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Effects of switching from oral to transdermal or transvaginal contraception on markers of thrombosis

Jeffrey T. Jensen^{1,4,*}, Anne E. Burke², Kurt T. Barnhart³, Carrie Tillotson⁵, Marci Messerle-Forbes¹, and Dawn Peters⁴

¹ Department of Obstetrics & Gynecology, Oregon Health & Science University, Portland, OR 97239

² Department of Obstetrics & Gynecology, Johns Hopkins University, Baltimore, MD 21205

³ Department of Obstetrics & Gynecology, and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA 19104

⁴ Department of Public Health & Preventive Medicine, Oregon Health & Science University, Portland, OR 97239

⁵ Biostatistics Shared Resource, Oregon Health & Science University, Portland, OR 97239

Abstract

Background—The study was conducted to determine the impact of switching from oral to transdermal patch or vaginal ring contraception on biomarkers of thrombosis.

Study Design—Current healthy oral contraceptive (OC) users were randomized to switch to either a contraceptive ring (CR) or patch (CP) and underwent phlebotomy to measure surrogate biomarkers of thrombosis (sex hormone binding globulin (SHBG), free protein S, and activated protein C-resistance (APC-r)) before switching, and during the 4th cycle of use of the new method.

Results—Of 142 reproductive age women enrolled, 120 sample pairs were available for analysis. SHBG increased significantly from baseline in CP users (mean change (95% CI) +29.9 nM (9.6, 50) but not in CR users -1.6 (-16.6, 13.5). Protein S decreased significantly from baseline in CP users (mean change -7.1% (-12.1, -2.1), but increased significantly in CR users +5.3% (1.1, 9.6). The APC-r ratio did not undergo a significant change from baseline in either group [CP +0.06 (-0.06, 0.18), CR +0.02 (-0.10, 0.14)] Compared to CR users, subjects using the CP had significantly higher SHBG (187.5 (167.0, 208), 146 (132.6,159.4), $p = 0.012$), significantly lower protein S (81.8 (76.8, 86.8), 93.6 (89.1, 98.1), $p = 0.001$), and similar APC-r ratios (2.99 (2.85,3.14), 3.09 (2.96, 3.22), $p = 0.3$) at the cycle 4 visit.

*Corresponding author: Jeffrey T. Jensen, MD, MPH, Mail code UHN-70 Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, Telephone: (503) 494-4469, Fax: (503) 494-5083, E-mail: jensenje@ohsu.edu.

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Conflict of interest

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Conclusion—OC users who switch to the ring exhibit beneficial changes in biomarkers of thrombosis while those switching to the patch display a shift favoring clot formation.

Keywords

Transdermal; Transvaginal; Hormonal Contraception; Thrombosis; Randomized

1. Introduction

Since receiving regulatory approval for marketing, both vaginal ring (NuvaRing™) and transdermal patch (Ortho Evra™) contraceptive delivery systems have become popular contraceptive options. Both of these products release ethinyl estradiol (EE), the same synthetic estrogen used in combination oral contraceptives (OCs). Since both routes of administration avoid hepatic first-pass metabolism and demonstrate lower peak levels of hormones than seen following oral dosing, the impact on hepatic induction of coagulation factors might be different from OC users [1].

Epidemiological studies have shown that both the estrogen dose and type of progestogen in a combination OC contribute to the increased risk of venous thrombosis seen in OC users compared to non-users [2]. A dose-dependent effect with estrogen is noted; OCs containing 50 mcg or more of EE are associated with a higher risk of thrombosis than formulations containing 20 to 30 mcg EE [3]. More recently, epidemiologic studies investigating the impact of the progestogen component of combined OCs have suggested that the so-called “third-generation” progestogens gestodene and desogestrel or the progestogen cyproterone acetate are more thrombogenic than OCs containing the “second-generation” progestogen levonorgestrel [4,5].

Steady-state levels of EE are higher in patch users than in ring users [1]. Highly publicized reports of fatal venous thromboembolism (VTE) in patch users in 2004 led to the addition of a specific warning regarding an increase in estrogen exposure (e.g., average steady-state concentrations of EE are 60% higher than in users of a 35 mcg EE OC) in the prescribing information for the product [6,7]. The results of epidemiologic studies have been inconsistent. A nested case-control study design using an insurance claims database found that the odds ratio for venous thromboembolism was 2.4 (95% CI 1.1–5.5) in patch users compared to users of OCs containing norgestimate, the parent compound of the progestogen norelgestromin used in the patch [8]. However, Jicks et al. [9,10], used a similar study design and found no increase in risk (OR 1.1 (95% CI 0.6–2.1)).

