

A randomized study over 13 cycles to assess the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on carbohydrate metabolism

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Abstract

In this open-label, randomized study we compared the influence of a new oral contraceptive containing 30 µg ethinylestradiol and 3 mg drospirenone (YasminTM) with a reference preparation containing 30 µg ethinylestradiol and 150 µg desogestrel (MarvelonTM) on variables of carbohydrate metabolism by means of oral glucose tolerance tests at baseline and in the 6th and 13th treatment cycle. The mean levels of fasting glucose and insulin were similar at baseline and after 13 treatment cycles, whereas C-peptide and free fatty acid levels decreased slightly in both groups. All blood glucose and insulin values measured in the oral glucose tolerance tests were within normal ranges, despite a slight increase in the mean areas under the curves of 0-3 h [AUCs (0-3 h)] of both variables from baseline to treatment cycle 13. Differences between both treatments were not statistically significant. The mean AUCs (0-3 h) for C-peptide were not markedly changed in any treatment group. Free fatty acid levels decreased by 42% in the drospirenone group and increased by 48.9% in the desogestrel group, in terms of means of individual changes. Both preparations were well tolerated and equally efficacious regarding contraception and cycle control. The mean body weight was slightly decreased in most cycles during treatment with the drospirenone combination, as compared to baseline, while it was slightly increased versus baseline in all cycles during treatment with the desogestrel combination. The combination with drospirenone had less impact on blood pressure than the combination with desogestrel. In conclusion, Yasmin, a combined low-dose oral contraceptive with 30 µg ethinylestradiol and 3 mg of the novel progestogen drospirenone, as well as the reference Marvelon, containing 30 µg ethinylestradiol and 150 µg desogestrel had little impact on carbohydrate metabolism when used for 1 year. The observed changes were small and not suggestive of a clinically relevant deterioration of carbohydrate metabolism.

Keywords: Oral contraceptives; Ethinylestradiol; Drospirenone; Desogestrel; Carbohydrate metabolism

1. INTRODUCTION

Oral contraceptives (OCs) are now used for more than 40 years and have been proved to be a highly efficacious and safe method for contraception. The hormonal components of OCs, estrogens (usually ethinylestradiol) and progestins, are known to have various metabolic effects, including effects on carbohydrate metabolism. Therefore, international guidelines, e.g., the "Note for guidance on clinical investigation of steroid contraceptives in women" [1], recommend to investigate the influence of OCs on variables of carbohydrate metabolism for safety reasons. Although slight decreases in glucose tolerance and increases in insulin resistance have been reported for some OCs by means of oral or intravenous glucose tolerance tests (oGTTs, ivGTTs) or glucose clamps [2,3], evidence for an increased risk to develop manifest diabetes has never been provided. However, a further investigation of the long-term consequences of OC use on carbohydrate metabolism is important because any chronic—even mild—hyperglycemia and/or hyperinsulinemia in the fasting state as well as during a glucose load may contribute to ischemic vascular diseases [4-8] and to the metabolic syndrome (or Syndrome X) described by Reaven [9].

Although the specific contributions of the estrogen and the progestin to the metabolic effects of OCs are not fully understood, it is evident that the dose of ethinylestradiol (EE) and the dose and type of the progestin—particularly its androgenic properties—affect the metabolic influence of OCs [10]. In this respect, the novel progestin drospirenone (DRSP), a 17- α -spiro lactone derivative, is particularly interesting because of its unique pharmacological profile with antiandrogenic and antiminerocorticoid activity in addition to its potent progestogenic activity [11-13]. The antiminerocorticoid activity, which has not yet been described for any other synthetic progestin, may reduce possible water retention in women using OCs [14].

The combination of 3 mg DRSP with 30 μ g EE (YasminTM) was recently approved for marketing as an OC in Europe and the US. The preparation is characterized by a high contraceptive efficacy in combination with excellent cycle control and a low incidence of adverse effects [15]. In an earlier study, Oelkers et al. [16] provided evidence for favorable metabolic effects of the preparations. However, more information is needed in order to judge its metabolic impact.

