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The relation of growth hormone to altered carbohydrate metabolism in women taking oral contraceptives

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SYNOPSIS Oral glucose tolerance tests were performed on a group of women before and during oral contraceptive administration and the plasma glucose, insulin, and growth hormone levels were studied. A significant impairment of glucose tolerance and an altered insulin response were observed in women taking oral contraceptives. The women had higher plasma growth hormone levels in the fasting state but this is not of primary aetiological significance in the development of altered carbohydrate metabolism.

Oestrogen-progestagen oral contraceptives have been shown to impair glucose tolerance (Gershberg, Javier, and Hulse, 1964; Wynn and Doar, 1966; Spellacy, Carlson, Birk, and Schade, 1968; Wynn and Doar, 1969) and cause elevated blood pyruvate and plasma insulin levels (Wynn and Doar, 1969). Although the mechanism of these effects is not yet established, Wynn and Doar (1969) and Doar and Wynn (1970) have drawn attention to the similarity between these changes and those produced by glucocorticoid therapy.

Fasting plasma growth hormone levels are elevated by oestrogens and oral contraceptives (Frantz and Rabkin, 1965; Garcia and Linfoot, 1966; Spellacy, Carlson, and Schade, 1967; Garcia, Linfoot, Manougian, Born, and Lawrence, 1967; Yen and Vela, 1968). Spellacy *et al* (1967) have postulated that the high plasma growth hormone levels are the cause of the impaired glucose tolerance in women on oral contraceptives since growth hormone has diabetogenic effects (Young, 1963). Yen and Vela (1968) found glucose tolerance to be unaltered in a group of women on contraceptive steroids but plasma insulin levels were higher. They attributed this effect to the excess growth hormone secretion found in these women.

In this paper we report our findings of plasma growth hormone glucose and insulin levels during oral glucose tolerance tests in women receiving oral contraceptives.

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Methods

Oral glucose tolerance tests (OGTT) were carried out on a group of 32 women by methods already reported (Wynn and Doar, 1966). All subjects acted as their own controls and were tested on an outpatient basis before and on the drugs, the average duration of administration being four months, except for four subjects who were studied when taking oral contraceptives and again three months after stopping. The oral contraceptives used were combined oestrogen-progestagen preparations. Blood samples were taken from an intravenous cannula, the first sample being withdrawn 30 minutes after its insertion. The fasting levels recorded of plasma glucose, insulin, and growth hormones are the means of two determinations separated by an interval of 10 minutes. One further subject who had been admitted to hospital was studied as an inpatient for both tests.

Plasma glucose estimations were determined by an automated glucose oxidase method (Cramp, 1967), plasma growth hormone by radioimmunoassay using charcoal for separation of bound and free hormone (Jacobs, 1969), and plasma insulin by a double antibody radioimmunoassay (Samols and Bilkus, 1964). For the hormone assays, both tests from the same patient were assayed in the same experimental run.

Composite values for the oral glucose tolerance test plasma glucose, insulin, and growth hormone curves were obtained by calculating the total area

between the curve and the abscissa, assuming straight lines between individual points (Wynn and Doar, 1966).

The significance of differences of means was assessed by Student's t test for paired samples, and the correlation between two variables by the product moment correlation coefficient.

Results

Mean oral glucose tolerance test plasma glucose, insulin, and growth hormone levels before and on therapy in 32 ambulant subjects are shown in Table I. The changes in glucose tolerance and plasma insulin levels are similar to those observed in a larger series reported from this unit (Wynn and Doar, 1969). With the exception of fasting values, the mean plasma glucose levels were significantly higher on treatment throughout the glucose tolerance tests. No significant change was found in mean plasma insulin levels in the fasting state or at 30 or 60 minutes after glucose, but thereafter the values on medication were significantly higher than those off therapy. The mean oral glucose tolerance test plasma growth hormone levels were significantly elevated during therapy, in the fasting state, and at 30, 60, and 90 minutes after glucose. Plasma growth hormone levels, however, fell after glucose administration in all subjects whether on or off therapy. Despite considerable individual variation of fasting plasma growth hormone levels, a rise during therapy occurred in 27 of 32 subjects (84%).

Significant increases in mean oral glucose tolerance test glucose, insulin and growth hormone areas occurred during oral contraceptive administration (Table II). No significant correlations, however, were found between the changes in any two of these indices. The changes of oral glucose tolerance test growth hormone area and glucose area found in 32 ambulant subjects during therapy are shown in Figure 1. From this figure it is clear that appreciable deterioration in glucose tolerance may occur in individuals with widely differing growth hormone responses.

