Conjugated estrogens and hypercoagulability

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A group of 11 menopausal women receiving 1.25 mg. of conjugated estrogens daily had coagulation tests to determine the development of hypercoagulability after taking 5 and 21 tablets. There was no essential change in thrombin generation or fibrinolytic activity as measured by euglobulin lysis time. There was a shift toward hypercoagulability in all three parameters of the thrombelastograms. The decrease of the antithrombin III activity was not as pronounced following the administration of conjugated estrogens as had been the change associated with oral contraceptives. Fibrin monomers were observed in some women during the first week of Premarin therapy.

ESTROGEN-CONTAINING oral contraceptives induce a hypercoagulable state characterized by a reduction of antithrombin III activity,[3, 10, 13, 16] premature and accelerated thrombin generation,[10, 16] and characteristic changes in the thrombelastogram[6, 13] during the first weeks of initiating birth control with these compounds. Corresponding investigations with oral conjugated estrogens have not been published, although one study investigated coagulation changes in menopausal women being treated with synthetic estrogens. A reduction of antithrombin III activity as measured by a coagulation technique was noted in this report.[1]

Material and methods

Eleven women, 44 to 61 (median 51) years of age, received 1.25 mg. of conjugated estrogens (Premarin) daily. Coagulation studies were completed a few hours prior to starting the medication and subsequently during days 5 and 21 of estrogen therapy.

The following coagulation tests were performed as detailed in the previous study with oral contraceptives[13]: thrombin generation, antithrombin III activity,[9] thrombelastography, and fibrinolytic activity. For this investigation with conjugated estrogens, a determination of fibrin monomers was added.[12] These tests are essential components of a panel of coagulation tests which are used to evaluate the presence of hypercoagulability.[14]

The statistical evaluations were carried out with the Wilcoxon and Rank Sum tests. The nonparametric multiple comparisons procedure was extremely conservative with this type of data. Therefore, significant results were definitely established, but nonsignificance could be interpreted more in the sense of "not proved."

Results

The results of the coagulation tests were as follows.

Thrombin generation. As a group, there was no essential change during Premarin therapy. Only one of the 11 women developed a definite shift toward hypercoagulability.

Antithrombin III activity. Fig. 1 shows the frequency distribution of antithrombin III times of 11 women before and after 21 tablets of conjugated estrogens as compared with those of 21 women prior to taking oral contraceptives and after 20 pills.

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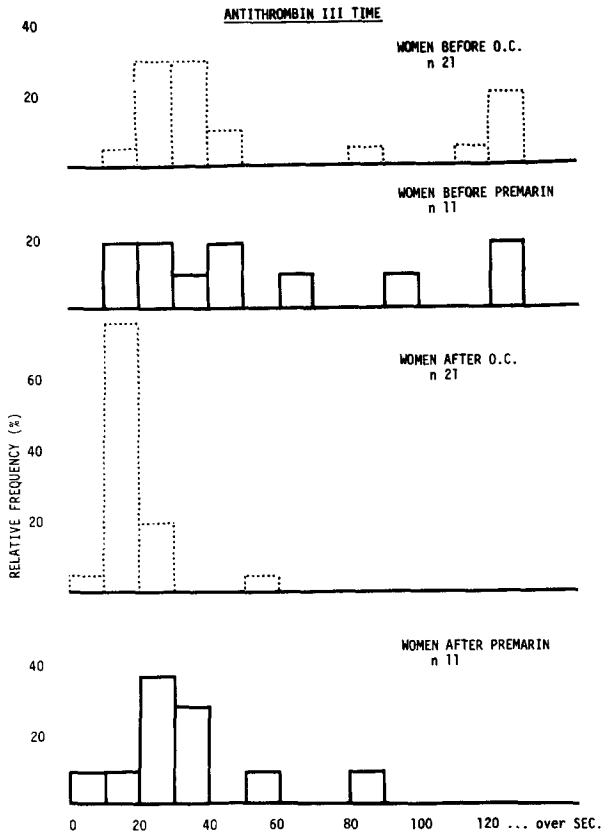

Fig. 1. Frequency distribution of antithrombin III times (seconds) of 11 women before and after 21 days of conjugated estrogens (Premarin, 1.25 mg. daily) (plain histograms) compared to 21 women before and after 20 days of oral contraceptive medication (estrogen content 80 μg of mestranol) (dotted lines). The data for oral contraceptives were taken from a previous publication.[13] Note the definite shift to shorter antithrombin III times with oral contraceptives and the less pronounced but similar effect with conjugated estrogens.