In the present study, we compared the effects of Yasmin with the marketed OC MarvelonTM containing 30 μ g EE in combination with 150 μ g of the 19 Nor-testosterone derivative desogestrel (DSG) on carbohydrate metabolism.

2. MATERIALS AND METHODS

The study was performed as an open-label, randomized, prospective study at one center in Belgium (Centre Hospitalier Universitaire de Liège, Domaine Universitaire du Sart Tilman-B.35-4000 Liège 1-Belgique) from January 1994 to June 1997. We compared Yasmin (Schering AG, Berlin, Germany) containing 30 μ g EE and 3 mg DRSP with Marvelon (Organon, Oss, The Netherlands) containing 30 μ g EE and 150 μ g DSG, as a reference preparation. The study protocol was approved by the appropriate ethics committee before the study started.

We recruited a total of 60 healthy women aged 18 to 28 years. A total of 54 volunteers started the study medication (27 in each treatment group) and were included in the full analysis set for the safety evaluation. Of these, 50 (25 in each group) were included in the per protocol analysis for the efficacy evaluation. Four volunteers were excluded from the per protocol analysis due to premature discontinuation of the study medication or other protocol deviations.

The women's wish for contraception for at least 13 cycles of 28 days each was a prerequisite for their participation in the study. New OC users as well as women who wanted to change their OC (switchers) were included in the study. Switchers were required to have at least two OC-free cycles, one wash-out cycle and one pretreatment cycle, before they started to take the study medication. The exclusion criteria were similar to the contraindications for OC use. Further exclusion criteria were the use of parenteral depot-contraceptives in the last 6 months before the start of the study, specified coexisting diseases such as diabetes or endocrinopathies, the intake of medications interfering with lipid or carbohydrate metabolism, diagnostically unclassified genital bleeding and a history of migraine accompanying menstruation. Smoking of up to 10 cigarettes per day was allowed. Each volunteer had a thorough medical and gynecological examination, including a cervical cytology examination using the Papanicolaou method and a pregnancy test, before start of treatment. All volunteers gave their informed consent prior to participation.

The volunteers were randomized to treatment with either Yasmin or Marvelon. The first tablet was to be taken on the first day of withdrawal bleeding. A 28-day treatment cycle consisted of 21 days with tablet intake followed by 7 days without intake. The treatment period lasted for 13 consecutive cycles, 28 days each. The study medications were supplied in calendar packs. When the scheduled intake time was missed, the women were to take the tablets until up to 12 h after the scheduled time. All deviations from the scheduled intake times had to be recorded in a diary.

The absolute change of the natural logarithm of the area under the curve (AUC) for glucose and insulin and the relative change of the lipid variables HDL-, HDL2- (high-density lipoproteins), and LDL-cholesterol (low-density lipoprotein) from pretreatment to treatment cycle 13 were the target variables in the study. Here we only report the results of the carbohydrate variables. The lipid results will be reported separately.

The laboratory samples were analyzed by two different laboratories at the University Hospital Center, Liège, Belgium. Only generally accepted methods were used for the laboratory analyses. Blood glucose was measured by the glucose oxidase method adapted to the Auto-Analyzer (Esat 6660; Eppendorf, Germany). Plasma insulin (immunoreactive insulin) was measured (in duplicate) by a modified double-antibody radioimmunoassay according to Hales and Randle [17] with a filtration instead of centrifugation [intra-assay coefficient of variation (CV) = 5.5%; inter-assay CV = 8.7%]. Plasma C-peptide was measured (in duplicate) by a radioimmunoassay according to Heding [18] (intra-assay CV = 3.1%; inter-assay CV = 10.8%). Plasma free fatty acids were measured by an enzymatic method [19] (intra-assay CV = 3.1%; inter-assay CV = 3.4%).

