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Can initial vaginal bleeding patterns in etonogestrel implant users predict subsequent bleeding in the first 2 years of use?☆

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ABSTRACT

Objectives: To evaluate if a simple method for characterizing vaginal bleeding patterns in etonogestrel contraceptive implant users can predict subsequent patterns and bleeding-related discontinuation over the first 2 years of use.

Study Design: We reanalyzed phase 3 study bleeding data for non-breastfeeding participants from the United States, Europe, Russia and Chile during the first 2 years of implant use to characterize and correlate bleeding patterns. We used 90-day reference periods with period 1.1 starting at Day 29 and ending at Day 118. We dichotomized bleeding patterns as "favorable" (amenorrhea, infrequent bleeding and normal frequency bleeding without prolonged bleeding) or "unfavorable' (prolonged and/or frequent bleeding) and tracked user groups based on these bleeding patterns in reference period 1.1 through Year 1 and from Year 1 through Year 2, respectively.

Results: We evaluated data from 537 and 428 women with up to 1 and 2 years use, respectively. Of the 325 (60.5%) women with favorable bleeding in reference period 1.1, 275 (84.6%) reported favorable bleeding also in reference period 2, 197 (60.6%) reported favorable bleeding throughout Year 1, and favorable bleeding in 75–85% of reference periods in Year 2. Among 212 (39.5%) women with unfavorable bleeding in reference period 1.1, 118 (55.7%) continued with unfavorable bleeding in reference period 2, while about 40%–50% reported favorable patterns in RP 2, 3 and/or 4. Initial favorable bleeding resulted in lower discontinuation rates than initial unfavorable bleeding in years 1 (3.7% vs 12.7%, $p \ll .0001$) and 2 (2.5% vs 16.5%, $p \ll .0001$).

Conclusion: Implant users with favorable bleeding in the first reference period are likely to continue with favorable bleeding over the next 2 years. Initial bleeding patterns predict overall continuation rates in years 1 and 2.

Implications Statement

When evaluating vaginal bleeding in any 90-day reference period over 2 years of etonogestrel implant use, approximately 80% of women with favorable and 40% with unfavorable bleeding patterns will have favorable bleeding in the next reference periods. These findings can facilitate counseling regarding bleeding for women using the etonogestrel implant.

☆ Conflicts of interest: Dr. Mansour serves on an advisory board for Merck & Co. and has received financial support to attend pharmaceutical advisory board meetings, undertake research studies, speak at educational meetings, webinars, conferences, along with travel grants from Bayer, Consilient Healthcare, HRA Pharma, Merck & Co, Mithra, Mylan, Pfizer and Vifor Pharma. Dr. Fraser serves on an advisory board for Merck & Co. and has given lectures, attended advisory boards and received research grants from Bayer Healthcare, Merck & Co, Vifor Pharma, Teva Pharmaceuticals and Daiichi-Sankyo Pharmaceuticals. Dr. Edelman has served on an advisory board for Merck & Co. and is an implant trainer (USA FDA required program in order to train new providers). Dr. Vieira serves on advisory boards for Merck & co. and Bayer, and Exeltis plus has given invited lectures for Merck and Bayer. Dr. Kaunitz serves on an advisory board for Merck & Co. Dr. Creinin serves on an Advisory Board for Lupin and Merck & Co. and is a consultant for Danco, Estetra, Exeltis, and Medicines360. The Department of Obstetrics and Gynecology, University of California, Davis, receives research funding for contraceptive research from Daré, HRA Pharma, Medicines360, and Merck & Co. and Sebela. Drs. Mansour, Fraser, Edelman, Vieira, Kaunitz and Creinin have not received any payment from Merck Sharp & Dohme Corp. for writing this article. T. Korver received personal fees from Merck Sharp & Dohme Corp. during the analysis of the data presented and A Pong, A Shah, J Lin, M Fox and H Rekers are employees of Merck Sharp & Dohme, a subsidiary of Merck & Co., Kenilworth, NJ, USA.

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1. Introduction

The etonogestrel subdermal contraceptive implant, first marketed in Europe in 1998 and the USA in 2006, has been used by more than 50 million women worldwide (personal communication, Merck). Continuation rates in clinical and observational studies are 80–90% at one and 65–75% at two years of use [1–3]. Acceptability and continuation rates are also high in younger users [4–7]. Vaginal bleeding issues comprise the main reason for implant removal, resulting in 13% of participants discontinuing implantable contraception over 3 years follow-up in USA and global phase III studies [1,5] and 16–19% in the first year in observational studies [7–9].

