COMPARATIVE STUDY ON THE EFFECT OF DIANE AND MICROGYNON 50 CONTRACEPTIVE ON THE HAEMOSTATIC MECHANISMS IN CHINESE SUBJECTS

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ABSTRACT

A longitudinal controlled study on the effect of Diane and Microgynon 50 (Micro 50) contraceptive pills on the haemostatic mechanisms in 59 Chinese subjects was carried out.

Diane, containing the potent anti-androgen progestagen, cyproterone acetate was used as a contraceptive and in subjects requiring anti-androgenic treatment and fertility control. Enhanced fibrinolytic activity with raised plasminogen and alpha$_1$ -antitrypsin (a_1-AT) was observed in all subjects after pill treatment. The changes observed after Diane treatment suggests a predispostion to hypercoagulation as evidenced by increases in Fibrinogen, Factors VII and X with accelerated Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and Reaction and Clotting Time (r+k). Maximum elasticity of the clot was raised after Diane 50 treatment when compared with pre-treatment levels. More changes in haemostasis were seen after treatment with Diane containing 35ug and 50ug ethinyl estradiol (EE) formulation than during Micro 50 treatment.

The results from this study show that Diane even with 35ug EE formulation caused coagulation changes which were more pronounced than the 50ug EE Microgynon. The finding is at variance with others that ascribe haemostatic changes observed to increased oestrogen content in a given pill formulation and so merits confirmation in a larger study.

Keywords: Effects of contraceptive pills on haemostasis

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INTRODUCTION

The association of increased risk of vascular complications with the use of oral contraceptive is well known (1, 2). The oestrogen component in the pill has been incriminated (3) so that lowering the oestrogen content in the pill combination has been recommended to reduce this risk (4). Oral contraceptives (OC) cause changes in the platelet function, coagulation and fibrinolytic systems both in Caucasian and Asian women (5-7) and these changes are similar to those seen in late pregnancy. Two preparations of the pill Diane, one containing 2mg of cyproterone acetate with a combination of 35ug EE (Diane 35) and the other, 2mg of cyproterone acetate with 50ug EE (Diane 50) were presented to a select group of subjects of proven fertility who sought contraception. They were between the ages of 20 to 42 years.

The study was designed to determine the long term effects of Diane and Micro 50 on the haemostatic mechanism of ethnic Chinese women in Singapore.

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MATERIALS AND METHODS

Fifty-nine Chinese women were recruited into this study after giving informed consent. The physical characteristics of the subjects are given in Table I. The first 20 subjects were allocated only to the Diane 50 group but subsequent subjects were randomly allocated to one of the three OC pills under study, ie. Micro 50, Diane 35 or Diane 50. The composition of Micro 50 contains 50ug EE and 125mg levonorgestrel, Diane 35 and Diane 50 formulations are as stated above. Each subject acted as her own control. Blood sampling was performed during the luteal phase of the menstrual period before treatment (Control) and 6 and 12 months after treatment. The blood samples were obtained at the same time of day (9am to

Table I
Physical characteristics

	Micro 50	Diane 35	Diane 50
n	14	14	14
Age $\bar{x}$ (SD) yrs	31.5 (4.9)	30.4 (3.6)	30.9 (5.7)
Age range (yrs)	22 - 40	26 - 37	20 - 42
Height $\bar{x}$ (SD) cm	155.9 (3.5)	156.2 (6.5)	156.1 (5.1)
Weight $\bar{x}$ (SD) kg	53.1 (4.2)	51.6 (6.9)	50.9 (10.8)
Sys BP $\bar{x}$ (SD) mmHg	115.1 (11.1)	112.0 (8.2)	116.5 (8.8)
Dia BP $\bar{x}$ (SD) mmHg	70.7 (9.2)	66.1 (6.8)	71.5 (7.0)
Smokers	nil	nil	nil

11am) on each occasion after at least half an hour's rest prior to venepuncture.

Using plastic syringes and 21G needles, 9 parts of blood obtained from a clean venepuncture was added to one part of cold 0.21M Hepes (Sigma) in 0.129M tri-sodium citrate (Merck) in cold plastic tubes and well mixed by inversion. The blood was spun in a refrigerated centrifuge for 15 min at 2000g. For platelet aggregation studies, the mixed blood was kept at room temperature and Platelet Rich Plasma (PRP) obtained after spinning at 180g for 5 min.

