EFFECT OF ORAL CONTRACEPTIVE ON BLOOD COAGULATION AND BLOOD FIBRINOLYSIS

by

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Introduction

Oral contraceptives are used to control the fertility in women by preventing ovulation. The common side effects reported during the use of oral contraceptive are mild and insignificant and to some extent simulate the physiological changes in women during pregnancy. One of the most significant effect of the 'Pill' is on the mechanism of blood coagulation and the fibrinolytic activity of the blood. Kollar and his co-workers in 1952 and Alexander and his co-workers in 1954 observed the rise in concentration of several blood coagulation factors during pregnancy and puerperium. Jorden in 1961 and Zilkha in 1964 observed that the administration of oral contraceptive results in pregnancy simulating effects and is associated with the occurrence of thromboembolic episodes in women. Over and above these observations, the relationship between the 'Pill' and blood clotting and thrombosis appeared quite complicated and workers in the field of haematology were reluctant to commit anything till 1967. In May 1967, a medical council subcommittee in the United Kingdom demonstrated the presence of a small but definite hazard of thrombosis in the cases using 'Pill'. The hazard related especially to the thrombosis affecting the deep veins, the lungs and the brain.

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Pharmacologically the 'Pill' or the oral contraceptives are a variable combination of oestrogens and progestogens. The changes in different blood coagulation factors, during the use of oral contraceptive, are thought to be oestrogen dependant and preparations with low oestrogen dosage may carry less risk. There would be no risk of inducing thrombosis if progestogens alone could be made into an acceptable and effective contraceptive.

In the years 1970 to 1973 a trial was conducted at Zanana Hospital, Udaipur, to evaluate the effects of low dose oral contraceptive on blood coagulation and its fibrinolytic activity. This paper presents some of the observations of the above mentioned trial.

Material and Methods

In the present study a large number of women taking low dose oral contraceptives were selected from the cases attending the family planning clinic of Zanana Hospital, Udaipur. In all 95 cases were observed. Thirty two cases started the oral contraceptive afresh and they were under regular observation upto the onset of 7th cycle of their therapy. They are termed as 'follow-up cases' in the text. Nineteen cases were those which were using one or the other conventional oral contraceptive for the last so many cycles. These cases were included to observe the long term effect of the oral contraceptives and are termed 'old cases'. Out of these 19 old cases, 8 cases visited the

clinic regularly for 7 cycles and they are also included in the follow-up cases. Thus, only 40 cases (32 fresh follow-up and 8 old follow-up) were under complete observation upto the onset of 7th cycle of their therapy. As such about 240 cycles in 40 cases have been observed. For the sake of comparison, 31 control cases, 10 pregnancy cases in different trimesters and 3 cases of thrombophlebitis were also included.

Out of 40 follow-up cases (32 plus 8), 16 were using Voldys-21 and 24 were using Ovral ED. The blood tests were conducted on the onset of 1st, 4th and 7th cycles of observation (termed as 1st, 2nd and 3rd visits in the text and tables). The blood tests conducted and the coagulation factors studied are as follows (The methods followed in conducting these tests are bracketed):

1. Bleeding time (Ivy *et al* 1940).
2. Whole blood coagulation time (Lee and White 1913).
3. Hess's Capillary resistance test (Dacie and Lewis 1963).
4. Clot retraction (Macfarlane 1939).
5. Prothrombin time (Quick 1942) and concentration (Factor II) (Tocantin and Kazal 1964).
6. Fibrinogen estimation (Factor I) (Cullen and Van Slyke 1920).
7. Assay of Factor V (Dacie and Lewis 1963).
8. Euglobulin lysis time for determination of fibrinolytic activity of blood (Buckell 1958).

Observations and Discussion

Bleeding Time and Coagulation Time: The oestrogenic hormones have been used in controlling the haemorrhage for many years. The successful control of bleeding has been observed in the genital tract as well as postoperative bleeding. The drug activates the intrinsic coagulation mechanism (Berkarda *et al* 1965; Akman *et al* 1966; and Balkuv *et al* 1966). On the other hand Heikinheimo and Kallionaki (1963) found that the oestriol had no effect on the coagulation mechanism. The effect of hormones on vascular system and ground substance was studied, and it was noted by them that in thrombocytopenic cases shortening of bleeding time occurs without increase in platelet count. These studies indicated that oestrogenic hormones have a role in control of haemorrhage by affecting mucopolysaccharides. It was demonstrated that oestriol succinate shortened bleeding time and corrected in vivo platelet adhesiveness with the method of Borchgrevink *et al* (1960). This was also noted by Winckelmann and Kohler (1964), De Vries and Rutgers (1965) and Akman *et al* (1965). This shortening of the bleeding time can be explained by the change in the ground substance. Poliwoda (1961), Heikinheimo and Kallionaki (1963), Kabakei (1967) and Ulutin (1969) have pointed out that with oestriol succinate, an improvement in the clinical bleeling tendency and shortening of prolonged bleeding time in cases of essential and secondary thrombocytopenia has been observed but the platelet count was unchanged. It seems that change in mucopolysaccharide is sufficient for the control of haemorrhage.

