

Fibrinogen Degradation Products and Coagulation Parameters in Women Taking Oral Contraceptives

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A study plan was designed to estimate the coagulation parameters like Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen level and fibrinogen degradation products (FDPs). In this study, coagulation parameters were compared in combined oral contraceptives (COCs) and control group. 40 subjects of COCs with 20 normal females without hormonal contraceptive were included in this study. Blood samples were collected for special coagulation parameters. FDPs were significantly elevated in subjects using COCs as compared to normal control. PT and APTT were shortened in COCs. Fibrinogen levels were increased significantly in COCs when compared with control groups.

Key words. Coagulation profile, fibrinogen degradation products:

The aim of contraception is to prevent fertilization of ovum or its implantation. It is estimated that 9 to 10 millions American women are presently on oral contraceptives^{1,2}. In one of the study, oral contraception is the safest known method of birth control provided the instructions are followed and 'the pill' is taken regularly. Most women find this an easy method. There is a good epidemiologic evidence of relationship between thrombotic events, both venous and arterial, and use of oral contraceptives^{3,4}.

It has been known since 1966 that oral contraceptives can increase the level of clotting factors. Post-menopausal hormone replacement studies with oestrogen have demonstrated the same effect on clotting factors, implying that it is the oestrogen rather than the progestogen component that is responsible for hypercoagulable state⁵. Jespersen et al (1990)⁶ noted decreased fibrinolytic activity in patients on oral contraceptives leading to hypercoagulable state.

There is enough literature on changes in blood coagulation in users of oral contraceptive and the induction of hypercoagulable state, which is defined as procoagulatory change in some coagulation tests (accelerated clotting in some coagulation tests or changes in clotting factors or inhibitors). There is a significant reduction in clotting times and activated partial thromboplastin time (APTT) after oral contraceptive use⁷. One of the studies showed a 50% increase of factor VII in women taking oestrogens and a fall in the relatively protective antithrombin III. Thus, the increase in factor VII would lead to a hypercoagulable state. The author also reported a raised level of fibrinogen in 'pill' users^{5,8,9}. In one of the study by Bonnar et al (1987)¹⁰, COCs affects blood clotting by increasing plasma fibrinogen and the activity of coagulation factors especially factors VII and X; anti-thrombin III is usually decreased. These changes create a state of hypercoagulability that appears to be counterbalanced by increased fibrinolytic activity. In one

study, factor VII levels increased sharply with oestrogen dosages, but increase was dose-related¹¹.

F VII activity was found to be increased during the treatment with low dose COCs with corresponding increase in fibrinolytic activity being reflected by higher levels of FDPs/D-dimers. In this study, there is balanced effect on the hemostatic system stimulating both procoagulatory and fibrinolytic activity^{12,13}.

Norris 1996¹⁴ described that F VII and X levels were significantly raised and there was also increase in fibrinogen level and FDPs with low dose COCs. Petersen and his colleagues in 1993¹⁵ studied that women taking low dose COCs had plasma levels of fibrinogen and F VII increased. Increased fibrinolytic activity was indicated by elevated levels of tissue plasminogen activators and reduced concentration of plasminogen activator inhibitors. There is increase in concentration of D-dimer and FDPs. Famodu et al in 1991¹⁶ studied the fibrinogen level in 100 women in COCs aged 17-46 years. The women on COCs had significantly higher plasma fibrinogen levels than control.

Methodology

A total of forty healthy females of child bearing age on oral contraceptive for the last (at least) three months were included in this study. Twenty age matched females, not taken contraceptives were also included as control subjects. Subjects were selected from Sir Ganga Ram Hospital, Services Hospital, Fatima Memorial Hospital and Lady Willington Hospital, Lahore.

Exclusion Criteria

Following women were not included in the study.

- Women with history of petichae or easy bruising before the start of oral contraceptives.
- Women with history of drug intake that is known to change the coagulation parameters.
- Women having past history of jaundice, diabetes mellitus, hypertension and nephrotic syndrome.

Grouping of the subjects

Group I

Twenty age-matched healthy females, not taking contraceptives were kept in this group. It is control group.

Group II

Forty patients using oral contraceptive for the last at least three months were included in this group. The oral contraceptive used by the group was "Lo-FEMENAL" which contains norgestrel 0.3 mg (Progestogen) with 0.03 mg ethinyl estradiol (oestrogen).

3.6ml of blood was mixed with 0.4 ml of 32 gm/l trisodium citrate for the estimation of prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen assay and Fibrinogen degradation products. Student's 't'-test and Chi-square test were used to analyze the results and data in this study.

Results

Out of 40 subjects studied in Group II 15% were in age group of 15-20 years, 72.5% were in the age group of 21-30 years and 12.5% were in the age group of 31-40 years. In group I (Control Group), 40% were in age group of 15-20 years, 55% of 21-30 years and 05% of 31-40 years (Table 1).

