

Original research article

A comparison of bleeding patterns and cycle control using two transdermal contraceptive systems: a multicenter, open-label, randomized study^{☆,☆☆,★★,★★★}

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Abstract

Objective(s): To investigate the bleeding pattern and cycle control parameters of a contraceptive patch containing 0.55 mg ethinyl estradiol (EE) and 2.1 mg gestodene (GSD) compared with a patch containing 0.6 mg EE and 6 mg norelgestromin (NGMN).

Study design: In this phase III, open-label, randomized, parallel-group trial, healthy women aged 18–35 years (smokers aged 18–30 years) received either the EE/GSD patch ($n=200$) or the EE/NGMN patch ($n=198$). Treatment consisted of one patch per week for 3 weeks followed by a 7-day, patch-free interval for seven cycles. Bleeding control was assessed in two 90-day reference periods.

Results: In reference period 1, mean number of bleeding/spotting days was comparable across treatment groups ($p>0.05$). However, in reference period 2, there were fewer bleeding/spotting days in the EE/GSD patch group (15.7 versus 18.4; $p<0.0001$). Mean number of bleeding/spotting episodes was comparable across groups for both reference periods, but bleeding/spotting episodes were shorter for the EE/GSD patch than the EE/NGMN patch during reference period 1 (5.13 days versus 5.53 days, respectively; $p<0.05$) and reference period 2 (5.07 versus 5.66; $p=0.0001$). Both treatment groups showed a similar frequency of withdrawal bleeding episodes; however, across all seven cycles, the length of these episodes was consistently shorter with the EE/GSD patch ($p<0.01$). There were no notable treatment differences in intracyclic bleeding.

Conclusion(s): Bleeding pattern and cycle control achieved with the EE/GSD patch was similar to that of the EE/NGMN patch.

Implications statement: The paper presents data on the bleeding pattern and cycle control parameters of an investigational transdermal contraceptive patch containing EE and GSD compared with an approved contraceptive patch containing EE and NGMN. This descriptive study found that bleeding patterns associated with the EE/GSD patch were similar to those of an EE/NGMN patch providing higher EE exposure.

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Keywords: Transdermal contraceptive patch; Bleeding pattern; Cycle control; Ethinyl estradiol; Gestodene; Tolerability

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1. Introduction

Daily oral contraceptives – presently the most common means of contraception in the developed world [1] – are highly effective when used correctly; however, poor compliance is common and can result in greatly reduced efficacy [2]. Moreover, oral contraceptives can be associated with rapid and large fluctuations in serum concentrations [3], large intra- and inter-individual pharmacokinetic variations in serum levels [4], and low bioavailability of ethinyl estradiol (EE; 38–48%) [5]. Transdermal contraceptives afford the user a number of advantages over oral administration of hormones, including

effective absorption and the provision of relatively constant serum concentrations [3,6].

Both EE and gestodene (GSD) are effectively absorbed into the systemic circulation via the transdermal route and are, therefore, suitable hormones for delivery through the skin for contraceptive purposes [3,7]. The use of EE in combined oral contraceptives (COCs) is well documented, and it is the most potent estrogen agonist currently available [8], while GSD is a well-researched progestin that has established safety and efficacy, with more than two decades of use in the European market for the purposes of birth control [9–11]. An additional advantage of GSD is the low absolute dose required for contraceptive efficacy [12], which allows for a small patch size.

One of the major reasons women discontinue use of hormonal contraceptives is abnormal uterine bleeding [13]. Therefore, it is essential that any new hormonal contraceptive entering the market is evaluated for its effect on both bleeding patterns and cycle control. The primary objective of the present study was to investigate, and reliably describe, these parameters for an investigational, transdermal contraceptive patch containing EE and GSD compared with an approved transdermal contraceptive patch containing EE and norelgestromin (NGMN).

2. Materials and methods

2.1. Study design

This study was a phase IIIa, multicenter, open-label, randomized, parallel-group trial conducted at 24 centers in three countries (Austria, Czech Republic and the Netherlands). The objective was to evaluate the bleeding pattern and cycle control parameters of two transdermal contraceptives: an 11 cm² EE/GSD patch (0.55 mg EE/2.1 mg GSD; Bayer Pharma AG, Berlin, Germany) resulting in the same systemic exposure as after oral intake of a COC containing 0.02 mg EE and 0.06 mg GSD [14] and a 20 cm² EE/NGMN patch (0.6 mg EE/6.0 mg NGMN; EVRA[®], Janssen-Cilag Ltd, High Wycombe, UK) resulting in the same systemic exposure as after oral intake of 0.0339 mg EE and 0.203 mg NGMN [15].

