Metabolic Effect of Conjugated Oestrogens (USP) on Glucose Tolerance

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SUMMARY

Synthetic oestrogens contained in normal contraceptives have been shown to cause a decrease in tolerance to oral glucose after prolonged use in young as well as in climacteric females.

To assess the effect of natural oestrogens on glucose tolerance, conjugated oestrogens (USP) (Premarin 1,25 mg) were administered cyclically for one year to a mixed group of 50 normal and diabetic postmenopausal women. Of the total group 38% developed a decrease in glucose tolerance on treatment, significant deviations from normal being found in 18%. Glucose tolerance was improved or the imbalance maintained in 60% of the diabetic and 'abnormal' group. In most instances the lowering of the glucose tolerance stabilised itself after 9 months' treatment in normals and diabetics, and was usually reversed on withdrawal of therapy.

It can be concluded that conjugated oestrogens may impair glucose tolerance in a low percentage of patients, but their effect appears to be much less than that of the synthetic oestrogens.

It is unlikely that conjugated oestrogens *per se*, will induce overt diabetes.

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Gershberg *et al.*[1] reported a decrease in tolerance to oral glucose after prolonged usage of hormonal contraceptives. Since then, this observation has been confirmed by several investigators who have established that it is the oestrogen component that is the activating factor.[2-5] Although these reports dealt primarily with young women on steroid contraceptives, the same effect has been noted when oestrogens were used in the treatment of the climacteric.[6,7]

Since most of the previous work was based on synthetic oestrogens taken over a relatively short period of time, a study was undertaken to determine glucose tolerance in postmenopausal women receiving conjugated oestrogens for one year. The investigation was initiated because of the increasing evidence that the oestrogen-deficient climacteric is associated with conditions such as osteoporosis, which can be prevented by long-term substitution therapy.[8]

The objectives of the trial were to establish the effect of prolonged therapy on glucose tolerance, and the reversibility of any impairment.

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PATIENTS AND METHODS

It was decided to investigate the effect of oestrogens on a group of White women attending a Climacteric Clinic without prior investigation of their carbohydrate balance, or relation to diabetes or pre-diabetes; 50 women were selected on a random sample basis and the objective of the trial was explained to them. All were ambulatory and in apparent good health. The mean age of the study group was 51 years (range 31 - 68 years), and their mean weight 66 kg (range 41 - 113 kg). The duration of the postmenopausal period varied from 6 months (surgical menopause) to 24 years, with a median value of 7,3 years. Each subject served as her own control. All were asked to maintain a normal diet before having the glucose tolerance test (GTT). The procedure was performed between 0800 and 1000 after an overnight fast. A fasting specimen of venous blood was obtained and the patient given 100 g glucose, dissolved in a tumbler of water. Further blood samples were taken at 60 minutes and 120 minutes. The patients were then put onto treatment—usually 1,25 mg/day conjugated oestrogen (Premarin) on a 3-week cyclic basis—and the GTT was repeated at the end of 3 and 9 months' treatment. At the end of a year's treatment medication was suspended for a month and the GTT repeated. The blood glucose was determined by a Technicon AutoAnalyzer, using a potassium ferrocyanide oxidation reduction reaction.

Statistical Analysis

The results were assessed in three ways; variations in individual response to treatment with Premarin were noted by either an improvement, a deterioration, or no alteration in glucose tolerance (Table I); to determine the effect of the duration of treatment and reversibility on glucose tolerance, the group was studied as a whole and the mean (± standard error of the mean) calculated for glucose at the three time intervals (fasting, 1 hour and 2 hours post-glucose), and at the four test intervals (baseline, 3 months, 9 months, and 1 month post-treatment) (Table II) (Fig. 1).