In the present study 60% of the cases were using Ovral ED and 40% were using Voldys-21. Majority of the cases in both the groups showed decrease in the bleeding time. Only 16.6% of the cases in the first group and 6.25% in the second group showed no change in the bleeding time. The coagulation time decreased in all the cases except in one using Voldys-

21. Statistically, no changes were observed in the bleeding time and coagulation time with both the drugs as shown in Tables I and II.

TABLE I
Range, Mean and Standard Deviation of Bleeding Time
(Minutes—Seconds)

Cases	Visits	Range	Mean	S.D.
Control	—	3–00 to 7–00	5–26	1–16
Follow-up	1st	3–10 to 6–15	4–16	1–06
	2nd	2–50 to 6–10	4–06	1–01
	3rd	2–50 to 6–10	4–00	0–56
Old	1st	3–00 to 7–00	4–08	1–01
	2nd	3–10 to 6–40	4–08	1–06
	3rd	3–00 to 6–40	4–08	1–17
Pregnancy	—	3–00 to 8–15	4–55	1–23

TABLE II
Range, Mean and Standard Deviation of Coagulation Time
(Minutes—Seconds)

Cases	Visits	Range	Mean	S.D.
Control	—	3–20 to 6–30	4–39	0–54
Follow-up	1st	3–10 to 6–55	4–36	1–09
	2nd	3–00 to 6–35	4–26	0–53
	3rd	3–00 to 6–00	4–18	0–52
Old	1st	3–13 to 7–10	4–14	0–58
	2nd	3–00 to 4–40	3–55	0–33
	3rd	3–20 to 4–40	3–46	0–34
Pregnancy	—	3–05 to 4–05	3–21	0–59

The above observations are well in agreement with the observations of other workers. Satterthwaite (1964); Pincus (1961); Brodsky *et al* (1964); Faust and Tyler (1966) and Caspary and Peberdy (1965) in their studies with Enovid showed that oral contraceptives had no effect on bleeding and coagulation time. Studies with Ortho-Novum, Provest, Oracon and Anovlar also showed no change in bleeding and coagulation time (Rice-Wray *et al* 1962; Livingston, 1963; Gould, 1963; Beaton 1964; Pincus, 1961).

Clot Retraction: Nour-Eldin and Lewis (1966) suggested that oral contraceptives produce an increase in factor VIII and they reduce the clot retraction and this aggravates the coincidental thrombus. But in the present study the clot retraction remained unchanged in all cases during the subsequent visits.

Hesses Capillary test: Throughout the present study this test was found to be negative.

Fibrinogen: It has been known for many years that fibrinogen level in-

creases in pregnancy. Kennan (1955), Fresh *et al* (1956), Gillman *et al* (1959), Davidson and Tomlin (1963) and Nossel *et al* (1966) have shown that fibrinogen level increases in pregnancy. Since oral contraceptives are a mixture of progestational and oestrogenic hormones, changes similar to pregnancy are expected with their use. Gross increase in the fibrinogen has been noticed in women using oral contraceptives.

In the follow-up cases using Voldys-21, an increase in fibrinogen level was noted in 67.7% of the cases. In 23.5% of the cases no change was observed and in 11.7% there was a slight lowering of the fibrinogen level. In the second group of study with Ovral-ED, 70.8% of the cases showed increase in plasma fibrinogen level. There was decrease in fibrinogen level in 20.8% and no change in the fibrinogen level in 8.3% of the cases. The mean value of fibrinogen level showing increase in 4th and 7th cycles is shown in Table III.

TABLE III

Range, Mean and Standard Deviation of Fibrinogen (mgm%)

Cases	Visits	Range	Mean	S.D.
Control	—	190 to 500	317.41	83.76
Follow-up	1st	190 to 700	329.37	103.20
	2nd	190 to 470	346.34	75.87
	3rd	270 to 500	362.31	68.11
Old	1st	270 to 700	386.31	115.68
	2nd	270 to 730	472.72	146.56
	3rd	270 to 730	423.34	195.5
Pregnancy	—	300 to 520	406.00	75.74

The increase in fibrinogen has also been observed by Phillips *et al* (1961), Sobrero *et al* (1963), Amundson and Pilgeram (1964), Brackman and Astrup (1964), and Ozsoylu and Corbacioglu (1966). Ozsoylu and Corbacioglu (1966) have observed a rise in fibrinogen level with oral contraceptives in cases of congenital afibrinogenemia. Some authors did not find any effect of Enovid on fibrinogen level (Mammen *et al* 1963; Repaport, 1962; Young *et al* 1965). Similarly, no effect was observed on fibrinogen level in cases using Provest, Ortho-Novum, Oracon and Norlestrin (Sobrero *et al* 1963; Young *et al* 1965; and Margulis *et al* 1965). The difference in the findings of different workers may be due to the fact that the factor of dose and duration remains a subject for consideration. The genetic factor and nutritional conditions in India might also be having its impact on the fibrinogen level.