Women using contraceptive pills may consider switching to either the patch or the ring to enjoy the benefits of long-acting contraceptive delivery systems. Although the absolute risk of thrombosis is low in healthy reproductive age women, not all hormonal contraceptive users are at low risk [11]. Compared to use of the pill, patch use results in a shift in hemostasis variables favoring clot formation [12–14]. In order to obtain more information on how transdermal and vaginal contraceptive delivery systems may affect thrombosis risk, we measured three surrogate markers of thrombosis risk in healthy OC users who agreed to be randomized to receive either the patch or ring: sex hormone binding globulin (SHBG), protein S, and activated protein C-resistance (APC-r). Our hypothesis was that, compared to ring users and former pill users, patch users will exhibit a net change in these markers favoring clot formation.

2. Materials and methods

2.1. Study population

All women enrolled in the Patch-Ring Acceptability Study (PARIS)[15], an open-label, prospective, multicenter, randomized comparative trial at three [Oregon Health & Science University (OHSU), the Johns Hopkins University, and the University of Pennsylvania] of the 10 study sites were asked to participate in a substudy investigating the effects of the contraceptive products on surrogate serum markers of thrombosis. All three participating sites obtained approval from their Institutional Review Board for the main study and substudy prior to initiation of the protocol. The details and findings of the PARIS study have been published [15]. Eligible subjects were satisfied current or recent users of a combined OC with no past experience using either the contraceptive ring or patch. Subjects agreed to discontinue their current oral contraceptive method and be randomized to either the patch or ring and continue use of the new method for four cycles. Group assignment was determined in the main PARIS study by a randomization sequence created using STATA 9.0 (Stata Corp., College Station, TX) statistical software, stratified by center with a 1:1 allocation using random block sizes of 2, 4 and 6. An individual unassociated with the clinical portion of the study prepared sequentially numbered opaque envelopes containing the product assignment, and research staff at the study site opened the next envelope for each enrolled subject.

Age, height, and weight were recorded for the substudy. BMI was calculated as weight (in pounds)/(height in inches)² × 703, and classified as underweight (BMI < 18.5), normal weight (BMI 18.5 – 24.9), overweight (BMI 25– 29.9), and obese (BMI >30) [16]. Subjects were asked about their current use of OCs, as well as the use of any OC in the last three months. For the purposes of data analysis, women who had used OCs within eight weeks of enrollment, but were not currently using the pill, were classified as recent users. All women enrolled in the study were either current or recent users of OCs.

All subjects underwent phlebotomy to obtain a blood sample for measurement of SHBG, protein S, and APC-r at the enrollment visit (prior to initiation of the patch or ring), and at the final scheduled follow-up visit during the first week of the fourth cycle of patch or ring use (or sooner if early discontinuation). Following separation of serum and plasma, samples were shipped frozen on dry ice to the Oregon Clinical & Translational Research Institute (OCTRI) Laboratory at Oregon Health & Science University where they were stored between –70 to –80°C until analysis. Samples from Johns Hopkins and Pennsylvania were stored at –70 to –80°C and shipped on dry ice to OHSU in batches. A unique identifying number was used to link the initial and follow-up samples to each other and to demographic data. Only subjects providing an initial and follow-up blood sample contributed data to the primary outcome. Women who discontinued the protocol prior to completing four months of use underwent the second blood draw within one week of stopping the ring or patch system.

2.2. Laboratory methods

The assays were performed in batches using the same standards following collection of all the samples. Protein S antigen determination was performed in the OCTRI Laboratory using a commercially available ELISA-based kit (Corgenix Inc, Denver, CO) that measures free protein S as a percent of normal, with a reference range of 73–149%. Only free protein S has biologic activity. The kit has an inter-assay coefficient of variance (CV) of 6.7%. SHBG levels were also measured in the OHSU OCTRI Laboratory using a chemiluminescent based immunoassay (Immulite, Siemens Medical Solutions Diagnostics, Tarrytown, NY) with an inter-assay CV of 6.2%, and a normal range for women of 20–175 ng/mL. APC-r was determined using a highly sensitive and specific plasma based functional clotting assay, (Pefakit APC-R Factor V Leiden assay, Pentapharm LTD, Basel, Switzerland) performed in

the OHSU Special Immunology and Coagulation lab (Hemostasis and Thrombosis Section). Results are expressed as ratios between activated partial thromboplastin time with and without activated protein C, with an inter-assay CV of 4.26%. The normal range is a value greater than 2.19, and a drop in APC-r ratio with this assay indicates a shift toward greater thrombosis risk.

2.3. Primary objective

The primary objective of this study was to compare the change from baseline to cycle four in levels of SHBG, protein S, and APC-r between women in the contraceptive ring (CR) and contraceptive patch (CP) groups.