The conduct of this clinical study met all local legal and regulatory requirements in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization Guideline E6: Good Clinical Practice. The protocol was reviewed and approved by each study site's internal ethics committee or review board, and written informed consent was obtained from each participant before the start of the study.

2.2. Study population

Participants were healthy women aged 18–35 years (18–30 years, if smokers) who were seeking contraception. When asked about contraceptive use in the 28 days prior to screening, 82.2% of women overall ($n=327$) reported having

used hormonal contraception, 7.5% ($n=30$) had used barrier methods and 10.3% ($n=41$) had not used contraception; percentages were similar in both treatment groups. Key exclusion criteria included pregnancy (fewer than three menstrual cycles since delivery, abortion or lactation before start of treatment), obesity (BMI >30.0 kg/m²), any disease or condition that could affect the pharmacokinetics of the study drug or worsen during hormonal treatment, undiagnosed abnormal genital bleeding, or abuse of alcohol, drugs or medicines. Women with a presence or history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction), or conditions that could increase their risk (e.g. hereditary predisposition), were also excluded.

2.3. Study treatment

There were two parallel groups receiving either the EE/GSD patch or the EE/NGMN patch, and participants were randomized (1:1) into one of these groups by means of an interactive voice response system. Before the start of the study, a computer-generated randomization list was produced, and each random number was assigned to either treatment group using randomization blocks of four.

In each study group, treatment consisted of a 21-day regimen per 28-day cycle (one patch per week for 3 weeks followed by a 7-day, patch-free interval) for seven cycles. Patches were applied to the outer upper arm, abdomen or buttocks. Application site could be changed between cycles, but all three patches within a single cycle were to be applied to a different location within the same general area (i.e. abdomen, buttocks or upper arm). Participants used diaries to record the dates new patches were applied, the application site, application deviations, the reason for patch removal (including complete or partial detachment), the dates they did not wear a patch, and whether back-up contraception was used.

If a patch was detached for less than 24 hours, it was to be reapplied; if no longer adhesive, a replacement patch was to be applied. In either case, the patch was to be worn until the next scheduled change. If a patch became detached for 24 hours or more, or the participant was unsure about how long the patch was detached, they were to restart the current cycle by applying a new patch. Restarting meant the application of three patches during the subsequent 3 consecutive weeks followed by a 7-day, patch-free interval.

The study included a screening visit, admission visit, four treatment visits (two visits during cycle 3 and two visits during cycle 7) and a final visit (after cycle 7, 21–28 days after removal of the last patch). Self-reported outcome measures with diary cards were the primary tool used to assess bleeding pattern and cycle control.

2.4. Study assessments

2.4.1. Efficacy assessments

Bleeding pattern was described in terms of number of bleeding/spotting days and episodes in each of two 90-day

reference periods. Cycle control was evaluated according to classifications of bleeding as either withdrawal (scheduled) bleeding (i.e. a bleeding or spotting episode that began during the hormone-free period or started not more than 4 days before the progestin withdrawal), or intracyclic (unscheduled) bleeding [16]. Bleeding intensity was categorized as none, spotting, light, normal or heavy [16]. Other efficacy assessments included the number of unintended pregnancies while receiving treatment up to 7 days after removal of the last patch, i.e. upon completing the 7-day, patch-free interval of cycle 7.

2.4.2. Safety and compliance assessments

Safety was assessed by means of adverse event monitoring, general physical and gynecologic examination (including breast examination by palpation), clinical laboratory tests, vital signs, body weight and height, and cervical smear testing. Laboratory evaluations included hematology, general serum chemistry, liver enzymes, carbohydrate metabolism and lipids. Treatment compliance, patch adhesion and unscheduled patch applications were evaluated based on information recorded by the participants in their diaries. Compliance was calculated as a percentage of actual versus planned treatment days per cycle.

