Conjugated equine oestrogens and blood clotting: a follow-up report

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Summary

A follow-up study of blood clotting and platelet aggregation was performed on 21 women who had received long-term hormone replacement treatment with conjugated equine oestrogens. The prothrombin time and factor VII and X values were significantly accelerated after three months, but there was no further increase with continual administration for 18 months. After 12 to 18 months' treatment, however, thrombin-induced platelet aggregation (Chandler's tube) was also significantly accelerated, which suggested a widening spectrum of effect. No overall acceleration of "intrinsic" clotting (partial thromboplastin time and thromboelastography) was found during the study, but the relatively small numbers may have been responsible.

Further efforts are therefore required to find formulations and doses of oestrogens which, while relieving menopausal symptoms, cause less acceleration of blood clotting and platelet aggregation.

Introduction

In a six-month, double-blind crossover study we showed that women taking conjugated equine oestrogens had accelerated blood clotting values.¹ Most of these women subsequently needed long-term maintenance treatment with oestrogens to control their menopausal symptoms. We therefore performed follow-up studies on blood clotting and platelet aggregation values during their long-term treatment. Our aim was to ascertain whether the acceleration of clotting observed in the first three months of oestrogen administration was sustained or intensified during a longer period of oestrogen treatment. We report here our findings after 18 months of the long-term study. By this time the women had received continuous oestrogen treatment for 21 or 18 months depending on whether they had received a three-month course of oestrogen or placebo before entry to the long-term study.

Patients and methods

Twenty-two of the 30 women originally studied requested long-term replacement treatment. They were given the minimum effective dose of conjugated equine oestrogens (Premarin) needed to suppress their hot flushes. Sixteen patients took 1.25 mg/day and six took 0.625 mg/day for three out of every four weeks. Two patients were excluded from the analysis because oestrogens were discontinued during the study—because of endometrial carcinoma in one case and loss of libido in the other.

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Coagulation studies were performed after three and six months' long-term treatment and then every six months. The laboratory tests were the same as those described previously.¹ The results were analysed, using the paired *t* test, against the women's baseline results recorded before entry into the preceding short-term double-blind study. The original random allocation of the patients into two groups of equal numbers was retained in this long-term follow-up. In the original trial those in group 1 had received oestrogen for the first three months and placebo for the second three months—that is, immediately before the start of the present study—whereas those in group 2 had received three months' oestrogen immediately before the start of this trial. Results in groups 1 and 2 were therefore analysed separately.

Results

At the entry to the long-term study, both groups of women showed significantly accelerated prothrombin times and factor VII and X values that were significantly faster than their baseline values ($P < 0.05$). Detailed results of the coagulation and platelet aggregation studies are given in the table.

Prothrombin time—The prothrombin time was significantly shorter after three months' long-term oestrogen administration in group 1, and this was sustained throughout the period of long-term replacement ($P < 0.05$). Women in group 2, who had already received oestrogen in the three months immediately before entry to the long-term study, had a significantly accelerated prothrombin time initially, and this was sustained throughout the study. There was, however, no statistical evidence of a progressive shortening of the prothrombin time in either group.

Partial thromboplastin time (PTT)—There was no change in the PTT values during long-term oestrogen administration.

Factor VII—Women in group 1 showed a significant shortening of the clotting time in the factor VII assay after three months' long-term treatment after three months, and this was maintained at later stages ($P < 0.05$). There was, however, no evidence of a progressive shortening of factor VII clotting times with long-term administration. Patients who had received oestrogen during the preceding three months (group 2) showed no evidence of a further acceleration, although clotting times in the factor VII assay continued to be significantly shorter than baseline times throughout the study.

Factor X—Factor X levels showed a similar pattern to that of factor VII. Values rose significantly in both groups, but there was no evidence of a cumulative rise.

Platelet aggregation (Chandler's tube technique)—In the original double-blind study there was no significant change after three months' oestrogen administration. Twelve months after the start of long-term

Detailed results of blood clotting and platelet aggregation tests in the two groups receiving long-term oestrogen replacement therapy. Results are means $\pm$ SD

Time during study	Prothrombin time (seconds)	Factor VII (seconds)	Factor X (%) *	Platelet aggregation (minutes)
Group 1				
Baseline ..	12.6 $\pm$ 0.55	13.1 $\pm$ 0.57	101 $\pm$ 3.2	9.8 $\pm$ 1.90
6 months ..	12.0 $\pm$ 0.97	12.1 $\pm$ 1.28	103 $\pm$ 8.0	10.6 $\pm$ 1.56
9 months ..	11.2 $\pm$ 0.79	11.1 $\pm$ 0.51	104 $\pm$ 4.2	9.8 $\pm$ 2.82
12 months ..	11.2 $\pm$ 0.75	10.8 $\pm$ 0.60	105 $\pm$ 4.7	8.9 $\pm$ 1.97
18 months ..	11.4 $\pm$ 0.95	10.8 $\pm$ 0.56	106 $\pm$ 3.6	8.7 $\pm$ 1.09
24 months ..	11.7 $\pm$ 0.58	11.0 $\pm$ 0.81	105 $\pm$ 4.5	8.4 $\pm$ 1.49
Group 2				
Baseline ..	12.3 $\pm$ 0.45	12.6 $\pm$ 0.59	98 $\pm$ 5.1	10.6 $\pm$ 1.41
6 months ..	11.4 $\pm$ 0.70	11.0 $\pm$ 1.06	106 $\pm$ 5.1	10.7 $\pm$ 1.43
9 months ..	11.3 $\pm$ 0.46	11.0 $\pm$ 0.80	106 $\pm$ 2.4	10.1 $\pm$ 2.00
12 months ..	11.7 $\pm$ 0.71	11.4 $\pm$ 1.20	105 $\pm$ 5.0	9.9 $\pm$ 1.48
18 months ..	11.8 $\pm$ 0.67	11.1 $\pm$ 0.73	105 $\pm$ 3.7	8.4 $\pm$ 1.00
24 months ..	11.9 $\pm$ 0.60	10.9 $\pm$ 0.72	106 $\pm$ 4.1	9.0 $\pm$ 1.39