Table I. Mean antithrombin times of women taking conjugated estrogens or oral contraceptives

Conjugated estrogens	*P*	*Oral contraceptives*	*P*
Control 55.2 sec.		Control 54.2 sec.	
After 5 tablets		After 10 pills	
40.0 sec.	<0.05	23.3 sec.	<0.001
After 21 tablets		After 20 pills	
35.1 sec.	<0.025	19.0 sec.	<0.001

Table II. Changes of the measurements of the parameters of the thrombelastograms as compared to the control values in women who were treated for 21 days with Premarin or 20 days with oral contraceptives

	Conjugated estrogens	*P**	*Oral contraceptives*	*P**
r	−3 mm.	0.07	−9 mm.	<0.001
α	+9.6°	<0.05	+13°	<0.001
β	+12.9°	0.014	+14°	<0.001

*Comparison with control values.

Table III. Comparison of the mean control values of the parameters r, α, and β of the thrombelastogram in menopausal women before taking conjugated estrogens and young women before taking oral contraceptives

	Conjugated estrogens	*Oral contraceptives*	*P*
r	15.0 mm.	22.10 mm.	<0.01
α	34.80°	29.67°	>0.1
β	52.0°	47.43°	>0.1

There was a definite shift to shorter antithrombin III times in both groups, although this shift was more pronounced after oral contraceptives.

The mean antithrombin III times for both groups and the statistical evaluation of the changes induced by the two hormone treatments are demonstrated in Table I. The mean control times for both study groups, the young women taking oral contraceptives and the menopausal women taking conjugated estrogens, were similar, P being $\simeq$ 0.95. However, the antithrombin III values after 20 days of oral contraceptives were significantly lower than the results after 21 days on conjugated estrogens. The difference between the two values was significant ($P < 0.01$).

Thrombelastograms. These graphs were continuous recordings of fibrin formation. Three parameters were studied: r, the time from recalcification of plasma to the beginning of fibrin formation; α, the rate of fibrin formation once it has started; and β, rate of over-all coagulability. It is obvious from Fig. 2 that there was a shift in all three parameters toward hypercoagulability in women taking either oral contraceptives or conjugated estrogens. In Fig. 2, the shorter the r (1 mm. corresponds to 1 minute) the quicker the initiation of fibrin formation. Conversely the rates α and β were expressed as degrees of an angle—the larger the angle the faster the rate. The changes in all three parameters of the thrombelastogram in women treated with conjugated estrogens or oral contraceptives and the statistical evaluations are listed in Table II. The

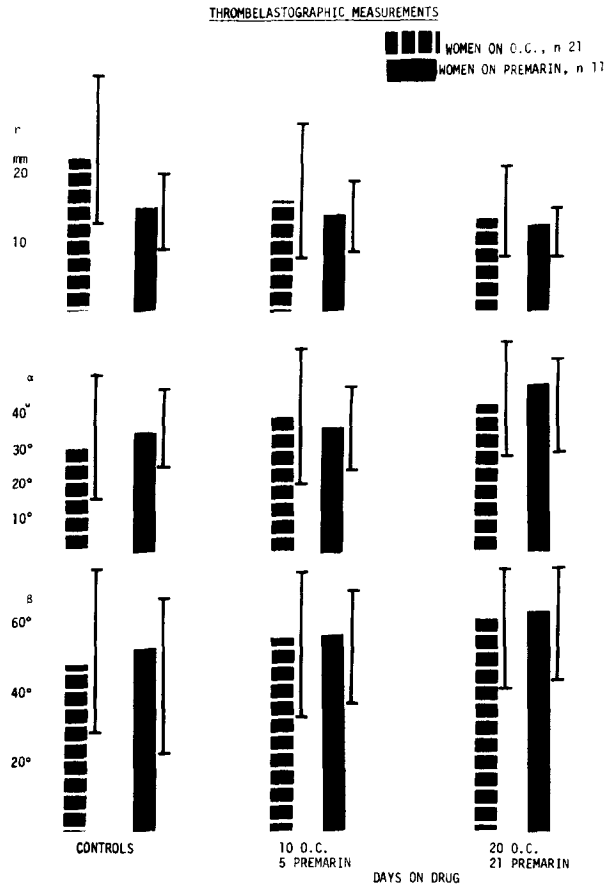

Fig. 2. Changes in three parameters of the thrombelastogram in women taking conjugated estrogens (plain histograms) and women using oral contraceptives (striped histograms). Note increasing shift toward hypercoagulability with both drugs.

