

EFFECTS OF ORAL CONTRACEPTIVES ON COAGULATING FACTORS

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Abstract — Thirty young, healthy, nonsmoking women (mean age approximately 28 years) taking low-dose oral contraceptive pills were recruited for the study of the effects of these pills on coagulating factors. Twenty subjects were taking LD pill (Ethinyl estradiol 0.03 mg, levonorgestrel 0.15 mg) and 10 others were taking Cilest (Ethinyl estradiol 0.035 mg, Norgestimate 0.25 mg) for six months. The control subjects did not receive any oral contraceptives or other medications. Our results showed that :

1. There is no significant difference between the effects of LD and Cilest (with a different progestin content) on coagulating factors.

2. No significant changes were observed between both LD users and controls in PT, APTT, and fibrinogen levels.

3. No significant changes were observed between both Cilest users and controls in PT, APTT, and fibrinogen levels.

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INTRODUCTION

Since the first report of a possible association between the use of combined oral contraceptives (OC_s) and thrombotic disease, the risk of cardiovascular complications, such as venous and arterial thrombosis and embolism, myocardial infarction, and cerebral thrombosis, has been under debate, and it must be concluded that the discussion has not reached a stage of final agreement. Several studies have suggested an increased risk of cardiovascular disease. However, these studies have been exposed to criticism, such as a lack of objective diagnosis and the involvement of additional risk factors, particularly smoking, age and obesity, which may account for a substantial portion of the observed cardiovascular complications. Several studies have provided evidence that the risk of cardiovascular event is related to the content of estrogen and progestogen. The strategy to reduce the side effects of OC_s has been the reducing dose of estrogen (1), and GO, OC_s containing 30µg of estrogen have been available. Also selective progestogens with a high affinity to the pituitary-ovarian axis, and reduced metabolic effects have been developed (2).

The thrombotic risk linked to oral contraceptive use is probably multifactorial, involving diverse alterations in hemostasis (3). Recent data imply that the plasma fibrinogen concentration is one of these factors. Abnormally high fibrinogen levels are associated with an

increased risk of myocardial infarction and/or stroke in the years to follow. This association is strong and independent of other, concomitant cardiovascular risk factors.

Therefore it is relevant to ask, what the effects of OC_s on fibrinogen are (4). The changes in various coagulation factors are related to the dose - dependent effect of estrogen, but the estrogen / progestogen ratio and the type of progestin also seems to be important (5). New progestines (e.g. norgestimate) exert less metabolic effects (2,6).

Variability between centres in the effects of OC_s on coagulation and fibrinolysis suggests that OC_s administration in different populations may not carry equal thrombotic risks (7). For example, there is some evidence that postoperative thrombosis may be less common in East Asian women. It is therefore important to examine the possibility that the adverse changes in the hemostatic system reported in the population of European origin following OC_s administration may not be relevant in other populations (7).

MATERIALS AND METHODS

Fifty healthy non smoking women (20 control, 20 LD users and 10 cilest users) between 18 and 35 years old were recruited for this study (8).

The oral contraceptive treatment was continued for at least six cycles and control group had not taken hormonal preparations for at least six months before the start of the study (4). Patients with diabetes mellitus, varicose veins, and hepatic, cardiac, or renal disease were excluded (1). Those who had, within the past two weeks, ingested medications known to interfere with hemostasis (ie, anti-platelet drugs, anticoagulants, aspirin (9), etc.) were also excluded (1); venous blood specimens were taken between days 15 and 26 of the last cycle.

The samples were collected in tubes containing 3.8% sodium citrate, were centrifuged immediately at 3500 rpm for 15 minutes. plasma was separated, and kept frozen at - 70°C until analysis (10).

The coagulation factors measured were Activated partial Thromboplastin time (APTT), prothrombin time

(PT) and fibrinogen amount. APTT and PT were determined according to the principles of routine techniques (3). Fibrinogen amount was determined by the clot weight method. All tests were carried out in department of physiology.

Neoplastine kit used for PT test and c.k. prest kit used for APTT test were obtained Diagnosticastgo (France).

Student t test was used to determine the level of significance of the observed changes within the groups.

Probability values < 0.05 were considered to be significant.

RESULTS

The following results were observed after oral contraceptive pills (oc₃) consumption:

1. There is not significant difference between the effects of LD and Cilest (with a different progestin content) on coagulating factors.
2. No significant changes were observed between both LD users and control on PT, APTT and fibrinogen levels.
3. No significant changes were observed between both Cilest users and control on PT, APTT and fibrinogen levels.