2.5. Statistical analyses

The analyses in this study were descriptive in nature and the study was not designed to show equivalence or non-inferiority. Thus, no formal sample size calculation was undertaken, but a study with 400 participants was expected to provide sufficient data to describe the menstrual bleeding pattern reliably based on results from previous studies [16].

All variables were analyzed according to their type using descriptive statistics (e.g. frequencies for categorical data and arithmetic mean, standard deviation [SD], minimum, quartiles, median and maximum for metric data). Statistical analyses were performed using SAS for Windows (Version 9.2; SAS Institute, Cary, NC, USA).

Analyses were based on the full analysis set (FAS), defined as all women who were randomized, had applied at least one patch, and for whom at least one observation after admission to treatment was available. A per-protocol set (PPS) was also defined, including all women from the FAS who had no major protocol deviations considered to affect the main efficacy variables.

Post-hoc statistical analyses were conducted in order to test for treatment differences in bleeding pattern and cycle control outcomes. Data related to the number of women with withdrawal bleeding, intracyclic bleeding, and the maximum intensity of these two measures, were analyzed using the Fisher's exact test or the χ^2 test. Data related to bleeding pattern outcomes and the length of withdrawal bleeding were analyzed using the two-sample t-test. These post-hoc tests were unrelated to any power analysis. No statistical analyses were undertaken to analyze between-treatment differences in the occurrence of adverse events.

3. Results

3.1. Study population

Of 432 women screened, 406 were randomized to one of the two treatment regimens. Unless otherwise indicated, data presented in the results section relate to the FAS, which included 398 women (200 in the EE/GSD group and 198 in the EE/NGMN group) (Fig. 1). A total of 245 women were included in the PPS (EE/GSD, $n=118$; EE/NGMN, $n=127$). Baseline demographics are shown in Table 1.

Major protocol deviations resulting in exclusion from the PPS (participants could have more than one) for EE/GSD and EE/NGMN were: treatment deviations in 71 women (35.5%) and 68 women (34.3%), respectively; study treatment despite not meeting inclusion/exclusion criteria in 12 women (6.0%) and 2 women (1.0%), respectively; and improper diary documentation in 4 women (2.0%) and 3 women (1.5%), respectively. Withdrawal by subject was 5.4% ($n=11$) for EE/GSD and 5.9% ($n=12$) for EE/NGMN.¹

3.2. Treatment compliance

Mean compliance was good in both treatment groups; 99.2% in the EE/GSD patch group and 99.4% in the EE/NGMN patch group.

3.3. Bleeding pattern

During treatment, the overall bleeding profile was largely similar between treatment groups with slightly fewer bleeding/spotting days in the EE/GSD patch group in reference period 2. For the FAS, the mean number of bleeding/spotting days in reference period 1 was comparable for EE/GSD and EE/NGMN (19.7 versus 20.6, respectively; $p>0.05$); however, in reference period 2 there were fewer bleeding/spotting days in the EE/GSD patch group (15.7 versus 18.4; $p<0.0001$). In the PPS, there were fewer bleeding/spotting days for the EE/GSD patch compared with the EE/NGMN patch in reference periods 1 and 2 ($p<0.01$ and $p=0.0001$, respectively). In the FAS, this was associated with fewer bleeding-only days in the EE/GSD patch group in reference periods 1 and 2 ($p=0.01$ and $p<0.0001$, respectively) for the comparison of mean data; the same finding was observed in the PPS ($p<0.05$ and $p<0.001$, respectively). The mean number of spotting-only days was similar between treatment groups for either analysis set ($p>0.05$).

Mean number of bleeding/spotting episodes was comparable for the EE/GSD and EE/NGMN patch groups in reference period 1 (3.3 versus 3.2, respectively; $p>0.05$) and reference period 2 (3.2 versus 3.3, respectively; $p>0.05$). Similar findings were reported for the PPS. Mean length of bleeding/spotting episodes was shorter for the EE/GSD patch than the

¹ One subject in the EE/NGMN group prematurely discontinued the study with mastodynia. The reason was recorded as "withdrawal by subject". However, the subject was included among those who discontinued the study due to a treatment-emergent adverse event.