estrogen-induced shifting of the three parameters of the thrombelastogram toward hypercoagulability was significant for both groups of women. Comparison of the control values before treatment reveals a shorter r value for the menopausal women as compared to the younger women who were going to receive oral contraceptives. This earlier start of fibrin formation in the menopausal women indicated a tendency toward hypercoagulability in this older age group. This difference as compared to the young women was significant, P being <0.01. The parameters α and β demonstrated a similar shift toward hypercoagulability in the menopausal women but differences were not significant. The data are given in Table III.

Fibrinolytic activity. There was no essential difference in the euglobulin lysis times measured before and during Premarin therapy.

Fibrin monomers. Prior to Premarin medication, 10 of the 11 women did not have detectable fibrin monomers in the blood. The one woman with a positive control test had a strong family history of thrombophilia. After 5 days of conjugated estrogen therapy, seven of the 11 women had positive tests for fibrin monomers. After 21 days of conjugated estrogen therapy only three had positive tests.

Comment

The assessment of hypercoagulability and its correlation to the various forms of intravascular clotting is a new and rapidly expanding field in hemostaseology. The basic aim is the development of diagnostic methods to identify those individuals who are prone to develop thrombosis and/or embolism and to help the clinician decide whether certain symptoms or syndromes might be caused by intravascular coagulation. In our opinion, there are various pathways for the development of a tendency toward intravascular clotting and, therefore, there is no single test which would discover all the causes. For this reason, we have developed a hypercoagulability panel which is used to identify potential "clotters."

The presence of a hypercoagulability does not necessarily signify that intravascular clotting must develop. If, however, an additional event takes place, such as vascular damage, prolonged stasis, surgical trauma, tissue trauma, inflammation, addition of certain medications, then thrombosis tendency as reflected by one or several hypercoagulability tests becomes an actual thrombosis danger. Theoretically, this additional event or events would have to be more pronounced in patients with a mild hypercoagulability in order to induce a severe thrombosis danger than in patients with a marked hypercoagulability. The shift in the parameters of the thrombelastogram and the appearance of fibrin monomers demonstrated that the conjugated estrogens induced a hypercoagulability tendency. Premarin at a daily dose of 1.25 mg. did not produce the dramatic changes in the blood tests for hypercoagulability that were evident in a previous investigation of oral contraceptives. Thus the alterations in the thrombin generation test and antithrombin III activity were not as evident with conjugated estrogens as the changes noted with oral contraceptive therapy. The antithrombin III activity was lowered, however, which reflects a shift towards hypercoagulability.

The thrombin generation test results in a curve and the position and shape of this curve in relation

to a standard curve indicate presence and extent of hypo- or hypercoagulability. Thus a shift of the curve downward means that more thrombin than normal is formed and a shift to the left demonstrates that the thrombin is formed at a faster rate than normal. A combination of both these events indicates the presence of hypercoagulability, the extent of which is indicated by the degree of change. Oral contraceptives caused a dramatic shift of the thrombin generation curve to the hypercoagulable side. There were only minor variations in the thrombin generation curves of the women taking Premarin. Each of the changes observed remained within the normal range except for one woman whose curve demonstrated a pronounced shift toward hypercoagulability. This individual observation of Premarin-induced hypercoagulability was statistically insignificant as compared to the study group. It is conceivable that this patient might be prone to intravascular clotting, especially if she would be exposed to any of those events which convert marked hypercoagulability into an actual thrombosis danger. It should be noted that the thrombin generation test is independent of the patient's own fibrinogen level. Therefore, in contrast to all other clotting tests, a hypercoagulable state can be discovered even with a low fibrinogen level.

