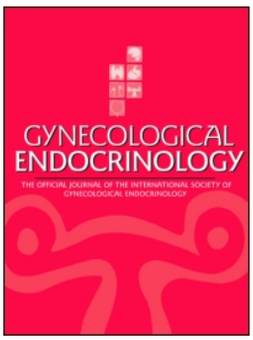

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DROSPIRENONE ONLY PILL AND HEMOSTASIS

Drospirenone as estrogen-free pill and hemostasis: coagulatory study results comparing a novel 4 mg formulation in a 24 + 4 cycle with desogestrel 75 μg per day

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Abstract

Introduction: A novel estrogen free contraceptive pill, with drospirenone 4 mg in a dosing regimen of 24 + 4, has been developed with a pearl-index of 0.51 (95% CI 0.1054; 1.4922). The aim of the following study was to determine if 4 mg DRSP has an impact on coagulation factors and thrombotic risks in comparison with desogestrel 75 μg.

Patients and methods: Thirty-nine patients received 4 mg DRSP 24 + 4 d and 29 desogestrel 75 μg per day continuously during nine complete cycles. Following hemostatic parameters were evaluated: Apc resistance, Antithrombin III, Protein C reactivity, Factor VII, Factor VIII, and D-Dimer.

Results: Factor VII decreased from 1.123 to 1.066 in the DRSP group and from 1.241 to 1.034 in the desogestrel group ($p = 0.0088$). The difference in change of mean Protein C activity from baseline to endpoint was −0.0332 in the DRSP versus −0.157 in the desogestrel group ($p = 0.0249$). D-Dimer values dropped in the DRSP group from baseline values of 264.9–215.0 ng/mL, whereas in the desogestrel group there was a rise from 201.4 ng/mL to 281.5 ng/mL.

Discussion: DRSP 4 mg was not associated with any meaningful changes on hemostatic parameters, indicating a lack of effect on hemostasis

Keywords

Hormonal contraception, ovary, uterus

History

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Introduction

Contraceptive pills were first introduced in the early 1950s. The first combined contraceptive pill contained the progestogen norethinodrel and high doses of estrogens (mestranol). Ethinylestradiol (EE)-containing CHCs were introduced in the 1960s with also a high dose of estrogen (up to 150 μg).

Several studies have shown that the use of these preparations was associated with an increased risk of venous thromboembolism [1] dependent on the dose of the estrogen component [2]. Subsequent studies showed that the risk was significantly reduced by lowering the dose of estrogen and this resulted in the introduction of newer preparations containing <50 μg EE [3–5]. The characteristics of the progestogen, when used in combination with EE, may also have an influence on the risk of thromboembolism [6]. In particular, some factors may play an important role in this respect such as the type and dose of estrogen with which it is combined; the route of admission; the dose of progestin; the duration of treatment and type of progestin [7].

Ethinyl estradiol has, due to its action in the liver, a procoagulatory effect by enhancing the factors responsible for coagulation and reducing the fibrinolytic factors. It is supposed that estradiol or estradiol valerate do not have such impact on the liver due to faster metabolization than ethinyl estradiol. Estradiol is metabolized in the liver to estrone and in turn estrone is converted into estrone sulfate, so that a significant lower biological activity is observed in comparison to ethinyl estradiol [8].

As Winkler [9] has shown, estrogens modify the dynamic balance of hemostasis by enhancing the coagulatory factors (e.g. Factor VII) and the anti-fibrinolytic factors (e.g. PAI-1). The amount of D-Dimers rise up consecutively due to the higher content of fibrin and its degenerated products in the blood.

This balance is also influenced by the amount of the ethinyl estradiol concentration that activates the coagulatory site and the dose of progestogen that activates more or less the anti fibrinolytic factors as e.g. PAI-1 [9].

On the contrary, progestogens per se do not increase the rate of thrombotic events with the exception of progestogens with a glucocorticoid partial activity [7].

The progestogen tree (see Figure 1) depicts the different partial effects of the different progestogens. Those as e.g. MPA, which has a partial glucocorticoid side effect, are associated with a higher rate of pro-coagulatory action due to the fact that they regulate the thrombin receptor and stimulate the procoagulatory activity at the vessel wall level.

As published by Schindler 2003, POP containing the progestogens chlormadinone acetate, megestrol acetate, norethisterone, and ethynodiol did not cause any significant changes in fibrinogen, factor II, V, VII, VIII or IX, AT-III, coagulation time, apt,

