THE EFFECT OF LONG-TERM STEROID CONTRACEPTION ON COAGULATION IN ASIAN WOMEN

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SYNOPSIS

Recently, Asian women who seemed to be less prone to thromboembolism were found to develop coagulation changes similar to Caucasians when they were on oral contraceptives containing synthetic oestrogens. Since progestogen only contraceptive is also very popular with Asian women, it was thought necessary to find out whether this contraceptive had any effect on the coagulation system after long term use.

A cross-sectional retrospective study of the effects of combined oral contraceptive pill (ethinyl oestradiol and norgestrel) and injectable progestogen contraceptive (medroxyprogesterone acetate) on coagulation, fibrinolysis and platelet function were investigated. There were 114 women who had been on oral contraceptive pills continuously for two years or more in the pill group and 127 women on two years or more of injectable progestogen in the progestogen group. They were matched for age, parity and ethnic group for the control group. The control groups were women who were not pregnant or recently pregnant, not on steroids of any kind and with no history suggesting coagulation disorders matched for age, parity and ethnic group.

In the pill group, overall clotting time such as PT, KCCT, were decreased. Coagulation factors I, II, V and X were increased, fibrinolytic activity and plasminogen were increased, and platelet count and function not significantly changed. Antithrombin III was decreased. Thromboelastographic studies showed no significant change.

In the progestogen group, there were very few coagulation changes. Fibrinogen was slightly increased. There was no change in fibrinolysis or platelet function.

INTRODUCTION

Recently, Asian women who seem to be less prone to thromboembolism (Chumnijarakij 1975) were found to develop coagulation changes similar to Caucasians when they were on oral contraceptives containing synthetic oestrogens (Tsakok 1976). These changes, however, were delayed (Tsakok 1978). It has been shown that in Caucasian women a hypercoagulable state is associated with a higher risk of thromboembolic disease both by epidemiological studies (Vessey 1969) and by individual investigation of thrombotic

patients (Ambrus 1975). Progestogen only contraception and medication, on the other hand, has shown little coagulation change (Poller 1971a). Since progestogen only contraception has been popular with Asian women, it was thought necessary to study whether this contraceptive had any effect on the coagulation system and especially after long term use.

MATERIAL AND METHODS

A cross-sectional retrospective study of the effects of:

(i) the combined oral contraceptive containing 50 μg ethinyl oestradiol and norgestrel/levonorgestrel.
(ii) the progestogen only injectable contraceptive 150 mg medroxyprogesterone acetate every three months

after continuous use for two years or more were studied.

The control groups for these above study groups were women matched for age, parity and ethnic groups who were not pregnant or recently pregnant, nor on steroids of any kind.

All patients in this study were married healthy volunteers. There were 114 women on oral contraception and 127 women on injectable contraception.

Preprandial venous blood was collected with plastic syringes after the patient had rested at least ten minutes. Plasma samples were obtained by mixing nine volumes of whole blood with one volume of Hepes citrate centrifuged at 4°C. Serum from blood added to epsilonamino caproic acid and thrombin was used for assay of fibrinogen degradation products.

Plain serum from clotted blood was used for electrophoretic tests. Blood added to edetic acid was sedimented and the plasma used for platelet count.

Most of the coagulation, fibrinolytic and platelet function tests were performed within an hour of the collection of blood which was kept at 4°C.

The overall screening tests performed were one stage prothrombin time (Biggs 1972), Kaolin cephalin clotting time (Biggs 1972) and thomboelastographic assays (Hartet 1948).

Coagulation factor assays performed were fibrinogen estimation (Ratnoff et al 1964), prothrombin assay (Denson 1971), Factor V assay (Shanberge et al 1967), Factor VII assay with beagle plasma (Thomson 1965), Factor VIII assay (Biggs 1955) and Factor X assay (Denson 1961).

Antithrombin III activity was measured by immunoelectrophoresis (Hedner 1973). Tests of fibrinolysis were plasminogen assay (Alkaersig et al 1959), α_2 macroglobulin estimation (Ganrot 1966) and serum fibrinogen degradation products (Merskey 1966). The fibrinolytic activity of plasma and resuspended euglobulin precipitate on fibrin plates were performed according to Nilsson and Olow (1962) and euglobulin lysis time (Nilsson et al 1962).