Laboratory Tests

The following haemostatic parameters were studied: Prothrombin Time (PT) using human saline brain (8), APTT (9), Haemotocrit, Platelet Count using Coulter Counter ZBI, Fibrinogen (10), coagulation Factor II (11), one stage assay for Factors V and VII (8) using artificially prepared human deficient plasma for Factor V (home-made) and Factor VII from Curtin Matheson USA, Factors VIII (12) and X (13), Antithrombin III (ATIII) clotting (14), Plasminogen Activator activity on fibrin plate (15), Fibrin (ogen) Degradation Products (FDP) (16), Platelet Aggregation using Adenosine Di-Phosphate (ADP) (Sigma) final concentration 10uM and 3ug equine collagen (Hormon Chemie, W Germany) (17). Laurell's rocket method (18) was used to determine Factor VIII R:Ag, alpha$_2$-Macroglobulin (a_2-M), a_1-AT, alpha$_2$-antiplasmin (a_2-AP), plasma plasminogen and ATIII using antibodies from Behring, W. Germany except for a_2-AP from Mochida, Japan. Thromboelastogram using PRP was performed; briefly, 0.4 ml of PRP was mixed with 0.4 ml of pre-warmed 0.125M $CaCl_2$ in 0.15M NaCl. 0.4 ml of this mixture was transferred to the cuvette in the Hellige Thromboelastograph D. Maximum elasticity and reaction and clotting (r+k) time was calculated after running for 2 hours. In some subjects some of the tests was not performed as insufficient sera or plasma was available.

Standards and Controls

Freeze-dried pooled Hepes-citrate plasma from at least 20 normal volunteers not on any medication was used as secondary standards. The pooled plasma was also used as normal control for PT, APTT, ATIII clotting assays. Factors VIIIC and VIIIR: Ag was calibrated against the 1st and 2nd International Standard from the National Institute for Biological Standards and Control (NIBSC) England. The locally prepared freeze-dried human brain thromboplastin used throughout this study had an International Sensitivity Index (ISI) of 1.16. Locally prepared Internal Reference Control was used for most assays in our internal quality control programme where cusum plot was used to monitor test variations. Commercial platelet control (Sarstedt, W Germany) was used as platelet control. As no standards or control are available for platelet aggregation studies the test variations were kept to a minimum by performing the test at about 90 min after blood collection. Streptokinase 100iu/ml (Behring) was used as internal reference control for plasminogen activator activity on fibrin plate.

Test variations

The coefficient of variation (CV) of the various tests using different batches of Reference Control Plasma or sera during the study period was summarised. For PT (1.2 – 4.4%), APTT (1.7 – 4.9%), Fibrinogen (4.5 – 7.5%), Factors II (4.1 – 7.0%), V (6.6 – 9.0%), VII (3.8 – 7.0%), VIIIC (6.0 – 9.0%), X (6.1 – 9.7%), VIIIR: Ag (6.8 – 8.9%), Plasminogen Activator activity (11.0 – 15.0%), Plasminogen (6.3 – 7.9%), ATIII clotting (2.3 – 2.8%), ATIII antigen (4.6 – 6.2%), a_2-AP (4.2 – 7.9%), a_2-M (4.0 – 5.6%) and a_1-AT (6.1 – 7.0%).

Statistical Analysis

This was carried out using the paired student's t-test. Each subject acts as her own control. The mean of pre-treatment levels was designated as 100% and compared to post treatment levels after 6 and 12 months of oral contraception. A p value of ≤ 0.05 was regarded as statistically significant.

RESULTS

Fifty-nine Chinese subjects were recruited, 14 each for Micro 50 and Diane 35 and 31 subjects for Diane 50 treatment. Physical characteristics of the subjects showed no statistically significant differences between the three groups of women studied (Table I). The haemostatic effects of the three contraceptive pills before and after treatment are shown in Tables II to VI. These include a broad spectrum of investigations which comprises Screening Tests (Table II), Coagulation Factors (Table III), Fibrinolytic Activity and Proteins (Table IV), Coagulation Inhibitors (Table V) and Platelet Function (Table VI).

