EFFECTS OF NORETHISTERONE ON COAGULATION AND FIBRINOLYSIS IN ASIAN WOMEN

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SYNOPSIS

High doses of norethisterone in 70 Asian women treated for endometriosis were found to affect the blood coagulation factors as well as the cellular components of the blood. Fibrinogen level was found to be decreased ($p < 0.01$). Prothrombin increased significantly ($p < 0.001$) at the initial three months' medication after which it gradually reverted to baseline values at nine months.

Factor V and X were significantly increased throughout the period of therapy ($p < 0.001$) whilst factor VIII showed no change. This is evidence that coagulation factors from the liver are affected by norethisterone whilst that from the vascular endothelium is not. The changes in coagulation factors resulted in a shortened prothrombin time and kaolin cephalin time in the initial period of treatment reflecting the initial increase in prothrombin level. Jaundice occurred in three patients when their prothrombin levels were at their highest for the individual patient. The adjustment and return to baseline levels did not occur in jaundiced patients although this was the trend in the other patients. Fibrinolytic activity as shown by the fibrin plate test was not changed, neither was the antithrombin III activity or the levels of fibrinogen/fibrin degradation product.

The cellular components of blood in patients treated with norethisterone was affected. The packed cell volume and platelet numbers were increased. This may be an androgenic effect of norethisterone.

Since the effect of norethisterone on coagulation factors is mainly via the effect of this progestogen in high doses on the liver, it would seem prudent to exclude liver dysfunction and previous liver disease before embarking on such form of treatment, and to monitor its effect during treatment.

This would apply to all patients to be given norethisterone whether it be at low dose or especially at high doses. This is because of the unpredictable effect of the drug on liver metabolism. Two patients who became jaundiced had 20 mg norethisterone per day for three months which was comparatively low dose in this study.

The results of this study should be considered when norethisterone is being contemplated for contraceptive use especially in Asian women, since they are known to be more prone to liver disease.

INTRODUCTION

Since its synthesis in 1951 (1), norethisterone has not only been the central element in the success of oral contraceptives, but has also played an important role in hormonal treatment of gynaecological conditions (2, 3, 4). Norethisterone, also known as norethindrone, is as successful as combined oestrogen-progestogen preparations in producing amenorrhoea in the treatment of endometriosis (3). The combination oestrogen-progestogen preparations have been reported to cause hypercoagulability in the blood (5-7) and to increase the risk of thrombovascular disease (8). A regime of progestogens-only was considered to be advantageous since it may not have these deleterious effects (9). The low dose of norethisterone used in contraceptive pills have previously been shown to be associated with very few coagulation changes even after six months of continuous medication (10, 11). Similary, there were few effects on the coagulation and fibrinolytic systems by other progestogen such as chlormadinone, medroxyprogesterone acetate and retroprogesterone (12-16), as compared to the combined preparations. The occasional finding of a prolonged bleeding time (14) increased fibrinolytic activity, decreased plasminogen, and decreased factor X by various studies indicated that hypocoagulability was more likely. No change in the prothrombin time or the level of factor VII and factor X could be detected after three months of high doses of parenteral norethisterone oenanthate (17). In monkeys which were given ten times the dose for human, only fibrinogen levels were found to be slightly increased while all other coagulation proteins showed no change (18).

Norethisterone undergoes various metabolic transformations in the body and is known to have some oestrogenic properties. Of interest is the metabolism of northisterone to 17-ethinyl oestradiol. Several investigators have reported increase urinary excretion of 17-ethinyl oestradiol after administration of norethisterone (19-21). It was calculated that from 12 mg of norethisterone administered, 1 mg of 17-ethinyl oestradiol could be formed (22). Under physiological conditions, there is evidence to show that norethisterone is not aromatised to 17-ethinyl oestradio (23). In the treatment of endometriosis, high doses of norethisterone are often prescribed to achieve amenorrhoea and pharmacological levels prevail. It would be advantageous if norethisterone even at high doses should not cause changes in the coagulation system. Unlike Caucasion women, Asian women are less prone to thrombovascular disease during their reproductive age (24, 25). However, Asian women who were on estrogen-containing pill do develop hypercoagulable changes. These changes developing at a later time than in Caucasion women comprise a decrease in antithrombin III levels (26) and a marked increased in fibrinolytic activity. Asian women are believed to have enhanced fibrinolysis when they are on the combined pill. The present study seeks to evaluate whether women on long-term, continuous high dose of norethisterone have any change in their coagulation or fibrinolysis system.

