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Bleeding and Cycle Control With the Newer Oral Contraceptive Formulations

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In response to scientific advances, manufacturers are now offering oral contraceptive (OC) formulations with an altered hormone-free interval (HFI). Some of these OCs have a 28-day cycle and shortened HFI of 4 days, whereas others have an extended regimen of 84 active-pill days and 7 days of low-dose estrogen that eliminates the HFI altogether.

There is evidence to support such alteration of the HFI. Ovarian follicular development can begin during a 7-day HFI,^{1,2} with ovulation occurring once follicles reach a critical diameter—regardless of OC use.³ Shortening the HFI from 7 days to 3 or 4 days can result in greater inhibition of ovarian follicular development⁴ and blunted activity of the pituitary-ovarian axis.⁵ There is also clinical evidence that extending the active-pill cycle can positively affect premenstrual symptoms by decreasing the frequency of menstruation.⁶ Improvements have been noted in daily self-reported mood scales (composite of anxiety, depression, and irritability), the Daily Record of Severity, and menstrual-related physical and emotional symptoms in women taking an extended-regimen OC.

These newer OC formulations have proven safety and efficacy that is qualitatively comparable to other products

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DISCLOSURE

Dr London reports he is on the speakers' bureaus of Berlex Laboratories; Duramed Pharmaceuticals, Inc; Eli Lilly & Company; Merck & Co, Inc; and Wyeth Pharmaceuticals.

in that class.⁷⁻⁹ To select the OC that best suits each patient, physicians need to understand the various methods used to evaluate these bleeding patterns (Table).

BLEEDING ASSESSMENT METHODOLOGY

Although the definition of a cycle has been uniformly defined, there are currently no standards for evaluating OC bleeding profiles.¹⁰ The first attempt to analyze and standardize OC bleeding patterns (the "Belsey criteria") came from the World Health Organization in 1986, but these guidelines were not universally accepted.¹¹⁻¹³ A renewed effort to establish standards has been proposed.¹⁴ However, until there is uniformity, cycle control data from clinical trials must be evaluated on an individual basis for each OC.

Registration trials of OCs universally use a patient daily diary to record bleeding and/or spotting. However, the diary instructions and contents are generally not described. Up until 2003, all studies used paper diaries or menstrual calendars, which may introduce recall bias¹⁵; electronic diaries have the advantage of real-time entry, mitigating some of this bias. Only one study in this review utilized an electronic diary.¹⁶ In addition to the Belsey criteria, bleeding/spotting may also be defined using the subjective model of "light" or "heavy," which varies among studies.¹⁰ Indeed, there are so many variations in bleeding criteria that the number of possible unscheduled bleeding/spotting days within a single 28-day cycle may range from as few as 13 to as many as 21. Furthermore, the incidence of unscheduled bleeding/spotting may be reported as mean or median

TABLE. Summary of Bleeding Assessment Methods

Formulation	Study Duration	Diary Type	Definition of Bleeding/Spotting	Criteria for Assessment	Analysis Population and Excluded Cycles
EE 30 mcg/ LNG 150 mcg x 84 d + EE 10 mcg x 7 d (91-d cycle) ⁷	1 y	Daily electronic	Not defined	Total days of bleeding/spotting during each 91-d cycle Mean and median bleeding/spotting days during evaluated 7-d low-dose EE monotherapy Mean and median bleeding/spotting days during 84-d combined active-pill interval, plus median "per patient month"	All data from ITT population were evaluated No cycles were excluded
EE 20 mcg/ DRSP 3 mg x 24 d + 4 d placebo (28-d cycle) ⁸	13 cycles	Diary cards	None = no vaginal bleeding; spotting = required only panty liners; light = less sanitary protection than normal menstruation; normal = like normal menstruation; heavy = > normal menstruation	Withdrawal bleeding was the first bleeding after hormone withdrawal All other was irregular bleeding 90-d reference period, with the first period starting on the first treatment day Presented mean data for full analysis set	Bleeding analysis conducted on the full analysis set and per-protocol set
EE 20 mcg/ NETA 1 mg x 24 d + 4 d placebo (28-d cycle) ⁹	6 mo	Not described	0 = none; 1 = light (< menstruation); 2 = normal (similar to menstruation); 3 = heavy (> menstruation); spotting = light bleeding requiring minimal or no sanitary protection	Mean number of intracyclic bleeding/spotting days and episodes recorded during cycles 2-6 Intracyclic and withdrawal bleeding by reference period Composite score for intensity of withdrawal bleeding calculated by multiplying the duration of withdrawal by average intensity Withdrawal bleeding = any bleeding from the last day of active drug intake to day 2 of next treatment cycle or any bleeding starting 4 d prior to last day of active drug intake and continuing at least through the first day after the end of active drug within the cycle	Bleeding analysis of MITT population Cycles with < 14 evaluable diary days excluded from per-cycle analysis Reference periods with < 56 evaluable diary days excluded from reference period analysis Number of excluded cycles not reported

EE = ethinyl estradiol; LNG = levonorgestrel; ITT = intent-to-treat; DRSP = drospirenone; NETA = norethindrone acetate; MITT = modified intent-to-treat.

within a cycle or within a predefined reference period. This variability in presentation inhibits comparison, leaving physicians no choice but to review each study and data set.