Platelet count was performed using the Coulter counter. Platelet function tests performed were platelet aggregation using a modification of the optical density technique of Born (1963) and platelet adhesiveness (Hellem 1960).

All the assays were subject to strict quality control, to take into account changing standards and reference materials.

Comparison between the study groups and their respective matched controls was made using students' t-test.

RESULTS

Tables I and II show the age and ethnic distribution of the study groups of women on pills and on injectables.

In each group, some investigations were not complete, either because the specimen was spoilt or the test was unavailable at that time. Therefore, the number of tests done is not the same as the study group number.

Figure I shows the overall screening tests.

Although there was a decrease in prothrombin time in both study groups, the decrease was more so in the pill group.

The Kaolin cephalin time was shortened in the pill group but not in the injectable group. There was no thromboelastographic change in both groups of patients.

Figure II shows the changes in coagulation factors. Fibrinogen level was increased in both groups.

Factor V, Factor VII, Factor VIII and Factor X were increased in the pill group but not in the injectable group. There was no change in either groups in prothrombin levels.

Figure III shows the changes in the fibrinolytic system. In only the depo group, the euglobulin clot lysis time is significantly increased. Fibrinolytic activity on fibrin plate was increased in the pill group but not in the injectable group. Plasminogen level was increased in the pill group only.

Figure IV shows the result of the inhibitor assays. No change was detected in the group on injectables whilst there was a significant decrease of antithrombin III and anti-Xa in the pill group. There was no change in the level of α_2 macroglobulin in both groups.

Figure V shows the platelet function tests which were not altered in both groups.

TABLE I AGE DISTRIBUTION

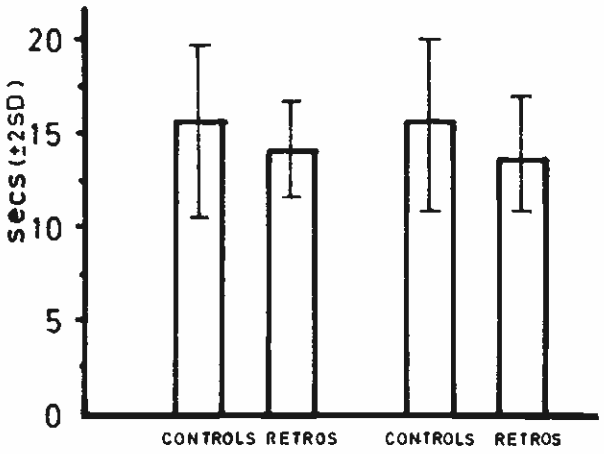
	20-25 yrs	26-35 yrs	36-45 yrs	46+yrs	Total
Depo	19 (15%)	49 (38.6%)	54 (42.5%)	5 (3.9%)	127
Pill	17 (14.9%)	56 (49.1%)	33 (28.9%)	8 (7%)	114

Comparison between two groups $p > 0.1$ (not significant)

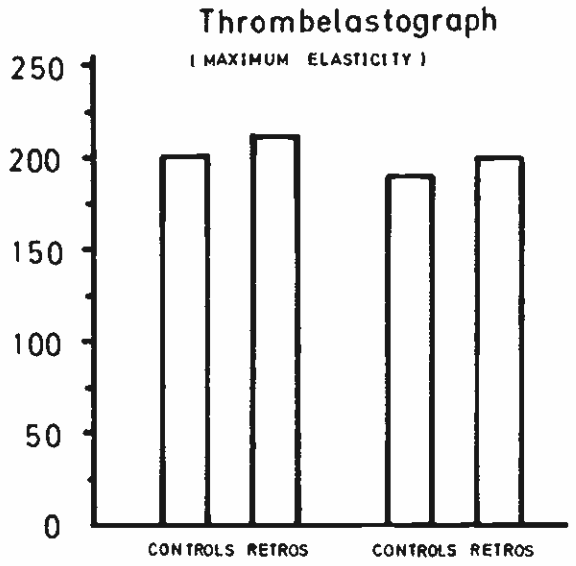
TABLE II ETHNIC DISTRIBUTION

	Chinese	Indian	Malay	Total
Depo	97	11	9	127
Pill	99	4	11	114
Comparison between two groups	p = 0.4 (NS)	p = 0.03 (*S)	p = 0.18 (NS)	