MATERIALS AND METHODS

The investigation was carried out in women volunteers diagnosed to have endometriosis by laparoscopy or laparotomy. Blood was taken before medication and at three monthly intervals whilst on treatment. The medical regime consisted of a starting dose of 15 mg norethisterone per day in divided doses. This dose was increased should there be breakthrough bleeding so that a period of at least six months amenorrhoea could be achieved.

Venous blood was collected into a plastic syringe with minimum stasis from patients after resting for 30 minutes for the following assays. The overall screening tests included were the one-stage prothrombin time (28) and kaolin cephalin clotting time (28). The packed cell volume was also measured. In addition, the following coagulation factor assays were performed: fibrinogen estimation (29), prothrombin assay (30), Factor V assay (31), Factor VIII assay (32), and Factor X (33). Antithrombin III activity was measured by clotting test (34) and immunoelectrophoresis (35).

Test for fibrinolysis were plasminogen assay (36), alpha-2-macroglobulin (37), and serum fibrinogen/fibrin degradation products (38). The fibrinolytic activity of plasma and resuspended euglobulin precipitate on plasminogen enriched fibrin plates were performed according to Nilsson and Olow (39). The plasma euglobulin clot lysis time (39) was also performed. Platelet count was performed using the Coulter Counter Platelet aggregation was performed using a modification of the optical density technique of Born (40) while platelet adhesiveness was measured by Hellem's method (41).

All investigations were subjected to internal and external quality control procedures. The results were analysed by self pairs. The results of each patient's coagulation tests at 3, 6 and 9 months were compared with their own baseline values. The means of the differences was then analysed by the paired t-test. This statistical evaluation was considered to be more appropriate than using analysis of variance since it was more specific.

DEMOGRAPHIC RESULTS

There were 70 women who were on norethisterone therapy for 3 months. Fifty-seven women continued to complete 6 months of treatment and 37 were treated for 9 months. The decreasing number of women in the study is due to the following reasons. Some, especially at 6 months, were taken off the study because they had completed their treatment. Most of those who dropped out after the third month from the coagulations studies were because they found it inconvenient to come for regular blood tests. Two women became jaundiced after three month's therapy and were taken off the treatment and the coagulations studies at the third month. None became sufficiently hypertensive during treatment to contraindicate continued therapy. The group completing 9 months of treatment consisted of those women whose endometriosis had not resolved clinically.

In all, three women in the study developed jaundice. One occurred at the completion of 9 months of therapy and two after treatment for three months as mentioned earlier. The dose of norethisterone used in the study varied from 15 mg/day to 40 mg/day for the first three months. In the second three months, the dose of norethisterone varied from 15 mg/day to 60 mg/day, and in the third three months from 15 mg/day to 80 mg/day. Even at the lowest dose, there is much more norethisterone than that present in contraceptive pills.

COAGULATION STUDY RESULTS

The results of the coagulation tests have been

tabulated in groups. Some of the coagulation tests have less than the number of women studied at each test period because certain tests were not available at the time of treatment or there was insufficient blood collected. The tables show the mean values of the test in question, and the mean difference in values from the baseline at 3, 6 and 9 months. (Table I, II and III) The coefficient of variation of methods used ranged from 0.8% to 9.2% except for fibrinolytic activity which was 19%.

SCREENING TEST — (Table I)

The screening tests consisted of the prothrombin time, kaolin cephalin time and the packed cell volume. The mean prothrombin time before treatment was 15.35 sec. The prothrombin time was significantly shortened by 0.95 sec by the third month. (p 0.01) This decrease in prothrombin time diminished by the 6th month to 0.67 sec which is still a statistically significant change. By the 9th month, however, the change had returned towards baseline values. The kaolin cephalin clotting time showed the same trend as the prothrombin time. At the third month the decrease from baseline values was highly statistically significant (3.88 sec less than baseline value of 55.95 sec). At 6 months the difference was less (2.93 sec) and by the 9th month the test has reverted to values before treatment.

