Illis, L., Kocen, R. S., McDonald, W. I., and Mondkar, V. P. (1965). *Brit. med. J.*, 2, 1164.
Jennett, W. B., and Cross, J. N. (1967). *Lancet*, 1, 1019.
Johnson, H. C., and Walker, A. E. (1951). *J. Neurosurg.*, 8, 631.
Joseph, J. (1942) *Brit. med. J.*, 1, 438.
Kalbag, R. M., and Woolf, A. L. (1967). *Cerebral Venous Thrombosis*, pp. 176–178. London.
Kendall, D. (1948). *Brain*, 71, 386.
King, A. B. (1950). *Arch. Neurol. Psychiat. (Chic.)*, 63, 471, 611.
Koek, H. C., and Schreuder, J. Th. R. (1951). *Acta psychiat. scand.*, 26, 353.
Krayenbühl, H. (1954). *Schweiz. Arch. Neurol. Psychiat.*, 74, 261.
Lemmi, H., and Little, S. C. (1960). *Arch. Neurol. (Chic.)*, 3, 252.
Lorincz, A. B., and Moore, R. Y. (1962). *Amer. J. Obstet. Gynec.*, 83, 311.
McNairn, J. (1948). *J. Obstet. Gynaec. Brit. Emp.*, 55, 630.
Martin, J. P. (1941). *Brit. med. J.*, 2, 537.
Martin, J. P. (1944). *Proc. roy. Soc. Med.*, 37, 383.
Martin, J. P. (1958). *Brit. med. J.*, 2, 315.
Martin, J. P., and Sheehan, H. L. (1941). *Brit. med. J.*, 1, 349.
Prakash, C., and Singh, S. (1960). *J. Ass. Phycns India*, 35, 363.
Richards, D. J. (1965). *Postgrad. med. J.*, 41, 702.
Scarff, J. E. (1944). *Proc. roy. Soc. Med.*, 37, 389.
Sinclair, M. A. McI. (1902). *Lancet*, 2, 204.
Stansfield, F. R. (1942). *Brit. med. J.*, 1, 436.
Stevens, H. (1954). *Neurology (Minneap.)*, 4, 723.
Stevens, H. (1958). *Ann. intern. Med.*, 49, 1022.
Stevens, H., and Ammerman, H. H. (1959). *Amer. J. Obstet. Gynec.*, 78, 104.
Symonds, C. P. (1940). *Brit. med. J.*, 2, 348.

Effects of Low-dose Oral Contraceptives on Blood Coagulation*

L. POLLER,† M.D., M.C.PATH.; ANNE TABIOWO,‡ B.SC.; JEAN M. THOMSON,§ F.I.M.L.T.

Brit. med. J., 1968, 3, 218–219

Summary: A study has been performed on the effect of Norinyl-1 and Ortho-Novin, two low-dose oral contraceptives, on blood-clotting factors. Ortho-Novin contains twice the amount of hormone as Norinyl-1. It was therefore possible to observe whether any changes detected were related to the dose of oestrogen-progestin combination. The women were tested in parallel with matched normal female controls and a group in the third trimester of pregnancy. Significant rises in factor VII and X levels were found with both low-dose preparations from the third month onwards. There was no difference between patients on Norinyl-1 and Ortho-Novin, and hence the clotting changes do not appear to be dose-dependent. The long-term effects on clotting factors of these low-dose oral contraceptive preparations remain to be investigated.

Introduction

In previous studies we found an increase in plasma clotting factors VII and X in women taking oral contraceptive preparations, and this rise became statistically significant from the third month onwards (Thomson and Poller, 1965; Poller and Thomson, 1966). The present investigations were designed to determine whether this effect depended on the dose of anti-ovulatory agent, and whether the time relationship of the consequent changes would be affected by the hormonal dose. Women volunteers were given two different preparations of relatively low hormonal content, one of which—Ortho-Novin—contained twice the dose (norethisterone 2 mg., mestranol 0.1 mg.) of the other—Norinyl-1. Parallel studies were performed on women controls and a group of patients in their third trimester of pregnancy.

Method of Study

The women of this investigation volunteered to co-operate in the study following an appeal for participants in a trial of low-dose oral contraceptives. Their clotting factors were studied before starting the "pill" preparations. They were tested at intervals of six weeks for three months, and then at intervals of three months for nine months. This report deals with the results to the nine-month stage.