Table 1 Age wise distribution in subjects of Control Group (I) and Oral Contraceptive Group (II)

Age (Years)	Group I		Group II	
	No.	%age	No.	%age
15-20	08	40	06	15
21-30	11	55	29	72.5
31-40	01	5	05	12.5
Total Subjects	20	100	40	100

The mean prothrombin time (PT) in Control Group (I) was 13.7 ± 2.05 with a range of 10-17 second. In group II (Oral Contraceptives), the mean PT was 12.8 ± 1.50 with a range of 10-14 second. PT was significantly shortened in group-II (Oral Contraceptives) when compared with Control Group (Table 2)

Table 2 Distribution of PT, APPTT, TT and Fibrinogen in Group I and II

Parameters	Group I (Control)	Group II (Oral)	Statistical Analysis
PT	13.7 ± 2.05	12.8 ± 1.5	I Vs II **
APTT	33.7 ± 1.52	32.6 ± 1.92	I Vs II **
TT	12.6 ± 1.27	11.9 ± 1.81	I Vs II **
Fibrinogen	305.9 ± 45.99	347 ± 80.9	I Vs II **

Key: ** (p<0.05) significant.

The mean APTT in Control Group (I) was 33.7 ± 1.52 with a range of 30-37 seconds and the mean APTT in Oral Contraceptive group (II) was 32.6 ± 1.92 with a range of 28-35 seconds. APTT was shortened in group II (Oral Contraceptives) when compared with the Control Group and difference was found to be significant (p<0.05) statistically (Table 2)

The mean TT in Control Group (I) was 12.6 ± 1.27 with a range of 10-15 second and in oral contraceptive (II) group was 11.9 ± 1.81 with a range of 8-15 seconds. On statistical evaluation, TT in Group II (Oral Contraceptives) was shortened as compared with the Control group and difference was significant (P<0.05) statistically (Table 2).

The mean value of fibrinogen in Control Group (I) was 305.9 ± 45.99 with a range of 248-330 mg/dl. The fibrinogen level in group-II (Oral Group) was 347 ± 80.9 with a range of 248-591 mg/dl. The fibrinogen levels in Group II (Oral Contraceptives) were elevated as compared with control group and difference was found to be significant statistically (p<0.05).

Fibrinogen Degradation Products

In the present study, all control group subjects (100%) had FDP levels in the range of < 5ug/ml. In Group II (Oral Group), 19 out of 40 subjects (47.5%) had FDP levels of $>5 \leq 20$ $\mu\text{g/ml}$ and 15 out of 40 subjects (37.5%) had FDPs levels in the range of > 0 $\mu\text{g/ml}$ and 6 out of 40 (15%) had FDP levels in the range of < 5 $\mu\text{g/ml}$. The FDP level was found to be increased in subjects taking oral contraceptives (Group II) as compared with control Group (Group I) and the difference was statistically highly significant (p<0.01) (Table 3).

Table 3 Comparison of Fibrinogen Degradation Products (FDPs) in Cases of Oral Contraceptives and Control Subjects

FDPs (ug/ml)	Control Group (I)	Oral Contraceptives (II)
<5	20	06
>5≤20	00	19
>20	00	15
Total subjects	20	40

Statistical Analysis (Chi-square test) II Vs I (p<0.001)

Discussion

Prothrombin Time

PT was found to be significantly reduced (p<0.05) in the subjects on oral contraceptives when compared with controls. These results are consistent with the findings of many workers who also observed reduced PT in oral contraceptive users^{8, 17, 18}

Activated Partial Thromboplastin Time

APTT was found to be reduced significantly (p<0.05) in subjects on oral contraceptives when compared with the control subjects. This reduced APTT may be due to the hypercoagulable effects of oestrogen present in COCs. These findings were consistent with the results of other workers who also observed reduced APTT in users of COCs^{8, 17, 18}

Thrombin Time

TT was found to be significantly reduced (p<0.05) in subjects on oral contraceptives when compared with the

controls (Group I). These results were consistent with the study of other authors who observed reduced TT in these subjects^{16,19,20}

Fibrinogen Level

Fibrinogen level was found to be significantly increased ($p < 0.05$) in subjects on oral contraceptives (Group II) when compared with the controls (Group I). These results were consistent with the findings of many workers who also observed increased fibrinogen level in COCs users^{16,19,20}

Fibrinogen Degradation Products

In the present study, FDPs were found to be highly significantly increased ($p < 0.001$) in the subjects on oral groups (Group II) when compared with the controls (Group I). This increased level of FDPs may be due to enhanced fibrinolysis. These findings were consistent with the results of many investigators who observed increased levels of FDPs in women taking oral contraceptives as compared to control group^{13, 21, 22}

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