (explaining at least 10% of the difference between the treatments), canonical coefficients were calculated and used to formulate an algorithm. The mean Z as well as the classification accuracy of each algorithm was calculated. Statistical analyses were performed using SAS for Windows V9.1.2 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

In the substudy, 74 and 73 subjects (n=147 total) started treatment with the continuous and the cyclic COCs, respectively. All subjects started treatment on one of the first five days of their menstrual cycle. The last subject enrolled started treatment approximately 6 months after the first subject did. Overall, 42 participants (25 in the continuous COC group and 17 in the cyclic COC group) did not complete the study. Of these participants, 32 discontinued from the study before sampling during pill pack 7 (19 in the continuous COC group and 13 in the cyclic COC group). In the analysis, subjects were excluded if they had only baseline values for a parameter or had only outlying on-treatment values for a specific test (determined in a blinded fashion). Subjects were also excluded from the carbohydrate and lipid analyses if their fasting status was unknown. The data set analysed consisted of 122 participants (61 in each treatment group). An overview of the demographics of the treated subjects is provided in Table 1.

Table 1 Demographic and other baseline characteristics

Characteristic	Continuous LNG 90 µg/ EE 20 µg (N=74)	Cyclic LNG 100 µg / EE 20 µg (N=73)	p-value*,**
Age	27.8 ± 8.58 (18–49)	27.1 ± 7.20 (18–47)	0.586*
Ethnicity n (%)			0.526**
White	66 (89)	62 (85)	
Black	5 (7)	4 (6)	
Asian	1 (1)	1 (1)	
Other	2 (3)	6 (8)	
Height (cm)	169 ± 6.7 (153.5–187)	170 ± 6.6 (156–186.5)	0.660*
Weight (kg)	64.9 ± 11.2 (45.2–96)	66.4 ± 9.5 (50–91.6)	0.397*
Body mass index (kg/m²)	22.6 ± 3.0 (17.3–30.3)	23.1 ± 3.1 (17.8–30.5)	0.329*
Smokes cigarettes, n (%)			0.546*
No	55 (74.3)	51 (69.9)	
Yes	19 (25.7)	22 (30.1)	
Number per day	6.3 ± 3.2 (1–10)	5.3 ± 3.6 (1–10)	0.354*

Data are mean ± standard deviation (range) unless otherwise indicated.
*One-way analysis of variance with treatment as factor
**p-value for chi-square

Metabolic parameters

Table 2 summarises the adjusted mean changes from baseline for carbohydrate and lipid measures and highlights the differences between the continuous and the cyclic groups. Fasting glucose, insulin, and HbA_{1c} levels were for the most part similar between subjects taking continuous LNG/EE 90/20 and those taking the 21-day, cyclic regimen of LNG/EE 100/20. The only significant change in HOMA-IR was a transient increase at treatment pill pack 7 in users of the cyclic COC (estimate of difference 15%, 95% confidence interval (CI) 1.8 – 30.0%, p<.05). After one year of use, however, there were no within-group or between-group differences observed for HOMA-IR.

Table 2 Baseline ± standard deviation and adjusted mean change ± standard error from baseline in carbohydrate metabolism, lipids, bone markers, and SHBG

