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Randomized controlled study of the influence of two low estrogen dose oral contraceptives containing gestodene or desogestrel on carbohydrate metabolism

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Abstract

This study compared the impact on carbohydrate metabolism of two combinedoral contraceptives (COCs). This open-label, single-center trial enrolled participants for a total of 15 cycles. Thirty-six women were randomized to receive either 20 μg ethinyl estradiol (EE) and 75 μg gestodene (GSD) or 20 μg ethinyl estradiol and 150 μg desogestrel (DSG) daily for 21 days out of 28. A glucose tolerance test was performed at baseline and cycles 6 and 13. The area under the curve (AUC) for glucose increased in both study groups. The change was statistically significant ($p = 0.036$) for the 20 EE/75 GSD group at cycle 6 versus baseline. Fasting blood glucose at cycle 13 was significantly ($p < 0.01$) higher for both treatment groups compared to baseline. No changes were found for fasting insulin and fasting C-peptide levels or for the AUCs of insulin or C-peptide. Both regimens were well tolerated. Gestodene and desogestrel in combination with 20-μg ethinyl estradiol induce similar changes in carbohydrate metabolism which are smaller than those described earlier for COCs containing higher estrogen doses or more androgenic progestins such as levonorgestrel.

Keywords: Carbohydrate; Oral contraceptive; Estrogen; Progestogen; Glucose; Insulin

1. INTRODUCTION

Since the first reports indicating that combined oral contraceptives (COCs) can alter carbohydrate metabolism, this issue has acquired increased significance in the field of hormonal contraceptive development. The main concern is that a decreased glucose tolerance and chronic hyperinsulinism may elevate the risk of cardiovascular disease by enhancing atherogenesis. The use of oral contraceptives by healthy young women usually results in a slight reduction in glucose tolerance. Although changes in blood glucose and insulin levels are often statistically significant, they are usually within the normal range and most fluctuations reported do not appear to be clinically relevant [1,2].

The newer progestins, such as desogestrel or gestodene, exert only minor or no androgenic effects in comparison with the older progestins such as levonorgestrel. This may provide an advantage, as it has been suggested that progestins with androgenic properties exert a more pronounced adverse effect on glucose metabolism [3].

We have examined two COCs, both containing the same low dose of 20 μg ethinylestradiol but with either gestodene or desogestrel as their progestin compound. We were interested in the metabolic impact that these low-dose COCs may have on carbohydrate metabolism, and whether the two different progestin components have different effects.

2. MATERIALS AND METHODS

The study was conducted as an open-label, single-center trial with two independent randomly allocated treatment groups, who were enrolled for a total of 15 cycles. Ethics committee approval was obtained and all participants gave their written informed consent.

Thirty-six women were randomized into two study groups. One group received the oral contraceptive combination consisting of 20 μg ethinyl estradiol with 150 μg desogestrel (20 EE/150 DSG; Mercilon®) and the other study group received 20 μg ethinyl estradiol with 75 μg gestodene (20 EE/75 GSD; Femoden 20®). After two initial cycles without treatment the pre-treatment values of the investigated parameters were recorded, that is, on Days 21 through 25 of the second pretreatment spontaneous cycle. The women then started pill intake on the first day of their withdrawal bleeding. In each of the 13 treatment cycles, the contraceptive pill was

administered for 21 days followed by a period of 7 days without medication.

Methods for determination of blood glucose, plasma immunoreactive insulin and C-peptide have been described elsewhere [4].

The area under the concentration-time curve (AUC) responses during a glucose tolerance test (OGTT) was used to indicate deteriorations in glucose tolerance. Around Days 21 through 25 of the second cycle without medication, an OGTT was performed to obtain a baseline value before starting the administration of study oral contraceptives. This first OGTT was preceded by randomization to the designated study group. In the medication phase an OGTT was again performed during the period of last pill intake in Cycles 6 and 13. The OGTT was performed in the morning, after at least 12 h of fasting and after 3 days of unrestricted diet (at least 250-g carbohydrate in their diet on each of the 3 days preceding the test). Blood samples (fasting values) were drawn before the 75-g glucose load was given and 30, 60, 90, 120, 150, and 180 min thereafter. The plasma levels of glucose, insulin, and C-peptide were assayed in each sample.