The 75-g-standardized oGTTs were carried out at baseline (during the last 7 days of the pretreatment cycle) and in treatment cycles 6 and 13 (on days 15-21 of the respective cycles). The volunteers were to eat a standard diet throughout the study with a carbohydrate intake of at least 300 g per day (total diet: 2500 kcal). During the last 3

days before the tests, strenuous exercise was not allowed. On the day of the test, 75 g glucose was administered in 300 mL water. The influence of the study treatments on carbohydrate metabolism was assessed by measurements of plasma glucose, insulin, C-peptide and free fatty acid levels. Blood samples were taken with a flexible catheter inserted into a superficial forearm vein at a fasting state before glucose was administered (together with the samples required for general clinical chemical variables) and in 30-min intervals for 3 h thereafter.

The patients' weight was determined every other day. The blood pressure was measured on all study visits. Adverse events, concomitant medication usage and treatment compliance, including a record of intake errors, and cycle control patterns, were recorded from the volunteers' diaries and the results of general questioning of the volunteers by the investigators. In the follow-up period, the volunteers were asked again about their general health during treatment and medical and gynecological examinations, including cervical cytology and routine laboratory examinations, were repeated.

2.1. Statistical methods

Statistical analyses were performed for both the full analysis and the per protocol set. All randomized volunteers who took at least one tablet of the study medication were included in the full analysis set. The per protocol set consisted of volunteers without major protocol deviations able to affect the target variables.

The absolute changes of the natural logarithm of the AUC for glucose and insulin from pretreatment to treatment cycle 13 were the target variables in the study. The AUCs were determined using the trapezoidal rule. The absolute changes of the natural logarithms of the AUCs were calculated as: natural logarithm of the value measured in cycle 13 minus natural logarithm of the value measured in pretreatment cycle.

For each target variable, the null hypothesis, which stated that the mean values were equal in both treatment groups, was tested against its alternative, which stated that the mean values in both treatment groups were not equal, using the two-sided t-test for two independent samples. The significance level α of 5% for these tests was not adjusted for multiple testing as appropriate for exploratory analyses.

Table 1: *Demographic characteristics at baseline*

	DRSP (n = 25)	DSG (n = 25)
Mean age (years) \pm SD	21.5 \pm 2.5	21.2 \pm 1.8
Range	18-28	18-25
Mean weight (kg) \pm SD	55.2 \pm 6.3	59.8 \pm 6.7
Range	41-69	51-72
Mean height (cm) \pm SD	165.2 \pm 5.8	165.0 \pm 5.2
Range	157-179	156-176
Mean Body Mass Index (kg/m ²) \pm SD	20.2 \pm 2.1	21.9 \pm 2.0
Range	16.6-25.2	19.3-25.8
Prevalence of smoking (% of volunteers)	16	28
Prior use of OCs (% of volunteers)	77.7	66.6
Volunteers with regular cycles (%)	100	100

3. RESULTS

3.1. Study population

A total of 63 volunteers were screened, 60 were randomized. Of these, 54 volunteers, i.e., 27 in the DSG group (Marvelon) and 27 in the DRSP group (Yasmin) started treatment. Fifty (25 in each group) had no major protocol violations and were included in the per protocol set. The demographic characteristics of both groups at baseline were well matched with the exception of body weight. The mean body weight was—by chance—4.6 kg higher in the DSG group than in the DRSP group (see Table 1).

3.2. Carbohydrate metabolism

3.2.1. Fasting levels

As shown in Table 2, the mean values for fasting glucose and insulin remained almost unchanged from baseline to cycle 6 and 13 in both treatment groups. Fasting C-peptide levels decreased from baseline to cycle 13 by $-3.4 \mu\text{mol/L}$ in the DRSP group and by $-17.8 \mu\text{mol/L}$ in the DSG group. Free fatty acid levels decreased by an average of $-48.8 \mu\text{Eq/L}$ in the DSG group compared to $-6.6 \mu\text{Eq/L}$ in the DRSP group.