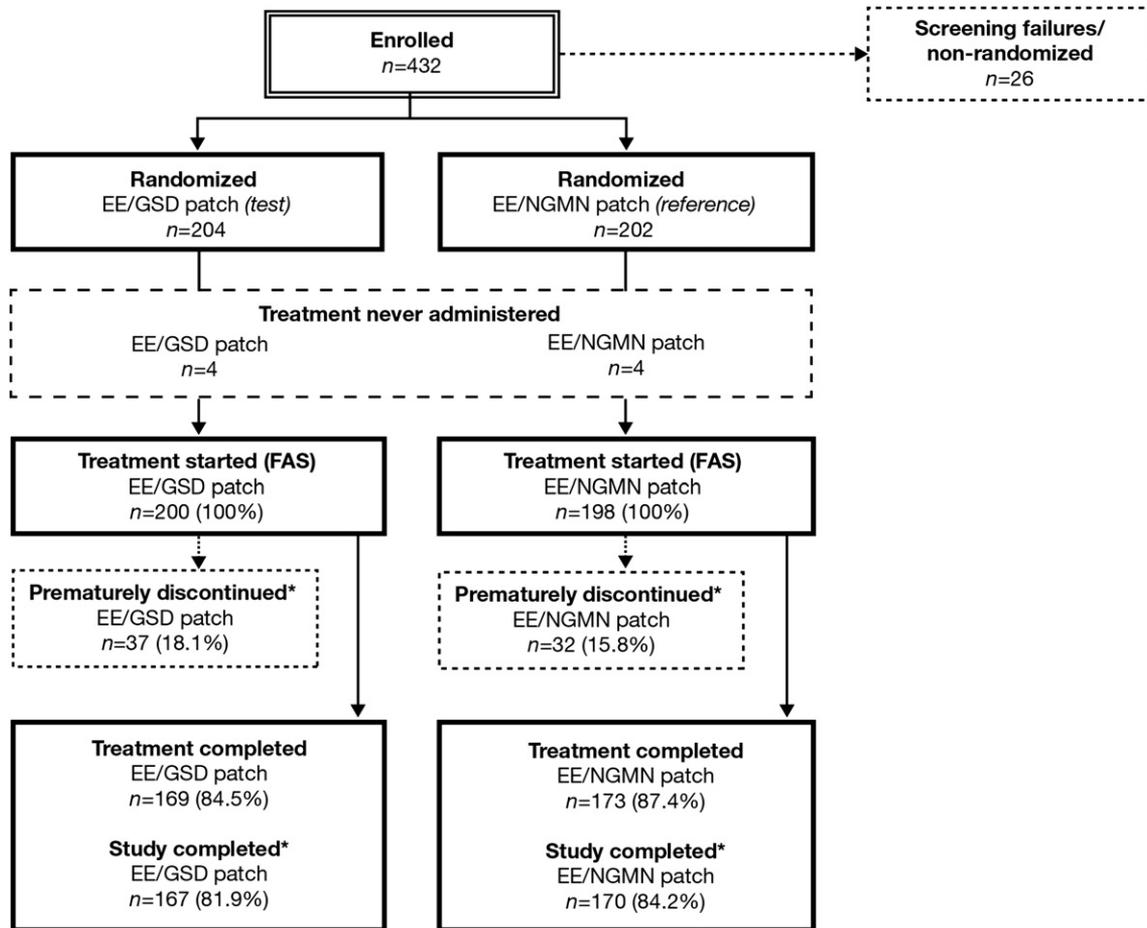


Fig. 1. Disposition of study participants. *The study was completed only if the participant had completed the treatment period and had performed the follow-up visit. EE/GSD patch, 0.55 mg EE/2.1 mg GSD; EE/NGMN patch, 0.6 mg EE/6.0 mg NGMN. EE, ethinyl estradiol; FAS, full analysis set; GSD, gestodene; NGMN, norelgestromin.

EE/NGMN patch for reference period 1 (5.13 days versus 5.53 days, respectively; $p < 0.05$) and reference period 2 (5.07 versus 5.66; $p = 0.0001$). Similar findings were reported for the PPS ($p < 0.001$ for reference periods 1 and 2). Results for bleeding pattern indices are summarized in Table 2.