ALTERING THE HORMONE-FREE INTERVAL

Three OC formulations were introduced in 2006 that shorten^{8,9} or eliminate the HFI.⁷ Methods of data collection and bleeding assessment differed in each case.

One trial evaluated a 91-day, extended-regimen OC that utilizes low-dose ethinyl estradiol (EE) during the usual

7-day HFI.⁷ All patients completed daily electronic diaries. Definitions of bleeding and spotting were not provided in the published report. Although intensity of bleeding was noted in the diary, the scale used by patients was not described. Data from patients in the intent-to-treat population were analyzed, and no cycles were excluded. Mean and median* numbers of reported days of scheduled bleeding and unscheduled bleeding were reported by cycle. The

*Mean refers to the average number of days reported for the population while the median refers to the midpoint value; half of the values will fall above it and half will fall below.

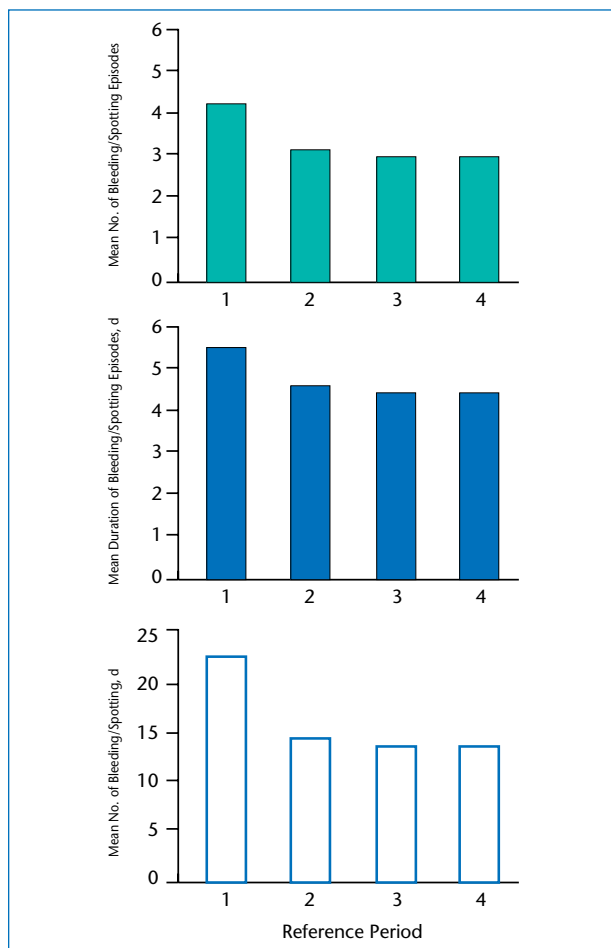
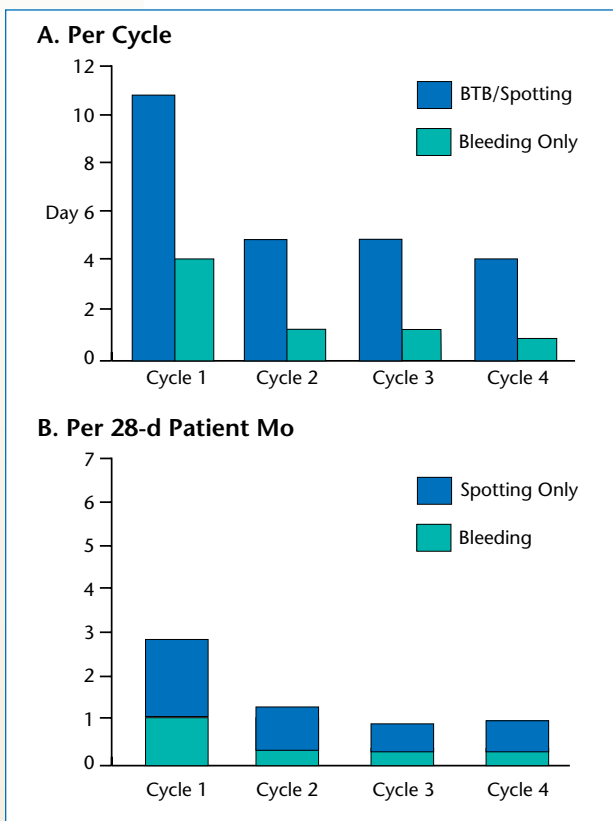


FIGURE 1. Median unscheduled bleeding and/or spotting and bleeding alone in a study of a 91-d, extended-regimen oral contraceptive utilizing continuous low-dose ethinyl estradiol per cycle (A) and per 28-d patient month (B).⁷

BTB = breakthrough bleeding.