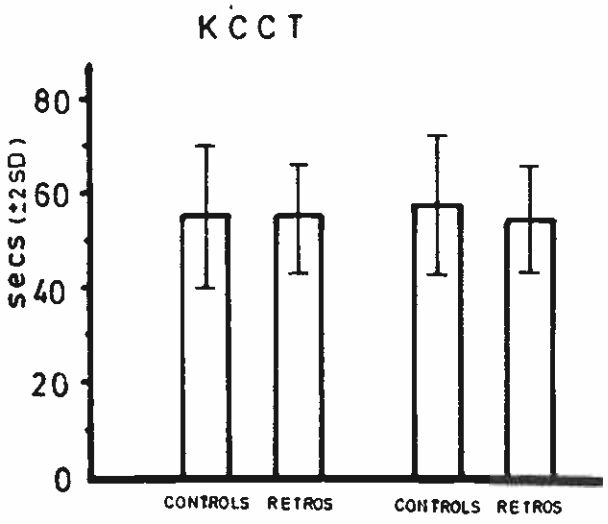
FIGURE 1



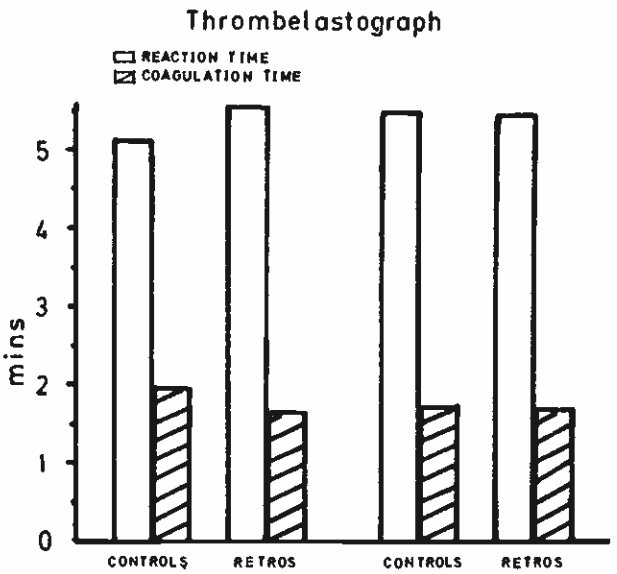
	Depo-Provera		Oral Pills	
n	111	114	107	109
mean	15·05	14·02	15·23	13·45
1 SD	2·26	1·29	2·24	1·39
p		< 0·0005		< 0·0005



	DEPO-PROVERA		ORAL PILLS	
n	55	96	49	91
mean	202·0	211·8	191·6	200·1
1 SD	49·8	53·2	43·9	53·4
p		0·15		0·15

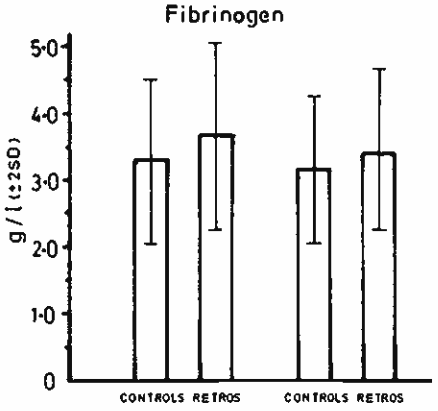


	Depo-Provera		Oral Pills	
n	117	115	107	109
mean	54·99	54·93	56·94	54·23
1 SD	7·45	5·85	7·25	5·55
p		0·475		< 0·003