Previous analyses have evaluated bleeding patterns in etonogestrel implant users from phase 3 studies [8,10]. These analyses assessed amenorrhea, infrequent, normal frequency, frequent, and prolonged bleeding patterns over eight 90-day reference periods based on World Health Organization (WHO) definitions (Table 1) [11]. Women with frequent or prolonged vaginal bleeding patterns more often discontinued the implant before 2 years of use [10]. However, these analyses did not track participants' bleeding patterns in later reference periods, based on their initial bleeding patterns. The absence of such information limits the use of existing published data for accurate patient counseling. Additionally, the prior analyses included 214 women from Southeast Asia (28.5% of the total population) who commonly report different bleeding patterns and lower discontinuation rates than women from other countries [10,12]. Discontinuation data from Europe/Chile and the USA showed little differences in prior analyses [10]. Accordingly, we have reanalyzed these data, excluding the subjects from Southeast Asia, to evaluate how early bleeding experiences in non-Asian women correlate with bleeding patterns during the first two years of implant use.

2. Materials and methods

Details of the 12 phase 3 open-label studies for etonogestrel implants have been previously published and include a total of 923 women [13]. Briefly, investigators enrolled sexually active women, 18 to 40 years old, with regular menstrual cycles and requesting contraception. Recruitment occurred in the late 1990s and early 2000s in 11 countries including the USA, Chile, Austria, Germany, Finland, Hungary, The Netherlands, Russia, Singapore, Thailand and Malaysia. Appropriate institutional ethics committees approved the study for each site.

Table 1
Definitions of favorable and unfavorable bleeding patterns

A. The characterization of bleeding patterns based on World Health Organization recommended definitions [10,11]
•Amenorrhea: no bleeding/spotting days throughout a 90-day reference period
•Infrequent bleeding: 1–2 bleeding/spotting episodes in a 90-day reference period
•Normal frequency: 3–5 bleeding/spotting episodes in a 90-day reference period
•Frequent bleeding: ≫5 bleeding/spotting episodes in a 90-day reference period
•Prolonged bleeding: any continuous bleeding/spotting episode lasting more than 14 days in a 90-day reference period. This may overlap with any of the other bleeding patterns except amenorrhea
B. Favorable and unfavorable bleeding patterns per reference period (as defined for this analysis)
Favorable bleeding patterns per reference period
•Amenorrhea
•Infrequent bleeding (1–2 episodes), without prolonged bleeding
•Normal frequency bleeding (3–5 episodes), without prolonged bleeding
Unfavorable bleeding patterns per reference period
•Frequent bleeding (6 or more episodes)
•Any prolonged bleeding

Reference period [each 90-day interval of use; for Reference Period 1, we excluded the first 28 days which shifted the first reference period, Reference Period 1.1, to Days 29 through Day 118 with an overlap (Day 91 to Day 118) between Reference Period 1.1 and Reference Period 2, (Day 91–180)].

For this analysis, we extracted bleeding data from the study diary databases, excluding women from Singapore (n=40), Thailand (n=130) and Malaysia (n=69). We summarized bleeding patterns over 90-day reference periods, based on the WHO-recommended definitions and characterizations of bleeding patterns [11] (Table 1). Using these definitions, we defined the patterns as favorable (amenorrhea, infrequent bleeding and normal frequency bleeding with no prolonged bleeding) or unfavorable (prolonged and/or frequent bleeding) (Table 1) [10]. We tracked user groups based on these bleeding patterns in reference period 1.1 through Year 1 and from Year 1 through Year 2, respectively. None of the Phase III trials allowed any hormonal treatments or other interventions for bleeding complaints.

In most trials, implants were fitted during Days 1–5 of participants' menstrual cycle, or the day after the last oral contraceptive was taken in the pack, just before the expected withdrawal bleeding. To minimize the effect of this bleeding on the analyses, we excluded the first 28 days of reference period 1, resulting in a shifted first reference period, reference period 1.1, running from Day 29 to Day 118 with an overlap (Day 91 to Day 118) between Reference Period 1.1 and Reference Period 2. Bleeding data in this overlap period were included both in Reference Period 1.1 and Reference Period 2 data. We excluded study participants with missing bleeding diary data in Year 1 and/or Year 2 from our analyses. We excluded study participants who discontinued implant use during the first 118 days (for bleeding or other reasons) because the analyses are based on the availability of complete bleeding diary data for at least Reference Period 1.1.