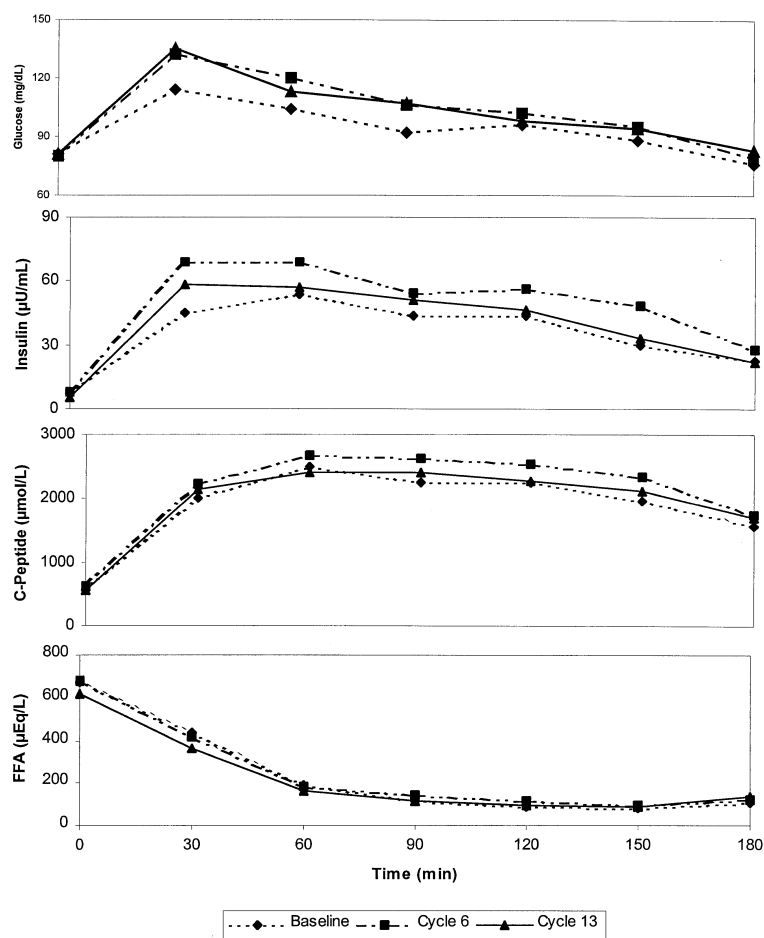
Table 2: Fasting plasma levels of glucose, insulin, C-peptide and FFA (mean \pm SD)

	Unit	Baseline		Cycle 6		Cycle 13		Absolute change baseline to cycle 13	
		DRSP	DSG	DRSP	DSG	DRSP	DSG	DRSP	DSG
Glucose	mg/dL	81.5 \pm 10.4	82.0 \pm 8.6	80.4 \pm 6.8	78.7 \pm 8.6	81.2 \pm 7.8	81.2 \pm 7.7	-0.32 \pm 11.6	-0.88 \pm 9.38
Insulin	$\mu\text{U/mL}$	7.2 \pm 5.1	6.2 \pm 2.9	8.3 \pm 5.5	6.8 \pm 4.1	5.6 \pm 4.1	6.5 \pm 4.9	-1.5 \pm 5.5	0.36 \pm 4.8
C-peptide	$\mu\text{mol/L}$	563 \pm 215	555 \pm 105	619 \pm 164	556 \pm 153	559 \pm 142	537 \pm 127	-3.4 \pm 184	-17.8 \pm 167
Free fatty acids	$\mu\text{Eq/L}$	670 \pm 294	712 \pm 274	679 \pm 210	717 \pm 264	621 \pm 230	705 \pm 225	-48.8 \pm 290	-6.63 \pm 258

3.2.2. oGTT

The mean levels of glucose, insulin, C-peptide and free fatty acids (FFA) in the oGTT at baseline and at cycles 6 and 13 are shown in Fig. 1 for the DRSP group and in Fig. 2 for the DSG group. Table 3 summarizes the AUCs and their absolute changes from baseline to cycle 13.

Fig. 1: Concentration curves of glucose, insulin, C-Peptide and FFA (means) assessed sequentially during OGTT before (baseline) and during use (6 and 12 cycles) of DRSP + EE.