In the Screening Tests (Table II) significant shortening of PT ($p < 0.001$) was seen after treatment with Diane

Table II
Screening Tests

	Micro 50			Diane 35			Diane 50		
	Pre	6mth	12mth	Pre	6mth	12mth	Pre	6mth	12mth
Haemoglobin									
n	13	13	11	13	13	12	30	30	25
mean (g/l)	128.4	130.9	130.5	120.9	132.0	127.0	126.8	126.2	128.9
SD	6.3	8.2	8.0	10.4	11.6	10.6	10.3	12.3	10.6
% diff from									
-Pre mean	100	102	101	100	109	105	100	100	103
p	-	NS	NS	-	<0.01	NS	-	NS	NS
PT									
n	14	14	12	14	14	13	31	31	25
mean (sec)	13.4	12.8	13.1	13.3	12.6	12.3	13.3	12.6	12.4
SD	0.4	0.5	0.7	0.6	0.8	0.5	0.6	0.7	0.7
% diff from									
-Pre mean	100	96	98	100	95	92	100	95	93
p	-	<0.001	NS	-	<0.01	<0.001	-	<0.001	<0.001
APTT									
n	14	14	12	14	14	13	31	31	25
mean (sec)	44.0	45.8	44.1	43.7	43.5	37.8	42.6	41.1	39.8
SD	3.7	4.8	2.8	2.9	2.8	2.5	3.1	4.6	5.5
% diff from									
-Pre mean	100	104	100	100	100	86	100	96	93
p	-	NS	NS	-	NS	<0.001	-	NS	<0.001
Hct									
n	14	14	12	13	13	12	31	31	25
mean (l/l)	0.40	0.39	0.40	0.39	0.38	0.38	0.39	0.39	0.39
SD	0.02	0.02	0.02	0.02	0.02	0.03	0.02	0.03	0.02
% diff from									
-Pre mean	100	98	102	100	97	97	100	100	100
p	-	NS	NS	-	NS	NS	-	NS	NS
TEG n	13	13	12	12	12	9	27	27	19
(r+k time)									
mean (min)	12.7	13.1	11.5	12.8	11.5	8.9	13.1	11.1	10.6
SD	3.3	2.2	1.6	2.8	2.3	1.0	2.4	2.0	2.8
% diff from									
-Pre mean	100	103	94	100	90	69	100	85	79
p	-	NS	NS	-	NS	<0.001	-	<0.001	<0.001
(Max Elast)									
mean(units)	114.5	109.2	113.2	98.9	96.3	104.4	100.8	114.7	115.5
SD	28.6	25.1	19.6	17.6	21.8	20.8	21.3	19.5	17.5
% diff from									
-Pre mean	100	95	97	100	97	106	100	114	120
p	-	NS	NS	-	NS	NS	-	<0.01	<0.01

whilst with Micro 50 treatment this was seen only at 6 months of treatment ($p < 0.001$). Significant shortening of APTT was evident only at 12 months of treatment in both the Diane groups. No significant changes were seen in haemotocrit levels in all three groups of subjects after treatment except for a slightly raised Haemoglobin concentration to 109% of the pre-treatment level ($p < 0.05$) at 6 months of Diane 35 treatment. In Thromboelastography (TEG) significant shortened r+k time ($p < 0.001$) with increased elasticity of the clot ($p < 0.01$) was observed in the Diane 50 group at 6 and 12 months of treatment. Significant shortened r+k time ($p < 0.001$) and tendency of raised elasticity was also seen at 12 months after Diane 35 treatment.

Significant increase in the levels of Fibrinogen ($p < 0.01$), Factors VII ($p < 0.001$) and X ($p < 0.001$) was seen in the Diane groups at 6 and 12 months of treatment (Table III). In Fibrinogen, the mean increase was from 110 to 124% of the pre-mean level; 124 to 135% increase for Factor VII and 121 to 147% for Factor X. Significant decrease ($p < 0.01$) in Factor V activity to 88% and 92% of pre-mean level was seen respectively at 6 and 12 months of Diane 50 treatment. Diane 35 treatment results in increases in Factor VIIIR: Ag at 6 ($p < 0.01$) and 12 months ($p < 0.001$) to 129% and 130% respectively and significant increase only at 6 months ($p < 0.01$) after Diane 50 treatment. An increasing trend in Factor VIIIC activity was seen after Diane 35 treatment which was significant only at 12 months ($p < 0.01$) to 149% of the pre-mean level. No significant change in coagulation factors was seen after Micro 50 treatment.