	Parameter	Continuous LNG 90 µg / EE 20 µg			Cyclic LNG 100 µg / EE 20 µg		
		Baseline	Pack 7	Pack 13	Baseline	Pack 7	Pack 13
Carbohydrates	Glucose (mmol/l)	4.77 ± 0.32	-0.00 ± 0.04	0.02 ± 0.05	4.76 ± 0.39	0.06 ± 0.04	0.04 ± 0.05
	Insulin (pmol/l)	57.19 ± 27.39	3.00 ±3.35	5.05 ± 2.90	55.18 ± 24.55	7.67 ± 3.16	4.09 ± 2.90
	HbA_{1C} (%)	5.14 ± 0.48	0.10 ± 0.07**	0.24 ± 0.10	5.13 ± 0.53	0.22 ± 0.06	0.14 ± 0.10
Lipids	Total cholesterol (mmol/L)	4.46 ± 0.81	0.25 ± 0.08*	0.23 ± 0.08*	4.52 −0.09 ± 0.88	± 0.07	−0.06 ± 0.08
	Triglycerides (mmol/L)	0.79 ± 0.26	0.23 ± 0.04*	0.20 ± 0.04	0.85 ± 0.23	0.10 ± 0.04	0.16 ± 0.04
	LDL (mmol/l)	2.54 ± 0.58	0.22 ± 0.06*	0.25 ± 0.07*	2.62 ± 0.59	−0.11 ± 0.06	−0.12 ± 0.07
	HDL (mmol/l)	1.47 ± 0.37	0.00 ± 0.03	−0.03 ± 0.03	1.47 ± 0.31	0.01 ± 0.03	−0.04 ± 0.03
	HDL_2 (mmol/l)	0.59 ± 0.21	−0.16 ± 0.02**	−0.15 ± 0.02	0.61 ± 0.24	−0.10 ± 0.02	−0.11 ± 0.02
	HDL_3 (mmol/l)	1.17 ± 0.20	−0.07 ± 0.03	−0.06 ± 0.03*	1.17 ± 0.20	−0.07 ± 0.03	−0.15 ± 0.03
	VLDL (mmol/l)	0.39 ± 0.13	−0.07 ± 0.02	−0.10 ± 0.02	0.39 ± 0.16	−0.11 ± 0.02	−0.10 ± 0.02
	Lipoprotein A (g/l)	0.08 ± 0.09	−0.02 ± 0.00	−0.02 ± 0.01	0.14 ± 0.15	−0.03 ± 0.00	−0.02 ± 0.01
Bone markers	Osteocalcin (µg/l)	30.33 ± 13.81	−8.02 ± 0.74	−6.87 ± 0.92	27.67 ± 12.04	−7.31 ± 0.69	−7.43 ± 0.89
	C-telopeptide (pmol/L)	6310 ± 2628	−1539 ± 174	−1391 ± 210	5997 ± 2475	−1313 ± 163	−1347 ± 202
Other	SHBG (nmol/l)	1201 ± 445	704 ± 77	791 ± 69*	1192 ± 469	579 ± 72	565 ± 68

Numbers of subjects analysed ranged from 49 to 59 for pill pack 7 and 42 to 51 for pill pack 13, depending on the variable
* p<.05 for between-group differences (analysis of covariance on data) for the same parameter at the same time point
** p<.05 for between-group differences (analysis of covariance on ranks) for the same parameter at the same time point

Table 3 Baseline mean ± standard deviation and adjusted mean change ± standard error from baseline in haemostatic parameters

	Parameter	LNG 90 µg/ EE 20 µg			LNG 100 µg / EE 20 µg		
		Baseline	Pack 7	Pack 13	Baseline	Pack 7	Pack 13
General	PT, sec	13.91 ± 0.96	-0.87 ± 0.08	-0.73 ± 0.08	13.99 ± 0.92	-0.70 ± 0.07	-0.61 ± 0.08
	APTT, sec	35.71 ± 5.45	-2.18 ± 0.38	-2.69 ± 0.33	35.64 ± 3.85	-2.69 ± 0.36	-2.42 ± 0.32
Procoagulation	Factor VII total, %	99.37 ± 23.13	21.33 ± 2.66	15.87 ± 2.82	94.92 ± 22.91	15.40 ± 2.45	15.00 ± 2.71
	Factor VII activated, U/l	49.67 ± 25.76	16.67 ± 3.67	13.48 ± 3.55	48.37 ± 23.35	11.15 ± 3.48	9.59 ± 3.40
	Factor VII clotting, kU/l	1.05 ± 0.18	0.03 ± 0.02	-0.04 ± 0.02	1.04 ± 0.16	-0.03 ± 0.02	-0.05 ± 0.02
	Fibrinogen, g/ l	3.17 ± 0.53	0.22 ± 0.07	0.14 ± 0.07	3.18 ± 0.62	0.25 ± 0.07	0.24 ± 0.07
Anticoagulation	Antithrombin III activity, kU/l	1.05 ± 0.10	-0.05 ± 0.02	-0.06 ± 0.01	1.05 ± 0.10	-0.03 ± 0.01	-0.04 ± 0.01
	Protein C antigen, %	92.40 ± 16.47	12.31 ± 1.42[a]	11.75 ± 1.56[a]	91.84 ± 15.19	7.95 ± 1.34	6.05 ± 1.50
	Protein C activity, kU/l	1.24 ± 0.19	0.08 ± 0.02	0.07 ± 0.02	1.22 ± 0.19	0.04 ± 0.02	0.03 ± 0.02
	Protein S antigen, kU/l	1.13 ± 0.20	-0.05 ± 0.02	-0.06 ± 0.03	1.09 ± 0.21	-0.09 ± 0.02	-0.08 ± 0.03
	Protein S activity, kU/l	0.92 ± 0.21	0.00 ± 0.02	-0.02 ± 0.02	0.84 ± 0.16	-0.02 ± 0.02	-0.03 ± 0.02
Profibrinolytic	t-PA activity, kU/l	0.69 ± 0.32	0.32 ± 0.05	0.22 ± 0.04	0.64 ± 0.28	0.32 ± 0.05	0.18 ± 0.04
Antifibrinolytic	PAI-1 antigen, ng/ml	30.64 ± 18.30	-21.79 ± 2.91	-22.95 ± 3.82	39.11 ± 32.43	-18.28 ± 2.73	-16.72 ± 3.67
Coagulation products	Fragment 1+2, nmol/l	824.50 ± 271.15	178.09 ± 35.28	135.37 ± 41.75	839.50 ± 309.19	140.31 ± 33.66	171.91 ± 39.56
	D-dimer, µg FE/l	115.86 ± 48.46	23.58 ± 8.52	18.69 ± 7.60[b]	120.55 ± 47.90	19.91 ± 7.91	37.12 ± 7.52