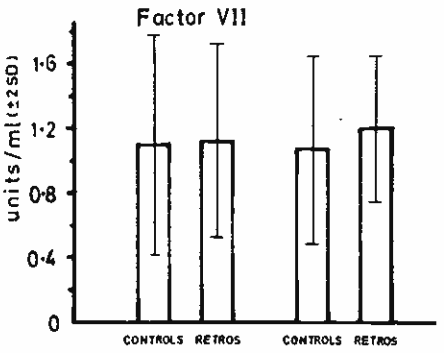


	DEPO-PROVERA				ORAL PILLS			
n	55	55	96	96	49	49	91	91
mean	5·11	1·96	5·53	1·66	5·48	1·70	5·45	1·68
1 SD	2·36	0·82	2·60	0·86	2·74	0·92	2·93	1·42
p			0·15	0·12			0·475	0·45

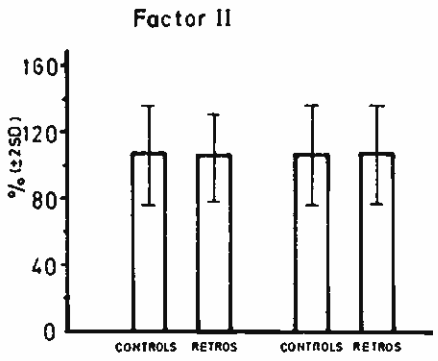
FIGURE II



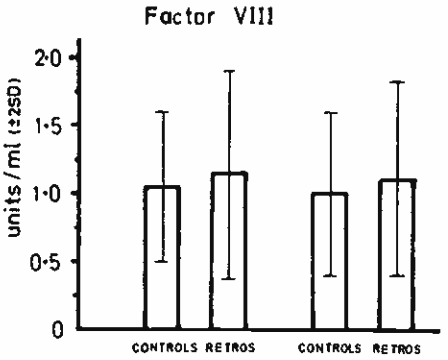
	Depo-Provera		Oral Pills	
n	122	121	111	110
mean	3·30	3·65	3·15	3·44
1 SD	0·61	0·71	0·56	0·60
p		<0·0005		<0·0005



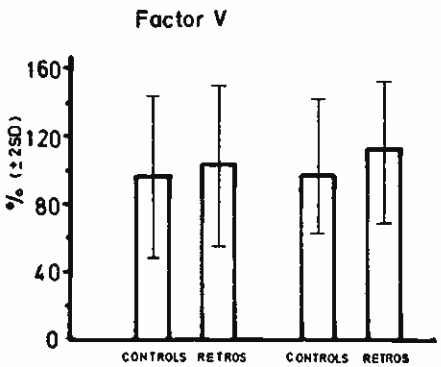
	Depo-Provera		Oral Pills	
n	60	66	62	64
mean	1·10	1·13	1·07	1·19
1 SD	0·34	0·30	0·30	0·36
p		0·30		0·005



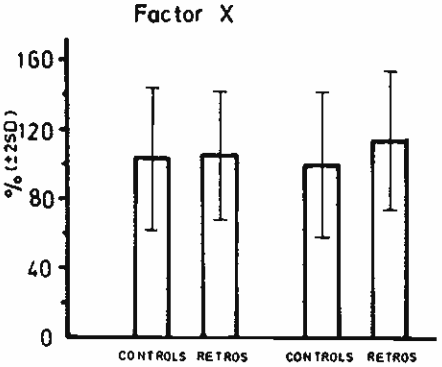
	Depo-Provera		Oral Pills	
n	124	125	114	114
mean	106·90	106·30	106·00	107·00
1 SD	14·64	13·99	14·79	14·82
p		0·38		0·38



	Depo-Provera		Oral Pills	
n	126	125	114	114
mean	1·05	1·14	1·00	1·11
1 SD	0·28	0·38	0·29	0·23
p		0·03		0·008