Enhanced fibrinolytic activity from 130% to 164% of pre-mean level and raised plasminogen antigen level from 128% to 144% was observed in all three groups after treatment. Increased FDP was seen in the Diane groups after treatment with decreased levels at 12 months of Micro 50 treatment, all the levels are within the normal range of ≤ 5ug/ml (Table IV).

Functional ATIII showed no change in all subjects even after 12 months of treatment except for the Diane 50 group whose ATIII antigen level decreased significantly to 92% at 6 months ($p < 0.001$) and to 93% at 12 months ($p < 0.05$) when compared with the pre-treatment level. No change in a_2-AP level was seen whilst a_1-AT was significantly raised ($p < 0.001$) in all subjects under treatment. An increase to 120% ($p < 0.05$) of the pre-treatment level for a_2-M was only seen at 6 months of Diane 35 treatment after which it dropped to 113% at 12 months treatment which was not statistically significant (Table V).

Significant increase in platelet numbers was observed in Diane 35 which increases to 148% at 6 ($p < 0.001$) and to 144% at 12 months ($p < 0.01$) of treatment whilst Diane 50 showed a rising trend at 6 months to 110%

Table III
Coagulation Factors

	Micro 50			Diane 35			Diane 50		
	Pre	6mth	12mth	Pre	6mth	12mth	Pre	6mth	12mth
Fibrinogen									
n	14	14	12	14	14	13	31	31	25
mean (g/l)	2.73	3.19	2.87	2.59	3.14	3.22	2.81	3.09	3.02
SD	0.35	0.93	0.42	0.39	0.58	0.69	0.38	0.48	0.37
% diff from									
-Pre mean	100	117	106	100	121	124	100	110	110
p		NS	NS	-	<0.01	<0.01	-	<0.01	<0.01
Factor II									
n	14	14	12	14	14	13	31	31	25
mean (%)	99.9	108.4	110.9	101.9	109.4	103.5	99.0	101.9	101.2
SD	18.1	12.8	17.9	13.2	11.8	9.0	10.6	19.1	12.7
% diff from									
-Pre mean	100	109	110	100	107	102	100	103	101
p	-	NS	NS	-	<0.05	NS	-	NS	NS
Factor V									
n	14	14	12	14	14	13	31	31	25
mean (%)	115.1	112.4	115.7	95.1	102.0	99.3	113.4	99.5	101.9
SD	21.9	20.6	31.5	20.9	19.9	18.0	22.3	14.9	19.4
% diff from									
-Pre mean	100	98	102	100	107	104	100	88	92
p	-	NS	NS	-	NS	NS	-	<0.01	<0.01
Factor VII									
n	6	6	8	13	13	13	20	20	17
mean (%)	132.7	118.8	123.4	111.5	138.1	150.2	118.7	147.6	148.8
	15.5	13.3	17.2	15.8	12.0	17.6	16.9	16.8	15.5
% diff from									
-Pre mean	100	90	104	100	124	135	100	124	126
p	-	NS	NS	-	<0.001	<0.001	-	<0.001	<0.001
Factor VIIIC									
n	14	14	12	14	14	13	31	31	25
mean (iu/ml)	0.87	0.95	0.87	0.83	0.95	1.24	0.97	0.96	1.15
SD	0.24	0.22	0.40	0.16	0.26	0.47	0.23	0.28	0.50
% diff from									
-Pre mean	100	109	100	100	114	149	100	99	122
p	-	NS	NS	-	NS	<0.01	-	NS	NS
Factor VIII R:Ag									
n	14	14	12	14	14	13	31	31	25
mean (iu/ml)	0.74	0.81	0.71	0.75	0.97	0.98	0.87	0.99	0.94
SD	0.17	0.43	0.35	0.18	0.24	0.29	0.26	0.33	0.26
% diff from									
-Pre mean	100	109	95	100	129	130	100	114	110
p	-	NS	NS	-	<0.01	<0.01	-	<0.01	NS
Factor X									
n	14	14	12	14	14	13	31	31	25
mean (%)	93.6	101.0	93.3	71.4	102.8	105.1	79.8	96.4	105.4
SD	15.9	23.4	22.1	17.1	15.2	17.9	14.0	16.0	15.5
% diff from									
-Pre mean	100	108	98	100	144	147	100	121	134
p	-	NS	NS	-	<0.001	<0.001	-	<0.001	<0.001

with significant increase to 120% ($p < 0.01$) at 12 months of treatment. A rising trend in platelet numbers to 108% and 115% at 6 and 12 months of treatment respectively was noted in the Micro 50 subjects. This was not statistically significant. Enhanced platelet aggregation to ADP and Collagen was observed at 12 months of treatment in both Diane 35 and 50 subjects. Stimulation with ADP to 155% ($p < 0.01$) and with Collagen to 121% ($p < 0.05$) in the Diane 35 group and in the Diane 50 group to 129% ($p < 0.01$) with ADP and to 114% ($p < 0.05$) with Collagen. No statistical significant enhancement in platelet aggregation in the Micro 50 group was observed (Table VI).