Numbers of subjects analysed ranged from 49 to 59 for pill pack 7 and 42 to 51 for pill pack 13, depending on the variable
* p<.05 for between-group differences (analysis of covariance on data) for the same parameter at the same time point
** p <.05 for between-group differences (analysis of covariance on ranks) for the same parameter at the same time point

Of the lipid measures, TC and LDL were significantly different between groups at pill packs 7 and 13 (Table 2). Smokers in both groups had a significant reduction in LDL, while non-smokers did not. In the cyclic group, the median change in LDL in smokers was −15.8% (n=12), and in non-smokers it was −0.66% (n=33; p=.04, Mann-Whitney).

The bone markers osteocalcin and C-telopeptide were affected similarly in the two groups throughout the study (Table 2). Statistically significant increases from baseline in SHBG (p<.001) were noted at pill packs 7 and 13 for both the continuous (73% and 77% increases, respectively) and the cyclic (58% and 59% increases, respectively) groups; after pill pack 13, the mean increase with the continuous COC was significantly higher than that with the cyclic COC (p=.021).

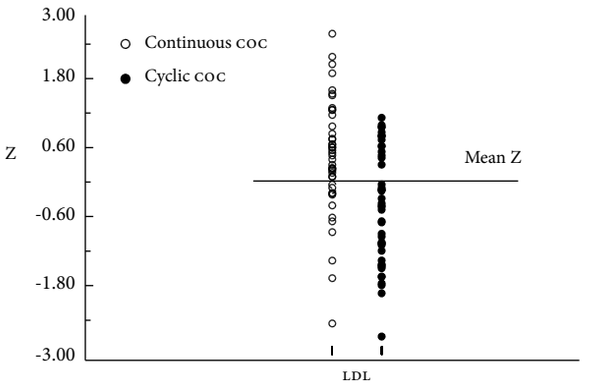
Table 3 summarises the adjusted mean changes from baseline for haemostatic variables. No significant between-group differences were observed for PT and APTT at pill packs 7 and 13, or for any procoagulation factors. Except for an increase from baseline in protein C antigen that was significantly greater for the continuous than the cyclic group at pill packs 7 (p=.028) and 13 (p=.010), but was not considered clinically important, no other between-group differences were observed for anticoagulation factors. Profibrinolytic (t-PA activity) and antifibrinolytic (PAI-1 antigen) variables were also similar between groups at pill packs 7 and 13. For products of coagulation, the increase from baseline for D-dimer was significantly less (p=.039) in the continuous versus the cyclic group at pill pack 13. However, the cyclic COC group had a greater increase from baseline at pill pack 13 than at pill pack 7. Of the 128 subjects who were tested at baseline for factor V Leiden, five tested positive for the heterozygous mutation. None of these or any other subjects reported adverse events related to thrombosis.

