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Effects of Low-dose Gestagen (Lynestrenol 0.5 mg) and Combination-type Oral Contraception (Lynestrenol 1 mg and Ethinyloestradiol 0.05 mg) on Blood Glucose and Serum Insulin Levels After a Glucose Load

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Summary. Forty 3-h oral glucose tolerance tests (OGTTs) were performed in 10 apparently healthy female volunteers aged 21–34 years, each serving four times as her own control. Each subject was taking either a low-dose gestagen contraceptive (lynestrenol 0.5 mg) or a combination-type pill (lynestrenol 1 mg + ethinyloestradiol 0.05 mg) alternatingly in four consecutive treatment cycles. Blood glucose and serum insulin did not differ significantly with either contraceptive (paired *t*-test).

Key words: Low-dose gestagen – Combination-type oral contraceptive – Comparison – Blood glucose – Serum insulin

Alterations of carbohydrate metabolism with hormonal oral contraceptives are attributed to the estrogen component of oral contraceptives [6, 9, 10, 18–20]. However, gestagens may also adversely influence glucose tolerance, especially those derived from 19-nortestosterone [12–15]. Both components can potentiate their effects as shown by Beck et al. [3] in the rhesus monkey, when neither component affected blood glucose or serum insulin when given alone, but combined therapy produced marked effects. Changes of glucose tolerance due to estrogens appear to be dose-dependent [18, 20]. Elevations of serum insulin are usually more pronounced than the rises in blood glucose [18, 20] and effects may already be seen in the 2nd treatment cycle [8]. With low-dose gestagens no adverse influences on glucose tolerance have been observed [2, 4, 7, 17].

In this study we examined the effect on oral glucose tolerance and serum insulin levels of gestagens alone and gestagens with added estrogen.

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Materials and Methods

Ten apparently healthy female volunteers, aged 21–34 years, who had been taking combination-type oral contraceptives for 6 months or longer before the start of the trial participated in the study. Each subject took either a low-dose gestagen (lynestrenol 0.5 mg = Exlutona, Organon), further referred to as L or a combination-type pill (lynestrenol 1 mg + ethinylestradiol 0.05 mg = Ovoresta, Organon), further referred to as C, alternatively in four consecutive treatment cycles. The starting preparation was selected at random. Each regimen was taken over 22 days and there followed 6 days without treatment before the patient was switched to the other type of oral contraceptive. On the 20th or 21st day of each treatment cycle an oral glucose tolerance test with 100 g glucose in 400 ml water was performed. Blood glucose and serum insulin levels were measured immediately before and every 30 min for 3 h after glucose ingestion.

Blood glucose was assayed enzymatically in duplicate (hexocinase-micromethod; coefficient of intra-assay variability 1.8%) and serum insulin by double-antibody radioimmunoassay in triplicate (coefficient of intra-assay variability 7.3%).

Figure 1 shows the means and standard deviations of blood glucose levels for the 20 OGTTs under L (points) and those for the 20 OGTTs under C (triangles). Figure 2 gives the corresponding serum insulin values where again the points represent the low-dose gestagen L and the triangles the combination pill C. When analyzing the data by means of the *t*-test for paired observations neither blood glucose nor serum insulin values yielded significant differences at the 5% level at any time of the OGTTs.

When pairs of sums of the half-hour glucose levels over 3 h were arranged for two consecutive OGTTs, one under L and one under C in the same subject, and the sum higher than the corresponding one was listed, 10 OGTTs yielded higher values with L than with C; in the remaining ten pairs of OGTTs the values with C exceeded those with L (Table 1).

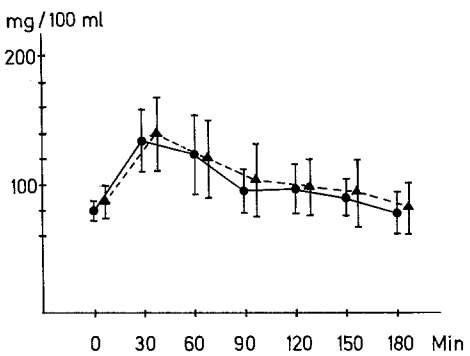

Fig. 1. Means and standard deviations of blood glucose values for 20 OGTTs done either during low dose gestagen therapy with lynestrenol 0.5 mg (points) or during combination-type oral contraceptive therapy with lynestrenol 1 mg + ethinyloestradiol 0.05 mg (triangles)