2.4. Secondary objectives

The secondary objectives were to assess the influence of prior OC use, OC type, and BMI on SHBG, protein S, and APC-r following use of the contraceptive ring or patch system. For purposes of data analysis, oral contraceptives were classified according to progestin type and estrogen dose. Dose of ethinyl estradiol was considered very low (20 mcg) or low (> 20 mcg). No subject reported use of a 50 mcg or higher pill. Progestins were classified as either 3rd generation (norgestimate, desogestrel), 1st and 2nd generation (levonorgestrel, norgestrel, ethynodiol diacetate, norethindrone), or other (drospirinone) [17].

2.5. Sample size

Sample sizes were based on the PARIS study, which expected to enroll 50 subjects at each of the three sites. We planned to enroll all of these women in the substudy (n=150). We estimated that enrolling 64 subjects in each group (assuming 15% dropout) would detect a difference in SHBG of 21.2 nmol/L (assuming a common standard deviation (SD) of 30 nmol/L) and conservatively assuming zero correlation between baseline and follow-up measurements) with 80% power (at significance level 0.05) using a paired t-test.

2.6. Statistical analysis

Simple comparisons for differences between baseline and follow-up measurements of APC-r, SHBG, and protein S were analyzed by two-tailed paired t-tests; differences in overall mean changes between contraceptive ring and contraceptive patch participants were analyzed by independent samples t-tests. Demographic differences between the contraceptive ring and contraceptive patch groups were assessed via t-tests and chi-square tests. p-values of less than 0.05 were considered statistically significant. We did not adjust the p-value for significance for multiple comparisons.

To adjust for confounders, linear mixed modeling was used to compare APC-r, SHBG, and protein S scores between the contraceptive ring and contraceptive patch groups. Primary predictors of interest included time (baseline vs. follow-up measurement), group (contraceptive ring (CR) vs. contraceptive patch (CP)), and OC use (current OC use vs. recent OC use). Potential confounders included in the analyses were study site (OHSU, John Hopkins, Penn); age (continuous); race (white vs. non-white); number of past pregnancies (0 vs. ≥1); and BMI (underweight/normal vs. overweight/obese). All possible two-way and three-way interactions were assessed between group, time, and OC use. Only interactions with a p-value of <0.05 were retained in the models.

Secondary analyses were conducted using linear mixed models to assess differences between groups among only the women who were current OC users at baseline (n = 102). Two separate models were analyzed: 1) with primary predictors group, time, and estrogen dose, and 2) with primary predictors group, time, and progestogen type. The same potential confounders and interactions were assessed as for the primary analysis described above.

All analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC).

3. Results

Between June 2005 and September 2006, 176 subjects were enrolled in the PARIS study at the three sites. Of these, 143 enrolled in the substudy and 131 contributed two blood samples. Labeling errors led to the exclusion of several samples (CR =1, CP = 6) leaving 120 subjects that contributed two samples suitable for analysis for paired analysis of APC-r and SHBG, and 119 for protein S (Fig. 1).

Of the 120 subjects in the analysis group, 65 received a contraceptive ring and 55 a contraceptive patch at randomization. Baseline characteristics were similar between the two treatment groups after randomization. The mean age of all 120 subjects was 27 years with the majority current OC users (85%), nulligravid (73%), white (81%) and non-Hispanic (97%) (Table 1). The demographics of the substudy sample were similar to those in the PARIS study [15].

For both the CR and the CP groups, the baseline values for APC-r ratio, SHBG, and protein S fell within the normal ranges for healthy premenopausal women, with no significant differences between treatment groups (Table 2).

Non-significant increases in APC-r ratio occurred during treatment in both CR (mean change 0.02 (95% CI -0.10, 0.14)) and CP (0.06 (-0.06, 0.18)) users, with no significant difference in the mean change between groups. In contrast, while SHBG declined slightly in ring users (mean change -1.6 nmol/L (-16.6, 13.5)), it increased significantly in patch users (mean increase 29.9 nmol/p (9.6, 50.1)). This difference in the mean change in SHBG was significant between the ring and patch treatments ($p=0.012$). While protein S increased significantly in CR users (mean change 5.3 (1.1, 9.6)), CP users demonstrated a significant drop in activity (mean decrease -7.1 (-12.1, -2.1), and these mean changes in protein S activity between treatment groups were significantly different ($p < 0.001$). Adjusting for BMI or other demographic characteristics did not alter the direction of the general conclusions.