Results are summarized in table 1.

Table 1. Effects of Contraceptives on PT, APTT and Fibrinogen levels.

Test	Control n=20	LD users n=20	Cilest user n=10
PT (sec)	13±0.17	13.2±0.247	12.6±0.16
APTT (sec)	36.55±0.64	34.8±0.97	34.6±1.3
Fibrinogen (mg/dl)	297.3±12.1	282.7±10.3	281.4±18.5

PT (prothrombin Time), APTT (Activated partial thromboplastin Time)

DISCUSSION

There is still ongoing debate on whether OC₃ use induces the development of hypercoagulability or increases the risk of deep venous thrombosis, especially if the newer low - dose formulations are used (11).

However, oral contraceptive consumption may contribute to the cardiovascular disorder partly via elevated fibrinogen level (12).

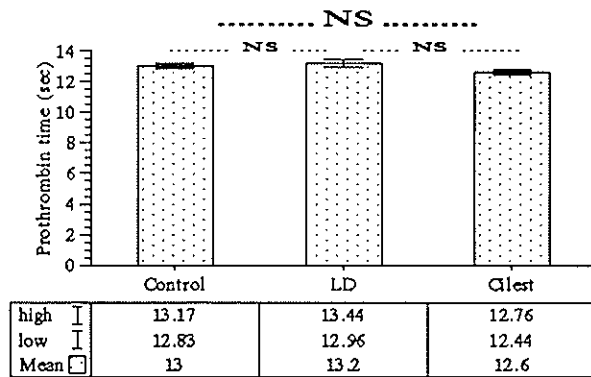


Fig.1. Changes of PT in three groups (LD users, cilest users and control group)

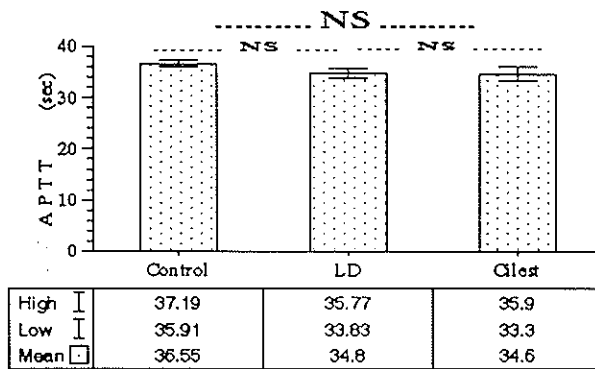


Fig.2. Changes of APTT in three groups (LD users, cilest users and control group)

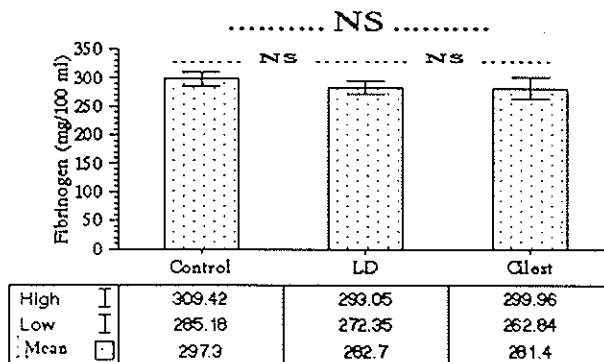


Fig.3. Changes of Fibrinogen in three groups (LD users, cilest users and control group)

In this study prothrombin time and Activated partial thromboplastin time, which measure the overall activity of the extrinsic and intrinsic coagulation pathways, (8) respectively, and fibrinogen levels showed no significant changes with both oral contraceptive formulations (with a different progestin content) and also showed no significant changes in oral contraceptive users (LD and Cilest) in comparison with control group. Therefore, low-dose oral contraceptive tablets (LD, Cilest) in Tehran (Iran) did not have any remarkable effect on coagulating factors mainly fibrinogen, and also, type of progestin (which is used in tablets) dose not have any significant effect in the various users.

Finally, it must be emphasised that the results reported here have been obtained in young healthy, non-smoking women.

In conclusion we suggest that family history of thromboembolism be included in the questions routinely asked before starting oral contraceptives, and antithrombin level be determined in select cases. It is to be hoped that future research will improve the ability to detect the small number who will suffer thromboembolism among the majority who use oral contraceptives without complication (1).

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