The women participating consisted of 31 patients on Ortho-Novin who had not previously taken oral contraceptives and 60 women on Norinyl-1. Of the latter group 34 had not previously taken oral contraceptives and 26 had been taking some other preparation within the preceding six months. An antenatal group consisting of 43 ambulatory patients in the third trimester of pregnancy attending Withington Maternity Hospital were studied as a control group. The normal group consisted of equal numbers of matched normal females tested at the same time as the oral contraceptive and antenatal patients.

To eliminate possible variables that occur in assays owing to alteration in reagents and other factors from day to day, each of the oral contraceptive groups was compared statistically with the simultaneous parallel group of normals and the antenatal patients.

Technique.—The method for prothrombin activity (Quick's test), cephalin time, and factor VII and factor X assays were as described previously. The method for the kaolin-activated cephalin time was the cephalin time method as described by Hjort *et al.* (1955), modified by the addition of kaolin.

Results

Of the original 91 patients 75 were still in the trial after their sixth monthly course and 56 patients were left after the ninth course. Of the three oral contraceptive groups 18 remained on Ortho-Novin and 21 and 17 respectively in the two Norinyl-1 groups after nine months.

When the results of the patients taking oral contraceptives were compared as groups with their parallel normal controls as well as with the parallel antenatal groups there was no significant difference in the prothrombin time results between any of the groups. Analysis of the cephalin times showed a significant shortening ($P=0.05$) with the unmodified test and with the kaolin-activated test from the sixth month onwards, but only when all the oral contraceptive patients were considered as a combined group.

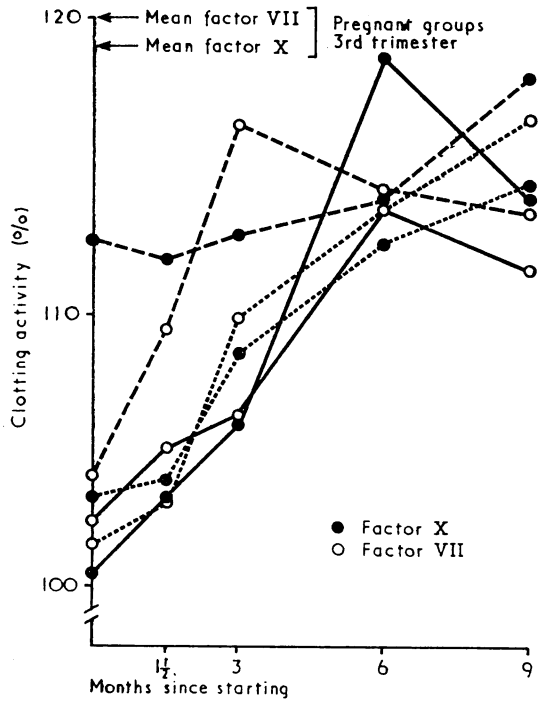
* This work was undertaken with the financial assistance of a grant for thrombosis research from Manchester Regional Hospital Board and a grant from the Council for the Investigation of Fertility Control. Syntex Pharmaceuticals Ltd. kindly provided the low-dose hormone preparation used in this study and patient data sheets.

† Consultant Haematologist.
‡ Research Technician.
§ Chief Research Technician.
Withington Hospital, Manchester 20.

The factors VII and X levels were significantly increased in the combined group and in each of the three individual groups of patients on oral contraceptives from the third month onwards. There was no significant difference between the patients on Norinyl-1 and Ortho-Novin when these were compared. The second group of Norinyl-1 patients—that is, those who had been on other preparations of oral contraceptives previously—showed a significantly raised level of factor X before starting Norinyl-1, which persisted and continued to rise progressively during the study. The Table gives the values for the individual assays, and these show progressive shortening in the tests, expressed as clotting-times. The Chart illustrates the results of factors VII and X assays. The percentage rise in clotting activity was calculated from the following formula:

$$\frac{\text{mean clotting-time control group (sec.)}}{\text{mean clotting-time "pill" group (sec.)}} \times 100$$

The results at the nine-month stage were still significantly less than those of the antenatal patients in their third trimester of pregnancy.



Factors VII and X levels. Rise in clotting activity (mean control times expressed as percentage of "Pill" groups). ——— Ortho-Novin group. . . . . Norinyl-1 group using pill for first time. – – – – Norinyl-1 group previously on other pill preparations.