The effects of OC use and formulation (e.g. progestogen type, estrogen dose) at baseline, are summarized in Table 3. In general, the direction of the effect for all of the assays mirrored the overall comparison. Current OC users showed smaller mean changes in SHBG [CR -9.6 (-26.4, 7.2), CP 18.4 (-0.5, 37.3), $p = 0.03$] and protein S [6.1 (1.5, 10.6), -4.6 (-9.8, 0.6), $p = 0.003$] than recent users [SHBG: 55.8 (11.0, 100.7), 81.3 (41.2, 121.4), $p = 0.4$; protein S: 0.3 (-11.9, 12.4), -18.3 (-29.2, -7.4), $p = 0.026$]. Few subjects ($n=16$) reported use of very low 20 mcg EE pills, and the confidence intervals for all comparisons were very broad. Results from subjects using estrogen doses > 20 mcg at baseline were the same as the overall group, with an increase in SHBG [CP 23.6 (0.6, 46.6), CR -12.0 (-28.0, 3.9), $p = 0.013$] and decrease in protein S [CP -6.5 (-12.2, -0.7), CR 7.5 (2.5, 12.6), $p = 0.001$] observed in patch users. Users of third generation progestins (e.g. desogestrel and norgestimate) did not experience changes in SHBG or protein S while using the patch, but showed a significant reduction in SHBG (mean change -17.4 (-34.5, -0.2)) and a non-significant increase in protein S (5.0 (-0.7, 10.6)). Former users of 1st/2nd generation progestins experienced non-significant increases in SHBG when switching to either new method, but protein S increased in CR (5.5 (-4.2, 15.3)) and decreased in CP users (-13.9 (-24.1, -3.8), $p = 0.007$). Since only 11 women (6 CR, 5 CP) reported use of drospirinone, these results were not separately analyzed. Similar to the overall comparison, OC use and type did not influence activated protein C resistance.

4. Discussion

Thrombosis represents one of the greatest risks of combined hormonal contraception, and the impact of a combined hormonal contraceptive method on coagulation pathways has important implications for safety. Our results demonstrate that OC users who switch to the contraceptive patch exhibit unfavorable changes in prothrombotic markers, while women switching to the contraceptive ring tend to show values more similar to non-users.

Oral contraceptive use produces changes in procoagulant, anticoagulant, and fibrinolytic parameters resulting in a net prothrombotic effect [2]. One suggested method of measuring the total effect is the thrombin generation-based activated protein C sensitivity ratio (APC-r) test [18]. The APC-r test has been shown to predict the risk of venous thrombosis in users of OCs as well as in non-users and men [19]. The direction of the effect of a hormone combination on APC-r supports observations noted in epidemiological studies of OC use and thrombosis [18]. However, APC acts as an anticoagulant through interaction with Factor V (see Figure 2) [20]. At least 90% of resistance to activated protein C is explained by point mutation in the gene for coagulation factor V, with the Leiden mutation most common [20]. Acquired resistance to APC then occurs primarily due to interactions with other plasma factors, principally protein S. Since the APC-r is sensitive to changes in multiple coagulation factors beyond Factor V Leiden it represents a milieu effect, rather than specific activity of Factor V. In other words, the APC-r assay is sensitive to a number of plasma factors affected by hormonal contraception that might influence blood clotting.

It is important to note that the APC-r test used in our study differs from the APC-r test, and is not expected to change with hormonal contraception [21]. Therefore, the similarity of our groups with respect to APC-r pre-treatment demonstrates the absence of a congenital defect in Factor V, and the absence of a change following switching to the CR or CP confirms that the impact of these hormonal therapies on the coagulation cascade is independent of factor V and related to other plasma factors.

Two studies have also suggested that an OC's effect on SHBG levels could possibly be an indicator of the thrombotic risk of that particular formulation [22,23]. The extent of the estrogen-related increase in SHBG depends not only on the dose of EE, but also on both the dose and type of progestogen [24–27]. This has led to the advancement of the use of SHBG levels as a marker of the total *estrogenicity* (the sum of estrogenic effect of EE and the anti-estrogenic effect of the progestogen) in an OC [22,28]. Odland et al. [22] found that SHBG levels were highest in users of pills shown in epidemiologic studies to have the highest risk of venous thrombosis. Consistent with these results, a randomized controlled trial comparing SHBG levels in women using a desogestrel-containing OC to levels in women using levonorgestrel-containing OCs confirmed higher levels of SHBG and APC-r in desogestrel-containing pill users [23].

Protein S is a vitamin K–dependent anticoagulant protein. Its major function is as a cofactor to facilitate the action of APC on its substrates (see Figure 2). Protein S deficiency usually manifests clinically as venous thromboembolism and may be hereditary or acquired. Protein S levels decrease in pregnancy and can fall into the abnormal-low laboratory range. However, low levels of protein S in pregnancy do not normally cause thrombosis by themselves [29].

