

References

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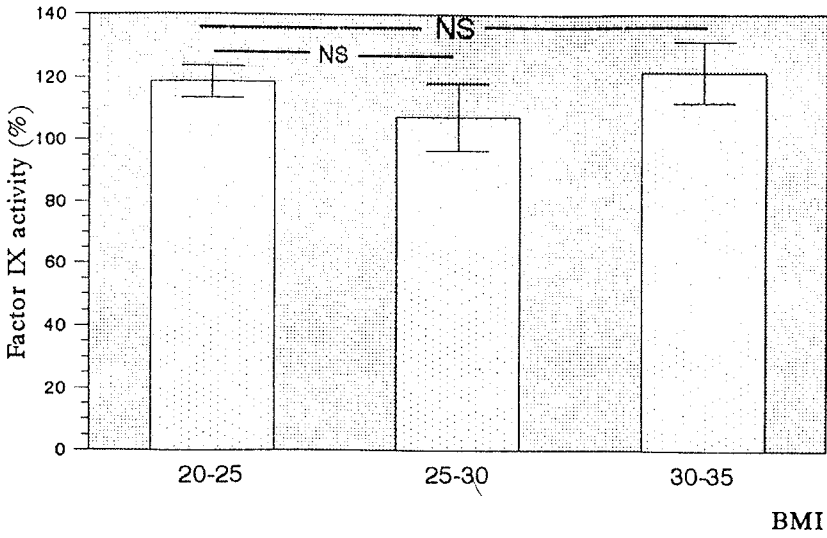


Fig 5 - Changes of factor IX activity (%) by different BMI in LD users.

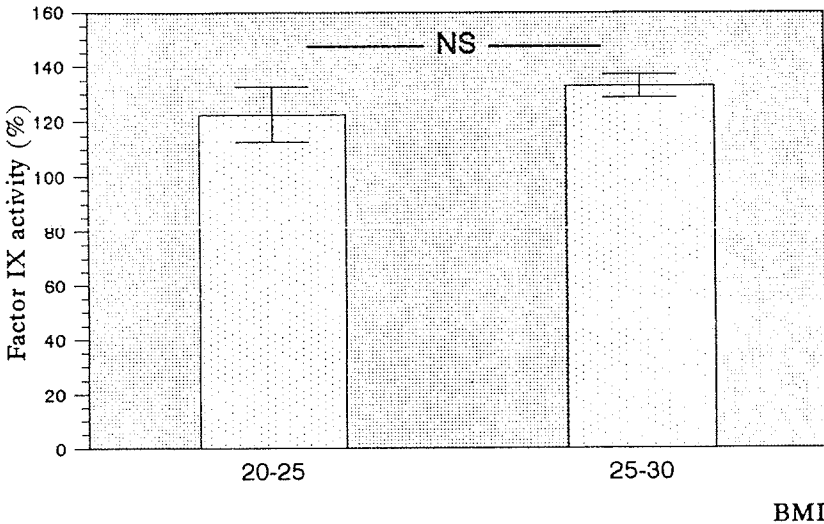


Fig 6 - Changes of factor IX activity (%) by different BMI in cilest users.

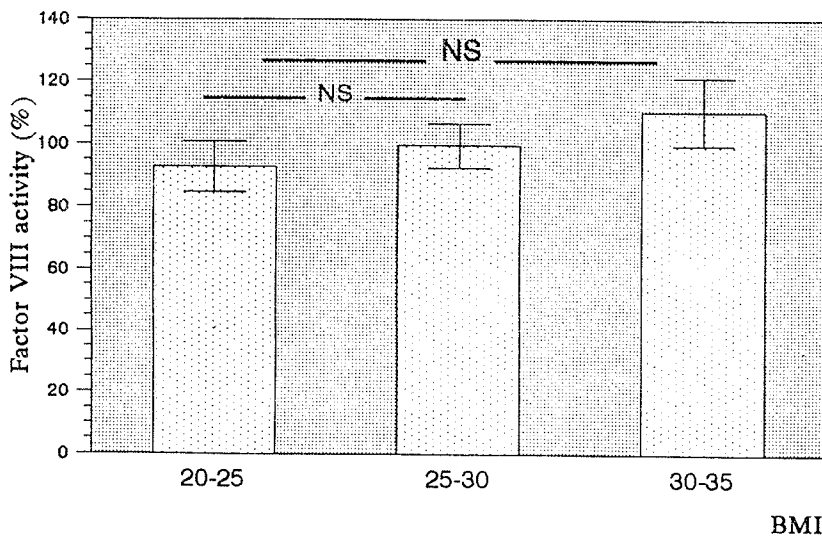


Fig 3- Change of factor VIII activity (%) by different BMI in LD users.