Results of Tests

	Cephalin Times (sec.)		Kaolin Activated Cephalin Times (sec.)		Factor VII		Factor X	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Group of Patients using Oral Contraceptive for First Time—Norinyl-1								
Before starting	70·76	5·64	48·25	5·34	17·8	1·758	18·51	1·934
2 months ..	69·84	6·02	46·17	4·35	18·00	0·95	17·97	1·016
3 months ..	66·22	8·19	46·22	5·12	17·15	1·38	17·45	1·184
6 months ..	61·48	4·35	43·28	4·75	16·83	1·28	17·07	1·334
9 months ..	61·10	3·12	44·10	3·59	16·29	1·385	16·67	1·337
Ortho-Novin								
Before starting	69·33	5·95	46·90	4·64	17·8	1·273	18·77	1·260
2 months ..	66·5	6·74	44·53	4·43	18·33	1·193	17·87	1·04
3 months ..	60·36	3·117	42·10	3·48	17·9	1·74	18·10	1·058
6 months ..	58·58	2·235	41·63	2·66	17·39	1·375	16·22	1·70
9 months ..	58·74	3·46	41·42	1·73	17·28	1·421	16·28	1·33
Group of Patients Previously on Other Oral Contraceptives—Norinyl-1								
Before starting	67·12	5·40	46·23	5·000	17·08	1·59	18·46	2·08
2 months ..	63·33	5·95	42·92	5·270	17·39	1·739	17·33	1·52
3 months ..	62·27	6·94	42·05	5·810	17·27	1·176	17·10	0·668
6 months ..	62·13	7·18	42·06	3·696	17·23	0·795	16·50	1·12
9 months ..	58·47	1·65	41·65	2·602	17·12	1·19	16·24	1·352
Antenatals								
	56·10	3·94	40·0	4·504	15·05	0·861	15·09	0·8

S.D. = Standard deviation.

Comment

This study on low-dose oral contraceptives confirms our previous reports that increases of factor VII and factor X result and reach a significant level after the third month. Both Norinyl-1 and Ortho-Novin contain smaller doses of hormones than the older proprietary preparations we studied previously. It was possible, therefore, that clotting-factor increases might not result or might be delayed with the reduced dosage. In this study we used one progestin–oestrogen combination exactly twice the hormonal content of the other preparation to see if a difference in degree of timing or clotting-factor increase resulted. In actual practice the coagulation response appeared to be identical. In other words, the changes do not appear to be a simple matter of dose-dependency.

Previously we have shown that after two years the rise in factor VII levels was of the same order of increase as occurs in the third trimester of pregnancy. In the present investigation women on oral contraceptives at nine months still showed less clotting-factor changes than women at the same period of normal pregnancy. Further studies must be carried out to see whether factor VII levels increase to the same extent as with the older, larger dose preparations after two years. It must be emphasized that the changes we have shown are only part of the spectrum of clotting-factor increases which occur during normal pregnancy, when the thrombosis risk, though increased, is still small, and the factor VII changes we showed previously in patients on oral contraceptives were not as marked as those present in venous thrombosis (Thomson and Poller, 1965). It is relevant to note that since our earlier studies were published a subcommittee of the Medical Research Council (1967) concluded that there can be no reasonable doubt that some types of thromboembolic disorders are associated with the use of oral contraceptives. It seems on first principles that such increases of clotting factors as we have recorded, though not direct evidence of a thrombotic tendency, must be regarded as undesirable, and the lack of success in reducing these changes by lowering the hormonal content is of course disappointing.

The lack of different factor VII levels between the two groups on Norinyl-1 is probably explained by the fact that in the group who had already taken oral contraceptives most of the patients had had a break of at least one month between taking their previous preparations and starting their course. These results partly confirm the view reported by Schrogie *et al.* (1967) that the effect of the oestrogen–progestin combination disappears within one month of stopping.

In contrast a persistent rise in factor X after stopping one preparation and changing to Norinyl-1 is noteworthy. The disappointing feature is the progressive rise in factor X that occurred on changing to Norinyl-1 and its persistence throughout our study. It is obvious that further work is required to determine whether the effects on clotting factors induced by oral contraceptive agents can be minimized by other approaches than simple reduction of dosage in a conventional combined preparation.

References

Hjort, P., Rapaport, S. I., and Owren, P. A. (1955). *J. Lab. clin. Med.*, 46, 89.
Medical Research Council (1967). *Brit. med. J.*, 2, 355.
Poller, L., and Thomson, J. M. (1966). *Brit. med. J.*, 2, 23.
Schrogie, J. J., Solomon, H. M., and Zieve, P. D. (1967). *J. clin. Invest.*, 46, 1114.
Thomson, J. M., and Poller, L. (1965). *Brit. med. J.*, 2, 270.