Our results are consistent with studies documenting similar changes in these markers between users of 2nd and 3rd generation OCs [4,5], and between users of OCs and the contraceptive patch [29]. Johnson et al. [29] randomized non-users of hormonal contraception to either the patch or a 35 mcg EE/250 mcg norgestimate-containing OC in a crossover design. Consistent with our findings, protein S decreased with both treatments in the Johnson study, with a larger decline seen in patch users. Resistance to APC also increased with both treatments, and was

significantly greater among patch users in one of the two assays used. In contrast, all of our APC-r ratios were within the normal range, with only small non-significant differences seen between or within treatment groups. This difference reflects the underlying sensitivity of the APC-r assay used in the two studies. Johnson measured the normalized APC sensitivity ratio (nAPCsr) using two thrombin generation assay methods that are sensitive to changes in multiple coagulation factors beyond Factor V Leiden. Our study used a functional APC-r ratio assay kit that shows no interference from changes in levels of protein C, protein S, lupus anticoagulants, or elevated Factor VIII levels.

Although we enrolled fewer subjects than planned, we were still able to find significant changes in both SHBG and protein S between treatment groups. We tested the main effect of use of the contraceptive patch or ring with possible interactions of BMI, recent or past OC use, and type of OC used, but did not enroll sufficient numbers to fully evaluate interactions. Small sample size in subgroups and the hazards of applying statistical tests over multiple outcomes limit our ability to make inferences about the effect of OC type used at baseline. Given the small observed differences seen in APC-r ratio using this assay, a much larger study would be needed to demonstrate a difference in this outcome.

Strengths of the study include the randomized design, and excellent participation. Of the 142 subjects who consented to participate, 120 (85%) contributed two samples suitable for analysis. All of the assays were performed at a central laboratory and run against the same standard curves.

It is important to recognize the limitations of using surrogate markers to assess risk of a hormonal product. Clarkston et al. [30] found that OC use protected cynomolgous monkeys from the negative impact of an atherogenic diet, even with unfavorable lipid changes. While the surrogate markers measured in our study support a shift favoring clot formation in patch users, epidemiologic studies of thrombosis have not consistently demonstrated an increased risk in women using the patch [9,10]. The largest case-control study of thrombosis in patch users to date by Jicks et al. [9,10] found no increase in risk (OR 1.1 (95% CI 0.6–2.1)). Furthermore, the overall risk of a thrombotic event in a healthy reproductive age woman is low, and the risk of thrombosis associated with pregnancy exceeds that of combined hormonal contraception [31]. However, subgroups that are at slightly higher risk of thrombosis (e.g., obese women) have not been well studied. It is unknown if small differences in prothrombotic markers produced using different combined hormonal contraceptives may influence the likelihood of a thrombotic event in women at increased baseline risk for thrombosis.

Our data support that users of OCs who switch to the contraceptive ring tend to exhibit favorable changes in biomarkers of clotting, while patch users undergo a shift toward a more pro-thrombotic profile. Given that OC users who switch to the ring are also more satisfied, and more likely to continue with the method than those that switch to the patch [15], clinicians may feel more comfortable recommending ring use to OC switchers and new patients.

