A COMPARATIVE STUDY OF BLOOD FIBRINOLYTIC ACTIVITY AND COAGULATION OF BLOOD IN PREGNANT WOMEN AND WOMEN TAKING ORAL CONTRACEPTIVES

by

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Blood coagulation and fibrinolysis are normally in a state of dynamic equillibrium. Thrombus formation would, therefore, occur either due to an increased coagulability or to decreased fibrinolytic activity of blood (Astrup and Sterndorff, 1956).

The 'pill' has been frequently blamed for rendering high risk of thrombo-embolic phenomenon to the user. Medical literature is replete with contradictory reports about the effect of oral contraceptives on fibrinolytic activity of blood. Some workers have reported a decrease (Tagnon *et al*, 1953), while others have found an increase (Brehn, 1964) of fibrinolytic activity following the use of oral contraceptives. Still others have found no significant change (Beller and Porges, 1967).

Aim of the present study was to study the effect of oral contraceptives on the coagulation and fibrinolytic mechanisms, and to compare the findings with changes during pregnancy.

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Material and Methods

A total of 100 cases were included in this study performed between February 1975 and November 1975.

(A) *Control Group*: It included 20 females in the age group of 18-40 years. They were selected from ward nurses and attendants of the patients admitted to the hospital. Precaution was taken to ensure that these cases had not consumed any drug at least 3 months prior to the investigation and that they were not suffering from any disease.

(B) *Pregnant Women*: Thirty pregnant women in the age group of 18-40 years were investigated during first, second and third trimesters of pregnancy.

(C) *Cases Taking Oral Contraceptives*: Fifty normal, healthy non-pregnant females in the age group of 18-40 years were selected for administration of oral contraceptives. Combined type of 'pill' was given "Ovral"—Wyeth Laboratories), which contains 0.5 mg. progestogen and 0.05 mg ethynylestradiol. All the investigations were done once before starting the course of oral contraceptives and then after 1 month, 3 months, 6 months and 9 months of their use.

Investigations

Following estimations were done in all the 100 cases:—

1. Fibrinolytic activity by estimating fibrinolysis time (Fearnley, 1957, modified by Mathur *et al*, 1964).
2. Coagulation time by the method of Lee and White (Dacie and Lewis, 1968).
3. Prothrombin time by employing modified Quick's method.
4. Plasma fibrinogen level (Wooton, 1964).

Results obtained were subjected to statistical evaluation.

Observations

The age range of cases in all the 3 groups is given in Table I. The cases under study were of different parity as shown in Table II.

Normal Controls:

Fibrinolysis time in this group ranged from 5 to 11.3 hours (mean 7.5 ± 1.82). Coagulation time ranged from 6 to 9.1 min. (mean 7.1 ± 0.94). Range of prothrombin time was 12 to 19 seconds (mean 15.8 ± 2.33). Plasma fibrinogen level ranged between 0.15 to 0.45 gm% (mean 0.31 ± 0.07). No particular relationship was found between results of these tests and age group of the control cases.

The results of fibrinolysis time, coagulation time, prothrombin time and plasma fibrinogen level in the other 2 groups of cases, along with the statistical data, are shown in Table III.

Pregnant Women:

Mean fibrinolysis time and plasma fibrinogen levels showed a tendency to rise as pregnancy advanced. However, statistically significant alterations were observed only during second and third trimesters. The fall in coagulation time was significant in all the 3 trimesters. No statistically significant change was found in the values of prothrombin time during pregnancy.