Packed cell volume increased significantly throughout the period of therapy. There was a 0.05—0.06 unit increase from the baseline value of 0.38 units. The screening tests consistently showed that blood took a shorter time to clot and that this change was most marked at the third month of treatment.

COAGULATION PROTEIN ASSAY S— (Table II)

There was a high statistical difference in the fibrinogen level before and after treatment. Fibrinogen levels decreased consistently throughout treatment with a decrease of 0.35—0.52 g/l from the baseline value of 3.34 g/l. This change is in contrast to many other coagulation proteins which showed consistent increase or an increase varying with the duration of norethisterone therapy or no change. Factor II levels increased significantly after 3 months of therapy (p 0.001). The increase was 8.7% from the baseline values of 106.6%. The increase diminished with continued treatment and by 9 months, prothrombin levels had reverted back to normal. The changing amount of prothrombin is reflected in the changes of coagulation clotting times. Both Factor V and Factor X levels were significantly increased throughout therapy while there was no change in the level of Factor VIII. The inhibitory activity of antithrombin III was not changed although antithrombin III molecules were significantly increased throughout the treatment period (p 0.001).

FIBRINOLYTIC SYSTEM — (Table III)

The measurement of plasminogen both by the caseinolytic and the immunoelectrophoretic methods revealed significant increases from baseline values throughout the treatment period. The euglobulin clot lysis time was significantly shortened showing that fibrinolytic activators were increased during the initial 6 months of treatment. By 9 months, the activator level had returned to baseline values. No significant change in fibrinolytic activity could be shown by the fibrin plate test. There was also no evidence of any change in level of fibrin/fibrinogen degradation products. Fibrinolytic inhibitor, alpha-2-macroglobulin, did not show substantial change.

PLATELET TESTS — (Table IV)

The platelet count was significantly increased by norethisterone treatment ($p < 0.001$). The magnitude of the change was substantial since the increase varied from 62.47 to 76.17 $\times$ $10^3/mm^3$ as compared to the baseline value of 274.15 $\times$ $10^3/mm^3$. Norethisterone therapy did not affect any of the platelet adhesiveness or aggregation function tests, but there were too few results in the platelet function studies to make any useful comment.

TABLE I

COAGULATION SCREENING TEST AND PACKED CELL VOLUME IN PATIENTS ON NORETHISTERONE

DIFFERENCES BETWEEN BASELINE VALUES AND VALUES AFTER NORETHISTERONE MEDICATION

Assay (UNITS)	Baseline value	Difference from Baseline after Norethisterone treatment					
	Mean Values	At 3 months		At 6 months		At 9 months	
		No.		No.		No.	
Prothrombin time (secs)	15.36	64	−0.95**	57	−0.67*	36	-0.18^{NS}
Kaolin cephalin clotting time (secs)	55.95	65	−3.88***	57	−2.93**	36	-0.87^{NS}
Packed cell volume (units)	0.38	67	+0.05***	53	+0.06***	34	+0.06***

NS = not significant
* = $p < 0.05$
** = $p < 0.01$
*** = $p < 0.001$

Paired t-test

TABLE II

COAGULATION FACTORS AND INHIBITORS IN PATIENTS ON NORETHISTERONE

DIFFERENCES BETWEEN BASELINE VALUES AND VALUES AFTER NORETHISTERONE MEDICATION

Assay (UNITS)	Baseline value	Difference from Baseline after Norethisterone treatment*					
	Mean Values	At 3 months		At 6 months		At 9 months	
		No.		No.		No.	
Fibrinogen g/l	3.34	70	−0.45***	57	−0.52***	37	−0.35**
Factor II %	106.60	70	+8.70***	57	+7.46**	37	+3.62^{NS}
Factor V %	101.37	70	+24.09***	56	+33.39***	35	+24.49***
Factor VIII u/ml	1.11	71	+0.06	57^{NS}	+0.04^{NS}	37	+0.04^{NS}
Factor X %	101.56	71	+16.72***	57	+17.40***	36	+17.53***
Activity Antithrombin III %	96.02	49	+0.27	32	−6.09*	19	−4.32^{NS}
Immuno-electrophoresis Anti III g/l	0.23	68	+0.02***	53	+0.02***	36	+0.03***
Anti XA %	92.83	68	+4.15*	54	+4.96*	37	+0.38^{NS}