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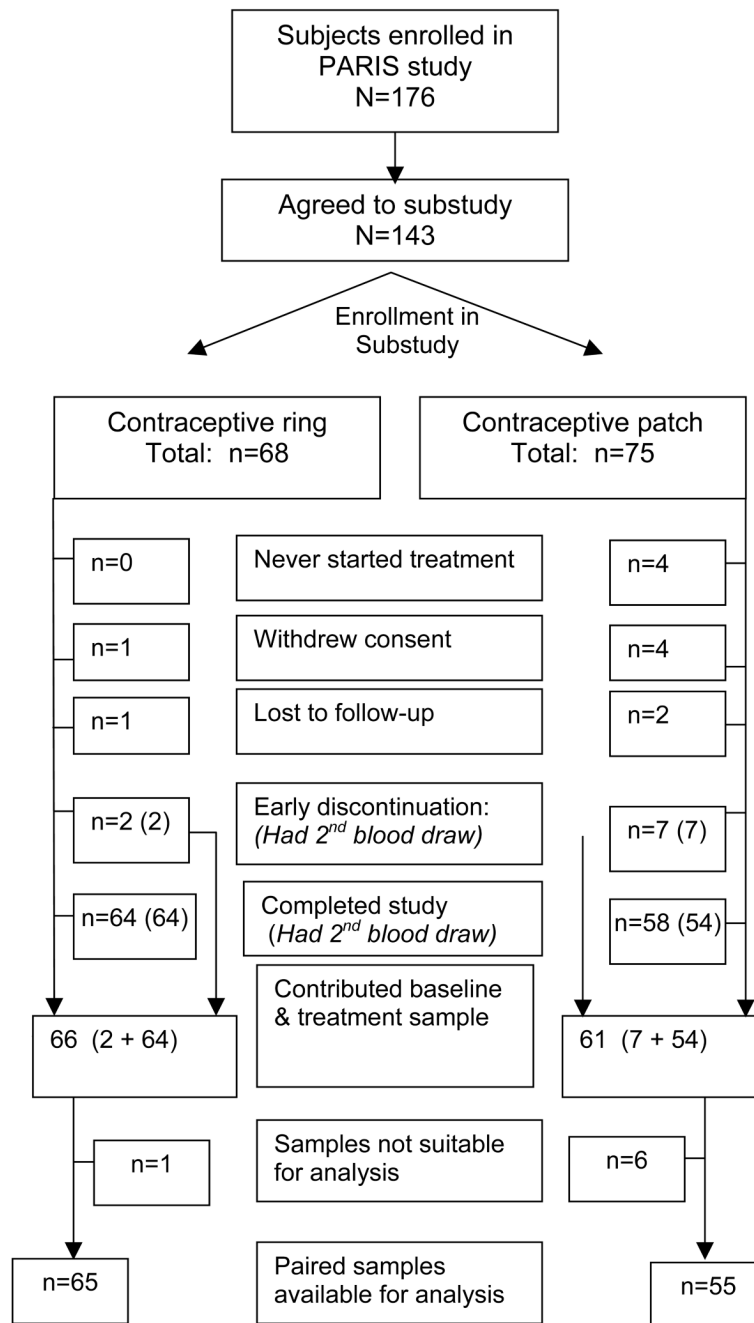


Fig. 1. Enrollment in substudy, and samples available for evaluation.

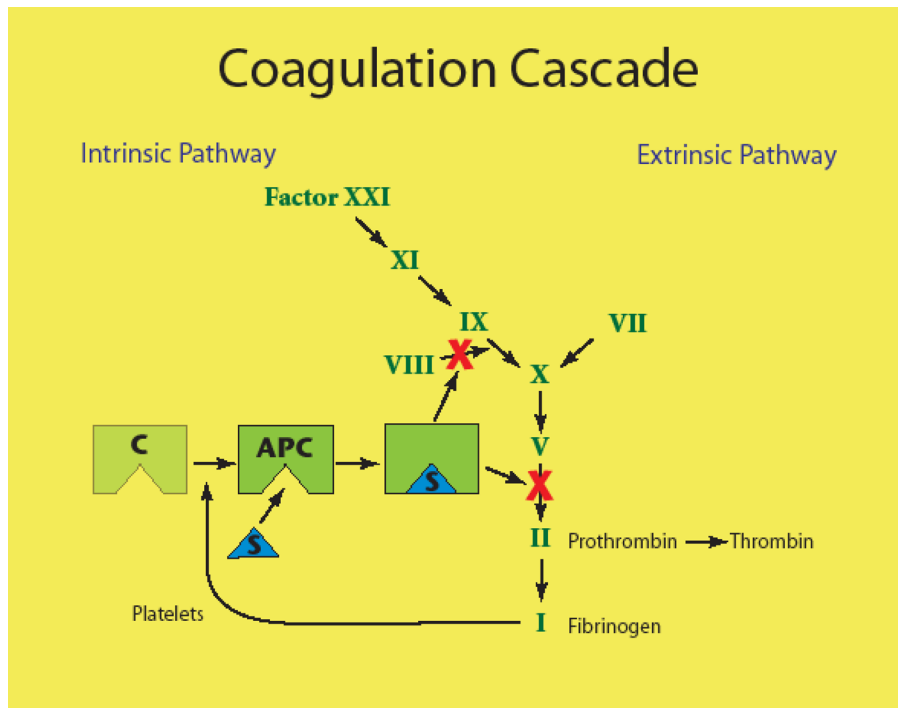


Fig. 2. A simplified illustration of the coagulation cascade. Activated protein C (APC) exerts an anticoagulant effect primarily through inhibition of factor V. Protein S is required for this interaction.

Table 1

Baseline characteristics of the study participants.