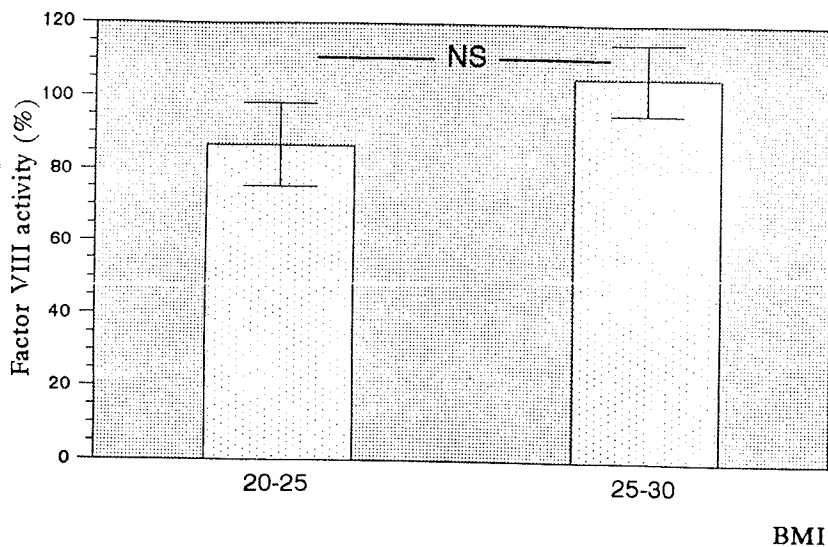


Fig 4- Changes of factor VIII activity (%) by different BMI in cilest users.

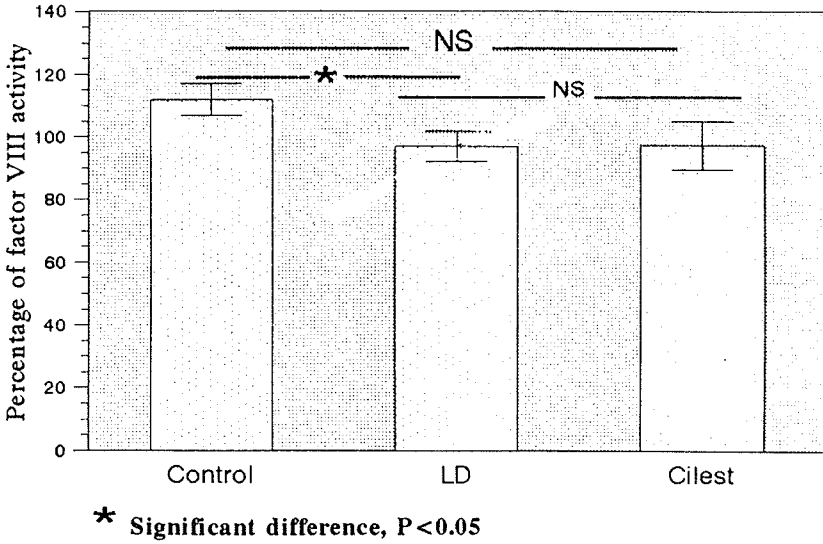


Fig 1- Change of factor VIII activity in three groups (LD users , cilest users and control group)