3.4. Cycle control

3.4.1. Withdrawal bleeding

In the FAS and PPS for both treatment groups, the frequency of withdrawal bleeding was similar ($p > 0.05$) (Fig. 2a). However, in the FAS and PPS, withdrawal bleeding episodes in cycles 1–7 were consistently shorter for the EE/GSD patch group compared with the EE/NGMN group ($p < 0.01$). The maximum intensity of withdrawal bleeding episodes was similar in both treatment groups ($p > 0.05$); except for cycles 1, 3 and 6 in the FAS and cycle 3 in the PPS, with lower intensities in the EE/GSD patch group) (Fig. 2b).

3.4.2. Intracyclic bleeding

In the FAS and PPS, the number of subjects with intracyclic bleeding/spotting episodes was similar in both treatment groups ($p > 0.05$) (Fig. 3a). Maximal length and intensity of

intracyclic bleeding/spotting episodes was also generally comparable in both the FAS and PPS population (Fig. 3b).

3.5. Unintended pregnancies

Overall, contraceptive efficacy in this study was good, with only one pregnancy reported in the EE/GSD patch group.

3.6. Safety

The percentage of women experiencing at least one treatment-emergent adverse event (TEAE) was 47.5% in the EE/GSD patch group and 39.9% in the EE/NGMN patch group. Overall, there was a numerically lower incidence of the EE-related TEAE of breast pain in the EE/GSD patch group compared with the EE/NGMN group (2 events in 1.0% of subjects versus 12 events in 4.0% of subjects, respectively).² The most common drug-related TEAEs are listed in Supplementary Table 1. Overall, 6.5% of subjects prematurely discontinued from study treatment due to

² Please note, the study was neither designed nor powered to show differences in the frequencies of adverse events.

Table 1
Demographics and baseline characteristics of participants at screening (FAS)

	EE/GSD patch ^a n=200	EE/NGMN patch ^b n=198
Age, height, body weight, body mass index: mean±SD (range)		
Age (years)	24.9±4.3 (18–35)	24.5±4.6 (18–35)
Height (cm)	167.3±5.9 (152–185)	167.9±5.9 (150–184)
Body weight (kg)	61.2±9.2 (45–89)	63.3±9.0 (42–89)
Body mass index (kg/m ²)	21.8±2.8 (17–30)	22.4±2.8 (17–30)
Race, n (%)		
White	200 (100)	198 (100)
Ethnicity, n (%)		
Not Hispanic/Latino	195 (97.5)	192 (97.0)
Hispanic/Latino	1 (0.5)	0 (0.0)
Not reported	4 (2.0)	6 (3.0)
Smoking history, n (%)		
Never	131 (65.5)	134 (67.7)
Former ^c	18 (9.0)	9 (4.5)
Current	51 (25.5)	55 (27.8)
Alcohol consumption, n (%)		
Abstinent	65 (32.5)	62 (31.3)
Light	130 (65.0)	136 (68.7)
Moderate	5 (2.5)	0 (0.0)

^a0.55 mg EE/2.1 mg GSD; ^b0.6 mg EE/6.0 mg NGMN patch is the only commercially available patch in study countries; ^cIncluding three subjects on the EE/GSD patch and one subject on the EE/NGMN patch with missing information.

EE, ethinyl estradiol; FAS, full analysis set; GSD, gestodene; NGMN, norelgestromin; SD, standard deviation.

TEAEs. Except for one (chest pain in the EE/GSD patch group), all other TEAEs that led to premature discontinuation were considered drug related, affecting 8.5% of subjects in the EE/GSD patch group and 4.0% of subjects in the EE/NGMN patch group. In the EE/GSD patch group, most drug-related discontinuations were due to skin reactions at the application site, whereas in the EE/NGMN patch group breast pain was the most common reason.

Generally, TEAEs were considered by the investigators to be either mild or moderate in intensity (EE/GSD patch: 23.5% and 22.0%, respectively; EE/NGMN patch: 13.6% and 25.3%, respectively). Serious TEAEs were reported by six women (EE/GSD: abortion [$n=1$], surgical removal of a pre-existing lipoma [$n=1$]; EE/NGMN: gastroenteritis [$n=2$], salpingo oophoritis [$n=1$], appendicitis [$n=1$]). None was considered to be causally related to study medication.