TABLE I
Age

Study groups	Age range (Years)	Mean age (Years)
A. Control	20-30	28.75
B. Pregnant	18-39	28.17
C. Women using oral Contraceptives	21-40	30.10

TABLE II
Parity

Parity	Control cases	Pregnant women	Cases taking oral contra.
P0	4	9	—
P1	3	7	13
P2	6	12	16
P3	3	2	17
P4	3	—	3
P5	1	—	1
Total	20	30	50

TABLE III
Results of Various Tests

Investigation	Title of data	Control group	Pregnant women			Women using oral contraceptives				
			1st Trim.	2nd Trim.	3rd Trim.	Before O.C.	After 1 month	After 3 months	After 6 months	After 9 months
Fibrinolysis time (hours)	Range	5.0 - 11.3	5.4 - 9.5	6.0 - 11.3	5.4 - 13.4	4.5 -13.3	4.5 - 13.0	5.1 - 12.7	5.3 - 15.0	4.9 - 15.0
	Mean (SD)	7.5 ± 1.82	7.46±1.14	8.86± 1.38	9.60± 2.1	8.08± 2.66	9.2 ± 2.6	9.08± 2.46	9.84± 2.72	10.64± 3.12
	't' as compared to control	—	0.072	0.025	3.672	—	2.12	1.95	3.27	4.42
	"p"	—	>0.05	<0.05	<0.05	—	<0.05	>0.05	<0.05	<0.05
Coagulation time (minutes)	Range	6.0 - 9.1	4.0 - 6.9	3.7 - 5.8	3.0 - 6.0	6.0 - 9.7	6.0 - 9.1	4.6 - 9.1	4.0 - 9.3	4.1 - 9.5
	Mean (SD)	7.10 ± 0.94	6.3 ± 0.81	5.03± 0.90	5.10±0.93	7.66± 1.14	7.18±0.95	7.14± 1.09	7.22± 1.31	7.10± 1.34
	't' as compared to control	—	3.209	7.829	7.418	—	2.29	2.33	1.79	2.25
	"p"	—	<0.05	<0.05	<0.05	—	<0.05	<0.05	>0.05	<0.05
Prothrombin time (seconds)	Range	12.0 -19.0	12.0 - 18.0	11.0 - 19.0	11.0 - 19.0	11.0 - 17.0	11.0 - 17.0	11.0 - 18.0	11.0 - 18.0	11.0 - 17.0
	Mean (SD)	15.80 ± 2.33	15.53±1.94	14.86± 1.87	15.66± 1.97	14.28± 2.08	15.52± 1.68	15.6 ± 1.83	15.28± 1.68	15.04± 1.71
	't' as compared to control	—	0.445	1.561	0.212	—	3.28	3.37	2.64	2.00
	"p"	—	>0.05	>0.05	>0.05	—	<0.05	<0.05	<0.05	<0.05
Plasma Fibrinogen (gm%)	Range	0.15 - 0.45	0.15 - 0.45	0.2 - 0.5	0.2 - 0.6	0.15 - 0.45	0.2 - 0.45	0.2 - 0.5	0.2 - 0.6	0.2 - 0.7
	Mean (SD)	0.32 ± 0.07	0.32 ± 0.07	0.37± 0.09	0.40±0.10	0.30± 0.06	0.32± 0.07	0.34± 0.07	0.36± 0.09	0.39± 0.13
	't' as compared to control	—	0.646	2.959	3.891	—	1.84	3.05	3.67	4.39
	"p"	—	>0.05	<0.05	<0.05	—	>0.05	<0.05	<0.05	<0.05

TABLE IV

Comparison of Results Obtained in Pregnant Women and in Women Taking Oral Contraceptives

Investigations	Groups compared					
	1st Trimester	After 3 months of O.C.	2nd Trimester	After 6 months of O.C.	3rd Trimester	After 9 months of O.C.
Mean Fibrinolysis time (Hrs.)	7.47	9.08	8.87	9.84	9.60	10.64
	('t' 3.37)		('t' 1.81)		('t' 1.62)	
	(p<0.01)		(p>0.05)		(p>0.05)	
Mean Coagulation time (Mts.)	6.30	7.14	5.03	7.22	5.10	7.10
	('t' 3.66)		('t' 8.08)		('t' 7.19)	
	(p<0.01)		(p<0.001)		(p<0.001)	
Mean Prothrombin time (Sec.)	15.53	15.60	14.87	15.28	15.67	15.04
	('t' 0.17)		('t' 1.01)		('t' 1.51)	
	(p>0.05)		(p>0.005)		(p>0.05)	
Mean Plasma Fibrinogen Level (gm%)	0.32	0.35	0.38	0.36	0.41	0.39
	('t' 1.86)		('t' 0.96)		('t' 0.73)	
	(p>0.05)		(p>0.05)		(p>0.05)	