We assessed implant discontinuation in each reference period due to bleeding or other reasons. We compared bleeding patterns and discontinuation rates for bleeding in Reference Periods 2, 3 and 4 in women who had favorable or unfavorable bleeding patterns in Reference Period 1.1. We also analyzed if favorable or unfavorable bleeding patterns in Reference Period 2 or 3 predicted similar outcomes.

Our primary outcome was the correlation between favorable or unfavorable bleeding patterns in Reference Period 1.1 and bleeding in the subsequent reference periods in Year 1. Secondary outcomes included the same correlations between Year 1 and Year 2 bleeding patterns, discontinuation due to bleeding and the impact of different definitions of prolonged bleeding on bleeding patterns and implant discontinuation. For the analyses of bleeding pattern correlation between the first and the second year, we defined the overall first year bleeding experience as favorable (two or more reference periods with favorable bleeding during Reference Periods 2, 3 and 4) or unfavorable (two or more reference periods with unfavorable bleeding during Reference Periods 2, 3 and 4). We then compared bleeding experiences and discontinuations in Year 1 (Reference Periods 2, 3, 4) with Year 2 (Reference Periods 5, 6, 7, and 8). We conducted a sensitivity analysis for all outcomes based on the definition of prolonged bleeding. The primary analysis used the WHO definition of prolonged bleeding as any continuous bleeding episode of≫14 days [11]; the sensitivity analyses evaluated differences using≫7 or≫10-day cut-offs.

We used Fisher's Exact Test for comparing discontinuation in women with favorable and unfavorable bleeding patterns in years 1 and 2, and a large sample test on Binomial proportion to test for changes in the percentage of favorable bleeding with a change of definition of prolonged bleeding from 7 to 10 days and from 10 to 14 days within each reference period. We performed statistical analysis using SAS (Carey, North Carolina) and considered a p≪.05 as significant.

3. Results

Characteristics of the 537 evaluable study participants for these analyses are listed in Table 2. Data concerning the last method of contraception used was available for 515 of the 537 women. We excluded 55

Table 2
Characteristics of Phase III etonogestrel implant bleeding analyses study participants

Characteristic	Participants n=537
Age (years)	27.5±5.6
Weight (kg)	61.7±9.2
Number of live births - n (%)	
0	199 (37.1)
1	137 (25.5)
2	138 (25.7)
≥ 3	60 (11.2)
Missing	3 (0.6)
Number of pregnancies	
0	128 (23.8)
1	119 (22.2)
2	150 (27.9)
≥ 3	140 (26.1)
Last contraceptive method	
Oral (COC, POP)	161 (30.0)
IUD	57 (10.6)
Implant	2 (0.4)
Condom, Foam, Diaphragm, Spermicide	255 (47.5)
Other	25 (4.7)
Never used	15 (2.8)
Missing	22 (4.1)

Data are presented as n (%) or mean ± standard deviation.

women from Year 1 and 46 women from Year 2 analyses due to missing bleeding diary data, leaving 537 (90.7%) women in Year 1 and 428 (72.3%) women in Year 2 analyses (Table 3, online appendix Table 1).

3.1. Correlation analyses Year 1

In Reference Period 1.1, 325 (60.5%) women reported a favorable and 212 (39.5%) an unfavorable bleeding pattern (Fig. 1 and online appendix Table 2). Thirty-nine women (7.3%) discontinued treatment in Year 1 due to bleeding and 68 (12.7%) did so for other reasons. Favorable bleeding in Reference Period 1.1 generally correlates with a continuation of favorable bleeding throughout Year 1 with favorable bleeding patterns during Reference Periods 2, 3 and 4 reported by 275 (84.6%), 250 (80.4%) and 80 (80%), respectively. Overall, 197 (60.6%) women with a favorable pattern in Reference Period 1.1 reported favorable bleeding in all Reference Periods in Year 1. Few women (n=12, 3.7%) with a favorable Reference Period 1.1. discontinued for bleeding reasons in Year 1.