For glucose and insulin plasma levels, the AUC corrected for the value at 0 min was used as the variable value. The AUC was calculated using the following equation : $AUC = 1/2\ [(1/2\ X_0 + X_{30} + X_{60} + X_{90} + X_{120} + X_{150} + 1/2\ X_{180}) - 6\ X_0]$ where $X_{0\text{-}180}$ is the parameter measured in blood samples at the different time points. AUCs are then expressed in concentration × 1 h. Statistical evaluation of the AUCs and of the fasting levels of glucose, insulin, and C-peptide was performed using Student's *t*-test for paired observations, comparing the pretreatment values with those after 6 months and 13 months of treatment, respectively. Results are expressed as estimates of treatment effects with 95% confidence intervals. For the AUCs of glucose and insulin, both treatment groups were compared using an analysis of covariance (ANCOVA) using the AUC of the pretreatment cycle as covariate. The results are presented as p-values and adjusted means. Episodes of bleeding and any adverse events were recorded throughout the trial.

Table 1: *Mean values ± SD for the various parameters studied*

Parameter (units)	Baseline	After 6 cycles of treatment	After 13 cycles of treatment
20 EE/75 GSD (n = 17)			
AUC glucose (g/L.h)	1.33 ± 0.77	1.81 ±0.91	1.69 ± 1.13
AUC insulin (IU/ml.h)	187 ± 58	261 ± 129	228 ± 119
AUC C-peptide (pmol/L.h)	2596 ± 981	2761 ± 739	2729 ± 790
Fasting glucose (g/L)	0.71 ± 0.08	0.71 ± 0.08	0.78 ± 0.07
Fasting insulin (IU/ml)	8.11 ± 5	8.0 ±3.5	7.0 ± 3.95
Fasting C-peptide (pmol/L)	418 ± 100	431 ± 90	377 ± 64
20 EE/150 DSG (n = 14)			
AUC glucose (g/L.h)	1.33 ± 0.8	1.6 ±0.9	1.98 ± 2.1
AUC insulin (IU/ml.h)	236 ± 81	275 ± 126	228 ± 110
AUC C-peptide (pmol/L.h)	2828 ± 620	2672 ± 674	3223 ± 2152
Fasting glucose (g/L)	0.68 ± 0.07	0.73 ± 0.1	0.76 ± 0.08
Fasting insulin (μU/ml)	6.5 ± 3.5	7.2 ± 3.2	6.0 ± 3.8
Fasting C-peptide (pmol/L)	404 ± 105	444 ± 77	381 ± 68

3. RESULTS

Thirty-six lean, healthy young women between 19 and 29 years of age were found to be eligible and were randomized for the study. In the pretreatment cycles, two women from the 20 EE/150 DSG group discontinued the trial. A further volunteer discontinued because she became pregnant during the second pretreatment cycle. During the course of the trial one woman in the 20 EE/150 DSG group and another one in the 20 EE/75 GSD group terminated the study for personal reasons.

Both study COCs were well tolerated, with nine women in the 20 EE/75 GSD group and four women in the 20 EE/150 DSG group reporting minor adverse events at least once during treatment. The most frequently reported symptoms were nausea (3 women) and acne (2 women). Bleeding which occurred outside the tablet-free interval was described as intracyclic bleeding, presenting either as scanty bleeding (spotting) or with the strength of a menstrual period (breakthrough bleeding). The incidence of spotting was high in the first treatment cycle in both groups and declined continuously afterwards. During the first treatment cycle, spotting was reported by 61% of women in the 20 EE/75 GSD group and by 41% in the 20 EE/150 DSG group. The range of slight intermenstrual bleeding varied from 0% to 23% for treatment cycles 2 to 6, and from 0% to 11% for treatment cycles 7 to 13.

One woman in the 20 EE/75 GSD group and three women in the 20 EE/150 DSG group reported an episode of heavier intermenstrual bleeding during study treatment.

The mean AUCs for glucose and insulin as well as the fasting values for glucose, insulin and C-peptide are given in Table 1. During study treatment, the AUC for glucose increased relative to the pretreatment levels in both study groups. Statistical significance ($p = 0.036$) was reached for the change in 20 EE/75 GSD at the sixth treatment cycle versus baseline values (Table 2). Fasting blood glucose measured at treatment cycle 13 was significantly ($p < 0.01$) higher for both the 20 EE/75 GSD and 20 EE/150 DSG treatment groups when compared to the pretreatment levels. However, no significant changes were found for the AUCs of insulin or C-peptide, or for fasting insulin and fasting C-peptide levels. Comparison of the mean AUCs for glucose and insulin for both oral contraceptives, adjusted for differences in their pretreatment values, did not reveal any difference between the groups at 6 and 13 months of study treatment (Table 3).