The statistical significance of the effect of treatment was based on the matched pairs test. Differences between 3 and 9 months' values and the baseline readings were analysed by means of the matched pairs *t*-test (Table III). A further indication was obtained by noting the change in glucose tolerance after the end of treatment. The changes from baseline to post-treatment, and from 9 months to post-treatment, were therefore similarly analysed

TABLE I. EFFECT OF CONJUGATED OESTROGEN ON GLUCOSE TOLERANCE IN 50 MENOPAUSAL WOMEN BEFORE, AFTER 3 AND 9 MONTHS' CONTINUOUS TREATMENT, AND 1 MONTH AFTER SUSPENSION OF TREATMENT (see text)

		Glucose tolerance worse		Glucose tolerance same	Glucose tolerance improved
		>Blood sugar	Blood sugar>		
Group	No.	GTT normal	GTT diabetic		
Diabetic	7	—	3	1	3
Abnormal	8	—	3	4	1
Normal	35	10	3	22	—
	—	—	—	—	—
Over-all effect	50	10	9	27	4

TABLE II. A COMPARISON OF THE MEAN (± SEM) BLOOD SUGAR LEVELS (IN mg/100 ml) IN A GROUP OF 50 POSTMENOPAUSAL WOMEN, BEFORE, DURING AND AFTER WITHDRAWAL OF TREATMENT WITH CONJUGATED OESTROGENS

Variable		Baseline	3 months	9 months	Post-treatment
Fasting	Mean	96,00	96,50	98,38	95,81
	± SEM	1,85	1,59	1,75	1,62
1-hour	Mean	143,87	154,47	147,94	139,24
	± SEM	5,84	6,97	7,03	6,87
2-hour	Mean	107,26	124,19	123,54	107,43
	± SEM	4,61	5,65	6,39	4,78

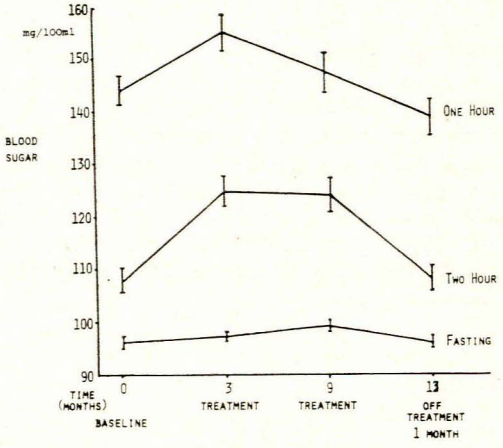

Fig. 1. Glucose tolerance in 50 menopausal women before, during and after treatment with Premarin. Mean values for group expressed in mg/100 ml (±SEM).

(Table IV). Using a Bonferonni inequality procedure, *t*-values above 3,2 were found to be significant at the 0,05 level, and those above 3,7 at the 0,01 level.

RESULTS

Patients were classified into three groups: those with fasting, 1-hour and 2-hour glucose levels below 120, 180 and 140 mg/100 ml respectively, were regarded as 'normal'; if one of the values exceeded these limits the patient was classified as 'abnormal'; if two or more values were elevated the patient was regarded as 'diabetic'.

Individual Response

Of the 50 patients admitted to the trial, 7 were found to be 'diabetic' after their initial glucose tolerance test, 8 were classified as 'abnormal', and 35 as 'normal' (Table I).

Subsequent glucose tolerance was said to be lowered if any one blood sugar recording varied by 40 mg/100 ml or more above the original baseline value. Only if it exceeded the limit of normality was the change categorised as 'diabetic'. Of the total group 19 (38%) showed some evidence of deterioration in tolerance, i.e. the 1-hour or 2-hour blood sugar levels were elevated above their baseline values at either the 3-month, 9-month or 'off-treatment' test intervals. However, in only 9 instances (18%) did these values exceed the limits of normality.