Women Taking Oral Contraceptives:

The investigations in this group were performed before starting oral contraceptives and after 1, 3, 6 and 9 months of their use. Statistically significant rise of prothrombin time over the control value for this group, was observed all over this period. Mean fibrinolysis time showed a significant rise only after 1, 6 and 9 months following the administration of 'pill'. Significant fall of coagulation time was observed only after 1, 3 and 9 months. The rise of plasma fibrinogen level was significant after 3, 6 and 9 months of using the 'pill'.

The alterations in fibrinolysis time, coagulation time, prothrombin time and plasma fibrinogen levels, observed during pregnancy and after the use of the 'pill' were compared. The values during first, second and third trimesters of pregnancy were compared respectively with those obtained after 3, 6 and 9 months of using oral contraceptives (Table IV).

It was found that values for mean fibrinolysis time after the use of oral contraceptives were higher as compared to values obtained during pregnancy. However, on applying statistical methods, it was observed that the difference between first trimester of pregnancy and 3 months after using the 'pill' was highly significant ($p < 0.01$), whereas the mean fibrinolysis time after 6 and 9 months of the use of oral contraceptives was not significantly different from that observed during second and third trimesters of pregnancy ($p > 0.05$).

The fall of coagulation time was more marked in pregnant women as compared to that seen in women taking oral contraceptives. This difference was highly significant in all the 3 groups compared ($p < 0.01$, < 0.001 and < 0.001 respectively).

The differences between the values of mean prothrombin time and mean plasma fibrinogen level during pregnancy and after administration of oral contraceptives, were not significant ($p > 0.05$).

All the cases were carefully followed-up for evidence of superficial or deep vein thrombosis. None of the cases developed such complications during the course of this study and upto 3 months after last investigations were performed.

Discussion

In the control group of the present series, fibrinolysis time ranged from 5 to 11.3 hours (mean 7.5 ± 1.82). This is comparable to the values reported by Mathur *et al* (1964) and Sinha *et al* (1960). Fearnley (1960) has reported lower values, viz., 2 to 10 hours, with a mean of 5 hours.

Our values for coagulation time, prothrombin time and plasma fibrinogen level compare well with the established and accepted values for normal individuals.

No significant relationship was found between these values and age of the individuals. Similar observation has been recorded by other workers (Fearnley, 1963: Mathur *et al*, 1964).

There was a progressive increase in fibrinolysis time, indicating a fall of fibrinolytic activity, with the advancement of pregnancy. This was statistically significant as compared to control, during second and third trimesters. Decrease of fibrinolytic activity during pregnancy has been observed by several workers (Gillman and Michael, 1959; Wardle and Menon, 1969; Nilson *et al*, 1970). There is only one report available, describing a rise of fibrinolytic activity during preg-

nancy (Ciulla and Luraschi, 1958—quoted by Poller, 1969).

Significantly decreased values of coagulation time during all trimesters point towards a state of hypercoagulability during pregnancy. Enhancement of coagulation system has been reported by Brakman *et al* (1967).

Prothrombin time did not show significant change during pregnancy as also reported by Donayre and Pincus (1965). However, Ambrus *et al* (1969) have found increase of prothrombin time during pregnancy.

Rise of plasma fibrinogen level was statistically significant during second and third trimesters of pregnancy. Gillman and Michael (1959) have observed that plasma fibrinogen increases during early months of pregnancy and remains elevated with puerperium.