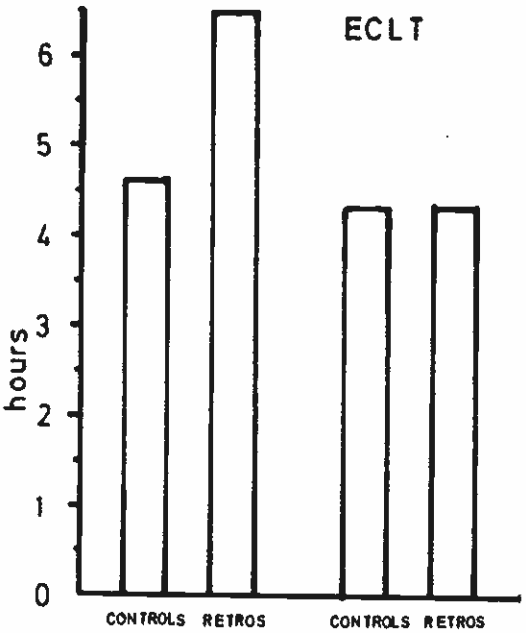


	Depo-Provera		Oral Pills	
n	125	126	114	116
mean	96·15	102·60	97·53	110·66
1 SD	23·97	23·05	22·45	21·24
p		0·02		<0·0005

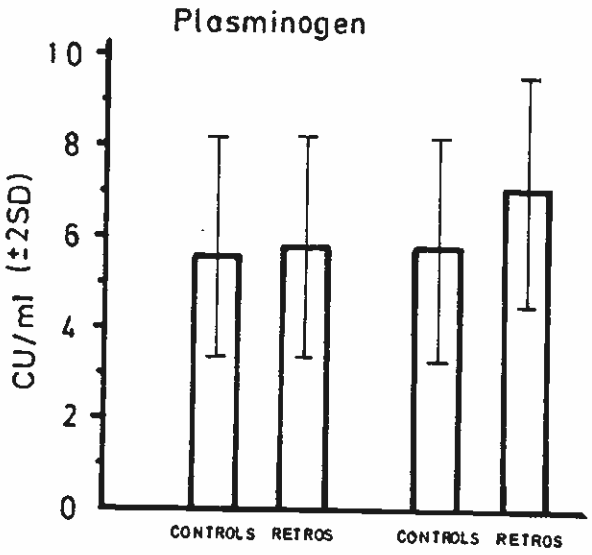


	Depo-Provera		Oral Pills	
n	127	123	114	114
mean	103·10	104·89	99·76	113·29
1 SD	20·59	18·40	20·84	19·90
p		0·23		<0·0005

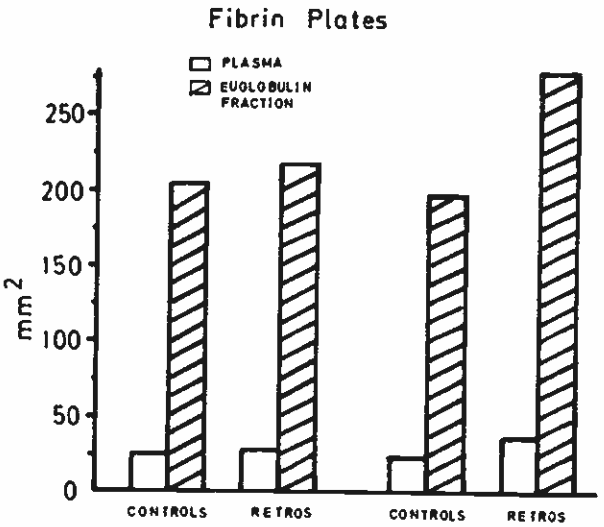
FIGURE III



	DEPO PROVERA		ORAL PILLS	
n	86	100	76	98
mean	4·58	6·46	4·30	4·30
1 SD	3·41	5·45	2·99	4·12
p		0·003		0·50

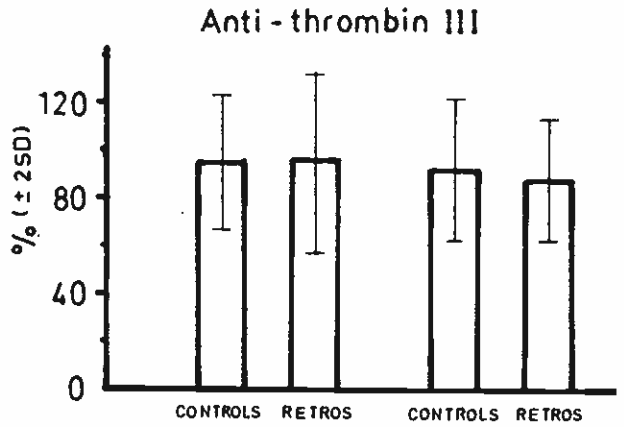


	Depo - Provera		Oral Pills	
n	114	99	103	99
mean	5·78	5·88	5·75	7·06
1 SD	1·22	1·21	1·22	1·25
p		0·28		<0·0005