Table 2

Mean number of bleeding/spotting days, mean number of bleeding/spotting episodes and mean length of bleeding/spotting episodes, shown by treatment group and reference period (FAS). Length of each reference period was 90 days and p-values for differences between treatment groups were $p>0.05$, unless otherwise indicated

	EE/GSD patch ^a		EE/NGMN patch ^b	
	Reference period 1 n=182	Reference period 2 n=169	Reference period 1 n=185	Reference period 2 n=174
Number of bleeding/spotting days				
Mean±SD	19.7±6.6	15.7±4.0 ^c	20.6±6.5	18.4±6.2 ^c
Median (range)	18.0 (9–48)	15.0 (7–30)	20.0 (8–48)	17.0 (4–59)
Number of bleeding/spotting episodes (days)				
Mean±SD	3.3±0.8	3.2±0.5	3.2±0.7	3.3±0.8
Median (range)	3.0 (2–7)	3.0 (2–5)	3.0 (2–6)	3.0 (1–7)
Length of bleeding/spotting episodes (days)				
Mean±SD	5.13±1.8 ^d	5.07±1.3 ^c	5.53±1.5 ^d	5.66±1.4 ^c
Median (range)	5.0 (3–23)	5.0 (2–10)	5.3 (2–16)	5.3 (3–12)

^a0.55 mg EE/2.1 mg GSD; ^b0.6 mg EE/6.0 mg NGMN patch is the only commercially available patch in study countries; ^c $p<0.0001$ for the comparison of EE/GSD patch versus EE/NGMN patch; ^d $p<0.05$ for the comparison of EE/GSD patch versus EE/NGMN patch; ^e $p=0.0001$ for the comparison of EE/GSD patch versus EE/NGMN patch.

EE, ethinyl estradiol; FAS, full analysis set; GSD, gestodene; NGMN, norelgestromin; SD, standard deviation.