Variable		Contraceptive ring n=65	Contraceptive patch n= 55	p-value ^b
Age at enrollment (years)		27.5 (6.5)	26.7 (5.5)	0.520
BMI	<18.5 Underweight	2 (3.1%)	2 (3.6%)	0.854
	18.5 – 24.9 Normal	49 (75.4%)	38 (69.1%)	
	25–29.9 Overweight	10 (15.4%)	10 (18.2%)	
	>30 Obese	4 (6.1%)	5 (9.1%)	
Pregnancies	0	50 (76.9%)	38 (69.1%)	0.334
	≥1	15 (23.1%)	17 (30.9%)	
Race	White	52 (80%)	45 (81.8%)	0.977
	Black	4 (6.2%)	3 (5.5%)	
	Asian	4 (6.2%)	4 (7.3%)	
	Other	5 (7.7%)	3 (5.4%)	
Ethnicity	Hispanic	1 (1.5%)	3 (5.4%)	0.332
	Not Hispanic	64 (98.5%)	52 (94.6%)	
OC use	Recent	8 (12.3%)	10 (18.2%)	0.369
	Current	57 (87.7%)	45 (81.8%)	
Current OC preparation (n %)	EE >20 mcg	48 (84.2%)	38 (84.4%)	0.974
	3rd generation progestogen	39 (68.4%)	27 (60.0%)	0.732

Progestins were classified as either 3rd generation (norgestimate, desogestrel), 1st and 2nd generation (levonorgestrel, norgestrel, ethynodiol diacetate, norethindrone, or other (drospirinone)

Table 2

Mean change in APC-r, SHBG, and protein S before (pre), and after (post) treatment with a contraceptive ring or contraceptive patch, all subjects

		APC-r ratio (95% CI) ¹	SHBG nmol/l (95% CI) ²	Protein S% (95% CI) ³
Contraceptive ring	Pre	3.07 (2.93, 3.20)	147.6 (128.5, 166.7)	88.3 (83.3, 93.3)
	Post			
	Mean change	3.09 (2.96, 3.22)	146.0 (132.6, 159.4)	93.6 (89.1, 98.1)
	p value	0.02 (-0.10, 0.14)	-1.6 (-16.6, 13.5)	5.3 (1.1, 9.6)
		0.698	0.834	0.014
Contraceptive patch	Pre	2.93 (2.79, 3.08)	157.6 (136.5, 178.8)	88.9 (82.9, 94.9)
	Post			
	Mean change	2.99 (2.85, 3.14)	187.5 (167.0, 208.0)	81.8 (76.8, 86.8)
	p value	0.06 (-0.06, 0.18)	29.9 (9.6, 50.1)	-7.1 (-12.1, -2.1)
		0.296	0.005	0.006
p-value between groups	Mean change	0.647	0.012	<0.001

¹ APC-r ratio normal range > 2.19

² SHBG normal range 20–175 ng/mL

³ Protein S % of normal activity, normal range 73–149%

Table 3

Effect of OC use status, and OC type on APC-r ratio, SHBG (nmol/L), and protein S (% of normal activity); Adjusted means with 95% confidence intervals (CI). The mean change is statistically significant within groups if the 95% CI does not include zero, and between groups if the p-value is <0.05.