The mean AUCs (0-3 h) for glucose and insulin increased from baseline to cycle 13. The increases were comparable in both treatment groups with 28.7 mg/dL*h in the DRSP and 22.2 mg/dL*h in the DSG group for glucose, and 14.3 μ U/dL*h in the DRSP and 7.8 μ U/dL*h in the DSG group for insulin. Differences between the treatment groups were not statistically significant. All individual blood glucose and insulin levels measured at any time during the study were within normal ranges and not suggestive of diabetes or impaired glucose tolerance in any case [20].

The mean AUCs (0-3 h) for C-peptide appeared to be unchanged throughout the treatment period in both groups. Free fatty acids decreased by 42 μ Eq/L*h vs. baseline in the DRSP group as compared to an increase by 48.9 μ Eq/L*h in the DSG group (Table 3).

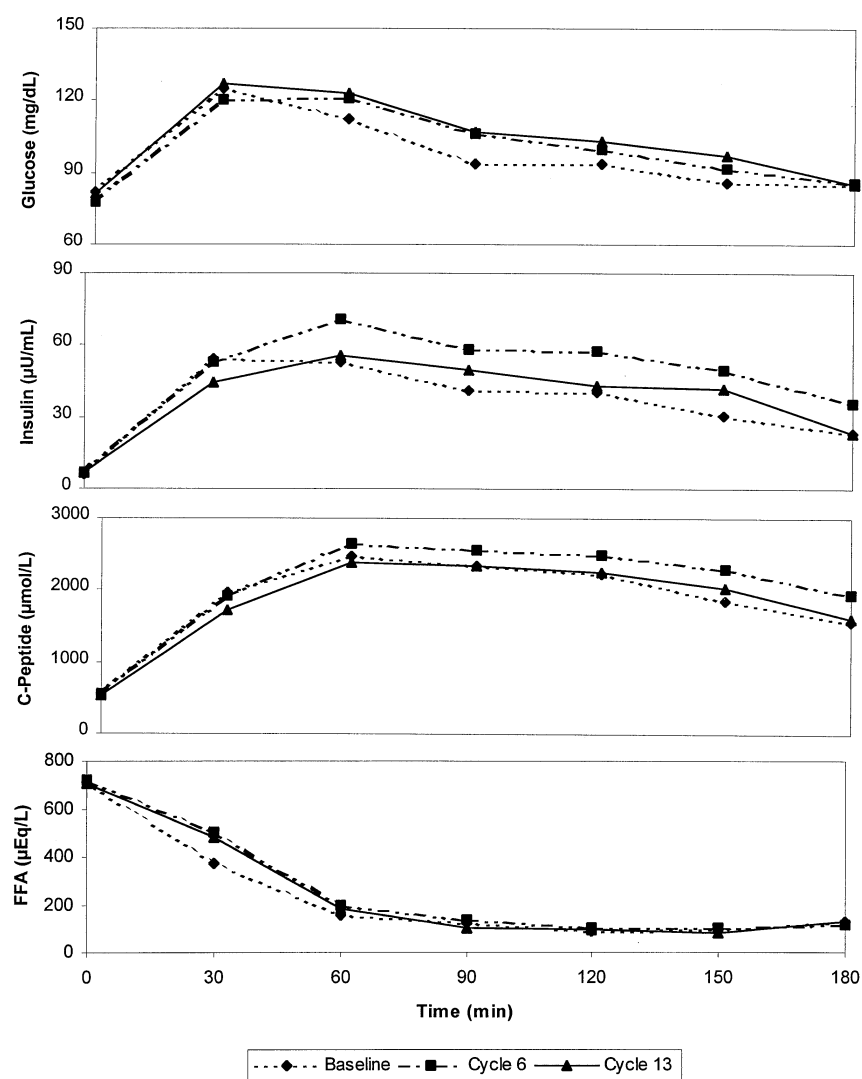
3.3. Contraceptive efficacy

None of the randomized volunteers became pregnant during the study.