Prothrombin time and Concentration: In the present study prothrombin time and prothrombin concentration were estimated by modified Quick's (1942) method and Tocantin and Kazal (1964) method respectively. In the cases using Voldys-21, the prothrombin time shortened in 93.7% of the cases and remained unchanged in the rest. The prothrombin concentration increased in 62.5% and decreased in 37.5% of the cases. The prothrombin concentration remained unchanged in one case.

In cases using Ovral ED, the prothrom-

bin time decreased in 62.5% and increased in 25% of the cases. No change was observed in 12.5% of the cases. Regarding prothrombin concentration, 75% of the cases showed increase and it was decreased in 25% of the cases. Hence it is evident that the majority of cases showed increase in prothrombin concentration with both the drugs as shown in Tables IV and V. These findings are in agreement with the work of Schrogie *et al* (1967), Hougie *et al* (1965), Donayre and Pincus (1965), Rapaport *et al* (1963) and Margulis *et al* (1965). While Mammen *et al* (1963), Egeberg and Owren (1963), Brodsky *et al* (1964) and Thomson and Poller (1965) did not observe any change in prothrombin values.

Factor V: In the present study with Voldys-21, a insignificant increase in factor V was observed in 52.5%, and decrease in 37.5% of the cases. On the other hand, with Ovral ED, there was insignificant increase in factor V in 45.8% of the cases and fall in 54.2%. As compared to control cases, no significant difference in factor V was observed. Similarly, on subsequent visits, Factor V was not altered significantly

TABLE IV

Range, Mean and Standard Deviation of Prothrombin Time

(Seconds)

Cases	Visits	Range		Mean		S.D.	
		Patient	Normal	Patient	Normal	Patient	Normal
Control	—	12–26	11.5–23	15.25	15.90	3.61	6.48
Follow-up	1st	12–24	12–22	17.26	17.53	3.07	3.36
	2nd	9–18	12–20	14.38	16.00	2.02	2.35
	3rd	12–22	12–22	14.96	16.80	3.39	2.64
Old	1st	12–22	14–23	16.10	18.42	1.49	1.76
	2nd	11.5–16	13.5–22	13.89	17.42	1.23	2.24
	3rd	12–14	14–16	13.25	15.01	0.28	0.39
Pregnancy	-	12–18	11–22	14.8	16.6	2.53	3.37

TABLE V

Range, Mean and Standard Deviation of Prothrombin Concentration (100% Normal)

Cases	Visits	Range	Mean	S.D.
Control	—	82.4 to 161.5	105.65	14.89
Follow-up	1st	90.4 to 180.00	107.50	5.2
	2nd	100.0 to 140.0	110.05	8.84
	3rd	100.0 to 146.0	111.76	9.61
Old	1st	100.0 to 128.0	109.87	7.15
	2nd	100.0 to 114.3	107.30	8.84
	3rd	100.0 to 116.0	107.88	5.15
Pregnancy	—	98.0 to 118.0	107.4	6.60

(Table VI). Other workers have also noted no change in Factor V (Mammen *et al* 1963; Donayre and Pincus, 1965; Rapaport *et al* 1963; Young *et al* 1965; and Margulis *et al* 1965).

Euglobulin Lysis Time: In the present study with Voldys-21, the euglobulin lysis time was increased in 68.7% of the cases and was decreased in 31.3%. In Ovral ED series the euglobulin lysis time was increased in 91.6% and decreased only in 8.4% of the cases. The increase in euglobulin lysis time in majority of cases is quite significant as compared with the control cases. Also when the pairs of mean in different cycles in follow-up cases were tested statistically, a significant mean difference was observed in 1st to 7th and 4th to 7th cycles (shown in Table VII). This statistically significant rise in euglobulin lysis time in the present study of follow-up cases is not in agreement with the previous workers (Brakman and Astrup, 1964; Donayre & Pincus, 1965; Brakman & Astrup, 1963; Powell *et al* 1965; and Menon, 1970). But none of these workers studies the changes in the euglobulin lysis time in subsequent cycles. They only compared their findings with the control cases. Hence, may be, they could not establish the changes in the subsequent cycles.