DISCUSSION

The increased risk of cardiovascular complications in women using combined oral contraceptives has been attributed to oestrogen content and this has led to a large number of studies concerning their effect on haemostasis. The present study is a prospective longitudinal controlled study involving 59 Chinese women who were treated with either Micro 50, Diane 35 or Diane 50. Multiple changes in haemostasis were observed especially after Diane treatment. Significant rises in plasminogen activator activity, plasminogen antigen and a_1-AT was seen in all three groups of subjects after treatment when compared with the pre-treatment levels. These are similar to our findings reported earlier in Asian subjects treated with 50ug EE OC pill formulations (7). The rise in a_1-AT an acute phase reactant protein which occurs in response to inflammation could not be explained. Accelerated PT, APTT and r+k times after Diane treatment with raised maximum elasticity of the clot after Diane 50 treatment was observed. These changes coincide with similar increases in Fibrinogen, Factors VII and X suggests a predisposition to hypercoagulation. Factor VII increases were observed only in the Diane subjects with no significant change in activity seen in Micro 50 subjects which is similar to our earlier findings in subjects treated with Micro 30 containing 30ug EE and 150mg levonorgestrel (19).

Table IV
Fibrinolytic Activity & Proteins

	Micro 50			Diane 35			Diane 50		
	Pre	6mth	12mth	Pre	6mth	12mth	Pre	6mth	12mth
Plasminogen Activator Activity									
n	13	13	12	14	14	12	30	30	25
mean (mm^2)	152.9	216.6	203.7	150.9	196.9	214.6	140.0	230.0	206.8
SD	41.5	75.2	76.6	46.4	40.9	46.0	48.5	111.0	45.2
% diff from									
-Pre mean	100	142	133	100	130	142	100	164	144
p	-	<0.05	<0.05	-	<0.01	<0.01	-	<0.001	<0.001
FDP									
n	14	14	12	14	14	13	31	31	26
mean (ug/ml)	1.66	1.97	0.95	0.96	2.81	1.86	0.99	2.32	1.84
SD	1.24	1.49	0.59	0.41	2.10	1.18	0.64	1.88	1.45
% diff from									
-Pre mean	100	118	56	100	292	195	100	230	164
p	-	NS	<0.05	-	<0.01	<0.05	-	<0.001	<0.05
Plasminogen									
n	14	14	12	14	14	13	31	31	26
mean (mg/dl)	11.5	16.1	15.5	11.8	15.1	16.6	11.6	16.5	16.4
SD	1.8	1.7	2.3	2.2	2.5	2.8	1.5	2.4	3.0
% diff from									
-Pre mean	100	140	132	100	128	141	100	142	144
p	-	<0.001	<0.001	-	<0.001	<0.001	-	<0.001	<0.001

