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Research Article

Effect of Four Hormonal Contraceptives on Platelet Count and Coagulation Parameters Under Real Conditions of Use After 6 Months of Treatment

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Abstract

Objectives

This study was designed for the purpose of evaluating the impact on platelet count, platelet distribution width, prothrombin activity, partial thromboplastin time, INR and fibrinogen concentration, after six months of treatment with four hormonal contraceptives by different administration routes, oral (2mg ACM/ 0.03mg EE and 3mg DRSP/ 0.03mg EE), transdermal (150mcg NGMN/ 0.02mg EE) and vaginal (0.015mg EE/ 120mcg ENG).

Study design

It is an observational, prospective, randomised, concurrent study in women with child-bearing potential (18-45 years) in daily clinical practice who visit the family planning clinic to ask for a hormonal contraceptive and meet all the study inclusion criteria, with no contraindicated use of hormonal contraceptive methods.

Materials and methods

328 women were included by a block randomisation system and were distributed as follows: 64 were assigned to the group on transdermal norelgestromin, 62 to the group on transvaginal release etonogestrel, 68 to the group on oral chlormadinone, 70 received oral drospirenone and 64 to a control group receiving no treatment. Laboratory tests were performed to measure all the abovementioned coagulation parameters before starting treatment and six months after receiving steroid hormones, except for the control group which was not administered any drug.

Results

A statistically significant increase was seen in platelet count and prothrombin activity in the group treated with norelgestromin. Partial thromboplastin time decreased on a statistically significant basis in all treatment groups and increased in the control group. The INR (International Normalised Ratio) increased on a statistically significant basis in the groups receiving norelgestromin and chlormadinone. Fibrinogen levels increased on a statistically significant basis in all treatment groups.

Keywords: Hormonal contraceptives; Lipid prolife; Risk cardiovascular disease

Introduction

The association between the use of Hormonal Contraceptives (HC) and the increased risk of cardiovascular diseases, such as Venous Thromboembolism (VTE) has been shown in several studies [1,2], evidencing a direct relationship between this risk and the dose of the oestrogen component of the formulation [3,4].

In this regard, in the past decades special attention has been paid to the influence of plasma lipoproteins as a cardiovascular risk factor, so that all issues related to an unfavourable lipid profile were associated with an increased cardiovascular risk.

Engel et al. [5], performed a coronary angiography in women suffering a myocardial infarction and found that 36% of those using oral contraceptives had diffuse atherosclerosis, while 79% of those not receiving them also had it and assured that in women with myocardial infarction and receiving oral contraceptives the infarction had no atherosclerotic but a thrombotic origin. This viewpoint supports the hypothesis of cardioprotection of oral contraceptives of microdoses including last-generation gestagens, as stated by Lobo et al. [6].

This study used low-dose HC, changing the gestagen component and the administration route authorised in recent years in the Spanish market. Therefore, the following HC combinations were administered for 6 months:

- **Transdermal route** (weekly administration): A Transdermal Release System (TRS) containing 6 mg of norelgestromin (NGMN)/ 0.600mg of Ethinyloestradiol (EE) was used, administering daily 0.203mg NGMN / 0.020mg EE.
- **Vaginal route:** A Vaginal Release System (VRS) was used that contains 11.7mg of Etonogestrel (ENG) and 2.7mg of EE. The ring releases by passive diffusion an average amount of 0.012mg

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of ENG and 0.015mg of EE, respectively, every 24 hours for a period of 3 months.

- **Oral route:**

Combined HC containing 2mg of Chlormadinone acetate (CMA) and 0.030mg of EE.

HC combined with 3mg of Drospirenone (DRSP) and 0.030mg of EE.

Methods

Study design

The study was performed following carefully the recommendations of the Declaration of Helsinki (Hong Kong, 1989) and the European Good Clinical Practice guidelines, so that all participants were duly informed in writing and gave their consent before starting the study.

The contraceptive was administered on the first day of the next menstruation and each patient was informed individually of the adequate dosage schedule of the HC included in the study.

The study was performed at the gynaecology clinic of the Municipal Health Centre of Vicalvaro, Madrid (Spain) between the months of October 2007 and May 2008.

It included women with child-bearing potential (18-45 years), with no contraindicated prescription of a combined hormonal contraceptive, not planning to get pregnant during the study (6 months) and visiting the gynaecology clinic to ask for a hormonal contraceptive method in the case of patients of the treatment groups, or completing a routine gynaecology review and not using any hormonal contraceptive method in the 6 months prior to the start of the study (control group).

The exclusion criteria applied to the study included contraindications in using HC, age under 18 years or older than 45 years, women potentially wishing to get pregnant within less than 8 months, women not agreeing to undergo clinical and laboratory controls within the timelines established in the study design and women reporting a history of non compliance with the established dosage schedule of contraceptives.