Women with an unfavorable bleeding pattern in Reference Period 1.1 reported less predictable future bleeding patterns in year one. As demonstrated in Fig. 1A and online appendix Table 2, of the 212 women in this group, 79 (37.3%), 92 (46.7%) and 89 (51.1%) reported a change to a favorable pattern in Reference Periods 2, 3 or 4, respectively, and the proportion of women who reported continuing unfavorable bleeding rates declined over time from 55.7% (n=118) in Reference Period 2 to 41.6% (n=81) in Reference Period 3 and 40.8% (n=71) in Reference Period 4. Of the 79 women who reported a change from an unfavorable pattern in Reference Period 1.1 to a favorable pattern in Reference Period 2; 51 (64.6%) also reported favorable bleeding in Reference Period 3. In Year 1, significantly more women (n=27, 12.7%) with an unfavorable pattern in Reference Period 1.1 discontinued due to bleeding compared to women with a favorable pattern (n=12, 3.7% p≪.0001).

3.2. Correlation analyses Year 2

Of the 428 women in the Year 2 analyses, 325 (75.9%) reported an overall favorable bleeding pattern in Year 1. We found similar correlation patterns as in Year 1. As shown in Fig. 1B and online appendix Table 2, favorable bleeding in Year 1 correlates with favorable Reference Periods 5, 6, 7 and/or 8 in 75–85% of women; 159 (48.9%) reported favorable bleeding throughout Year 2 with a low discontinuation rate for bleeding (n=8, 2.5%). The trends reported in Year 1 in women with unfavorable bleeding continued in Year 2 as well. Of the 103 women with unfavorable overall Year 1 bleeding patterns, 31–52% reported a change to favorable bleeding over Reference Periods 5 to 8, with rates of unfavorable bleeding declining from 52% to 38% of women over Reference Periods 5 to 8. As in Year 1, discontinuation rates for bleeding in this group were higher (n=17, 16.5%) than in women with a favorable pattern (n=8, 2.5%; p≪.0001).

3.3. Correlations of bleeding patterns in preceding reference periods with those in the next reference period

We observed that the bleeding pattern an individual woman experiences in any reference period beyond Reference Period 1.1 generally correlates with future bleeding. A favorable bleeding pattern reported in any reference period is followed by reporting of continuation of favorable reference periods in 75% to 85% of women, unless one of the prior reference periods is reported as unfavorable, in which case the rate is 55–70% (see online appendix Table 3). In Year 2, women with reported unfavorable bleeding in any reference period have similar likelihood of a favorable or unfavorable pattern in the next reference period, approximately 35–55%. Women have their implant removal more frequently when they report the previous reference period as unfavorable (see online appendix Table 3).

Table 3
- Prolonged bleeding sensitivity analyses for bleeding pattern definitions and discontinuation among women using an etonogestrel implant.

Prolonged bleeding duration	≫14 days			≫10 days			≫7 days		
Number and % of participants with favorable/unfavorable bleeding									
		Favorable n (%)	Unfavorable n (%)		Favorable n (%)	Unfavorable n (%)		Favorable n (%)	Unfavorable n (%)
Reference Period 1.1	537	325 (60.5%)	212 (39.5%)	537	264 (49.2%)	273 (50.8%)	537	211 (39.3%)	326 (60.7%)
Reference Period 2	508	354 (69.7%)	154 (30.3%)	508	311 (61.2%)	197 (38.8%)	508	257 (50.6%)	251 (49.4%)
Reference Period 3	463	342 (73.9%)	121 (26.1%)	463	302 (65.2%)	161 (34.8%)	463	234 (50.5%)	229 (49.5%)
Reference Period 4	430	320 (74.4%)	110 (25.6%)	430	282 (65.6%)	148 (34.4%)	430	216 (50.2%)	214 (49.8%)
Discontinuations for bleeding									
In Year 1		12 (3.7%)	27 (12.7%)		8 (3.0%)	31 (11.4%)		5 (2.4%)	34 (10.4%)
In Year 2		8 (2.5%)	17 (8.0%)		7 (2.7%)	18 (6.6%)		6 (2.8%)	19 (5.8%)

Reference Period 1.1 (Days 29–118); Reference Period 2 (Days 91–180); Reference Period 3 (Days 181–270); Reference Period 4 (Days 271–360).
Favorable pattern: Amenorrhea, Infrequent bleeding without prolonged bleeding, normal frequency without prolonged bleeding.
Unfavorable pattern: Prolonged (≫14 days) and/or frequent bleeding.
Definition changes for the duration of bleeding that is called prolonged bleeding change the proportions of women who have favorable or unfavorable bleeding patterns, but does not impact on the discontinuation rates per pattern of bleeding.