The pattern of the thrombelastogram, in contrast to the thrombin generation, is dependent on the patient's fibrinogen level and what appears to be the reactability of the patient's fibrinogen. Therefore, two patients might have the same thrombin generation pattern, but in one patient the reactability of the fibrinogen for the thrombin formed during the clotting process might be greater than in the other patient and this difference will be discovered by the thrombelastogram. The thrombelastogram is an automatic recording of the growing strength of the fibrin during its formation. We measure it by three parameters: r, the time elapsing from recalcification of the plasma sample until the fibrin formation starts; the angle α, which reflects the speed of fibrin formation once it has started; the angle β, which practically combines α and β and reflects therefore the over-all coagulability.

The parameters of the thrombelastogram showed definite changes in menopausal women treated with conjugated estrogens. All three parameters, r, α, and β, demonstrated a marked shift toward hypercoagulability; fibrin formation started earlier was faster and the over-all coagulability was increased. Similar observations were noted in women taking oral contraceptives. These parameters of the thrombelastogram for oral contraceptives and Premarin are compared in Fig. 2. This figure indicates the important finding that the control values of these three parameters for the menopausal women were more "hypercoagulable" than the control values of the younger women taking oral contraceptives. The difference is statistically significant ($P < 0.01$) for r. These findings should be taken into consideration when prescribing conjugated estrogens, particularly if there is a personal or family history of intravascular clotting.

Antithrombin III activity is a protective mechanism against intravascular clotting, the spontaneous fibrinolytic activity being the second line of defense. Antithrombin III neutralizes thrombin traces which might result from low-level intravascular thrombin formation, thus preventing or reducing the formation of intravascular clots. Antithrombin III offers little protection against pronounced intravascular thrombin formation which might result from a pronounced plasmatic hypercoagulability as detected by an abnormal thrombin generation. A patient with a normal or high antithrombin III activity, however, is more fortunate under these conditions than a patient with reduced or no antithrombin III activity. A shortening of antithrombin III times demonstrates a reduction of antithrombin III activity, and corresponding loss of a protective mechanism against intravascular clotting due to the loss of the body's ability to neutralize thrombin traces. The pivotal role of a marked reduction or total absence of antithrombin III activity is hereditary thrombosis tendency[4, 7, 11] and in certain cases of thromboembolism[5, 9] is increasingly recognized. Fig. 1 shows the pronounced shortening of antithrombin III times with oral contraceptives. The resulting values are below the lower limits of normal for the majority of women. The women on conjugated estrogens demonstrate a shortening of the antithrombin III times, indicating a shift toward lower antithrombin III activity, but the average values remain within the normal limits for women of that age. Consequently, the loss of protection against intravascular clotting provided by antithrombin III was considerably less at a conjugated estrogen dosage of 1.25 mg. daily, when the women are considered as a group. However, as noted for the thrombin generation test, there can be individual patients in whom the antithrombin III activity is lowered by Premarin to a "nonprotective" level.

The test for fibrin monomers corroborates the

observation of the shift of the parameters of the thrombelastograms toward hypercoagulability. This test detects the presence of nonpolymerized fibrin traces in the blood, indicating that some intravascular thrombin formation has taken place, but it does not necessarily imply that insoluble fibrin has been or will be formed. The test for fibrin monomers was positive in only one of the 11 women before taking conjugated estrogens and this patient had a family history of thrombophilia. After Premarin, the fibrin monomer test became positive in several women, more so after five than after 21 tablets. Again, this finding is an indication that conjugated estrogens might produce a potential for intravascular clotting. These laboratory results are not surprising in view of the clinical observations that conjugated estrogens may contribute to the development of pulmonary embolism,[8, 15] particularly if the estrogen dosage is elevated (5 mg.),[2] and possibly to transient blindness.[17]

Based on this pilot study, it is concluded that Premarin produces a tendency toward hypercoagulability. This tendency could become pronounced in an individual patient, since the data obtained with the thrombelastograph showed a shift toward hypercoagulability and were suggestive for an enhanced clotting tendency in this age group of menopausal women. Although Premarin induced less hypercoagulability than oral contraceptives, its use should be discontinued 2 or 3 weeks prior to angiography or elective surgery and in patients complaining of severe headaches, particularly of the migraine type. Before prescribing conjugated estrogens, the physicians should obtain and evaluate any signs of actual or potential intravascular clotting and family history of thromboembolism, cerebral vascular accidents, or myocardial infarction.

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