Table 2: *Changes in experimental parameters from pretreatment (baseline) to 6 and 13 cycles after start of treatment*

Parameter	6 cycles treatment minus baseline		13 cycles treatment minus baseline	
	Estimate	**95% confidence interval**	**Estimate**	**95% confidence interval**
20 EE/75 GSD				
AUC glucose	0.48	0.034 to 0.92*	0.36	-0.11 to 0.83
AUC insulin	74	-5 to 153	41	-30 to 112
AUC C-peptide	165	-549 to 879	76	-590 to 742
Fasting glucose	0.005	-0.06 to 0.04	0.07	0.03 to 0.11**
Fasting insulin	-0.11	-2.6 to 2.3	-1.1	-3.1 to 0.92
Fasting C-peptide	13	-39 to 65	-41	-104 to 21
20 EE/150 DSG				
AUC glucose	0.3	-0.2 to 0.8	0.68	-0.5 to 1.8
AUC insulin	39	-24 to 103	-8	-77 to 60
AUC C-peptide	-156	-565 to 253	395	-972 to 1763
Fasting glucose	0.05	-1.7 to 0.11	0.08	0.02 to 0.1***
Fasting insulin	0.7	-1.1 to 2.6	-0.5	-3.6 to 2.6
Fasting C-peptide	40	-7.8 to 87	-23	-91 to 45

p-values are for comparison between treatment value to baseline: * $p = 0.036$; ** $p = 0.001$, *** $p = 0.008$.

Table 3: *Comparison of both treatments: analysis of covariance (ANCOVA) for the area under the curve (AUC) for plasma glucose and insulin*

Parameter	Treatment cycle	Adjusted means		p-value
		20 EE/75 GSD	**20 EE/150 DSG**	
AUC insulin	6	268	268	0.9
	13	231	225	0.9
AUC glucose	6	1.81	1.65	0.6
	13	1.69	1.98	0.6

4. DISCUSSION

It has previously been reported that past or current oral contraceptive usage does not influence the subsequent risk of diabetes [5]. Furthermore, there is no evidence that the changes in carbohydrate metabolism induced by combined oral contraceptives (COCs) have an adverse impact on microvascular disease or atherosclerotic processes in healthy women [6]. However, glucose intolerance and hyperinsulinism may be factors predisposing to arterial disease, particularly if additional risk factors such as obesity, family history of diabetes, age, and previous history of gestational diabetes are present [1,7].

In view of the fact that there is convincing evidence that hyperinsulinemia is a good predictor of myocardial infarction and other forms of arterial disease [8], it is desirable to use COCs which exert minimal impact on glucose tolerance. Although the OGTT is a somewhat static, single-point picture of the homeostasis of carbohydrate metabolism, and does not provide full information on the physiological process of insulin resistance induced by COCs in an individual woman, it may nevertheless help to evaluate the relative impact of different COCs on carbohydrate metabolism.

A number of studies have suggested that both the estrogen as well as the progestin component in hormonal contraception may be responsible for inducing insulin resistance. On the progestin side, it is interesting to note that with long-acting progestin-only injectable contraceptives, a significant increase in fasting blood glucose and 2-h blood glucose after glucose load can be observed [9]. However, when using the more sophisticated glucose-clamp technique, Shamma et al. [10] found evidence of a hyperinsulinemic response to glucose and increased insulin resistance in women using implants of levonorgestrel, a gonane progestin with a chemical structure related to DSG and GSD. Similar observations were made earlier with oral levonorgestrel during OGTTs [11]. The estrogen component of COCs is also implicated in lowering insulin sensitivity; among others authors, Kojima et al. [12] using an insulin tolerance test, showed that even low hormone doses, such as 20 μg (EE) administered alone, causes a reduction in insulin sensitivity. The effect of different combined OCs on overall glucose tolerance has accordingly been postulated to be a result of a combination of estrogen-induced insulin resistance and progestin-associated changes in insulin half-life or pancreatic secretion [13]. However, these pharmacodynamic effects cannot be easily ascribed to the estrogen or the progestogen component as the nature of these synthetic, alkylated, steroids may be different, their dose and the ratio estrogen/progestogen may also differ.