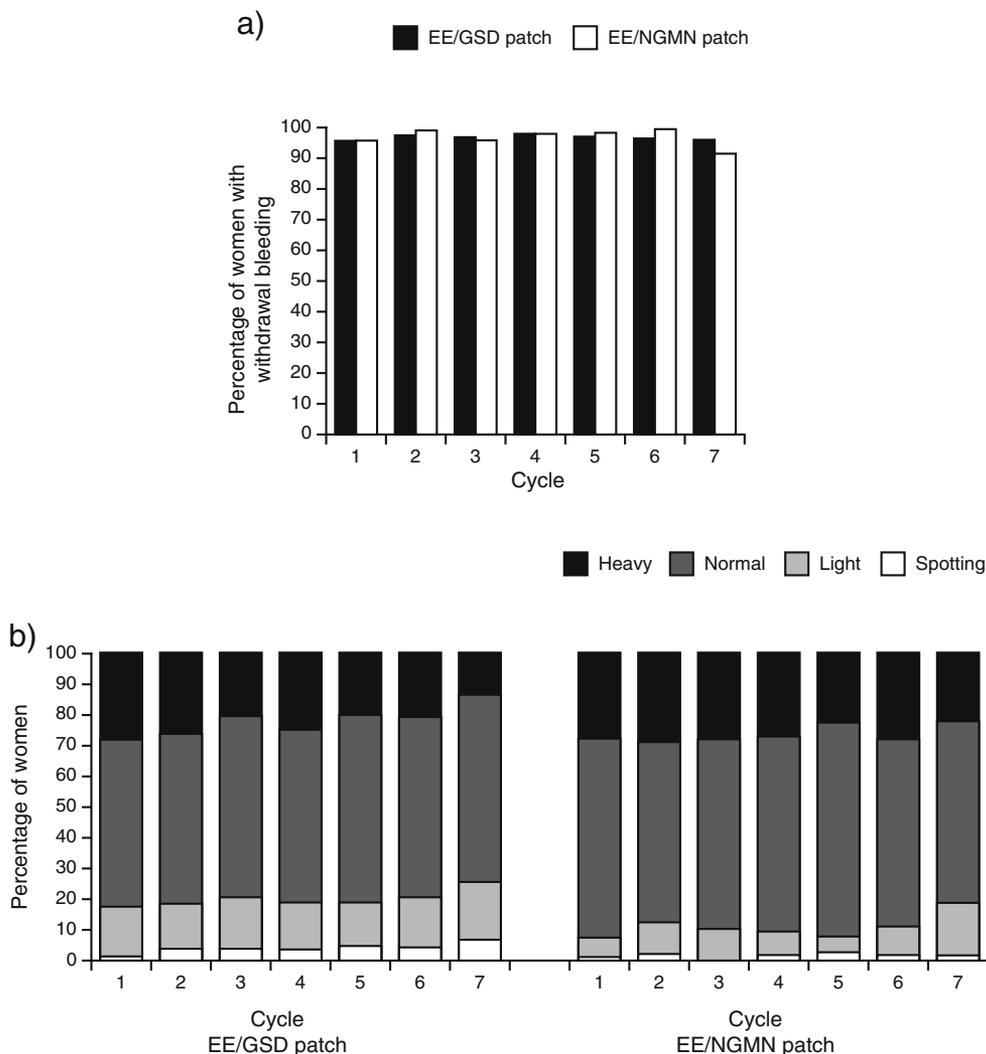


Fig. 2. a) Percentage of women with withdrawal bleeding, by treatment and cycle (FAS); b) Percentage of women with withdrawal bleeding, by maximum intensity, treatment and cycle (FAS). EE/GSD patch, 0.55 mg EE/2.1 mg GSD; EE/NGMN patch, 0.6 mg EE/6.0 mg NGMN. EE, ethinyl estradiol; FAS, full analysis set; GSD, gestodene; NGMN, norelgestromin.

4. Discussion

The results of this study show that the EE/GSD patch was associated with a very good bleeding profile. Despite the estimated 50% lower EE delivery rate of the new patch [14], bleeding control was largely comparable to that of the conventional 0.6 mg EE/6.0 mg NGMN patch, with a slightly lower number of bleeding/spotting days in both reference periods for the EE/GSD patch.

The cycle control results from this study are largely consistent with those of other methods of hormonal contraception. In a direct comparison with a 0.02 mg EE/0.1 mg levonorgestrel pill, the EE/GSD patch was largely comparable in terms of bleeding pattern and cycle control [17]. Furthermore, in a historical comparison with a 3 mg drospirenone/0.02 mg EE pill and a 0.015 mg desogestrel/0.02 mg EE pill, the EE/GSD patch displayed similar bleeding pattern and cycle control [18].

Overall, contraceptive efficacy in this study was good, with only one pregnancy reported in the EE/GSD patch group. The findings reported here are in line with those of a phase III study of the contraceptive efficacy of the EE/GSD patch, which found that the Kaplan–Meier probability of contraceptive protection after 364 treatment days was 98.8% and the adjusted Pearl Index was 0.81 [19].

In both treatment groups, compliance was very high and the patch was generally well tolerated. The percentage of women who discontinued because of adverse events was low in both groups. One advantage of the EE/GSD patch is the approximately two-fold lower EE delivery rate [14], which in this study was reflected in a numerically lower incidence of the EE-related adverse event of breast pain compared with the EE/NGMN group.³ The tolerability of the two patches was otherwise similar.

³ Please note, the study was neither designed nor powered to show differences in the frequencies of adverse events.