Discriminant analysis

Of the four data sets analysed (change from baseline of all data and of the haemostatic variables, and the pill pack 13 values of all data and of the haemostatic variables), only the change from baseline of LDL in the all-data set was found to be discriminative of the treatments and associated with partial R-square ≥.1 (p-value; partial R-square) (p=.0012; 0.1645). The canonical coefficient calculated for LDL was 13.0; thus, the following algorithm was formulated: $Z = 13 \times \Delta \log LDL$

For the continuous and the cyclic COC, the mean Z was 0.43 and −0.41, respectively, and the classification accuracy was 72% above the average Z and 67% below the average Z, respectively (Figure 1).

Figure 1 Scatter plot of the discriminating function $Z_{CFBa}=13 \times \Delta \log LDL$, based on the change from baseline of low-density lipoprotein (LDL). Above the mean Z lie 72% of the observations of the women taking their combined oral contraceptive (COC) continuously, and beneath it, 67% of the observations of the participants taking their COC cyclically



DISCUSSION

Although additional differences were observed in lipids at pill pack 7, after one year of use, the cyclic LNG/EE 100/20 and the continuous LNG/EE 90/20 groups were found to differ only in TC, LDL, HDL_3, protein C antigen, D-dimer, and SHBG levels. These differences observed between the two treatment groups may be a consequence of the continuous vs. cyclic nature of the regimen, and/or different doses of LNG between the formulations. The temporary changes in HOMA-IR, TGS, and HDL_2 are considered to have no implications for the risk of arterial disease, since these effects are transient, whereas atherosclerosis is a process that takes years rather than months to develop.

The adjusted mean percentage increases in TC (7%) and LDL (11%) after one year in the continuous COC group are comparable to data obtained by other study groups with the well-established second-generation COC containing 30 µg EE [5]. Increased LDL is a risk factor for VTE. A higher oestrogen/androgen ratio has been shown to lead to a relatively lower LDL and higher HDL in cyclic COC users [6;7]. Since this ratio is greater for the continuous than for the cyclic COC tested (20/90 vs. 20/100), the LDL increases were expected to be smaller in the continuous group than in the cyclic group. Given that our results indicate the opposite, the greater rise of LDL in users of the continuous COC may be a result of continuous exposure to the androgenic LNG, despite its lower dose compared to that in the cyclic COC regimen.

In benchmarking the LDL results of the cyclic preparation with those in the literature, we encountered different data, ranging from increases of 3.2% [8] to 10.5% [9], to 10.6% [10] to 11.5% [11], and 16.9% [12]; whereas we recorded an adjusted mean decrease of 3.3%. The variability in results we observed may be due to the wide range in individual percentage changes (from −37% to 24%) in our study. The divergent results obtained in different studies may stem from the difference in the populations studied. In our study, the only demographic variable that influenced LDL was smoking. Smokers in both the continuous and the cyclic COC groups, but not non-smokers, were found to have a significant reduction in LDL. Evidence that the percentage of smokers in the population could affect the mean change in LDL associated with cyclic COC use was noted in the study of Skouby et al. [11], in which the percentage of smokers was low (about 8%) and the average increase in LDL was 11.5%. In the study by Endrikat et al. [8], around 70% of the users smoked, and the increase in LDL was only 3.2%. Apparently, smoking is an important determinant of the effect of COCs on lipids. As increased levels of LDL enhance the process of atherosclerosis, according to our results the change in LDL levels is more unfavourable in non-smokers using one of the studied treatments long-term, than in smokers.

The milder decrease of HDL_3 in users of the continuous COC can be considered a beneficial effect on VTE risk compared to the cyclic preparation [13]. This difference also suggests that, in contrast to LDL, HDL_3 levels might be more sensitive to the oestrogen/progestin ratio than to the extent of exposure to LNG.