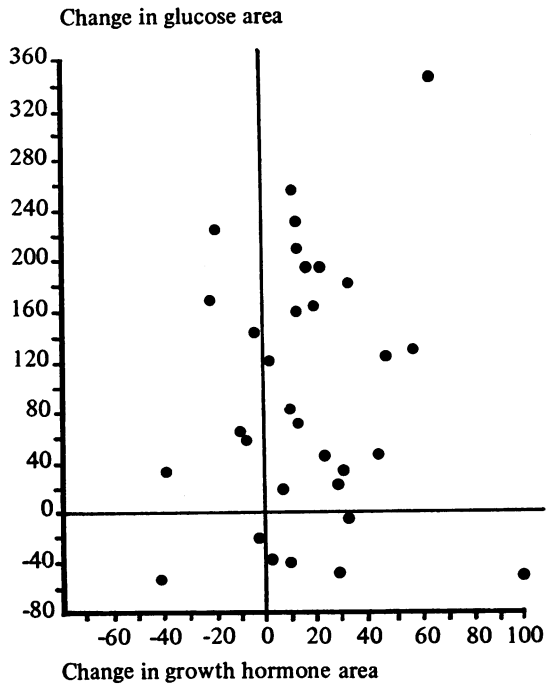

Fig. *Changes in oral glucose tolerance test glucose and growth hormone areas produced by oral contraceptives.*

Oral Glucose Tolerance Test	*Untreated*	*On Oral Contraceptives*	*P*
Glucose area	678 ± 102	772 ± 114	< 0·001
Insulin area	324 ± 148	370 ± 167	< 0·01
Growth hormone area	31 ± 23	47 ± 34	< 0·01

Table II *Oral glucose tolerance test glucose, insulin, and growth hormone areas (±SD) in 32 subjects untreated and taking oral contraceptives*

Time (min)		*0*	*30*	*60*	*90*	*120*	*150*	*180*
Plasma glucose (mg/100 ml)	A	84 ± 10	137 ± 22	133 ± 30	119 ± 28	110 ± 19	96 ± 19	83 ± 20
	B	87 ± 8	147 ± 23	146 ± 29	142 ± 30	129 ± 23	114 ± 21	104 ± 21
	P	NS	<0·05	<0·01	<0·001	<0·001	<0·001	<0·001
Plasma insulin (μu/ml)	A	19 ± 13	78 ± 37	73 ± 43	59 ± 33	53 ± 28	37 ± 20	27 ± 18
	B	20 ± 11	75 ± 38	70 ± 30	78 ± 47	66 ± 38	51 ± 25	40 ± 19
	P	NS	NS	NS	<0·01	<0·05	<0·001	<0·001
Plasma growth hormone (ng/ml)	A	13·5 ± 11·8	4·6 ± 5·8	1·6 ± 2·1	0·6 ± 0·8	2·3 ± 4·0	8·5 ± 10·7	13·6 ± 16·2
	B	21·3 ± 14·2	8·8 ± 8·4	3·8 ± 8·3	1·5 ± 1·9	3·4 ± 4·9	11·1 ± 11·8	14·5 ± 13·0
	P	<0·01	<0·01	<0·001	<0·01	NS	NS	NS

Table I *Mean (±SD) plasma glucose, insulin and growth hormone levels during oral glucose tolerance tests on 32 ambulatory subjects* (A) *before and* (B) *during oral contraceptive administration*

Time (min)	0	30	60	90	120	150	180
Untreated							
Plasma glucose (mg/100 ml)	60	105	115	125	125	95	70
Plasma HGH (ng/ml)	5	2	2	3	4	30	35
Plasma insulin (μu/ml)	7	44	45	43	47	28	11
On oral contraceptive							
Plasma glucose (mg/100 ml)	84	171	215	210	175	117	76
Plasma HGH (ng/ml)	1	1	1	—	1	15	19
Plasma insulin (μu/ml)	11	58	68	75	65	37	20

Table III *Oral glucose tolerance test plasma glucose, insulin, and HGH values obtained on a 37-year-old subject studied as an hospital inpatient before and two months after oral contraceptive administration*

The results for the subject who was studied as an inpatient for both tests are recorded in Table III. The subject was 37 years old, para 2, not obese, and had no family history of diabetes. After two months on oral contraceptives (Anovlar 21—norethisterone acetate 4 mg, ethinyloestradiol 0·05 mg) glucose tolerance was impaired, plasma insulin levels increased, but plasma growth hormone levels were not noticeably affected.

Discussion

The observation in this study that fasting plasma growth hormone levels are elevated in women taking oral contraceptives confirms the results of other workers on the effects of oestrogen and oestrogen/progestagen combinations (Frantz and Rabkin, 1965; Garcia and Linfoot, 1966; Garcia *et al*, 1967; Spellacy *et al*, 1967, Yen and Vela, 1968). Although an increase in the fasting growth hormone level was found in 84% of subjects, a striking finding was the marked individual variation in the degree of change observed and the wide range of growth hormone values encountered. The finding of statistically significant mean changes at individual points during the oral glucose tolerance tests (Table I) or of a mean change when glucose tolerance is assessed as the area under the curve (Table II) does not necessarily imply that there is a causal relationship between the variables investigated. When the association between plasma glucose and growth hormone is tested by examining the correlation between changes induced by oral contraceptives in the total areas during oral glucose tolerance tests, no significant correlation emerges. Furthermore, reference to the Fig. illustrates the wide range in change of the oral glucose tolerance test growth hormone area produced by contraceptive steroids which may occur for a given change in glucose tolerance. These findings suggest that elevated growth hormone is not the main factor in causing the impaired glucose tolerance in women taking oral contraceptives.