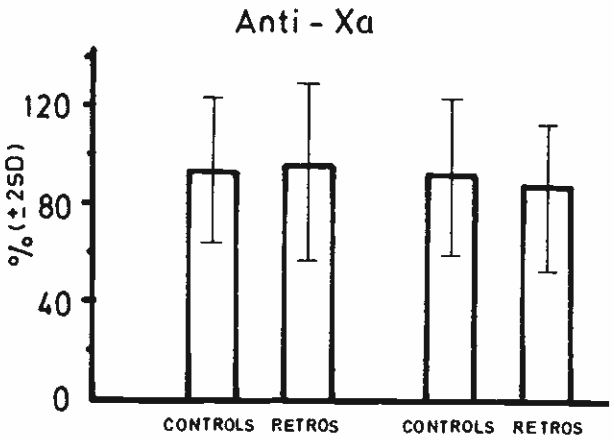


	DEPO - PROVERA				ORAL PILLS			
n	75	75	92	92	78	78	99	99
mean	24·1	203·5	26·5	215·9	22·6	198·4	36·6	279·4
1 SD	33·8	79·0	37·6	80·3	33·7	76·2	39·9	123·1
p			0·32	0·15			0·008	<0·0005

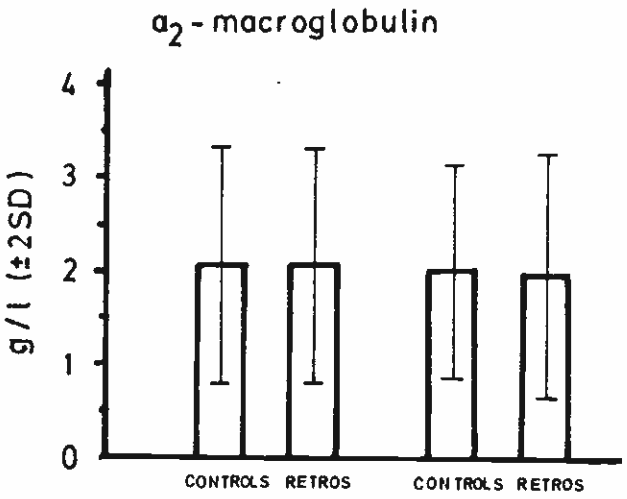
FIGURE IV



	Depo - Provera		Oral Pills	
n	96	39	97	48
mean	94·96	95·49	91·92	87·88
1 SD	14·28	19·09	14·03	12·89
p		0·43		0·05

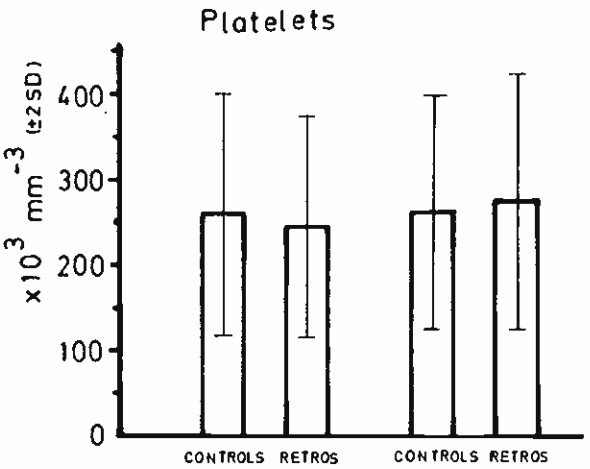


	Depo - Provera		Oral Pills	
n	104	49	100	52
mean	93·54	95·00	91·22	87·08
1 SD	14·90	17·19	15·97	13·69
p		0·30		0·05