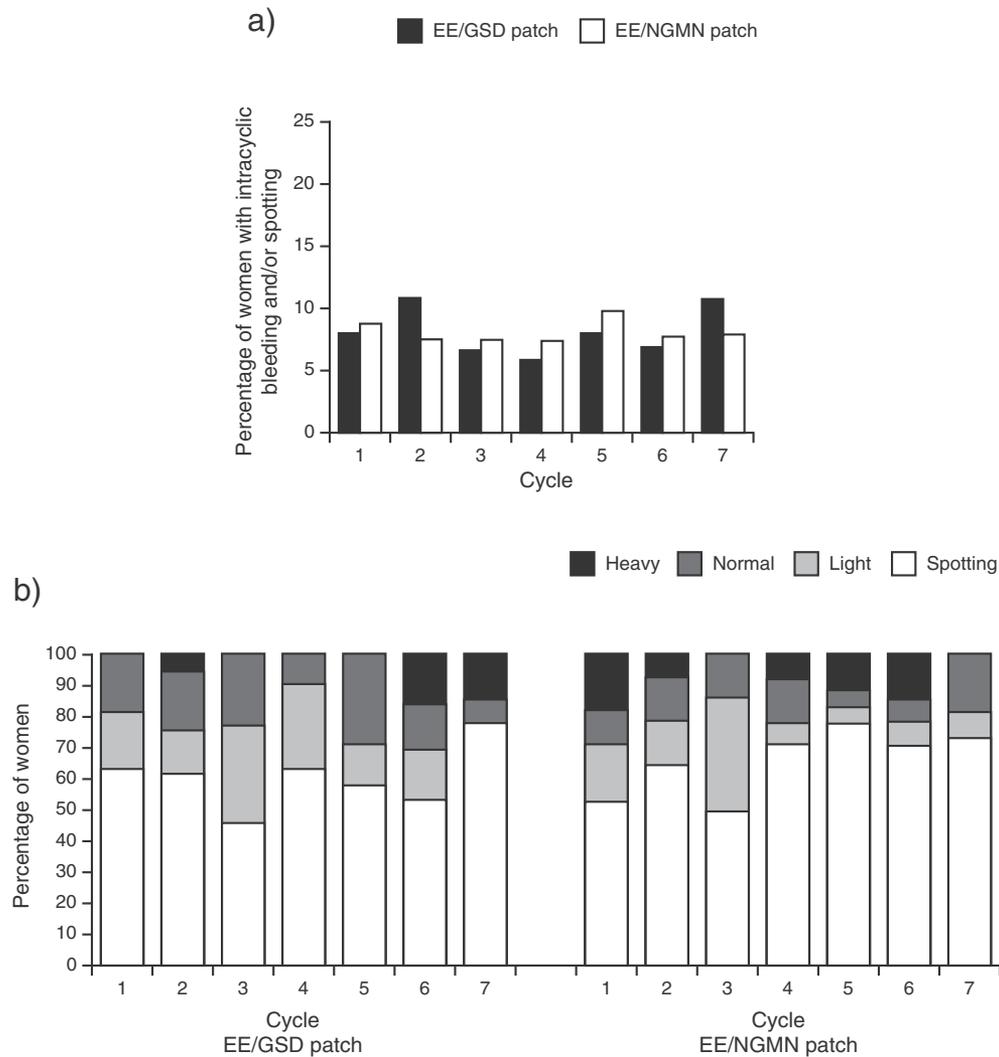


Fig. 3. a) Percentage of women with intracyclic bleeding/spotting episodes, by treatment and cycle (FAS); b) Percentage of women with intracyclic bleeding/spotting episodes, by maximum intensity, treatment and cycle (FAS). EE/GSD patch, 0.55 mg EE/2.1 mg GSD; EE/NGMN patch, 0.6 mg EE/6.0 mg NGMN. EE, ethinyl estradiol; FAS, full analysis set; GSD, gestodene; NGMN, norelgestromin.

In terms of study limitations, small sample size restricts the extent to which the data can be used to evaluate pregnancy and safety outcomes; although, the aforementioned phase III study provides reassuring data on pregnancy outcomes, as assessed in a larger number of women ($n=1,631$) [19]. Despite this, the risk of rare but pertinent events such as venous thromboembolism cannot reasonably be assessed here. Additional study limitations include the lack of *ad hoc* hypotheses and evaluation of clinically-relevant differences. Furthermore, given the descriptive nature of these analyses, the data should not be over-interpreted to imply benefit. An additional point for consideration is the prevalence of current smokers in this study, which was relatively high and could potentially have affected bleeding patterns. However, as the percentage of current smokers was similar for both groups (25.5% of subjects in the EE/GSD patch group and 27.8% of subjects in the EE/NGMN group)

it is unlikely that this variable affected the outcomes of the comparative analyses presented here.

Where possible, this study was conducted in concordance with WHO terminology and definitions [16]. Future analyses of bleeding data could benefit from the use of more standardized terminology, thus allowing for more direct comparison of data between studies [20]. Use of real-time electronic diary recordings could also improve the accuracy of data collection, and studies with larger groups of participants could benefit from stratification and analysis by prior patch use.

In conclusion, the results of this exploratory study indicate that bleeding pattern and cycle control achieved with the EE/GSD patch are similar to that of the older EE/NGMN patch, despite the lower EE delivery rate of the former.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.contraception.2014.10.003>.

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