*Expressed as percentage of values in normal controls.

conjugated oestrogen treatment there was, however, a significant acceleration in platelet aggregation in both groups ($P < 0.05$). The shortening was still present six months later, at the end of the follow-up.

Thromboelastography—There was no change in reaction time (r), thrombin phase (k), or maximum amplitude (ma).

Discussion

Prothrombin time and clotting times in factor VII and X assays are accelerated in women who have had three months' hormone replacement treatment with conjugated equine oestrogens, but there is no evidence from these tests of a cumulative effect. The pattern of increase of factors VII and X was similar to that recorded with combined oestrogen-progestogen oral contraception,^{2,3} but, unlike the contraceptive, conjugated oestrogens produced no further acceleration in these assays when they were given for longer than three months.

At 12 months the thrombin phase of platelet aggregation, measured by the Chandler's tube technique, also became significantly accelerated. This test is a sensitive index of changes in intrinsic clotting that affect the thrombin phase of platelet aggregation and is not specific for platelet function. The importance of this finding is not clear, but the result does suggest that there is a widened spectrum of adverse effects and that other changes may be taking place in the coagulation mechanism in addition to those monitored.

The absence of any changes in the PTT test and thromboelastography in this study might suggest that conjugated equine oestrogens have less overall effect on intrinsic blood coagulation than combined synthetic oestrogen-progestogen contraceptives. After six months' treatment with the latter there was a significant reduction of PTT and of r values in the thromboelastogram.³ The oral contraceptive study was, however, performed on larger groups, though only when these were combined was a significant result achieved. Groups of 31 and 34

women on different individual formulations of combined oestrogen-progestogen preparations did not show a significant shortening of the PTT. The present group of 20 menopausal women studied for 18 months of continual oestrogen administration is much smaller than the groups in our oral contraceptive studies. Too much reliance, therefore, cannot be placed on the negative findings.

Different dose regimens or dose equivalents of oestrogen may produce varying effects in haemostatic tests. Alternatively, Davies *et al*⁴ found smaller changes in blood clotting with oestriol succinate treatment than with the synthetic oestrogen ethinyloestradiol in a group of menopausal women who were treated sequentially. This might be taken to support the view that different types of oestrogen cause varying rates of acceleration of the haemostatic mechanism. These problems still need to be resolved.

Further efforts are therefore still required to find formulations and doses of oestrogens which, while relieving menopausal symptoms, do not accelerate blood clotting and platelet aggregation.

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Evaluation of fetal wellbeing by antepartum fetal heart monitoring

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Summary

The value of antenatal fetal heart rate monitoring was assessed in 301 patients. Tracings from each patient were classified as "reactive" or "non-reactive." Perinatal mortality, fetal distress in labour, caesarean section for fetal distress, and the incidence of low Apgar scores were all significantly increased in the non-reactive group.

Introduction

Since the results of intrapartum fetal monitoring correlate closely with the immediate neonatal outcome,¹⁻⁴ close attention to fetal

heart rate patterns during the antenatal period might be of value in assessing fetal wellbeing. Antepartum fetal heart rate patterns may be studied by means of the oxytocin challenge test or a "non-stress" test. Though the oxytocin challenge test is useful in evaluating the condition of the fetus before birth,⁵⁻⁸ it is time-consuming, may cause hyperstimulation, and is not easily repeatable. We therefore report the results of a non-stress⁹⁻¹² approach to antepartum fetal heart monitoring.

Materials and methods

From 1 July 1975 to 30 June 1976, 800 tracings were obtained from 301 patients with singleton pregnancies. The indications for monitoring are listed in table III. Heart rate and fetal activity patterns were recorded with three conventional fetal heart rate monitors: the Roche CTG5 (phonocardiography; 225 tracings), the Roche 540 (ultrasoundography; 554 tracings), and the Hewlett-Packard 8030ACTG (electrocardiography; 21 tracings).

Fetal movements may be detected (a) by auscultation via the fetal heart rate sensor, (b) by observing or palpating the maternal abdominal wall, (c) subjectively by the patient, or (d) from a transient rise on the uterine contraction channel. Fetal movements were sometimes not noticed by the patient or shown on the uterine contraction record or

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