

## Effects of estrogens and progestagens on the primary variables of haemostasis

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### ABSTRACT

**Background:** The present study aims at determining the effect of two combined oral contraceptives on the primary variables of haemostasis in a group of healthy Albanian women.

**Methods:** In this study were included, 49 women between the ages of 24 and 51 years, twenty nine of them taking ethinylestradiol 30 µg and gestodene 75 µg and twenty of them taking ethinylestradiol 30 µg and levonorgestrel 75 µg for 1-2 months. The subjects had no history of thromboembolic disease. Plasma was used for measuring levels of PT, fibrinogen, factors V and VIII, before and after pill use. Collected data were analyzed using SPSS 20 software.

**Results:** Comparison of values of the parameters before and after treatment showed that concentrations of fibrinogen and factor VIII were significantly increased following treatment ( $p < 0.05$ ), while we noted no significant changes in the level of factor V. Prothrombin time and activated thromboplastin time were reduced during treatment ( $p > 0.05$ ).

**Conclusions:** The results show that changes in the haemostatic primary variables after combined oral contraceptive administration are significant which might increase the risk for thrombotic situations.

**Keywords:** Estrogens, Progestagens, Blood coagulation, Factor VIII, Factor V

### INTRODUCTION

The massive use of female hormones for birth control began in the 1960s with the availability of oral contraceptives. It is estimated that worldwide 100 million women use an oral contraceptive.<sup>1</sup> With such a large number of women taking OC, even the smallest increase in risk of side effects will affect the lives of many. Female hormones have a variety of side effects, of which thrombosis is the most frequent and most important.<sup>2</sup> Knowledge of such risks and efforts to reduce them are of crucial importance.

It is also known that the use of combined hormonal contraceptives (containing both estrogen and progestogen) is associated with an increased risk of venous thromboembolic events.<sup>1</sup>

The first thrombotic side effect of oral contraceptives was reported in 1961, when a nurse developed pulmonary embolism after starting an oral contraceptive containing 100 µg oestrogen (mestranol) and norethynodrel as progestogen.<sup>3</sup> For a long time, it was believed that oestrogens in postmenopausal hormone replacement therapy had no effect on thrombosis, or would even lower the risk, even though early studies in men for whom oestrogens were tried as treatment for coronary disease showed an increased risk of thrombosis.<sup>4</sup> It was later reported that oestrogens in hormone replacement therapy also increase the risk of venous thrombosis.<sup>5</sup>

Thrombotic risk was reduced when so-called low-dose oral contraceptives containing 50 µg or less of estradiol became available. However, a number of subsequent epidemiological studies<sup>6</sup> suggested that women who use

third generation pill containing the progestagens desogestrel (DSG) or gestodene (GSD) may have higher risk of venous thrombosis than women who use a second generation oral contraceptive (OC) containing levonorgestrel (LNG). The further increased thrombotic risk in third generation OC users was, however, questioned in later publications.<sup>7,8,9</sup> The discussion that followed was hampered by the fact that there was neither a good biological explanation for the thrombotic effect of the pill nor for the difference in risk between second and third generation oral contraceptives.<sup>10</sup>

The present study aimed at determining the effect of two combined oral contraceptives (containing ethinyl estradiol and levonorgestrel or gestodene) on five primary haemostatic variables in a group of healthy Albanian women.

## METHODS

### Study design

The investigation was conducted at Ana Diagnostic Center in Tirana, Albania. All participants signed an informed consent form before were included in the study. Healthy women requesting contraception were included and followed up for two months, while smokers and those with contraindications to combined oral contraceptives (COCs) were not followed up for this study. Twenty women were instructed to use COC with 30 µg EE and 75 µg GSD and 16 were instructed to use COC with 30 µg EE and 75 µg LNG, initiating pill intake on the first day of the cycle. Clinical and laboratory assessments were carried out prior to initiation of medication and after 2 months of COC use.

### Laboratory methods

All participants were submitted to a blood collection to perform the APTT, PT, fibrinogen, factor V and factor VIII laboratory test. Blood samples were centrifuged at 1500 rev/min for 15 min to extract plasma. APTT, PT, fibrinogen, factor V and factor VIII were measured using coagulometry (BFT II analyzer, kits and reagents from Siemens Diagnostic Healthcare, Marburg, Germany).

## Statistical analysis

Student's *t*-test for paired samples was used for numerical variables with normal distribution to compare values of the coagulation factors at two time intervals (pre-treatment and after 2 months of COC use). Data are given as mean and SD,  $p < 0.05$  was considered statistically significant. SPSS 20 software was used for running all statistical calculations.

## RESULTS

Mean and SD of the parameters before and after treatment with COCs are reported in Table 1. Paired samples T-test showed that concentrations of fibrinogen and factor VIII were significantly higher after two months of treatment with 30 µg EE/75 µg GSD than prior to treatment. Similar results were obtained with treatment with 30 µg EE/75 µg LNG in the level of FVIII, while the increasing of fibrinogen was not significant ( $p > 0.05$ ). Prothrombin time (PT), activated partial thromboplastin time (APTT) and FV were significantly reduced in women taking 30 µg EE/75 µg GSD, though there was no significant change in this variables in women taking 30 µg EE/75 µg LNG (Table 1).

Statistical analysis indicated difference in the effect of different COCs on the levels of APTT, fibrinogen, PT, FV and the same effect on F VIII level.

## DISCUSSION

In the present study, users of third generation combined oral contraceptives showed significant changes in the primary haemostatic variables. The changes were within the normal range and are not associated with an increase in VTE risk. The results found a large effect of oestrogen and progestogen on some of the variables. A greater change in FV, FVIII, APTT, fibrinogen and PT was observed in the GSD group compared with the LNG group, but we must also take in account that the baseline for these variables was different between groups. In two other studies<sup>8,11</sup> comparing COCs containing GSD with those containing LNG, there were no significant changes in PT between the two groups.

**Table 1: Effects of COCs on the primary variables of haemostasis.**

Parameters	30 EE/ 75 GSD			30 EE/ 75 LNG		
	Baseline	After COC use	p value	Baseline	After COC use	p value
PT (s)	11.5 ± 0.4	10.3 ± 0.6	0.000	11.3 ± 0.9	11.9 ± 1.4	0.165
APTT (s)	31.4 ± 4.4	27.6 ± 1.5	0.000	28.7 ± 1.8	28.6 ± 2.5	0.867
FV (%)	110.3 ± 9.3	98.6 ± 11.6	0.000	86.7 ± 8.1	86.5 ± 10.8	0.196
FVIII (%)	107.1 ± 8.1	115.03 ± 14.6	0.01	86.6 ± 9.8	102.8 ± 10.0	0.000
Fibrinogen (g/l)	2.8 ± 0.2	3.5 ± 0.3	0.000	2.7 ± 0.77	3.2 ± 0.64	0.06

Factor VIII was increased after two months of treatment with both COCs. High factor VIII, and fibrinogen levels have been found to be related with a thrombophilic situation.<sup>12,13,14</sup> Nevertheless, it is important to note that changes observed in coagulation parameters during the use of COCs by healthy women cannot explain the increased risk of thromboembolic disease; hence caution should be taken in interpreting results in aspects of clinical trial.

## CONCLUSION

In conclusion, the use of a COCs containing 30 µg EE/75 µg GSD and 30 µg EE/75 µg LNG for a period of two months in healthy women with no associated risk factors caused significant changes in the primary haemostatic parameters suggestive of a higher prothrombotic risk. The clinical significance of these findings should be established in a larger study with associated risk factors, such as smoking, and over a longer period of COC use.

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