The similar changes in glucose and insulin levels as well as in insulin resistance expressed in HOMA-IR after 13 pill packs are indicative of the similarity of the effect of the treatments on carbohydrate metabolism. Our observations suggest that one year of use of the continuous LNG/EE 90/20 COC does not affect the risk of developing the metabolic syndrome, as defined by the National Cholesterol Education Program [14], even though alterations in lipid metabolism were different from those observed with the tested cyclic COC.

With regard to the risk of VTE, both treatments affected nearly all measured haemostatic variables similarly. The few differences included protein C antigen, which increased more with the continuous COC. The continuous COC was associated with less of an increase in D-dimer, and F1+2 increased at pill pack 13 to a similar extent as with the cyclic COC (22% and 27%, respectively). The difference between groups in the changes in haemostasis parameters was small, but indicated a more favourable profile related to the continuous LNG/EE 90/20 COC compared with the cyclic LNG/EE 100/20 COC with regard to risk of VTE. In light of the other differences in haemostatic variables, any difference between groups in the effect on haemostasis in vivo is unclear.

The difference in SHBG levels (77% increase from baseline for continuous COC versus 59% for cyclic COC use) points to a different extent of net oestrogen exposure associated with the treatments. The larger increase in SHBG levels observed with the continuous COC is in line with the fact that LNG counteracts the oestrogen effect on SHBG levels in a dose-dependent manner. According to a review by Odlind et al., a greater steroid-induced increase in SHBG is associated with a higher risk of VTE [15]. There is, however, little experimental evidence that substantial differences in the effect of SHBG on haemostasis are involved in the pathophysiology of VTE in general. In this study, there was no evidence for a link between changes in SHBG and in haemostatic variables.

A pharmacokinetic study of the continuous COC showed that LNG and EE reached steady state after 21 days; thus, no accumulation with longer use was expected (Data on file, Pfizer Inc. 2009). We also found no pharmacodynamic evidence of accumulation of EE with the continuous regimen since fibrinogen, which is known to respond to oestrogens but not to progestogens or androgen [16], did not show a cumulative change over time.

In this study, there was no pharmacodynamic evidence of accumulation of EE found for the continuous regimen. Conversely, data collected in this study cannot rule out with certainty a difference in LNG accumulation with continuous use versus cyclic use. Finally, DA of the data identified the change from baseline of LDL as the strongest discriminator between the two treatments. However, this can explain no more than 16% of the difference between the treatments, and consequently can classify the treatments poorly.

The main limitation of this study is that the doses of LNG are not identical between the continuous and cyclic treatment regimens. However, since the primary goal of the study was to determine the metabolic effects of continuous LNG/EE 90/20, it was best to compare to a cyclic regimen that had the closest formulation. Thus we were limited to Alesse™/ Loette™, currently approved by regulatory agencies, which contains 100 µg LNG and 20 µg EE. We acknowledge that any differences between the therapies may be due not only to their continuous vs. cyclic nature, but also to the difference in progestin dose. It may be important to realise that the statistically significant differences we found in surrogate markers of arterial disease and VTE are not necessarily clinically relevant. Further, 34% and 23% of the subjects who started treatment in the continuous and cyclic groups, respectively, did not complete the study, thus limiting the conclusions of our results. However, these are typical discontinuation rates for studies on COCs [17;18].

In conclusion, after 13 pill packs of use, the continuous regimen of LNG/EE 90/20 and the cyclic regimen of LNG/EE 100/20 affected carbohydrate metabolism, lipid profile, haemostatic variables, bone markers, and SHBG similarly in most cases. The larger increase in SHBG with the continuous COC is consistent with a higher net oestrogenic effect due to a lower dose of LNG. Based on the presented results, it can be concluded that the continuous COC regimen does not expose users to much different changes in a large series of metabolic variables, and most likely not to a higher risk of cardiovascular disease, than observed with the established, second-generation COCs. Whether this conclusion also applies to long-term use of continuous COCs can only be determined in prospective studies assessing relevant clinical endpoints.

REFERENCES

1 Machado RB, Fabrini P, Cruz AM, Maia E, da Cunha BA. Clinical and metabolic aspects of the continuous use of a contraceptive association of ethinyl estradiol (30 microg) and gestodene (75 microg). Contraception 2004 November;70(5):365-70.