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FIGURE 2. Bleeding patterns during the 90-d reference periods for a 28-d oral contraceptive regimen with shortened hormone-free interval (ethinyl estradiol 20 mcg/drospirenone 3 mg).⁸

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median for unscheduled bleeding days was also reported “per patient month.” The mean for scheduled bleeding ranged from 2.7 days in cycle 1 to 2.2 days in cycles 3 and 4. The medians for unscheduled bleeding/spotting days and bleeding-only days in the first cycle were similar to those reported with another 91-day, extended-regimen product, and declined sharply in subsequent cycles (Figure 1). The median for unscheduled bleeding only per 28-day patient month declined from 1.0 in cycle 1 to 0.3 in cycles 2 to 4. The authors noted that no comparisons could be made to other OCs because of the “wide variability in collection method and data analysis.”⁷

Another report described the bleeding patterns associated with an OC that reduced the HFI to 4 days.⁸ Paper diary cards were utilized to classify bleeding patterns according to a subjective scoring system based on experience with menstruation. The study used a 90-day reference period and presented mean data.¹¹ The mean number of bleeding/spotting days and the mean duration of bleeding episodes decreased from reference period 1 to reference period 2, and remained low and stable to the end of reference period 4 (Figure 2). Bleeding patterns were

assessed for the full analysis set and the per-protocol set, with data reported for the full analysis set. The authors noted that reference period analysis allows for direct comparison of vaginal bleeding patterns among different OCs, and avoids the arbitrary definitions required by analysis based on a treatment/menstrual cycle. While the use of the reference period analysis across studies could standardize analysis of bleeding data, it does not delineate scheduled versus unscheduled bleeding nor does it provide clinicians or their patients with meaningful clinical data.

The third OC approved in 2006 also utilized a 28-day regimen with a shortened HFI. It was evaluated in a 6-month randomized study comparing a traditional 21/7 norethindrone acetate (NETA)/EE regimen to a 24/4 NETA/EE regimen.⁹ Patients completed daily dairies (type not specified) that rated bleeding based on menstrual experience. The mean number of intracyclic bleeding/spotting days (excluding withdrawal bleeding) was assessed for cycles 1 through 6. In addition, data for both

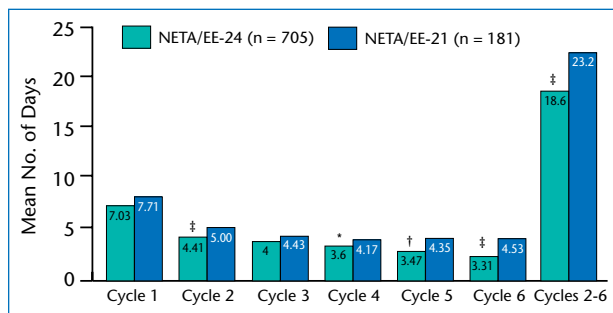


FIGURE 3. Mean number of all bleeding days in patients in the MITT population receiving NETA/EE-21 (n = 181) or NETA/EE-24 (n = 705).

MITT = modified intent-to-treat; NETA = norethindrone acetate; EE = ethinyl estradiol.⁹

*P < .05 versus NETA/EE-21.

†P < .01 versus NETA/EE-21.

‡P < .001 versus NETA/EE-21.

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intracyclic and withdrawal bleeding were summarized by reference period (two periods of three 28-day treatment cycles). Withdrawal bleeding was defined as any bleeding from the last active-pill day to day 2 of the next treatment cycle, or any bleeding from 4 days prior to the last active-pill day through the first day of the HFI within that cycle. The severity of withdrawal bleeding was calculated by multiplying duration by average intensity. Cycles with fewer than 14 evaluable diary days were excluded, as were reference periods with fewer than 56 evaluable diary days. The totals for excluded cycles and reference periods were not reported. The mean number of intracyclic bleeding/spotting days ranged from 2.12 in cycle 1 to 0.95 in cycle 6. Mean duration of withdrawal bleeding ranged from 3.60 days to 3.95 days in cycles 1 through 5, decreasing to 2.66 in cycle 6. There was a mean 18.6 bleeding/spotting days in cycles 2 through 6 (Figure 3). The authors concluded that shortening the HFI to 4 days improved the bleeding profile compared with a 7-day HFI.

CONCLUSION

Although each of these studies provides statistically sound data, the variable methodology for assessing bleeding does not allow for even subjective comparison. Therefore, each study must be evaluated independently within the confines of the methodology used. Conventional methods of defining unscheduled and scheduled bleeding/spotting need to be adapted for OC regimens that alter the HFI. Each of the studies had faults and lacked uniformity, but the regimens have nonetheless demonstrated cycle control that is subjectively comparable to traditional 21/7 OCs after a period of adjustment. Until evaluation standards are adopted, physicians should judge each new product or regimen based on their own clinical experience, not subjective comparisons or claims of superiority. The US Food and Drug Admin-

istration addressed current issues influencing the approval of hormonal contraceptive products in a recent advisory meeting—including clinical trial design, expected efficacy and safety outcomes, and measures of acceptability to patients.¹⁷ While no specific conclusions were drawn, the agency has indicated a goal of issuing guidance to manufacturers regarding study trial design.

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