All the diabetics were diagnosed for the first time at their initial attendance and no specific treatment was ordered except for advice regarding the avoidance of excessive carbohydrate and fat in their diet. Strict supervision of their 'diabetes' was not enforced. It is therefore interesting to note that glucose tolerance actually improved or stayed the same in 4 patients and deteriorated in only 3. Similarly, of the 8 patients classified as 'abnormal' the majority (5) either improved or maintained their degree of abnormality; the other 3 patients exhibited a definite decrease in glucose tolerance.

No change in glucose tolerance was noted in 22 (63%) of the 'normal' group; moderate elevations (more than 40 mg/100 ml above baseline values, but still within normal range) occurred in 10 normal subjects (29%). The increase in the glucose values in the latter category invariably involved the 1-hour blood sugar sample, and may in part have been related to the rather large loading dose of glucose (100 g) used in the series. Three 'normal' patients

TABLE III. STATISTICAL ASSESSMENT OF THE EFFECT OF CONJUGATED OESTROGENS ON GLUCOSE TOLERANCE BY CALCULATING THE MEAN CHANGE IN TOLERANCE (FOR THE GROUP) AFTER 3 AND 9 MONTHS TREATMENT (see text)

Variable		3 months - baseline	9 months - baseline
Fasting	**Mean diff. (mg/100 ml)**	**−0,05**	**2,77**
	t	**−0,02**	**1,18**
	P	**NS**	**NS**
1-hour	**Mean diff. (mg/100 ml)**	**7,63**	**2,50**
	t	**1,18**	**0,36**
	P	**NS**	**NS**
2-hour	**Mean diff. (mg/100 ml)**	**18,47**	**16,17**
	t	**3,64**	**2,69**
	P	**S**	**NS**

TABLE IV. STATISTICAL ASSESSMENT OF THE EFFECT OF CONJUGATED OESTROGENS ON GLUCOSE TOLERANCE (FOR THE GROUP) BY NOTING THE MEAN CHANGE IN TOLERANCE AFTER WITHDRAWAL OF TREATMENT (see text)

Variable		Post-treatment - baseline	Post-treatment - 9 months
Fasting	**Mean diff. (mg/100 ml)**	**−0,47**	**− 2,84**
	t	**−0,20**	**− 1,85**
	P	**NS**	**NS**
1-hour	**Mean diff. (mg/100 ml)**	**−4,49**	**−10,22**
	t	**−0,70**	**− 2,14**
	P	**NS**	**NS**
2-hour	**Mean diff. (mg/100 ml)**	**−0,19**	**−14,80**
	t	**−0,04**	**− 2,62**
	P	**NS**	**NS**

(9%) developed 'diabetic' GTT curves subsequent to treatment. All 3 were elderly (68, 68 and 65 years respectively), 2 were obese (77 and 77,5 kg), and 2 had hypertension (blood pressure 200/105 and 155/90 mmHg). The abnormality in glucose tolerance persisted in 2 patients (6%) one month after conjugated oestrogen treatment had been stopped. Since they were both asymptomatic they were classified as 'chemical' diabetics.

Group Response

The change in glucose tolerance of the total group (irrespective of their initial classification), is reflected in Fig. 1 and Table II. From this it can be seen that the fasting blood sugars are largely unaffected, a marginal increase occurring only after 9 months of treatment. The respective mean values for the baseline, 3-month, 9-month, and post-treatment values were 96,00 ± 1,85, 96,50 ± 1,59, 98,38 ± 1,75, and 95,81 ± 1,62 mg/100 ml. A more distinctive change is noted at the 1-hour time interval. After 3 months' treatment the mean value rose from the original baseline level of 143,87 ± 5,84 to 154,47 ± 6,97 mg/100 ml. After a further 6 months' treatment with conjugated oestrogens the 1-hour value settled to a level midway between the previous two, viz. 147,94 ± 7,03 mg/100 ml, and returned to a value lower than the original baseline 139,24 ± 6,87 mg/100 ml, when assessed one month after suspension of treatment. These changes are all within normal limits and were not statistically significant (Tables III and IV).

