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REGULAR ARTICLE

# Effects of the contraceptive patch, the vaginal ring and an oral contraceptive on APC resistance and SHBG: A cross-over study

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**KEYWORDS**
Activated Protein C Resistance;
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**Abstract**

*Introduction:* The transdermal patch (20 μg ethinylestradiol + 150 μg norelgestromin daily) and the vaginal ring (15 μg ethinylestradiol + 120 μg etonogestrel daily) are new contraceptives, designed to deliver a low dose of hormones, suggesting a low exposure. However, few data are available about their risk of venous thrombosis. The objective was to investigate the effect of the patch, the ring, and an oral contraceptive (30 μg ethinylestradiol + 150 μg levonorgestrel daily) on activated protein C sensitivity ratio (APC-sr) and on sex hormone-binding globulin (SHBG) levels in plasma.
*Materials and methods:* After a two month wash-out, 13 volunteers were randomly assigned to either the patch followed by the oral contraceptive or vice versa, or the ring followed by the oral contraceptive or vice versa. All treatments lasted two cycles and were separated by a wash-out of two cycles. APC-sr and SHBG levels were determined on day 18–21 of the second cycle of the wash-out and of each treatment period.

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*Results:* Compared to the oral contraceptive, both the patch and the ring led to higher APC resistance (mean difference APC-sr 1.1; 95% CI 0.67–1.52 and 0.55; 95% CI 0.11–1.00, respectively) and higher SHBG levels (mean difference 210 nmol/l; 95% CI 134–286 and 148 nmol/l; 95% CI 48–248, respectively). *Conclusion:* The activity of the protein C system in plasma was impaired more by contraceptive patch and vaginal ring than by an oral contraceptive containing the second generation progestagen levonorgestrel.


## Introduction

Recently, two new combined contraceptive formulations, the transdermal patch (Ortho-Evra® or Evra®) and the vaginal ring (Nuvaring®), have been introduced on the market. The rationale of their development was to provide administration alternatives for the combined oral contraceptive (OC) and to improve convenience and thus compliance [1]. Furthermore, dose delivery by the transdermal and transvaginal route is unaffected by gastrointestinal disturbances, and there is no first-pass liver effect. These two new formulations are designed to deliver a low daily dose of hormones to the systemic circulation, and thus to have few side effects [1]. The contraceptive patch was designed to deliver 20 μg ethinylestradiol (EE2) and the contraceptive vaginal ring 15 μg EE2 per day to the systemic circulation, while a widely used second generation OC (Microgynon 30®) has a daily oral dose of 30 μg EE2. However, recently published data from a randomized cross-over study showed 60% higher average serum levels of EE2 in users of the patch compared to users of this second generation OC [2]. Few data are available about the risk of venous thrombosis in patch and ring users. This is remarkable, because both contraceptives contain a third generation progestogen, *i.e.* the patch contains norelgestromin, the primary active metabolite of norgestimate and the vaginal ring etonogestrel, a metabolite of desogestrel [3]. From 1995 onward, several studies have shown that combined oral contraceptives containing a third generation progestogen are associated with a two-fold higher risk of venous thrombosis than OCs containing levonorgestrel, which is classified as a second generation progestogen [4–7]. Recently, three studies have reported conflicting data about the incidence of venous thrombosis among users of the transdermal patch compared to norgestimate-containing OCs [8–10]. Cole et al. [8] found significantly more cases of venous thrombosis in patch users than in OC users (incidence rate ratio 2.2), whereas Jick et al. [9,10] found no difference (incidence rate ratio 1.1). No data are available about the risk of venous thrombosis of the vaginal ring.

OCs are associated with changes in procoagulant, anticoagulant and fibrinolytic parameters, resulting in a net prothrombotic effect [11,12]. The overall effect of contraceptives on the anticoagulant and procoagulant pathways can be measured by a thrombin generation-based activated protein C (APC) resistance test, the outcome of which has been demonstrated to associate well with the risk of venous thrombosis [13]. Also, several studies have shown that SHBG levels in women using OCs are a measure of total estrogenicity, and therefore may serve as an additional marker for the thrombotic risk of those formulations [14–16]. Furthermore, sex hormone-binding globulin (SHBG) levels follow the same pattern as the APC resistance in women using OCs [15,16]. The aim of our study was to investigate the effects of the transdermal patch and the vaginal ring on APC resistance and SHBG levels in plasma, and thus to predict the risk of venous thrombosis in users of these contraceptives.

## Methods

### Study design and participants

We recruited 13 healthy female volunteers aged 18 to 45 years between January and December 2005 through advertisements in local newspapers and through posters in general practioners' practices and public and university buildings. Exclusion criteria were contraindications for oral contraceptive use as stated by the World Health Organization [17], pregnancy during the three months before the study, use of anticoagulants or platelet aggregation inhibitors, and chronic or serious acute illness. Written informed consent was given by all participants. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

The volunteers were required not to use any hormonal contraception for at least two normal menstrual cycles (wash-out at baseline), and were then randomly assigned for the first time to one of two groups. Women of the first group received a