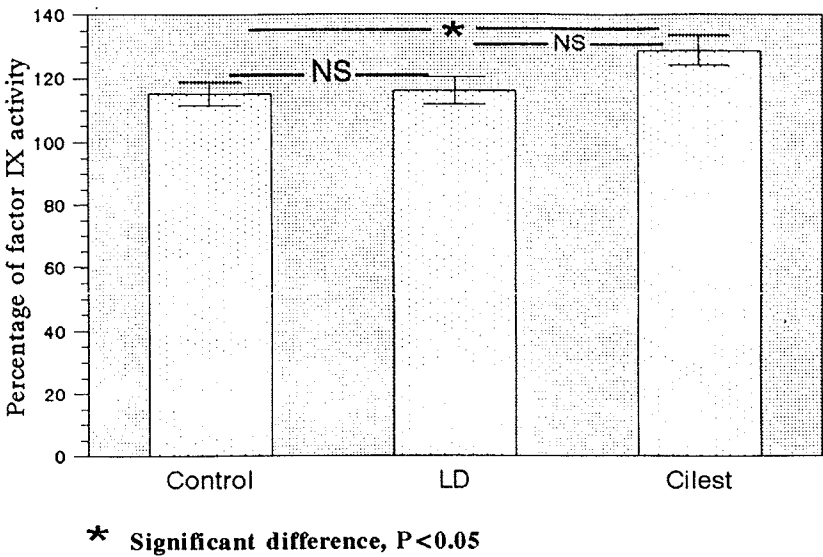


Fig 2- Changes of factor IX activity in three groups (LD users , cilest users and control group).

Table 3- Effect of oral contraceptives on factors VIII and IX in over weight and obese subjects in compare to normal weight.

BMI	LD users			cilset users	
	20-25 n= 9	25-30 n=6	30-35 n=4	20-25 n=4	25-30 n=6
	mean + SE	mean + SE	mean + SE	mean + SE	mean + SE
factor VIII (%)	92.78+ 7.95	99.6+ 7.02	110.37+ 10.75	86.5+ 11.5	105.0+ 9.8
factor IX (%)	118,66+ 5.1	107.5+ 10.76	121.75+ 9.6	122.5+ 10.1	133.0+ 4.22

Table 1- Classification of BMI

Classification	BMI
Under weight	< 20
Normal	20 - 25
Over weight	25 - 30
Obese	30 - 40
Severely obese	> 40

Table 2- Effects of oral contraceptives on factors VIII and IX.

Test	Control n= 20	LD users n= 20	cilest users n= 10
	Mean + SE	Mean + SE	Mean + SE
Factor VIII (%)	112.0 + 5.05	97.17+4.9*	97.6+7.67
Factor IX (%)	115.05 + 3.7	116.15 + 4.33	128.8 + 4.75*

* Significant difference from control group , $P < 0.05$.

iron deficiency anemia , benign breast disease , functional ovarian cysts , and endometrial and ovarian cancers. Although evidence of these protective effects is strong , some data regarding the health effects of oral contraceptives are difficult to interpret and contribute to ongoing controversies about potential health risks. Study finding and controversies about the relation between oral contraceptive use and both cardiovascular disease and cancers are most noteworthy, because these conditions are serious and potentially affect large numbers of women.

Most data for the relation between oral contraceptive use and the risk for cardiovascular disease are from studies conducted in the United States and Europe during the 1970s , of oral contraceptive preparations containing at least 50 μ g of estrogen.

Studies of oral contraceptive use and cardiovascular disease indicated that any harmful effects are limited to current users ; past users appear not to have any increased risk (4).

Epidemiological data support the notion that first generation high-dose oral contraceptives (containing > 80ug of estrogen) increased the incidence of thromboembolic events. The quantitative interpretation of these data is difficult because results were often confounded by life-style factors and inadequate diagnostic procedures. With the introduction of modern low-dose combination oral contraceptives , the incidence of thromboembolic events decreased markedly. Although all combined oral contraceptives induce statistically significant changes in hemostatic factors , these changes are generally within normal ranges , and their clinical significance is questionable (5). Obesity has no effect on factors VIII and IX in oc users.

In conclusion , it dose not appear that oral contraceptive use is associated with hyper coagulability. We suggest including family history of thromboembolism in the questions routinely asked before starting oral contraceptives , and obtaining antithrombin levels 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.

Factor VIII and IX activity were determined according to the principles of one stage clotting method.

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

Probability valuse <0.05 were considered to indicate significance.

Results

The following results were observed after oral contraceptive pills (OCP) consumption (table 2).

- 1- There is not a significant difference between the effects of LD and cilest (with a different progestin content) on factors VIII and IX (fig. 1 and fig. 2).
- 2- No significant changes observed between both cilest users and control on factor VIII but a significant increase ($P<0.05$) on factor IX activity was observed (fig. 1 and fig. 2).
- 3- No significant changes observed between both LD users and control on factor IX but a significant decrease ($P<0.05$) on factor VIII activity was observed (fig. 1 and fig. 2).

