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Affect of Combined Oral Contraceptives on Routine Coagulation Parameters

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SUMMARY

The present study was designed to estimate the coagulation parameters like fibrinogen degradation products (FDPs), fibrinogen levels, thrombin time (TT), Prothrombin time (PT) and activated partial thromboplastin time (APTT). In this study, 40 subjects on combined oral contraceptives (COCs) with a contraceptive duration from 3-18 months and 20 normal females without hormonal contraceptives were included. Blood samples were collected for coagulation parameters in accordance with the standard protocol. FDPs and fibrinogen levels were significantly elevated whereas PT, APTT and TT were shortened in subjects using combined oral contraceptives (COCs) as compared to normal controls.

Key words: Coagulation parameters, Combined oral contraceptives.

INTRODUCTION

Barnes[1] described that 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. He also noted that thromboembolism, coronary thrombosis or a cerebral vascular accident are the most serious risks of use of oral contraceptives. There is a good epidemiologic evidence of relationship between thrombotic events, both venous and arterial, and use of oral contraceptives. Oodds[2] also described thrombosis as one of the major complications of oral contraceptive intake. The relative risk for all oral contraceptive users of 2.8 times than non-user rate was recorded.

Jespersen et al.[3] noted decreased fibrinolytic activity in patients on oral contraceptives leading to hypercoagulable state. Kunz et al4 has also reported that there is a vast body of literature on changes in blood coagulation in users of oral contraceptives 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). They found a significant reduction in clotting times and activated partial thromboplastin time after oral contraceptive use.

Kelleher[5] reported a 50% increase of factor Vllc in women taking oestrogens and a fail 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. It is generally accepted that these alterations are induced by the oestrogenic component and are dose related[6,7]. The proposed study is aimed at recording coagulation changes in women taking oral contraceptive and to compare the coagulation pattern in subjects not taking hormonal contraceptives.

Bonnar et al.[8], reported that 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. Studies show that coagulation effects depend on the dosage of oestrogen and type of progestogen used in COCs.

In another study, factor VII levels increased sharply with oestrogen dosages, but increase with 50

µg oral contraceptive was significantly higher than that occurring with 30 µg preparation. Similar results were noted with factor X. Levels of coagulation inhibitor antithrombin III decreased significantly in patients receiving 50 ug COCs.[9] Norris and Bonnar[10] observed that low dose COCs exerts a balanced effect on hemostatic system stimulating both procoagulatory and fibrinolytic activity as demonstrated by simultaneous rise in factor VII levels as well as increased fibrinolytic activity reflected by higher levels of FDPs/D-Dimers, in patients on combined oral contraceptives. Petersen[11] studied that women taking low dose COCs had increased plasma levels of fibrinogen and factor VII. 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.[12] showed that women on COCs had significantly higher plasma fibrinogen levels than controls, thus causing hyper-fibrinogenemia.

SUBJECTS AND METHODS

Forty healthy females of child bearing age on hormonal contraceptives for at least three preceding months were included in this study. Twenty, age matched females, not taking any contraceptives were included as controls.

Exclusion Criteria

Following women were not included in the study.

i. Women with history of patichae, or easy bruising before the start of oral contraceptives.
ii. Women with history of drug intake that is known to change the coagulation parameters.
iii. 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 contraceptives for at least three preceding months were included in this group. The oral contraceptive used by this group was "Lo-FEMENAL" which contains norgestrel 0.3 mg (Progestogen) with 0.03 mg ethinyl estradiol (oestrogen).

RESULTS

In group I (control group), 40% were in age group of 15-20 years, 55% of 21-30 years and 5% of 31-40 years. 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 (Table 1).

Table 1: Age-wise distribution in subjects of control group (I) and oral contraceptive group.

Age (Years)	Group I (Control)		Group II (Contraceptive)	
	No.	%	No.	%
15-20	8	40.0	6	15.0
21-30	11	55.0	29	72.5
31-40	1	5.0	5	12.5
Total	20	100.0	40	100.0

The mean prothrombin time in control group was 13.7±2.05 with a range of 10-17 seconds. In group II (oral contraceptives), the mean PT was 12.8±1.50 with a range of 10-14 seconds. PT was significantly shortened in group II (oral contraceptives) and difference was highly significant while comparing I vs II (Table 2).

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 significantly shortened in group II (oral contraceptives) when. compared with the control group.

The mean TT in control group (1) was 12.6±1.27 with a range of 10-15 seconds 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 was significantly shortened as compared with the control group.

Table 2: Distribution of PT, APTT, TT and fibrinogen in groups I and II.

Parameters	Group I (Control)	Group II (Contraceptive)	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**

**Highly significant.

The mean value of fibrinogen in control group (I) was 305.9:t45.99 with a range of 248-330 mg/dl. The fibrinogen level in group II was 347±80.9 with a range of 248-591 mg/dl. On statistical evaluation the fibrinogen levels in group II were significantly elevated as compared with group I.

Fibrinogen degradation products

In the present study, all control group subjects (100%) had FDP levels in the range of <5 pg/ml. In group II (oral group), 19 out of 40 subjects (47.5%) had FDP levels of >5 ≤20 µg/ml and 15 out of 40 subjects (37.5%) had FDPs levels in the range of >20 µg/ml where as 6 out of 40 (15%) had FDP levels in the range of <5 µg/ml which were normal. The FDP level was found to be increased in subjects taking oral contraceptives (group II) as compared with control group (Group I) (Table 3).

Table 3: Distribution of fibrinogen degradation products in cases of hormonal contraceptives and control subjects.

FDPs (µg/ml)	Group I (Control)	Group II (Oral contraceptives)
< 5	20	6
> 5 ≤ 20	0	19
> 20	20	15
Total	20	40

Statistical analysis (Chi-square test) II vs I (P<0.001)

DISCUSSION

Prothrombin time

In the present study, 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 other workers who observed lowering of PT in oral contraceptive users[6,14,15].

Activate" Partial Thromboplastin Time

In the present study, APTT was found to be significantly reduced (p<0.05) in subjects on oral contraceptives when compared with the control subjects (Table 2). 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 decreased APTT In users of COCs[6,14,15]

Thrombin Time

In this study, TT was found to be significantly reduced (p<0.05) in subjects on oral contraceptives when compared with the controls. These results were consistent with the study. of other authors who observed reduced TT in these subjects[13,16,17].

Fibrinogen Level

In the present study, fibrinogen level was found to be significantly increased (p<0.05) in subjects on oral contraceptives when compared with the controls. These results were consistent with the findings of many authors who observed increased fibrinogen level in COCs users[13,16,17].

Fibrinogen Degradation Products

In the present study, FDPs were found to be significantly increased (p<0.001) in the subjects on oral contraceptive when compared with the controls. These increased levels 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 COCs contraceptives as compared to control group[10,18-20].

CONCLUSIONS

The present study confirms that use of low dose COCs results in stimulating both procoagulatory and fibrinolytic activity. Increased procoagulant activity is demonstrated by shortening of PT, APTT and TT, as well as by increased levels of fibrinogen in patients using low dose COCs. On the other hand increased fibrinolytic activity is demonstrated by the increase in FDPs.

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