3.4. Prolonged bleeding sensitivity analysis

Sensitivity analyses of changing the cut-offs for prolonged bleeding from≫14 days (the WHO standard) to≫7 or≫10 days on favorable and unfavorable bleeding patterns are reported in Table 3. As expected, a less stringent definition of prolonged bleeding results in higher proportions of reference periods categorized as unfavorable bleeding and a change of definition of prolonged bleeding from ≫7 to ≫10 days or ≫10 to ≫14 days results in a highly significant (p≪.0001) increase in the proportion of favorable bleeding in each of the reference periods over Year 1. However, the discontinuation rates in Year 1 in the women having a favorable or an unfavorable pattern in Reference Period 1.1 are not impacted by the changes in prolonged bleeding definitions (≫7 to≫10 to≫14 days) (p-values 0.71and 0.6, respectively). The same is true for Year 2 (p-values 0.96and 0.59, respectively).

4. Discussion

Our overall findings show that most women who have an initial favorable bleeding pattern continue with this pattern for the next 2 years. To aid counseling, women with a favorable bleeding pattern in any reference period can be informed that there is approximately an 80% chance of this favorable pattern continuing to the next reference period. Women with an initial unfavorable bleeding pattern are more likely to have unpredictable bleeding in the future; they can be counseled that there is an approximately 50% chance that their bleeding pattern will