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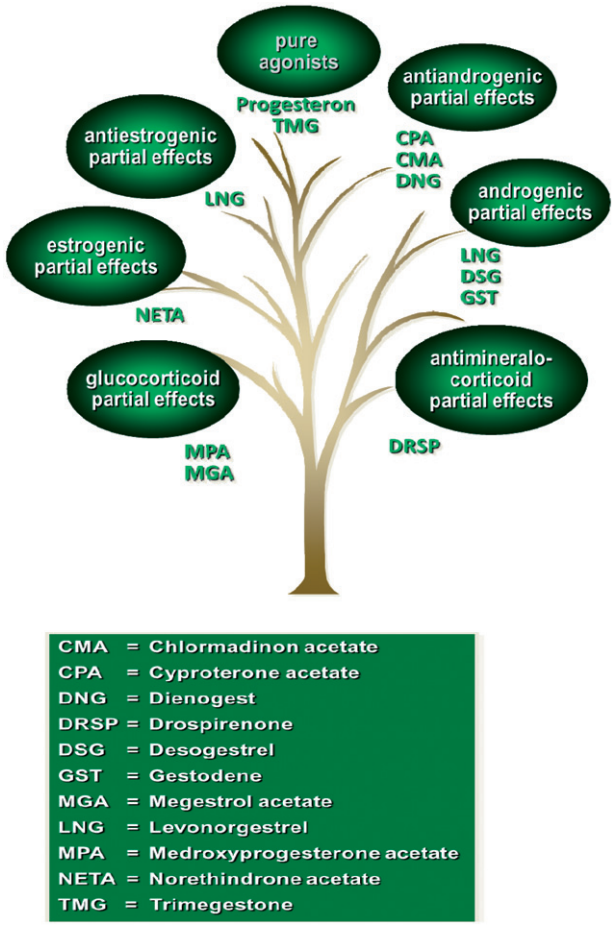

Figure 1. The progestin tree. Modified from HPG Schneider [15].

thrombocyte aggregation, plasminogen, a-2-microglobulin, a-1-antitrypsin, or fibrinolytic activity.

Desogestrel 75 µg and levonorgestrel 0.03 mg per day were associated with a reduced coagulatory activity, as evidenced by reduced factor VII activity and reduced plasma concentration of prothrombin fragment 1 + 2 [7].

First studies with drospirenone (DRSP)

A novel drospirenone (DRSP) only pill was developed to improve compliance and side effects. DRSP is a unique progestin derived from spirolactone with anti-mineralocorticoid and anti-androgenic properties. The 4 mg dose of DRSP was selected after completion of PK/PD studies. Multiple dose exposure of DRSP 4 mg demonstrated a lower exposure of DRSP compared with 3 mg/20 mg ethinyl estradiol and additional testing with DRSP 4 mg demonstrated inhibition of ovulation with DRSP 4 mg similar to that of desogestrel [10].

In a recently published study, the pearl-index of 4 mg DRSP in a regime of a daily use for 24 d followed by a placebo for 4 d was 0.51 (95% CI 0.1054; 1.4922). No reports of deep vein thrombosis, pulmonary embolism, or hyperkalemia were documented [11].

The aim of this comparative study versus desogestrel 75 µg was to determine if 4 mg DRSP in this new formulation and has an impact on coagulation factors and possible thrombotic risks from a hemostatic point of view

Patients and methods

Thirty-nine patients received 4 mg drospirenone in a regime intake of 24 d followed by four placebos and 29 patients desogestrel 75 µg per day as a comparative group continuously for a period of time of nine complete cycles. Laboratory data for the following hemostatic parameters were evaluated: Apc resistance, Antithrombin III, D-Dimer, Clotting factor VII, Clotting factor VIII, and Protein C reactivity. Data were evaluated after randomization before starting the intake and after 9 months of treatment and the values compared using a 2-sample *t* test.

Results

At baseline mean (SD), values of clotting factor VII were lower in the DRSP group (1.123 (0.2486 SD)) than in the group receiving desogestrel (1.241 (0.2607 SD)). At endpoint, the mean values of factor VII were comparable between the groups, but the change from baseline to endpoint was more pronounced in the DRSP group leading to the statistically significant difference ($p = 0.0088$, 2-sample *t* test) between the groups.

Mean protein C activity in the DRSP group at baseline was also lower than in the desogestrel group (1.140 (0.2052 SD)) versus (1.293 (0.2447 SD)); $p = 0.0069$, 2-sample *t* test. An identical change was found for the endpoint values (1.108 (0.1688 SD) for DRSP) versus (1.136 (0.2230 SD) for desogestrel). The difference in change of mean Protein C activity from baseline to endpoint was −0.0332 in the DRSP versus −0.157 in the desogestrel group; $p = 0.0249$, 2-sample *t* test. The differences in change of clotting factor VII and Protein C activity during the trial may be attributed to the baseline level differences (Figure 2).

A relevant reduction in the amount of D-Dimer could be observed in the DRSP group. From baseline values of 264.9 ng/mL, they dropped to 215.0 ng/mL whereas in the desogestrel group, there was a rise from 201.4 ng/mL to 281.5 ng/mL. This shows that DRSP lowers the production of fibrin products so that it has no coagulatory effects. The differences in the analyzed other parameters (APC resistance, ATIII activity and clotting factor VIII) were statistically not significant before and after the treatment (Table 1).