NS = not significant
* = $p < 0.05$
** = $p < 0.01$
*** = $p < 0.001$

Paired t-test

TABLE III

FIBRINOLYTIC INHIBITORS FIBRINOLYTIC TEST IN PATIENTS ON NORETHISTERONE

DIFFERENCES BETWEEN BASELINE VALUES AND VALUES AFTER NORETHISTERONE MEDICATION

Assay (UNITS)	Baseline Value	Difference from Baseline after Norethisterone treatment					
	Mean Values	AT 3 months		AT 6 months		At 9 months	
		No.		No.		No.	
Plasminogen (casein) u/ml	2.58	62	+0.26**	46	+0.27*	32	+0.51**
Plasminogen (Immuno) cu/ml	5.21	67	+1.32***	54	+1.37***	37	+1.56***
ECLT hrs	5.08	56	−2.35***	44	−2.24***	31	+0.45^{NS}
Fibrin Plate mm^2	197.96	45	+22.02	39	+38.49^{NS}	22	+51.95^{NS}
FDP ug/ml	2.88	69	+0.12^{NS}	36	−0.01^{NS}		
Alpha 2 macro g/l	2.07	65	−0.15*	49	+0.02^{NS}	33	−0.08^{NS}

NS = not significant
* = $p < 0.05$
** = $p < 0.01$
*** = $p < 0.001$

Paired t-test

TABLE IV

PLATELET COUNT & PLATELET FUNCTION TESTS IN PATIENTS ON NORETHISTERONE

DIFFERENCES BETWEEN BASELINE VALUES AND VALUES AFTER NORETHISTERONE MEDICATION

Assay (UNITS)	Baseline Value	Difference from Baseline after Norethisterone treatment					
	Mean Values	At 3 months		AT 6 months		At 9 months	
		No.		No.		No.	
Platelet count $10^3/mm^3$	274.15	68	+62.47***	54	+62.76***	35	+76.17***
Platelet adhesiveness %	35.14	38	+4.00^{NS}	25	+2.12^{NS}	18	+1.67^{NS}
Platelet aggregation Max. transmission with Collagen %	63.91	11	+4.73*	6	−5.83^{NS}	3	+6.33^{NS}
Platelet aggregation Max. transmission with ADP %	55.56	17	−11.59*	16	−5.81^{NS}	8	−12.13^{NS}
Platelet aggregation velocity with Collagen mm/min	243.41	22	−18.77^{NS}	9	+11.44^{NS}	5	−54.00*
Platelet aggregation velocity with ADP mm/min	232.39	31	−32.94*	23	−15.61^{NS}	15	−62.53*

NS = not significant
* = $p < 0.05$
** = $p < 0.01$
*** = $p < 0.001$

Paired t-test

RESULTS OF JAUNDICED PATIENTS

There were two Indian women and one Chinese woman who developed jaundice. In two, jaundice occurred after the third month of treatment. In the third, jaundice occurred after completion of 9 months of treatment. Two were nulliparous whilst the remaining had had 3 pregnancies. They were normotensive on all records and weights did not vary much from baseline reading. All their coagulation tests were not different from the mean of the whole study group except for prothrombin levels. The patient who completed 9 months of treatment started with the lowest prothrombin level of the study group and ended with the highest prothrombin level. Jaundice seems to occur when prothrombin levels were found to be at their highest.

DISCUSSION

The results presented in this study have few previous comparison in the human. This is because these studies have been performed on women who have been on therapeutic doses of norethisterone. The minimum amount of norethisterone given in a three-month period was 1680 mg. The three monthly dose of norethisterone oenanthate for contraception is 200 mg. Therefore, in these patients, this is at least 8 times the dose of norethisterone used for contraception. In animals, (rhesus monkeys), high doses of norethisterone oenanthate (18) produced no changes in protein analyses except for an increase in fibrinogen.