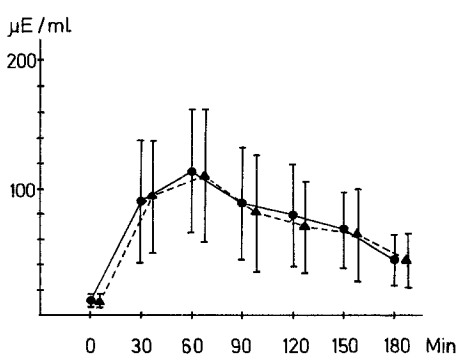

Fig. 2. Means and standard deviations of serum insulin values for 20 OGTTs done either during low-dose gestagen therapy with lynestrenol 0.5 mg (points) or during combination-type oral contraceptive therapy with lynestrenol 1 mg + ethinyloestradiol 0.05 mg (triangles)

Table 1. Sums of blood glucose values. Non-quantitative "higher-lower" comparison of sums of half-hour blood glucose values over 3 h arranged in pairs of oral glucose tolerance tests of two consecutive treatment cycles in the same subject, one during low-dose gestagen therapy with lynestrenol 0.5 mg (L) and the other during a combined therapy with lynestrenol 1 mg + ethinyloestradiol 0.05 mg (C)

Comparison no.	Sum of 3-h blood glucose values during low-dose gestagen therapy (L) (mg/dl)	L > C	Sum of 3-h blood glucose values during combined therapy (C) (mg/dl)	C > L
1	581		721	×
2	778	×	735	
3	537		642	×
4	627		670	×
5	739		769	×
6	909	×	681	
7	621		676	×
8	674	×	543	
9	719		733	×
10	780	×	642	
11	646		734	×
12	585		746	×
13	770	×	673	
14	800	×	585	
15	709		746	×
16	954	×	770	
17	631		873	×
18	818	×	678	
19	607	×	568	
20	978	×	745	
		10		10

When the same analysis was made with the insulin values, the values with L exceeded those with C, and in the remaining ten pairs the values with C exceeded those with L (Table 2).

The number of pathologic OGTTs as defined by the 2-h blood glucose values exceeding 120 mg/dl or the sum of the 1-h and 2-h values exceeding 300 mg/dl was five, three with L and two with C.

Discussion

Low-dose gestagen oral contraceptives are reported to exert no measurable influence on carbohydrate metabolism [2, 4, 7, 17]. Similarly, low-dose estrogens as used in treatment of postmenopausal women appear to be without adverse effects on glucose tolerance [16]. There are conflicting findings on combinations of estrogens and gestagens as used in combination-type oral contraceptives with [1, 8–10] and without [5, 11] deterioration of glucose assimilation. These discrepancies might be due to problems arising from the large variability of blood glucose and serum insulin responses in OGTTs

Table 2. Sums of serum insulin values. Non-quantitative "higher-lower" comparison of sums of half-hour serum insulin values over 3 h arranged in pairs of oral glucose tolerance tests of two consecutive treatment cycles in the same subject, one during low-dose gestagen therapy with lynestrenol 0.5 mg (L) and the other during a combined therapy with lynestrenol 1 mg + ethinyloestradiol 0.05 mg (C)

Comparison no.	Sum of 3-h serum insulin values under L (μU/ml)	L > C	Sum of 3-h serum insulin values under C (μU/ml)	C > L
1	469		689	×
2	748	×	611	
3	639	×	548	
4	756	×	492	
5	475		542	×
6	384		663	×
7	292		403	×
8	312		637	×
9	413	×	344	
10	324		359	×
11	750	×	727	
12	764		814	×
13	464	×	408	
14	143		169	×
15	509	×	474	
16	364		541	×
17	629	×	379	
18	331		354	×
19	349	×	292	
20	369	×	366	
		10		10

between different individuals and even in the same subjects. To minimize bias with a small number of volunteers we tried to standardize the basic conditions by testing the same subjects four times, each serving as her own control with respect only to the two treatment schemes used in this study. A statistical comparison of the means of glucose and insulin values appeared to be of little value in view of the individual variability demonstrated by the standard deviations shown in Figs. 1 and 2. Our experimental model allowed a comparison of the differences in glucose and insulin values in the same subjects by means of the *t*-test for paired observations, which yielded no significant differences. When the differences in glucose and insulin values were analyzed on a nonquantitative "higher-lower" basis, as was done with the sums of glucose values over 3 h in Table 1 and with corresponding insulin values in Table 2, again no differences between the estrogen-free gestagen therapy (L) and the combined therapy (C) could be found as regards glucose tolerance.

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