3.4. Tolerability

A total of 18 (33%) of the 54 treated volunteers had a total of 35 adverse events. Most adverse events were described as mild and transient. The most common adverse event was breast pain. In each treatment group, one serious adverse event (appendectomies) was recorded. Both serious adverse events had no causal relationship to the treatments.

Fig. 2: Concentration curves of glucose, insulin, C-Peptide and FFA (means) assessed sequentially during OGTT before (baseline) and during use (6 and 12 cycles) of DSG + EE.



Physical and gynecological examinations showed few abnormal findings, all of which were not considered treatment-related.

Blood pressure differences between baseline and cycle 13 were small and not relevant in both groups. The mean systolic blood pressure decreased from baseline to cycle 13 by -2.2 mmHg in the DRSP group and increased by +2.5 mmHg in the DSG group. The mean diastolic blood pressure increased by +0.2 mmHg in the DRSP group and by +2.9 mmHg in the DSG group.

The mean body weight for almost all cycles during treatment with DRSP was virtually unchanged from baseline (mean change on cycle 13: +0.03 kg). During treatment with DSG, the mean body weight for all cycles was slightly elevated vs. baseline (mean change on cycle 13: +0.54 kg).

The overall levels of the safety laboratory values before and after treatment did not suggest an influence of the study preparations. The incidence of laboratory abnormalities was low and not appreciably different in the baseline and the posttreatment examinations. Individual deviations from normal laboratory ranges were transient, generally small and not clinically relevant.

Table 3: Carbohydrate profile, AUCs (0-3 h) (mean \pm SD)

	Unit	Baseline		Cycle 6		Cycle 13		Absolute change baseline to cycle 13		p-value ^a
		DRSP	DSG	DRSP	DSG	DRSP	DSG	DRSP	DSG	
Glucose	mg/dL*h	287 \pm 49	299 \pm 44	319 \pm 32	312 \pm 52	316 \pm 52	321 \pm 45	28.7 \pm 48.6	22.2 \pm 39.6	0.57
Insulin	μ U/mL*h	116 \pm 51	117 \pm 53	158 \pm 66	154 \pm 60	130 \pm 55	125 \pm 58	14.3 \pm 67.5	7.8 \pm 61.8	0.62
C-peptide	μ mol/L*h	6.0 \pm 1.3	5.9 \pm 1.2	6.7 \pm 1.5	6.5 \pm 1.4	6.2 \pm 1.7	5.9 \pm 1.4	0.22 \pm 1.7	-0.07 \pm 1.5	0.57
Free fatty acids	μ Eq/L*h	649 \pm 223	630 \pm 190	676 \pm 206	735 \pm 208	607 \pm 165	679 \pm 172	-42.4 \pm 222	48.9 \pm 214	0.24

^a Test was performed on the natural logarithm of the AUCs.

4. DISCUSSION

In this randomized study, we investigated the influence of the new OC Yasmin containing 30 μ g EE and 3 mg DRSP on carbohydrate metabolism variables during 13 cycles of treatment in healthy female volunteers in comparison to the marketed OC Marvelon containing 30 μ g EE and 150 μ g DSG as a reference.

Several studies [2,21,22] have shown that Marvelon has only a small influence on carbohydrate metabolism. Yasmin contains the progestin DRSP, a 17- α -spiro lactone derivative with a unique pharmacological profile that combines potent progestogenic with antiandrogenic and the unique antimineralocorticoid activity. In this study, we investigated the impact of the novel combination on carbohydrate metabolism to proof the safety of the preparation [23].

Our data show that a 1-year treatment with the combinations of EE with DSG or DRSP does not affect the levels of glucose and insulin, whereas the levels of C-peptide and free fatty acids were slightly decreased. Our data for the reference preparation confirm the results of Si et al. [22] and Crook et al. [2]. The data for the combination of EE with DRSP are in accordance with preliminary results from Oelkers et al. [16]. None of the preparations caused any major changes of the fasting blood levels of the carbohydrate variables, even during long-term use. The data are not suggestive of a negative influence of the preparations regarding the cardiovascular disease risk of the users [24]. Fasting levels of plasma C-peptide and the molar ratio C-peptide:immuno-reactive insulin (data not shown) remained unchanged throughout the entire study in both treatment groups. This observation, which was made earlier for the combination of EE with DSG [2], suggests that basal, fasting insulin secretion by the pancreas is almost unchanged during 1-year use of these preparations.