Only fibrinogen levels were substantially decreased. This is in contrast to all other coagulation proteins produced by the liver at the initial three months which increased. The results are also in contrast to previous reports of increased fibrinogen levels in rhesus monkeys given similar doses of norethisterone (18) and no change in human female on low doses (10, 43, 17, 11). Decrease in fibrinogen levels was found in 20 patients with familial type III, IV and V hyperlipoproteinemia given norethisterone acetate (43). These patients also had increased prothrombin levels otherwise, other factors were unchanged. These patients had been given norethisterone acetate at 20 mg/day.

Prothrombin levels in the present study showed a transient effect. The increase is more in the initial period after which the difference from baseline diminished. The changes in other coagulation proteins do not alter with time. Coagulation proteins from the liver showed increases such as Factor V, Factor X whilst Factor VIII which is synthesised by the vascular endothelium is not affected.

Norethisterone seems not to affect fibrinolytic activity in contrast to other types of progestogens such as medroxyprogesterone acetate (16, 44). The plasminogen activator level in the blood is however increased. Greig (45) found no change in fibrinolytic

activity in African women on norethisterone but the dose was only 0.36 mg daily. This could be the result of the balance between increased levels of plasminogen and increased levels of plasminogen activators found in the study. Fibrinolytic inhibitors were not substantially increased.

The inhibitor of thrombin, antithrombin III, was significantly increased as measured by the immunoelectrophoretic method. Although antithrombin III molecules were increased, as has been observed by others (43, 45, 46), no increase in antithrombin III activity could be demonstrated.

Fibrinogen/fibrin degradation products remained unchanged. The increase in coagulation proteins, the shortening of the clotting time of blood, and the increase of platelet count would contribute to a hypercoagulatory state. The hypercoagulatory state seems to be most accentuated at the third month, after which there is an adjustment towards pretreatment levels. Coagulation factors produced by the liver become adjusted to the effects of norethisterone. If adjustment by the liver does not occur, it seems, then there is decompensation with the development of jaundice. In the 3 patients who became jaundiced prothrombin levels were at their highest when jaundice developed. Other coagulation proteins and fibrinolytic components changed with the same trend as the whole group.

The cellular changes are not the result of altered liver function. The highly significant increase in platelet count and the packed cell volume could be due to the androgenic effect of norethisterone and the latter change also from the amenorrhoea. The androgenic effect of norethisterone is quite well recognised in animal experiments (47, 48, 49), causing virilising signs in female fetuses (50, 51). However, their effects on platelets and erythrocytes are less well known in human. In patients with hypoplastic anaemia, androgenic steroids are given to raise platelet count and haematocrit levels (52, 54, 27).

Thus, norethisterone seems to have two types of effects on blood coagulation components. The androgenic effect causes increase in cellular component red blood cells and platelets. It is possible that leucocytes may also be increased. The second effect on coagulation components is via the effects on liver function. The increase in coagulation and fibrinolytic components is thought to be due to increased synthesis by the liver caused by a stimulating effect of norethisterone on the liver. From animal experiments it is known that norethisterone levels build up in a staircase fashion when given orally and the drug is slowly excreted (55). In animals it affects the liver by stimulating its growth and also affects its drug and protein metabolising activity (56) often by reducing this enzyme activity. The effect is dose dependent, also species and even sex dependent (57). It is known that norethisterone has cholestatic effects (58, 61). In particular it has more pronounced retention effects on bromsulphthalein (59, 60, 42, 43). Jaundice is a well known complication of androgen therapy. Some of the coagulation changes found in this study may be due to the decrease in metabolism of the coagulation proteins causing a build up in blood levels.

In contrast, fibrinogen levels are significantly decreased throughout norethisterone therapy. In normal women, norethisterone has been found either to cause to change in fibrinogen levels (9, 14, 17) or an increase (46). Only in hyperlipoproteinemic women was fibrinogen decreased with norethisterone treatment. The Asian women studied here were clinicaly normal. Their lipid levels, however, were not measured nor were they known to have hyperlipidaemia. This unusual effect of norethisterone may be peculiar to Asian women. Asian people are known to develop jaundice frequently, have a higher incidence of hepatomas and in whom neonatal jaundice is the rule rather that the exception. Although the women's routine liver function tests when on norethisterone were within normal limits, perhaps additional liver function tests in this group may explain the unexpected decrease in fibrinogen level.

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