The study was planned with a duration of 6 months, during which 2 visits were completed: baseline and final visit.

The following procedures were scheduled at the baseline visit: clinical history, cervicovaginal smear, transvaginal ultrasonography, verification of normal laboratory ranges for: lipid profile and blood biochemistry; blood pressure, height and weight measurement and calculation of Body Mass Index (BMI).

After 6 months of treatment, a second visit was scheduled for evaluating the same parameters as at the baseline visit, also including treatment compliance and potential adverse events resulting of the use of HC.

Laboratory measurements

The blood samples were obtained by venous puncture. About 12ml of blood were taken, that was distributed as follows: 3ml of blood in an 8% EDTA 0.05ml glass tube for haematology and 4ml in a glass tube without anticoagulant for biochemistry. For haematology tests a Coulter autoanalyser was used and for the biochemistry tests, a Siemens ADVIA® 1650 Chemistry System analyser.

The reference controls for the different laboratory measurements used the controls Lyphochek® and Assayed Chemistry Control (Biorad).

The specific laboratory measurements performed on coagulation parameters were: Platelet count, platelet distribution width, prothrombin activity, partial thromboplastin time, INR and fibrinogen (g/dL).

Statistical analysis

All parameters are summarised with their respective descriptive statistics.

The comparisons of the biochemical parameters were performed by the Student's T test and the single factor Anova test. For the statistical data analysis the statistical package SPSS v 15.0 was used.

A value of $p<0.05$ was considered to be statistically significant.

Results

Distribution of the study participants

A total of 328 women with child-bearing potential were included and randomised into the following groups: EE/NGMN (n=64); EE/ENG (n=62); EE/ACM (n=68); EE/DRSP (n=70); Control (n=64).

No discontinuations due to adverse events occurred during the 6 months of the study.

Baseline characteristics

The baseline demographic data included (Table 1) age, weight, height, BMI and age at the first menstruation (menarche), with no significant differences in the baseline demographic data when performing the single factor Anova test between the different study groups.

	EE/NGMN (n=64)	EE/ENG (n=62)	EE/ACM (n=68)	EE/DRSP (n=70)	Control (n=64)
Age (years)	28.00±1.54	28.77±1.66	29.79±1.75	28.51±1.47	33.66±1.47
Weight (kg)	62.38±3.29	60.14±3.03	60.81±1.34	61.36±1.97	64.00±2.95
Height (cm)	161.65±2.03	161.12±1.22	161.44±1.61	162.26±6.04	161.62±1.44
BMI	23.31±0.95	22.67±0.99	23.02±0.65	23.14±0.76	24.13±0.99
Menarche (years)	12.34±0.32	12.77±0.41	12.26±0.37	12.66±0.25	12.66±0.36

Table 1: Baseline demographic data.

The results obtained in our study show that very few changes are identified in platelet count and they are not clinically significant (Figure 1). Only the group on norelgestromin showed a statistically significant increase and levels remained within normal ranges. This is consistent with other studies on the matter that have shown slight platelet hyperactivity and no increase in platelet released products, such as B-thrombomodulin and platelet factor IV.

With regard to prothrombin activity, which evaluates the extrinsic, common coagulation pathway, the result obtained was a minor increase in all treatment groups, with the levels being within normal ranges and with no clinical or statistical significance (Figure 2). This

parameter is generally used to monitor the haemostatic system when oral anticoagulants are used.

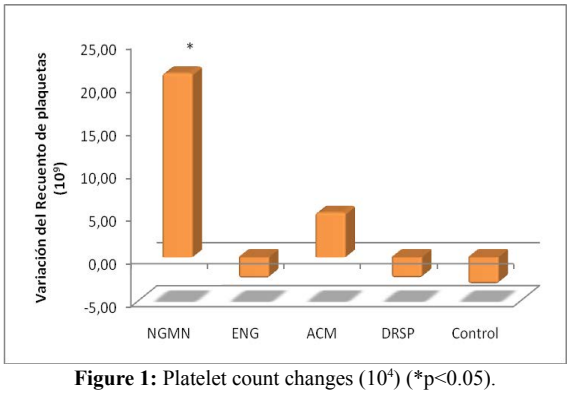

Figure 1: Platelet count changes (10^4) (*p<0.05).

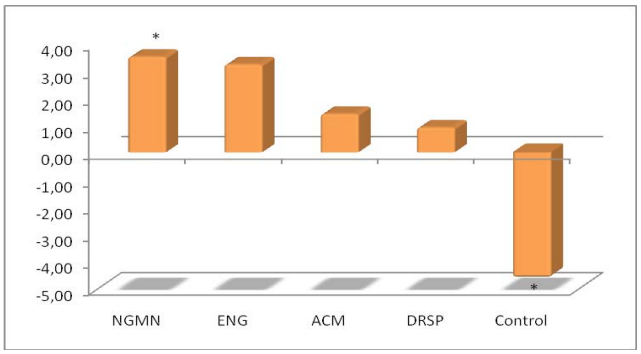

Figure 2: Changes in prothrombin activity (%) (*p<0.05).