That growth hormone may exert a diabetogenic influence is well known (Young, 1963), but in acromegaly there is an abnormal pattern of growth hormone response to stimuli in addition to the elevated values found, and glucose administration rarely causes suppression of plasma growth hormone levels (Sönksen, Greenwood, Ellis, Lowy, Rutherford, and Nabarro, 1967). However, in the present study suppression after glucose occurred in all subjects, and, although the levels remained higher throughout the test when on treatment, the decrement in plasma growth hormone level from the fasting state to the 90-minute sample was greater than when untreated. This pattern of suppression of growth hormone release following glucose administration in subjects on oestrogens or combined oestrogen/progestagen preparations has also been observed by other workers (Frantz and Rabkin, 1965; Garcia *et al*, 1967; Yen and Vela, 1968).

Frantz and Rabkin (1965) introduced the terms 'ambulatory' and 'basal' growth hormone levels to differentiate between values found in outpatients tested one to three hours after awakening in the morning, following an overnight fast, and those found in hospitalized subjects soon after waking and before the occurrence of any significant activity. In their study they found that in the ambulatory state women had raised levels compared with men and that administration of an oestrogen caused further elevation in plasma growth hormone. However, under basal conditions plasma growth hormone levels for men, women, and oestrogen-treated subjects were all low. This variability in growth hormone secretion underlines the difficulty in obtaining meaningful data for fasting plasma growth hormone levels in outpatients who have travelled variable distances to the hospital and have been subjected to the growth-hormone-provoking effect of exercise (Roth, Glick, Yalow, and Berson, 1963) or stress (Greenwood and Landon, 1966) to a greater or lesser extent. The need for adequate control data and the effects of minor forms of stress with regard to growth hormone secretion have been emphasized in recent reports (Best, Catt, and Burger, 1968; Czarny, James, Landon, and Greenwood, 1968).

If, as Frantz and Rabkin (1965) have suggested, the increased growth hormone secretion in patients on oestrogens is mediated by an increased pituitary sensitivity to the various stimuli causing growth hormone release, then the higher plasma growth hormone levels found in our ambulant subjects on

combined oestrogen/progestagen preparations are to be predicted. Our observations on the one subject studied under basal conditions confirm the finding of low plasma growth hormone levels (see Table III) and show that at the individual level a subject may have distinct deterioration of glucose tolerance due to oral contraceptive therapy without elevated plasma growth hormone levels.

A further feature of the altered carbohydrate metabolism in women on oral contraceptives is the finding of elevated blood pyruvate levels (Wynn and Doar, 1969). However, neither acromegalic patients (Doar and Wynn unpublished observations) nor healthy subjects following the acute administration of a single injection of growth hormone (Doar, Maw, Simpson, Audhya, and Wynn, 1969) show these blood pyruvate changes after glucose administration.

As a result of these findings we are unable to substantiate the hypothesis of Spellacy *et al* (1967) that the impaired carbohydrate tolerance in women on oral contraceptives is a direct result of high plasma growth hormone levels. Yen and Vela (1968) did not find any impairment of glucose tolerance in the subjects they studied on contraceptive steroids, but implicated the increased plasma growth hormone levels as the cause of the hyperinsulinism they found in their subjects on treatment. In the present study no significant change was found in the mean fasting plasma insulin level but significantly higher mean values were recorded during the latter half of the test when on therapy and there was a significant increase in the area under the plasma insulin curve. However, a significant correlation was not found between the change in area under the plasma growth hormone curve and the change in area under the plasma insulin curve, which makes it unlikely that the elevated fasting plasma growth hormone levels in ambulant women on oral contraceptives is of primary importance in the pathogenesis of the altered insulin secretion to glucose administration.

The variation in the fasting plasma growth hormone levels in this study illustrates the difficulty encountered in determining plasma growth hormone changes in subjects on an outpatient basis when it is impossible to eliminate completely factors such as stress and exercise which are known to exert a powerful stimulus to growth hormone secretion. But the results show that the higher plasma growth hormone levels observed in women on oral contraceptive therapy are not the initiating cause of the impaired glucose tolerance. In addition a recent cross-sectional study (Spellacy, Buhi, Spellacy, Moses, and Goldzieher, 1970) of women taking contraceptive steroids has failed to show any difference in growth hormone response after glucose administration between subjects with abnormal and those with normal glucose tolerance. However, further knowledge of changes in diurnal growth hormone secretion in women on oral contraceptives both in the basal and ambulatory states is needed to determine whether growth hormone has any indirect effect in initiating metabolic abnormalities in response to glucose. In this report the observed changes in plasma growth hormone are best explained by the hypothesis of Frantz and Rabkin (1965) that there is increased pituitary sensitivity present in subjects taking oestrogen-containing medication and that the high plasma growth hormone levels are probably physiological reflections of the various stresses involved in outpatient studies.

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