Accordingly, high-dose COCs containing 50 μg ethinylestradiol and high progestin doses modulate glucose tolerance more markedly than lower dose preparations containing 35 μg ethinylestradiol or less [13]. When formulations containing the same progestin but in which the estrogen dose has been reduced from 50 to 20 μg are used, the degree of hyperinsulinemia is also reduced [14].

The effect on carbohydrate metabolism, measured by the OGTT, in the long-term use of a COC containing 30-µg ethinylestradiol with 75 μg gestodene has been reported. Slight increases in glucose and insulin during treatment were observed, although these changes were not clinically relevant [15-17]. Reports on the effect on carbohydrate metabolism of monophasic preparations containing 20-µg ethinylestradiol and 150-µg desogestrel show the same pattern of slightly impaired glucose tolerance [16,18-20].

In this prospective randomized study, we compared 2 preparations containing the same dose of 20 μg ethinylestradiol but different 19-nortestosterone derivatives from levonorgestrel as progestins, both DSG and GSD being characterized by far less androgenic action than their parent progestin, levonorgestrel [3]. The glucose responses to OGTTs increased after administration of both preparations, and fasting glucose values were found to be higher after 13 months of treatment by 10 to 12% when compared to the pretreatment levels. However, all fasting values were within the clinically normal range. This is in line with earlier observations that the effect on fasting glucose levels are more accurately evaluated in trials lasting for at least 12 months as shorter durations often do not show an influence on fasting levels [3]. In the present study, the COCs investigated did not show any statistically detectable difference in the AUCs for glucose except at six months of use of EE + GSD versus baseline—a short-lived change. Once more, no abnormal value of blood glucose was recorded during the OGTTs. No statistical difference in the AUCs was detectable between both preparations used. This small decrease in glucose tolerance at 6 and 13 cycles of OC use is in good correlation with observations published earlier [21].

When insulin is cleft from its precursor proinsulin molecule, C-peptide is released into the portal vein in an 1:1 ratio with insulin and can therefore be used as a marker for pancreatic insulin secretion. Changes in fasting insulin levels did not parallel the observed trend of a slight increase in glucose values seen during the study, and simultaneously no change in fasting levels of C-peptide was recorded during the use of both OCs, supporting the observation that fasting insulin concentrations remained unaffected. The fact that no hyperinsulinemia nor increased pancreatic insulin secretion was observed in either treatment group may indicate that the reduction in dose to 20 μg ethinylestradiol in combination with low dosages of progestins as well, triggers to a lesser degree peripheral insulin resistance.

There was a very slight divergence, albeit not statistically significant in this study, in the insulin responses during OGTTs performed at 13 cycles of use of either OC : a slight decrease in AUC for insulin (-3.4%) versus baseline was recorded during use of EE + DSG and a moderate increase (+21%) during use of EE + GSD while pancreatic insulin response (depicted by the AUCs for C-peptide) did not change. Note that the apparent small increase in C-peptide AUC at 13 cycles of EE + DSG use is because of an outlier value. These observations of a somewhat increased response in circulating levels of insulin during use of the COC containing gestodene and decreased levels with desogestrel, while C-peptide concentrations do not change, may indicate a different impact of these steroids on liver function. Hypothetically, desogestrel may increase the hepatic clearance of insulin, a concept that has been previously suggested [13]. Regardless of the mechanism, both oral contraceptives in this study produced a smaller elevation in the plasma insulin response to glucose load than older preparations

particularly those containing levonorgestrel, reinforcing their positive safety profile. However, any predicted benefit in terms of reducing arterial disease will be difficult to demonstrate epidemiologically because of the rarity of the disease in young women [14].

We conclude that the progestins gestodene and desogestrel in combination with 20 μg ethinylestradiol induce similar changes in carbohydrate metabolism. These changes are small and are in good agreement with other studies concerning low-dose COCs containing the same progestins. It is interesting to note that previous studies have indicated that low-dose COCs containing new progestins such as DSG and GSD induced less decline in glucose tolerance and less insulin resistance than older COCs containing high dosages of older progestins such as levonorgestrel. These new OCs may therefore, provide related clinical advantages.

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