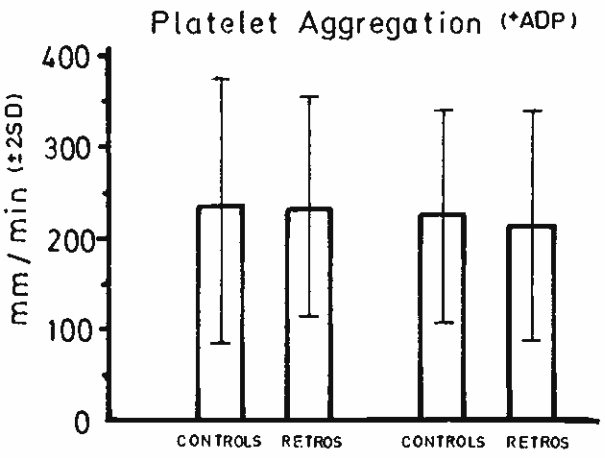


	Depo - Provera		Oral Pills	
n	107	99	104	103
mean	2·04	2·04	1·99	1·93
1 SD	0·64	0·63	0·57	0·65
p		0·475		0·25

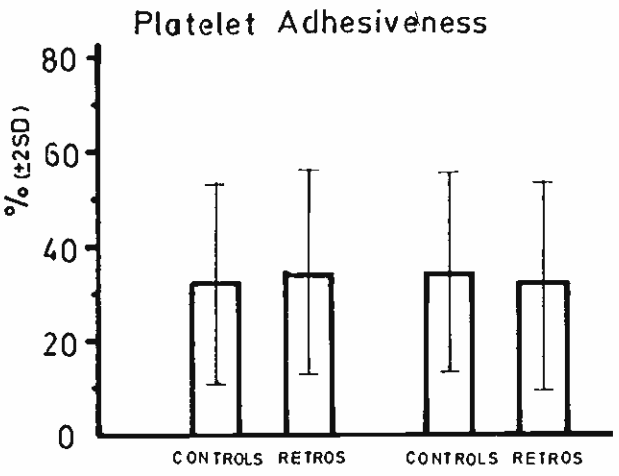
FIGURE V



	Depo - Provera		Oral Pills		
n	120	124	105	112	
mean	259	244	262	276	x10³
1SD	71·2	63·9	69·0	76·0	x10³
p		0·07		0·08	



	Depo - Provera		Oral Pills	
n	53	98	46	93
mean	230·8	233·5	224·5	213·9
1SD	72·3	60·2	58·0	63·5
p		0·40		0·18



	Depo - Provera		Oral Pills	
n	53	96	38	98
mean	32·2	34·4	34·0	31·9
1SD	10·5	10·9	10·3	11·4
p		0·12		0·15

DISCUSSION

From the data presented, there is evidence that a reactive condition is induced by long term use of oral pills containing 50 μg of ethinyl oestradiol. The increase in coagulation factors and the decrease in antithrombin III with a decrease in prothrombin and Kaolin cephalin time all point to a hypercoagulable state similar to that reported in Caucasians. However, in Asians, fibrinolytic activity is increased and this seems to effect a haemostatic balance as evidenced by no change detected in the thromboelastographic studies.

In the group of women using progestational injectable only, there are few coagulation changes. Only fibrinogen level was increased. The haemostatic balance was not disturbed.

Therefore, in both groups, haemostatic balance seems unchanged; the balance being at a higher level in the pill group. However, there seems to be a definite advantage of the progestational injectable contraceptive in that it causes less coagulation changes and demands less haemostatic readjustment.

On the basis of this information, however, one is unable to predict the clinical significance of these coagulation changes as to the risk of increasing thromboembolism by each type of contraceptive. Progestational agents have been reported to cause impaired venous tone and decreased mean linear velocity of venous blood resulting in a tendency to stasis. This would favour thrombosis especially in the presence of blood hypercoagulability.

More work has to be done before progestogen only contraception can be pronounced safer than the combined oestrogen containing contraceptive in the point of view of thromboembolic risk.

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