Discussion

It is currently well established that the estrogens in combined hormonal contraceptives are the main responsibles for the elevated risk of thromboembolic events. Epidemiological studies have shown that also the progestogen component, when used in combination with estrogens, may be involved in the etiology of venous and arterial diseases. This reflects an influence of progestogens on synthesis, release, and activation of pro-and anticoagulatory and fibrinolytic factors on the function of platelets and endothelium and possibly on smooth muscle cells [7].

The use of combined contraceptives results in an acceleration of coagulation and fibrinolysis as demonstrated by Kuhl [12], Winkler [9], and Schindler [7] by an increase of various markers of hemostasis and fibrin turnover.

This is induced by the marked action of ethinyl estradiol on hepatic and vascular function as also documented by the rise of SHBG. Progestins with pronounced androgenic properties, e.g. levonorgestrel may counteract the estrogen induced changes in the hepatic synthesis of hematological factors unlike other progestogens with anti-androgenetic properties or with neutral androgenetic properties may not.

As shown before by Schindler [7], desogestrel or levonorgestrel used as a POP has no effect on the hemostatic system and they showed an overall potentially favorable effect on hemostasis. Hemostatic markers are not the only parameters that influence the occurrence of thrombotic events, but they represent a very important component that influences these clinical events. For any 10 IU/dl increment of factor VIII, the risk for a single or recurrent episode of venous thrombosis increases by 10% and 24%, respectively [13].

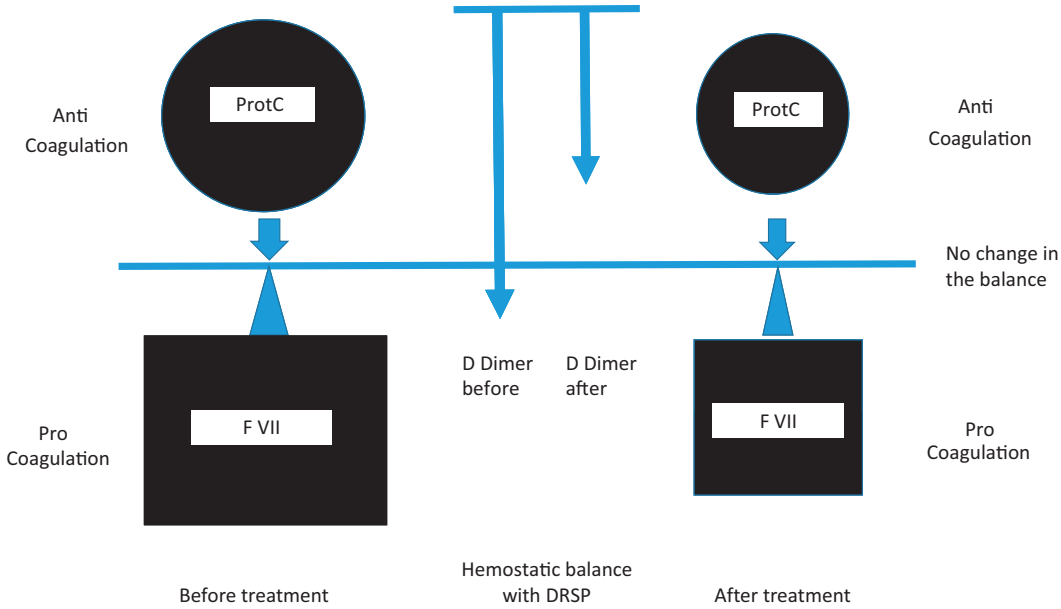

Figure 2. Balance of hemostasis after treatment with 4 mg drospirenone (DRSP).

Table 1. Development of hemostatic factors under treatment with 4 mg drospirenone (DRSP) in a 24 + 4 cycle.

	APC resistance	ATIII	F VII	F VIII	Protein C	D-Dimer (ng/ml)
	Reference range	Reference range	Reference range	Reference range	Reference range	
Baseline	2.711	0.946	1.123	0.939	1.14	264.9
Endpoint	2.998	0.99	1.066	1.012	1.108	215

Statistically significant different for the clotting factor VII, Protein C, and D-Dimer.

Platelet count also was performed in this study. No drug-induced immune thrombocytopenia (ITP) case was observed in both treatment groups suggesting that the observed increase of ITP by Gabe et al. [14] in combined drospirenoene/ethinylestradiol users was due to the estrogen effect. DRSP does not induce ITP.

DRSP 4 mg, in a 24 + 4 regime over 9 months, had no effect on the investigated hemostatic parameters. The use of this novel estrogen free pill can therefore be considered as safe in regard to potential changes of the blood coagulation as there is no effect on the liver dependent coagulation factors. Due to its pharmacological properties and the demonstrated good bleeding profile, DRSP 4 mg represents a valid alternative not only to POPs but also to COCs, given that the drug will not confer any additional risk in terms of thromboembolic events. The anti-androgenetic and anti-mineralocorticoid effects of DRSP should also translate into a reduction of possible adverse side effects, like acne and weight gain, ultimately leading to a high level of acceptability and compliance.

Declaration of interest

P.A. Regidor is an employee of Exeltis, Germany; E. Colli is an employee of Exeltis, Spain.

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