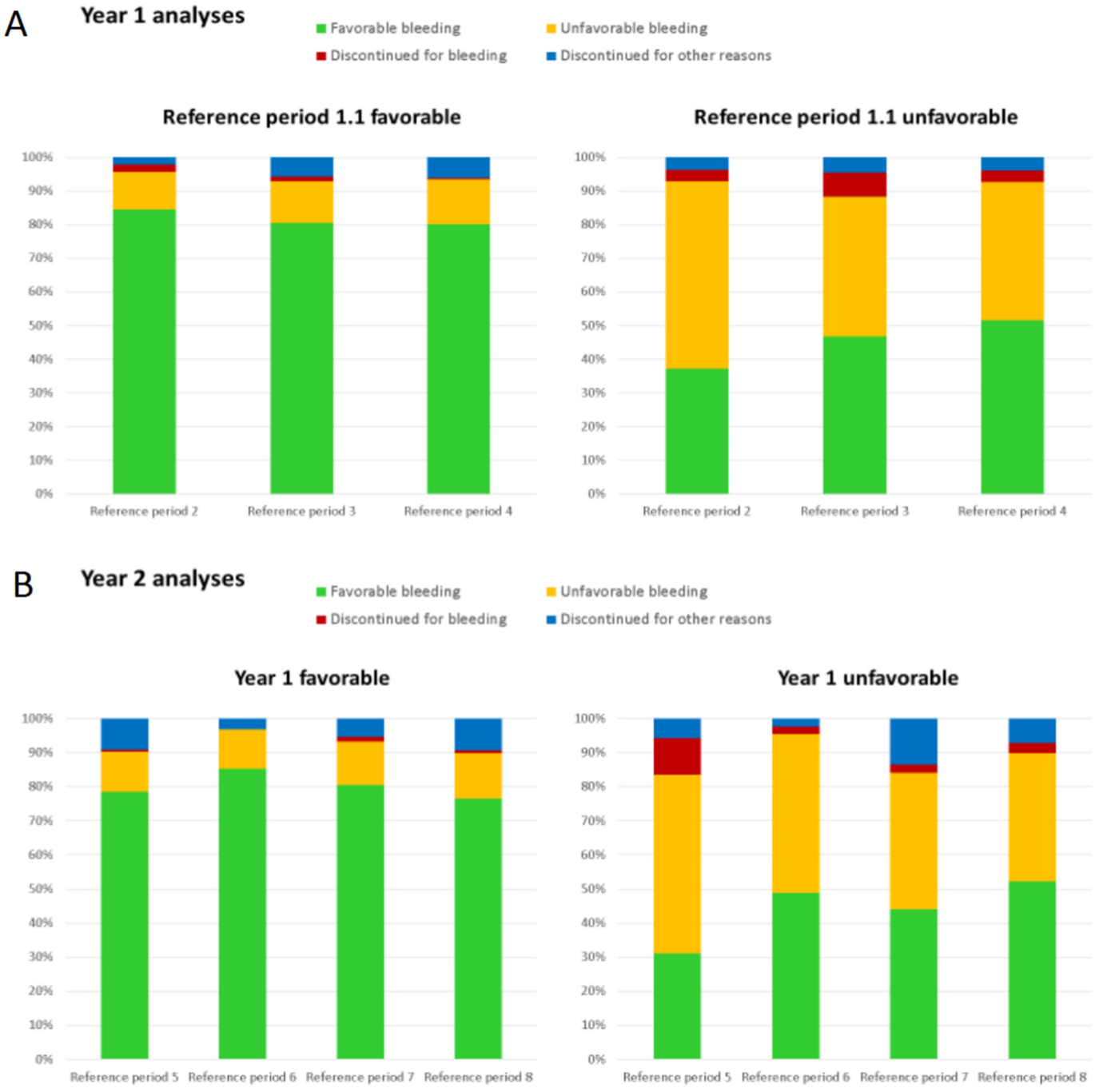

Fig. 1. A) Bleeding patterns and discontinuation data in Reference Period 2, 3 and 4 in correlation with favorable and unfavorable bleeding patterns in reference period; B) Bleeding patterns and discontinuation data in Year 2 (Reference Periods 5, 6, 7 and 8) in correlation with the bleeding pattern in Year 1 being defined as favorable or unfavorable.

improve over time. The likelihood of a favorable bleeding pattern during Reference Periods 2, 3 and 4 are 37.3%, 46.7% and 51.1% respectively, and of unfavorable patterns in Reference Period 2 is 55% and about 40% in Reference Periods 3 and 4.

This is the first report to demonstrate how predictive analyses of progestin-only contraception bleeding data can facilitate counseling in potential etonogestrel implant users. Previous publications have focused on data analyses of the number of bleeding days or patterns in groups of users rather than individuals [10]. This current analysis evaluates bleeding from the patient's perspective by identifying 'favorable' and 'unfavorable' patterns from previous publications and the discontinuation rates associated with these patterns. Being sensitive to religious and cultural influences along with known differences in bleeding patterns among Asian women when using progestin-only contraception [12], we focused our attention on non-Asian women. A subsequent analysis is planned to examine bleeding data in Asian women.

Prediction of future bleeding patterns in women with unfavorable bleeding is more complex than in women with favorable bleeding. About 40–50% of women with an unfavorable pattern in any one reference period are likely to have more favorable bleeding in the next reference period but bleeding in future reference periods can vary. Attrition bias may influence these findings as women with unfavorable patterns are more likely to discontinue etonogestrel implant use.

The initial analysis of this dataset, reported in 2008, suggested that the pattern experienced during the first three months of implant use was broadly predictive of future bleeding patterns for many women [10]. Our re-analyses provide greater detail about the correlation between both favorable and unfavorable bleeding pattern rates across two years and how individual patterns correlate with future bleeding.

We wanted to be sure that the WHO Belsey 1986 criteria [11], which are more than 30 years old, did not lead us to misclassify women's patterns as favorable when "prolonged" bleeding is classified as lasting for more than 14 consecutive days. Women may be intolerant of prolonged bleeding even at lesser durations. For this reason, we assessed whether≫7 or≫10 days of prolonged bleeding may be better at predicting outcomes. Importantly, shortening the definition of prolonged bleeding did not result in any difference in discontinuation rates. However, the data from the Phase 3 trials is more than 15 years old and it is possible that more contemporary data would result in a different finding.

The dataset for this analysis has complete bleeding data for only 2 years, which limits our ability to attempt predictions for the third year of use. Additionally, because the studies did not uniformly assess weight and height, we cannot evaluate the relationship between BMI and bleeding patterns. Most notably, the dataset was not set up to allow analyses for continuation of amenorrhea based on individual bleeding patterns. However, group analysis of amenorrhea over two years with the etonogestrel implant done in 2008 shows that women experience amenorrhea in 22% of the reference periods and this pattern appeared to be acceptable, as indicated by high continuation rates in such women [10]. Although we used diary data from Days 90–118 in both Reference Periods 1.1 and 2, the overlap of this data does not appear to hide any changes in bleeding patterns as correlations between Reference Period 1.1 and Reference Periods 2, 3 and 4 are largely the same.

Future research could help answer important clinical questions, including changes in bleeding patterns in women from different demographic and ethnic backgrounds and in women at the extremes of body weight. In addition, exploring the change in patterns with replacement of the etonogestrel implant would help provide clearer counseling messages.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2019.05.017.

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