With regard to partial thromboplastin time (Figure 3), also called kaolin cephalin time, with a value dependent on coagulation factor VIII concentration and useful in the assessment of the intrinsic pathway, we found a statistically significant reduction in all treatment groups and a minor change in the control group. Despite the results obtained, the levels were within normal ranges.

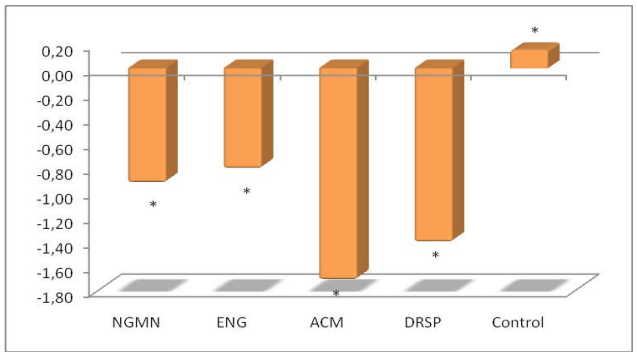

Figure 3: Changes in aPTT (s) (*p<0.05).

With regard to the INR value (International Normalised Ratio), which is a standard form in the assessment of prothrombin time, the results evidence minor changes in this parameter, despite finding statistically significant differences in the norelgestromin and chlormadinone groups.

Once the results obtained were analysed for fibrinogen values (Figure 4), a statistically significant increase was seen in all treatment groups, with minor differences between them.

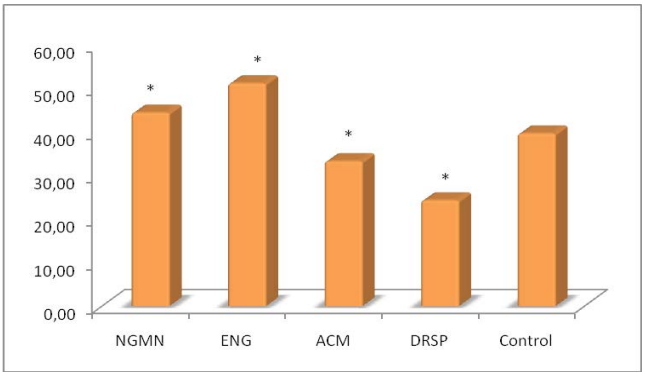

Figure 4: Changes in fibrinogen concentration (mg/dL) (* p<0.05).

The changes in the coagulation parameters can exclude the influence of smoking, given the homogeneity of the percentages of female smokers in the different treatment groups (Table 2).

Treatment Groups			Frequency	Percentage
EE/NGMN	Valid	NO	44	688
		SI	20	313
		Total	64	1,000
EE/ENG	Valid	NO	46	742
		SI	16	258
		Total	62	1,000
EEIACM	Valid	NO	46	676
		SI	22	324
		Total	68	1,000
EE/DRSP	Valid	NO	52	743
		SI	18	257
		Total	70	1,000
CONTROL	Valid	NO	46	719
		SI	18	281
		Total	64	1,000

Table 2: Smoker.

Overall for the parameters tested in the haemostatic system study, despite the differences found after administration of hormonal preparations for six months, the changes are within the interindividual coefficient of variation.

Discussion

Contraception is not a modern practice. The efforts to limit reproduction are as old as couples. Contraceptives are one of the synthetic substances most commonly used all over the world for preventing pregnancy, though they are not free from risks and require adequate medical assessment before starting administration.

Combined hormonal contraceptives contain two substances, independently from the administration route used. A non-natural synthetic oestrogen, the most common being ethinyloestradiol. The metabolism of this compound changes on an individual basis and among the different populations In fact, with the same doses the positive or negative effects can be highly variable [7-9]. Throughout the extensive experienced obtained with these compounds, high significance has been attached to the dose of the oestrogen component and its relationship with unwanted side effects, such as thromboembolism and circulatory problems [7,10,11].

The second component is gestagen or progestagen. This compound has changed markedly in the past 20 years, as new products have been obtained, with lower doses and a significant reduction of side effects, such as androgen signs and lipid profile changes [12-15].

Conclusion

Given the data obtained, an increase within normal ranges is seen in the plasma concentration of fibrinogen and prothrombin activity in all women receiving steroid hormones. The higher increase in the platelet count corresponded to the group treated with the ethinyloestradiol and norelgestromin transdermal administration formulation. Furthermore, except for the control group, a reduction was seen in INR and a PTT, regardless of the administration route and gestagen used, with values within normal ranges.

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