2 Machado RB, de Melo NR, Maia H, Jr., Cruz AM. Effect of a continuous regimen of contraceptive combination of ethinylestradiol and drospirenone on lipid, carbohydrate and coagulation profiles. Contraception 2010 February;81(2):102-6.

3 Teichmann A, Apter D, Emerich J, Greven K, Klasa-Mazurkiewicz D, Melis GB et al. Continuous, daily levonorgestrel/ethinyl estradiol vs. 21-day, cyclic levonorgestrel/ethinyl estradiol: efficacy, safety and bleeding in a randomized, open-label trial. Contraception 2009 December;80(6):504-11.

4 Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. Diabetes Care 2002 July;25(7):1177-84.

5 Kemmeren JM, Algra A, Grobbee DE. Effect of second and third generation oral contraceptives on lipid metabolism in the absence or presence of the factor V Leiden mutation. J Intern Med 2001 November;250(5):441-8.

6 Burkman RT. Lipid metabolism effects with desogestrel-containing oral contraceptives. Am J Obstet Gynecol 1993 March;168(3 Pt 2):1033-40.

7 Crook D, Godsland I. Safety evaluation of modern oral contraceptives. Effects on lipoprotein and carbohydrate metabolism. Contraception 1998 March;57(3):189-201.

8 Endrikat J, Klipping C, Cronin M, Gerlinger C, Ruebig A, Schmidt W et al. An open label, comparative study of the effects of a dose-reduced oral contraceptive containing 20 microg ethinyl estradiol and 100 microg levonorgestrel on hemostatic, lipids, and carbohydrate metabolism variables. Contraception 2002 March;65(3):215-21.

9 Scharnagl H, Petersen G, Nauck M, Teichmann AT, Wieland H, Marz W. Double-blind, randomized study comparing the effects of two monophasic oral contraceptives containing ethinylestradiol (20 microg or 30 microg) and levonorgestrel (100 microg or 150 microg) on lipoprotein metabolism. Contraception 2004 February;69(2):105-13.

10 Young RL, DelConte A. Effects of low-dose monophasic levonorgestrel with ethinyl estradiol preparation on serum lipid levels: A twenty-four month clinical trial. Am J Obstet Gynecol 1999 November;181(5 Pt 2):59-62.

11 Skouby SO, Endrikat J, Dusterberg B, Schmidt W, Gerlinger C, Wessel J et al. A 1-year randomized study to evaluate the effects of a dose reduction in oral contraceptives on lipids and carbohydrate metabolism: 20 microg ethinyl estradiol combined with 100 microg levonorgestrel. Contraception 2005 February;71(2):111-7.

12 Kiran G, Kiran H, Ekerbicer HC. Serum lipid and lipoprotein changes induced by preparations containing low-dose ethinylestradiol plus levonorgestrel. Aust N Z J Obstet Gynaecol 2003 April;43(2):145-7.

13 Lamarche B, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, Despres JP. Associations of HDL_2 and HDL_3 subfractions with ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. Arterioscler Thromb Vasc Biol 1997 June;17(6):1098-105.

14 Expert Panel on Detection Evaluation , and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001 May 16;285(19):2486-97.

15 Odlind V, Milsom I, Persson I, Victor A. Can changes in sex hormone binding globulin predict the risk of venous thromboembolism with combined oral contraceptive pills? Acta Obstet Gynecol Scand 2002 June;81(6):482-90.

16 Oral Contraceptive and Hemostasis Study Group. The effects of seven monophasic oral contraceptive regimens on hemostatic variables: conclusions from a large randomized multicenter study. Contraception 2003 March;67(3):173-85.

17 Chavez A, DelConte A. A comparison of cycle control with monophasic levonorgestrel/ethinylestradiol 100 micrograms/20 micrograms versus triphasic norethindrone/ethinylestradiol 500-750-1000 micrograms/35 micrograms: a multicenter, randomized, open-label study. Eur J Contracept Reprod Health Care 1999 June;4(2):75-83.

18 Archer DF, Maheux R, DelConte A, O'Brien FB. Efficacy and safety of a low-dose monophasic combination oral contraceptive containing 100 microg levonorgestrel and 20 microg ethinyl estradiol (Alesse). North american Levonorgestrel Study Group (NALSG). Am J Obstet Gynecol 1999 November;181(5 Pt 2):39-44.