TABLE VI

Range, Mean and Standard Deviation of Factor V (40% Normal)

Cases	Visits	Range	Mean	S.D.
Control	—	28.0 to 53.3	39.60	6.09
Follow-up	1st	32.0 to 55.4	40.51	6.89
	2nd	30.0 to 63.3	41.44	6.81
	3rd	30.0 to 52.0	39.96	8.05
Old	1st	20.6 to 56.0	40.40	8.82
	2nd	32.0 to 45.9	38.66	7.00
	3rd	33.3 to 56.0	42.11	6.19
Pregnancy	—	30.0 to 42.0	35.1	4.12

TABLE VII

Range, Mean and Standard Deviation of Euglobulin Lysis Time (Hours—Minutes)

Cases	Visits	Range	Mean	S.D.
Control	—	1–20 to 7–50	2–33	1–13
Follow-up	1st	1–00 to 4–55	20–07	0–40
	2nd	1–10 to 3–30	2–17	0–34
	3rd	1–40 to 3–55	2–48	0–34
Old	1st	1–10 to 3–40	2–22	0–34
	2nd	1–08 to 3–40	2–05	0–47
	3rd	1–45 to 2–55	2–26	0–29
Pregnancy	—	2–55 to 5–55	4–27	1–23

TABLE VIII

Showing Comparison of Mean Values of Different Blood Tests in Control, Pregnancy and Thrombophlebitis Cases with Old Cases in Groups

Comparison	Fibrinogen (mgm.%)	Prothrombin Concentration (100% N)	Prothrombin Time (Seconds) Patient	Prothrombin Time (Seconds) Normal	Factor V (40% N)	Euglobulin Lysis time (Hr. — Min.)	Bleeding time (Min. — Sec.)	Coagulation time (Min. — Sec.)
Control	317.41	108.65%	16.25	15.90	33.60%	2–33	4–26	4–39
Pregnancy	406.00	107.40%	14.80	16.60	35.10%	4–27	4–55	3–21
Thrombophlebitis	433.33	112.00%	18.66	18.00	34.00%	3–16	5–43	3–48
Group I	372.00	111.00%	14.50	16.22	42.34%	2–32	4–36	3–43
Group II	337.50	110.80%	15.25	16.75	41.57%	2–35	3–50	4–04
Group III	515.00	111.80%	12.25	16.25	36.42%	2–55	3–57	4–52
Group IV	115.00%	433.00	14.00	17.00	36.50%	2–35	3–20	3–45

The rise in euglobulin lysis time suggests the fall in fibrinolytic activity of the blood. This fall in fibrinolytic activity and corresponding rise in the blood coagulation factors may lead to thromboembolism. But in the present study the rise in coagulation factors is insignificant and the account of fibrinolytic system at present time is tentative and incomplete and the methods and techniques available for their study are still at an early stage. In these conditions it is premature to form a firm opinion on the oral contraceptives, blood coagulation and the fibrinolytic activity of the blood.

In order to observe the long term effects of oral contraceptives, the nineteen 'old' cases studied were divided into four groups according to the duration of the use of oral contraceptives. These groups are:

Group I 4 to 10 cycles.
Group II 11 to 15 cycles.
Group III 16 to 30 cycles.
Group IV 31 cycles and more.

The mean values of bleeding time, coagulation time, prothrombin time, prothrombin concentration, Factor V, fibrinogen and euglobulin lysis time in these different groups of old cases have been compared with the mean values observed in the control, pregnancy and thrombophlebitis cases. This comparison is shown in Table VIII. The differences in these values are statistically non-significant.

Summary and Conclusion

Forty cases were studied with complete follow-up. Eleven 'old' cases visited the clinic irregularly. Thirty-one control cases, 10 pregnancy cases in different trimesters and 3 cases of thrombophlebi-

tis were also included in the study. Thus in all 95 cases were studied.

Except in 'old' cases Ovral ED and Voldys-21 were used in the present trial.

The bleeding time and coagulation time in the present series of follow-up cases were found to be shortened. The mean shortening in bleeding time was 16 seconds and in coagulation time was 18 seconds.

Plasma fibrinogen levels were found to be raised in subsequent cycles in the follow-up cases. The mean rise was 32.93 mgm%.

Prothrombin concentration was increased in majority of cases. The mean increase in prothrombin concentration was 4.28% in follow-up cases.

No significant change was observed in Factor V level when compared with the controls.

Rise in euglobulin lysis time in subsequent cycles of the follow-up cases was observed. The mean rise was 41 minutes.

Above observations were statistically tested. The equality of pairs of means were tested by 't' test. All were found statistically non-significant except in the follow-up cases of euglobulin lysis time.

Since the advent of oral contraceptives the subject of their effect on blood coagulation and blood fibrinolysis is discussed to a great length. The findings of various workers in the field are incomplete and highly controversial. The methods and techniques presently available are also at an inceptive stage.

The present study reveals that oral contraceptive when used for a short duration has insignicant effects on blood coagulation and the fibrinolytic activity of the blood.

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