Effect	Group	Time	APC-r ratio (95% CI) ¹	SHBG nmol/L (95% CI)	Protein S % (95% CI) ³
OC use status					
Current OC use (n = 102)	Contraceptive ring (n = 57)	Pre	2.93 (2.75, 3.11)	145.0 (121.1, 169.0)	85.1 (78.2, 92.0)
		Post	2.93 (2.75, 3.11)	135.4 (111.5, 159.3)	91.2 (84.3, 98.1)
		Mean change	-0.003 (-0.12, 0.12)	-9.6 (-26.4, 7.2)	6.1 (1.5, 10.6)
Contraceptive patch (n = 45)	Pre	2.80 (2.62, 2.98)	159.2 (135.0, 183.4)	83.1 (76.1, 90.1)	
	Post	2.81 (2.63, 2.99)	177.6 (153.4, 201.8)	78.5 (71.5, 85.5)	
	Mean change	0.01 (-0.12, 0.14)	18.4 (-0.5, 37.3)	-4.6 (-9.8, 0.6)	
	Between groups p-value ⁴	0.737	0.030	0.003	
Recent OC use (n = 18)	Contraceptive ring (n = 8)	Pre	2.65 (2.29, 3.02)	51.1 (2.8, 99.5)	91.7 (77.9, 105.6)
		Post	2.86 (2.50, 3.22)	106.9 (58.6, 155.3)	92.0 (78.2, 105.8)
		Mean change	0.21 (-0.11, 0.52)	55.8 (11.0, 100.7)	0.3 (-11.9, 12.4)
Contraceptive patch (n = 10)	Pre	2.82 (2.50, 3.14)	99.2 (56.2, 142.1)	101.7 (89.4, 113.9)	
	Post	3.10 (2.78, 3.42)	180.5 (137.6, 223.4)	83.4 (71.1, 95.7)	
	Mean change	0.28 (-0.003, 0.56)	81.3 (41.2, 121.4)	-18.3 (-29.2, -7.4)	
	Between groups p-value ⁴	0.861	0.403	0.026	
Effect of estrogen dose					
E/E = 20 mcg (n = 16)	Contraceptive ring (n = 9)	Pre	3.03 (2.65, 3.42)	144.6 (89.9, 199.3)	97.7 (83.9, 111.4)
		Post	2.92 (2.53, 3.31)	147.9 (108.3, 187.5)	95.8 (82.0, 109.6)
		Mean change	-0.11 (-0.41, 0.18)	3.3 (-33.5, 40.0)	-1.9 (-13.5, 9.9)
Contraceptive patch (n = 7)	Pre	2.68 (2.28, 3.09)	176.2 (121.0, 231.3)	79.4 (64.9, 93.2)	
	Post	2.57 (2.17, 2.98)	166.5 (113.7, 219.3)	84.7 (70.2, 99.2)	
	Mean change	-0.11 (-0.45, 0.23)	-9.7 (-63.2, 43.8)	5.3 (-8.0, 18.5)	
	Between groups p-value ⁴	0.993	0.692	0.427	
E/E >20 mcg (n = 86)	Contraceptive ring (n = 48)	Pre	2.94 (2.74, 3.15)	142.0 (114.8, 169.3)	82.8 (75.5, 90.0)
		Post	2.96 (2.76, 3.17)	130.0 (108.1, 151.8)	90.3 (83.1, 97.6)
		Mean change	0.02 (-0.11, 0.15)	-12.0 (-28.0, 3.9)	7.5 (2.5, 12.6)
Contraceptive patch (n = 38)	Pre	2.84 (2.64, 3.05)	152.0 (124.8, 179.1)	83.7 (76.3, 91.1)	
	Post	2.88 (2.67, 3.09)	175.6 (149.3, 201.9)	77.2 (69.7, 84.7)	
	Mean change	0.04 (-0.11, 0.18)	23.6 (0.6, 46.6)	-6.5 (-12.2, -0.7)	
	Between groups p-value ⁴	0.854	0.013	0.001	
Effect of progestogen type					
1st/2nd Generation (n = 25)	Contraceptive ring (n = 13)	Pre	2.94 (2.62, 3.28)	90.9 (47.2, 134.6)	86.1 (74.2, 98.0)
		Post	2.89 (2.56, 3.23)	109.6 (76.6, 142.6)	91.6 (79.7, 103.6)
		Mean change	-0.05 (-0.30, 0.19)	18.7 (-11.4, 48.4)	5.5 (-4.2, 15.3)
Contraceptive patch (n = 12)	Pre	2.83 (2.50, 3.15)	96.0 (58.2, 133.8)	89.8 (78.2, 101.5)	
	Post	2.98 (2.66, 3.30)	151.0 (110.3, 191.7)	75.9 (64.3, 87.5)	
	Mean change	0.15 (-0.11, 0.41)	55.0 (15.4, 94.6)	-13.9 (-24.1, -3.8)	
	Between groups p-value ⁴	0.259	0.149	0.007	
3rd generation (N = 66)	Contraceptive ring (n = 39)	Pre	2.98 (2.76, 3.20)	153.8 (126.1, 181.5)	85.0 (77.2, 92.9)
		Post	3.00 (2.78, 3.21)	136.4 (114.2, 158.7)	90.0 (82.2, 97.9)
		Mean change	0.01 (-0.13, 0.16)	-17.4 (-34.5, -0.2)	5.0 (-0.7, 10.6)

Effect	Group	Time	APC-r ratio (95% CI) ¹	SHBG nmol/L (95% CI) ²	Protein S % (95% CI) ³
	Contraceptive patch (n = 27)	Pre	2.80 (2.56, 3.04)	184.1 (156.8, 211.5)	80.8 (72.3, 89.3)
		Post	2.74 (2.51, 2.98)	185.1 (156.0, 214.3)	80.4 (71.8, 89.1)
	Between groups p-value ⁴	Mean change	-0.06 (-0.23, 0.12)	1.0 (-25.4, 27.4)	-0.4 (-7.2, 6.5)
			0.542	0.249	0.235

¹ APC-r ratio, normal range > 2.19

² SHBG, normal range 20–175 ng/mL

³ Protein S % of normal activity, normal range 73–149%

⁴ For comparison of pre-post mean change between ring and patch users within each category

Progestins were classified as either 3rd generation (norgestimate, desogestrel), 1st and 2nd generation (levonorgestrel, norgestrel, ethynodiol diacetate, norethindrone, or other (drospironone)).