A substantially greater mean increase in the 2-hour levels was noted at both 3 months (124,19 ± 5,65 mg/100 ml), and 9 months (123,54 ± 6,93 mg/100 ml), when compared with the initial value of 107,26 ± 4,61 mg/100 ml. The 2-hour blood sugar levels returned to normal on withdrawal of therapy (107,43 ± 4,78 mg/100 ml).

The statistical significance of these changes was assessed by calculating the mean difference between the 3-month, 9-month and baseline values (Table III), and the mean change between the 'after-treatment' and baseline, and the 'after-treatment' and 9-month values (Table IV). The only statistically significant difference was the mean increase observed in the 2-hour value after 3 months' treatment (Table III). Although the mean 2-hour level at 9 months was also raised, it was not found to be of statistical significance. There was a substantial (but not significant) decrease in both the 1- and 2-hour glucose levels after treatment had been withheld for a month (Table IV).

Clinical Response

The clinical response of the patient to treatment with conjugated oestrogens, and their effect on blood pressure and weight will be presented elsewhere.[9] In brief, all reported a definite improvement in menopause-related symptoms, e.g. 'hot flushes' and pruritus vulvae. There were no untoward side-effects related to the taking of conjugated oestrogens apart from occasional episodes of breakthrough bleeding.

DISCUSSION

This study has shown that the natural oestrogens have a glucogenic potential. The term 'glucogenic' (rather than diabetogenic) is preferred since it differentiates between a reversible pharmacological side-effect and a more permanent iatrogenically-induced pathological state. When compared with other series, the incidence of disturbed carbohydrate balance was surprisingly low. Thus 38% of our patients showed some deviation from normal, a significant difference being found in only 18%. This figure is rather surprising since the trial was conducted over a period of one year and involved elderly women, many of whom were obese and hypertensive, and so predisposed to abnormal glucose tolerance. One of the few comparable studies was that conducted by Goldman and Ovadia.[7] Their trial involved 30 patients who had received 1,25 mg Premarin daily for 3 months; 73,3% of their postmenopausal patients showed a decrease in carbohydrate tolerance as measured by the intravenous GTT. Wynn and Doar[5] and others[3,4] evaluated glucose tolerance in young women on the contraceptive pill taken for periods varying from 6 months to 8 years. They recorded a deterioration in oral glucose tolerance in some 39 - 78% of their patients. In one series, 13% of the study group developed chemical diabetes while on treatment.[5]

The sum of evidence from these and other investigations suggests that it is the synthetic oestrogen component in the contraceptive pill which accounts for the commonly-found impairment of glucose tolerance. The precise mechanism of this impairment has not yet been agreed upon. Defective pancreatic response, increased growth hormone levels, a decrease in the rate of utilisation of glucose by the tissues, hepatic factors and altered endogenous glucocorticoid activity, have all been incriminated.[4,10] Utian[11] has shown that different oestrogens have different degrees of therapeutic efficacy in terms of their ability to lower plasma calcium and cholesterol levels. The same is probably true for their undesirable side-effects. According to the present study it would appear that the natural oestrogens have a lesser over-all glucogenic side-effect.

Posner *et al.*[12] recently recorded reduced tolerance to intravenous glucose administration during the first 6 months of treatment with an oral contraceptive (Enavid), but noted that this abnormality disappeared in patients who had been followed up for 18 months. Di Paola *et al.*[13] also found that the effect of mestranol on carbohydrate metabolism was transient since the percentage of abnormal tests decreased after 9 months and reached normal levels after 12 months. By following patients for more than a year one can frequently detect a biphasic effect in which disturbed carbohydrate balance is followed by a normalisation of tolerance. This recovery in glucose tolerance is thought by some to be due to a hypertrophy and hyperplasia of the pancreatic islands.[13] There was a slight, but definite, trend in the present study to an improvement in glucose tolerance with the progression of treatment, this being more apparent at the 1-hour post-glucose interval.