Table V
Coagulation Inhibitors

	Micro 50			Diane 35			Diane 50		
	Pre	6mth	12mth	Pre	6mth	12mth	Pre	6mth	12mth
AT III (functional)									
n	14	14	12	14	14	13	31	31	25
mean (%)	101.0	105.0	102.9	99.4	99.7	97.1	105.0	103.2	102.6
SD	7.3	10.3	7.9	9.7	9.5	7.1	6.6	10.0	7.8
% diff from									
-Pre mean	100	104	101	100	100	98	100	98	98
p	-	NS	NS	-	NS	NS	-	NS	NS
AT III (Ag)									
n	14	14	12	14	14	13	31	31	25
mean (%)	0.232	0.240	0.230	0.218	0.208	0.218	0.240	0.221	0.223
SD	0.025	0.019	0.014	0.028	0.024	0.020	0.020	0.030	0.026
% diff from									
-Pre mean	100	104	98	100	95	100	100	92	93
p	-	NS	NS	-	NS	NS	-	<0.001	<0.05
a_1 - Antitrypsin									
n	14	14	12	14	14	13	30	30	25
mean (g/l)	1.78	2.79	2.49	1.83	2.81	2.91	1.80	2.91	2.80
SD	0.36	0.69	0.47	0.19	0.82	0.43	0.34	0.58	0.45
% diff from									
-Pre mean	100	156	141	100	154	159	100	162	154
p	-	<0.001	<0.001	-	<0.001	<0.001	-	<0.001	<0.001
a_2 - Antiplasmin									
n	13	13	12	14	14	13	31	31	26
mean (mg/dl)	5.93	5.72	5.77	5.16	5.54	5.64	5.42	5.53	5.69
SD	1.05	0.88	0.71	0.89	1.03	0.99	0.77	0.73	0.83
% diff from									
-Pre mean	100	96	96	100	107	109	100	101	104
p	-	NS	NS	-	NS	NS	-	NS	NS
a_2 - Macroglobulin									
n	14	14	12	14	14	13	31	31	25
mean (g/l)	2.17	2.66	2.32	2.13	2.55	2.40	2.53	2.57	2.61
SD	0.71	0.92	0.87	0.39	0.51	0.59	0.70	0.80	0.75
% diff from									
-Pre mean	100	123	108	100	120	113	100	102	102
p	-	NS	NS	-	<0.01	NS	-	NS	NS

Table VI
Platelet Function Studies

	Micro 50			Diane 35			Diane 50		
	Pre	6mth	12mth	Pre	6mth	12mth	Pre	6mth	12mth
Platelets									
n	14	14	11	13	13	12	30	30	24
mean ($x10^9/l$)	186.3	202.1	208.7	171.4	253.0	246.0	224.0	248.8	261.8
SD	59.8	45.2	61.7	49.3	73.4	48.5	59.3	60.8	54.3
% diff from -Pre mean	100	108	115	100	148	144	100	110	120
p	-	NS	NS	-	<0.001	<0.01	-	NS	<0.01
Platelet Aggregation (+ADP)									
n	12	12	11	13	13	12	26	26	23
mean (%max T)	59.5	58.6	54.6	43.5	49.0	67.8	47.8	52.3	62.0
SD	17.0	8.5	9.7	15.8	17.6	17.4	14.6	21.3	18.2
% diff from -Pre mean	100	98	95	100	113	155	100	109	129
p	-	NS	NS	-	NS	<0.01	-	NS	<0.01
Platelet Aggregation (+ Collagen)									
n	12	12	11	12	12	13	27	27	25
mean (%maxT)	61.0	57.8	66.0	61.5	56.4	74.4	58.0	60.0	66.4
SD	14.4	9.6	7.0	12.6	10.6	12.7	13.8	20.4	12.5
% diff from -Pre mean	100	95	107	100	92	121	100	103	114
p	-	NS	NS	-	NS	<0.05	-	NS	<0.05

Functional ATIII and antigen showed no significant changes after Diane 35 or Micro 50 treatment except that in Diane 50 a decrease in antigen level was observed after 6 and 12 months of treatment. A_2-AP, the naturally occurring plasmin inhibitor was not affected by the OC treatment which was similar to other studies involving Chinese subjects (20).

The increase in platelet numbers after Diane treatment was evident with enhanced platelet aggregation to both ADP and Collagen suggesting enhanced platelet activation after Diane treatment.

Least haemostatic changes were seen with Micro 50 treatment. Increased fibrinolytic activity and plasminogen was also observed in all three groups of subjects after treatment suggesting that plasminogen is available for fibrinolytic activity to keep the vasculature patent. This is contrary to the report by Astedt et al (21) who reported abnormally low fibrinolytic activity in oral contraceptive users. An increase in coagulation factors has been attributed to the oestrogen component of the pill. In our study on Chinese subjects, more haemostatic changes were observed after Diane than Micro 50 treatment. It appears therefore that Diane treatment either with 35ug or 50ug EE formulation may enhance one's predisposition to hypercoagulation but this condition is countered by the increased fibrinolytic activity observed to keep the vasculature patent as evidenced by a population well known for its low predisposition to thromboembolic disease (22).

The results of this study suggest that the Micro 50 combination pill causes fewer changes in the haemostatic mechanisms and should be preferred if only contraception is required. When Diane 35 or 50 are used for its antiandrogenic properties especially on long term treatment it would be advisable to monitor the coagulation changes so that they do not reach pathological levels.

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