For studying the effects of oral contraceptives, we studied 50 cases after 1, 3, 6 and 9 months of their use. The values before the use of the 'pill' served as control for the subsequent values. Thus, every case in this group served as its own control. These values were slightly different from the values of control group (Group A), because selection of cases for giving oral contraceptives was done irrespective of previous history of ailment or termination of pregnancy in recent past. Hence these values did not match exactly with the values of our control group.

The rise in fibrinolysis time (fall in fibrinolytic activity) was statistically significant after 1, 6 and 9 months of using the 'pill'. Reduction of fibrinolytic activity after use of oral contraceptives has been reported (Margulis *et al*, 1965; Schubert *et al*, 1968) and after administration of oestrogens in cases of prostatic carcinoma (Tagnon, 1953). There are other workers who did not find any significant change (Sobrero *et al*, 1963; Bennet *et al*, 1966; Menon *et al*, 1970).

Hedia and Monkhouse (1971) found increase in fibrinolytic activity after the use of oral contraceptives. However, Bick and Thompson (1972) suggested that this increase might be a compensatory protective mechanism and this simple assay might help to detect women who are prone to thrombo-embolic problems while using oral contraceptives.

Fall of fibrinolytic activity found in the present series would tend to theoretically emphasize that use of 'pill' is accompanied by the risk of thrombo-embolism. However, none of our cases had subsequent thrombo-embolic complications. Thus, fall of fibrinolytic activity is not critical enough to lead to clinical thrombo-embolism.

Significant fall of coagulation time was observed after 1, 3 and 9 months of the use of the 'pill'. Similar observations have been recorded by Margulis *et al* (1965) and Schubert *et al* (1968). Astedt (1972), on the other hand, has not found any appreciable change.

Prothrombin time has been reported to rise after the use of oral contraceptives (Rutherford *et al*, 1964; Ambrus *et al*, 1969). Similar observations have been recorded in the present series.

The rise of plasma fibrinogen level was significant after 3, 6 and 9 months of the use of 'pill'. Our results are comparable to those reported by Brakman and Astrup (1964) and Ambrus *et al* (1969). Some workers have not observed any significant change in plasma fibrinogen level after the administration of oral contraceptives (Brakman *et al*, 1970).

Various changes observed after 3, 6 and 9 months of the use of oral contraceptives were compared statistically with

those occurring during the first, second and third trimesters of pregnancy. Changes of prothrombin time were not significant ($p > 0.05$). Rise in plasma fibrinogen level was comparable in both conditions. Fall in fibrinolytic activity was more after 3 months of using the 'pill' as compared to that occurring during the first trimester of pregnancy. Fall in coagulation time occurred to a greater degree during pregnancy.

From our observations, it appears that the changes in fibrinolysis time, coagulation time and plasma fibrinogen level point towards a hypercoagulability state during pregnancy as well as after the use of oral contraceptives. However, in the light of clinical follow-up of our cases, it is concluded that these changes are not enough to manifest clinically as thromboembolic complications. It is also concluded that the risk of a state of hypercoagulability after the use of oral contraceptives is not greater than that during pregnancy.

Drill (1972) concluded that the incidence of superficial and deep vein thrombosis is not increased during pregnancy or when oral contraceptives are administered. However, Menon (1969) has observed that the changes indicating hypercoagulability of blood occur to a greater degree during pregnancy than after the use of oral contraceptives.

Summary

Effects of oral contraceptives and pregnancy on blood coagulation and fibrinolytic mechanisms have been investigated. The changes of fibrinolysis time, coagulation time and plasma fibrinogen level indicate a state of hypercoagulability during pregnancy as well as after the administration of oral contraceptives. However, clinical follow-up of these cases clearly shows that these changes are not critical enough to produce overt thromboembolism. It is also concluded that chances of developing a state of hypercoagulability after the use of oral contraceptives are not greattr than those during pregnancy.

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