Of greater significance is the reversibility of the glucogenic effect of conjugated oestrogens. Thus all post-treatment values were substantially reduced, e.g. the 1-hour value decreased from 147,94 ± 7,03 to 139,24 ± 6,87 mg/100 ml; and the 2-hour value from 123,54 ± 6,30 to 107,43 ± 4,78 mg/100 ml. These values were either lower or the same as the original baseline figures.

Wynn and Doar[5] found a striking improvement in oral glucose tolerance shortly after oral contraceptives had been discontinued. They nevertheless expressed the fear that this improvement might not be permanent, and that the initial impairment of glucose tolerance, together with the commonly-associated increased plasma insulin levels, would accelerate the development of clinical diabetes mellitus and its associated complications. In the present series, 3 patients who had normal glucose tolerance at the beginning of the trial subsequently developed tolerance curves suggestive of diabetes mellitus. On withdrawal of therapy this abnormality persisted in 2 of them. Superficially it might seem that the fears expressed by Wynn and Doar[5] were justified. However, with the exception of 1 patient, definite prediabetic features such as hypertension were present.[14] In addition all 3 patients (who were over 65 years old) were at an age when glucose tolerance is commonly said to deviate from the normal. Thus Heikinheimo,[15] in a study based on 1 500 patients, concluded that older age group patients (especially females) invariably showed higher blood glucose values 2 hours after the administration of glucose than a younger age group. It is probable that gross aberrations of glucose tolerance only occur in patients who are already prediabetic, in very much the same way as pregnancy only affects the GTT adversely in potential or latent diabetics. It is also well known that although repeated pregnancies may temporarily cause an aggravation in glucose tolerance in diabetics, it has no adverse effect on the pathogenesis of the vascular lesion.[16,17] Cognisance should also be taken of the observations of Garcia and Wallach[10] who did not observe an increase in the incidence of overt diabetes among patients who had been on the contraceptive pill for 10 - 12 years. It is therefore most unlikely that the administration of oestrogens over many years to healthy postmenopausal non-diabetic women would cause the development of diabetes mellitus or its associated vasculopathies. In fact, women who have a tendency to decreased glucose tolerance when on oestrogen therapy, might even benefit by having their diabetes diagnosed earlier. By instituting dietary control and, where necessary, additional antidiabetic therapy, one may be able to exert a beneficial effect on the pathogenesis of the disease, and reduce, if not prevent, its associated long-term morbidity.

Despite the acknowledged glucogenic effect of oestrogen, it is important to emphasise that this form of therapy is not contra-indicated in overt diabetics. This view is endorsed by Pyke.[18] Javier *et al.*[3] produced evidence to suggest that oestrogen might actually improve glucose tolerance in the mild maturity-onset diabetic. Approximately 60% of patients in our diabetic and abnormal groups either maintained or improved their glucose tolerance while on treatment with conjugated oestrogens.

CONCLUSION

If prolonged use of oestrogens is envisaged in the treatment of postmenopausal women, therapeutic preference must be given to those preparations with the greatest efficacy and the least side-effects. Using our patients as their own control, this study has shown that whereas conjugated oestrogens do have a glucogenic tendency, the degree of abnormality tends to decrease with prolonged treatment and is usually reversible within one month of stopping treatment. Furthermore, considerably fewer of our patients had aberrations in glucose tolerance (38%), when compared with the 57 - 80% incidence of abnormalities in tolerance after prolonged usage of the synthetic oestrogens (mestranol and ethinyl oestradiol) in younger women. Prolonged oestrogen therapy may precipitate chemical diabetes in predisposed individuals, and it is therefore suggested that all persons on prolonged supportive hormone therapy be tested annually for abnormal tolerance. Since it is the 2-hour post-glucose value that is usually affected by oestrogen therapy,[2] control can easily be exercised by the simple expedient of screening patients annually with a 2-hour post-glucose check. This may be conveniently and accurately performed with the Dextrostix test strip.[19]

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