The effects of overweight and obesity on factors VIII and IX in oc users were as follows (table 3).

There is not a significant difference ($P<0.05$) between normal , overweight and obese subjects on factors VIII and IX in LD users and cilest users (fig 3,4,5,6).

Discussion

Millions of world women now use oral contraceptives and many millions more used them in the past. with so many women involved , it is imperative that the health risks and benefits of oral contraceptive use should be fully described.

The contraceptive benefit of oral contraceptive use is clear ; oral contraceptives are highly effective for prevention of pregnancy. This benefit translates into health benefits , particularly in developing countries , where increased health risks are associated with pregnancy and child bearing.

Noncontraceptive health benefits of oral contraceptive use are less easily summarized but well documented. Oral contraceptives protect against seven important conditions : ectopic pregnancy , pelvic inflammatory disease,

Despite an overall reduction of thrombotic events in users of low-dose oral contraceptives, recent epidemiologic data are consistent with an increased risk of deep venous thrombosis and pulmonary embolism in treated women. The thrombotic risk linked to oral contraceptive use is probably multifactorial, involving diverse alterations in hemostasis. It is generally accepted that these later alteration are induced by the estrogen component of oral contraceptives and are dose related (2).

Further observations, especially from the Royal College of General Practitioners study, implied that the progestin component could also be important, at least for arterial diseases. These observations enhanced the development of newer progestational agents, and subsequently, oc formulations containing desogestrel, gestodene and norgestimate were introduced (5).

Human factor VIII is a complex protein which possesses the procoagulant activity deficient in classic hemophilia (hemophilia A).

Factor VIII circulates with minimal coagulant activity. Trace amounts of thrombin or factor X_a increase the coagulant activity of factor VIII.

Factor VIII serves as a cofactor for the enzymatic cleavage of factor X to factor X_a by factor IX_a .

Activation of factor IX requires the presence of calcium ions, hence in cirtated plasma, the coagulation reactions donot proceed further than the activation of factor XI.

Activated factor IX forms a catalytic complex with factor VIII on a membrane surface, which efficiently converts factor X to its activated form (6):

$$\text{factor X (factor IXa):(factor VIII) + membranes + ca}^2 \xrightarrow{\hspace{1.5cm}} \text{Factor Xa.}$$

Materials and methods

Fifty healthy and nonsmoking woment (20 controls, 20 LD users and 10 cilest users) who were between 18 and 35 years old were enrolled in the study.

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.

Venous blood specimens were taken between days 15 and 26 of the cycle.

The samples were collected in tubes containing 3.8% sodium citrate, and they were centrifuged immediately at 3500 rpm for 15 minutes, plasma was separated and kept frozen at -70°C until analysis (3).

EFFECT OF ORAL CONTRACEPTIVES (LD AND CILEST) ON CLOTTING FACTORS VIII AND IX

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Key words: *Oral contraceptive, Factor VIII, factor IX*

Abstract

Based on epidemiologic data , women who take oral contraceptives seem to have an increased risk of developing thromboembolic disease. The thrombotic effects of oral contraceptive (oc) are probably mediated , at least partly , through their effects on the coagulation system. Plasma levels of several clotting factors have been shown to be elevated in oc users , and this increase is graduated according to the dose of estrogen. In this study fifty healthy and non smoking women , aged 18-35 years , were randomly assigned to treatment with 2 different ocs: a monophasic pill containing 30 µg of ethinyl estradiol plus 150µg levonorgestrel (LD) and a monophasic pill containing 35µg ethinylestradiol plus 250µg norgestimate (cilest).

Factor VIII plasma values were significantly decreased ($P<0.05$) only in women treated with the preparation LD , but the levels of factor VIII were not significantly different in the group treated with cilest.

Factor IX plasma values were significantly increased ($P<0.05$) only in women treated with the preparation cilest , but the levels of factor IX were not significantly different in the group treated with LD.

In LD and cilest users factors VIII and IX were not significantly changed ($P<0.05$) in overweight and obese subjects in comparison to normal weight.

Introduction

Soon after the introduction of the first generation of contraceptive pills, anecdotal reports of deep venous thrombosis (DVT) in pill users appeared in the literature. Observational studies corroborated these reports (5).

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