OCs, particularly those with high doses of potent 19-nortestosterone derivatives may cause a state of insulin resistance, as suggested by a slight reduction of oral glucose tolerance in the presence of slight hyperinsulinism [25-28]. In agreement with this general observation, the present study showed slightly elevated plasma glucose and insulin AUCs during the oral glucose tolerance tests after 1 year of use of the preparation, compared to baseline. However, all blood glucose and insulin levels remained within normal ranges and well below the threshold of impaired glucose tolerance. Differences between both treatments were not statistically significant. Our data confirm previous results for the combinations of EE with DRSP [16] or DSG [2]. A slight decrease in glucose tolerance which was similar in magnitude to the decrease observed in this study was found in a study with a combination of the same dose of DSG (150 μ g) with a lower dose of 20 μ g EE [23,29]. C-peptide AUCs

are a measure of pancreatic insulin secretion. In the present study, the C-peptide AUCs remained virtually unaffected in both groups during 13 treatment cycles, indicating no significant changes in insulin secretion and thus probably no deterioration of insulin sensitivity. In addition, it is emphasized that no abnormal values for blood glucose, plasma insulin or C-peptide were recorded in the postglucose load period, indicating that there was no shift towards an impaired glucose tolerance [20] for any of the volunteers during this study. The results for the AUCs of free fatty acids during the oGTTs were almost unchanged and, in contrast to the observation of Singh and Natrass [30], do not point to any abnormality of free fatty acids responsiveness to the antilipolytic action of insulin.

As mentioned above, all blood glucose and insulin levels measured during the oGTTs remained within normal ranges, despite a slight increase of the AUCs (0-3 h) of both variables after 1 year of treatment. None of the fasting or postglucose load values of blood glucose and plasma insulin reached the level of impaired glucose tolerance during use of either preparation. During the physiological menstrual cycle of untreated women, slight decreases in glucose tolerance and insulin sensitivity have been described for the luteal phase when both estradiol and progesterone are secreted, in comparison to the follicular phase when only estradiol is secreted [31]. The changes observed in carbohydrate metabolism during the use of low-dose OCs in this study were similar in magnitude to the changes occurring during the physiological menstrual cycle and not sufficient to induce an increase in the incidence of diabetes mellitus [32]. This is in contrast to the changes induced by older, high dose OCs, which may slightly deteriorate glucose tolerance and cause hyperinsulinemia [33].

Godsland [28] summarized observations (also by our group [23,34]) of progestogen-induced variations in plasma insulin half-life, presumably related to alterations in hepatic clearance of insulin. In the present study, no obvious changes in insulin half-life were observed. The modest increase in insulin AUC was apparently closely related to a slight increase in pancreatic beta cell function, as reflected by a very small increase in C-peptide levels.

In accordance with the findings of other groups, both preparations were well tolerated and equally efficacious in terms of contraception and cycle control [14,15]. Compared to baseline, the mean body weight during treatment with the DRSP combination was slightly decreased in most cycles, while it was slightly increased vs. baseline in all cycles during treatment with the DSG combination. The combination with DRSP had less impact on blood pressure than the combination with DSG confirming the findings of previous publications [14,16]. The favorable influence of the combination with DRSP on body weight and blood pressure is presumably due to the antimineralocorticoid effect of DRSP.

In conclusion, Yasmin, a low-dose OC containing EE and the novel progestogen DRSP, as well as the reference Marvelon, containing the same EE dose and DSG as progestogen had little impact on variables of carbohydrate metabolism after 13 treatment cycles. Observed changes were small and not suggestive of a clinically meaningful deterioration of carbohydrate metabolism or an increase in risk for cardiovascular disease.

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