Extended-regimen oral contraception may be one of contemporary medicine’s best-kept secrets,1 de- clared Dr David J. Portman, and so began this experts’ roundtable. Despite approval of 91-day extended-regimen oral contraceptives (OCs) by the US Food and Drug Administration (FDA) in 2003, women continue to receive OCs in traditional 28-day cycles: 21 days of active treatment with a 7-day hormone-free interval (HFI) (ie, placebo). This 21/7 regimen provides safe and effective contraception, but, in some regards, is a historical relic associated with the inconveniences of monthly prescription refills, 13 physiologically unnecessary withdrawal bleeding episodes, and hormone withdrawal and menstrual-like symptoms, which, may adversely affect long-term adherence.

History of the Hormone-Free Interval

The original intent of the 21/7 OC regimen was psychological, not physiologic, said Dr Portman. When OCs were first introduced, the medical community was concerned that amenorrhea—an indication of EC effectiveness—would induce anxiety about OC failure rather than foster confidence in its efficacy. Thus, the 28-day cycle was designed to mimic menstrual menstruation, thereby assuring women they were not pregnant. The HFI provided the “illusion of natural menstrual cyclicity,” explained Dr Portman, but with no physiologic benefit.

However, the HFI is not without a physiologic effect. The onset of the HFI is linked to a rebound in hormonal and ovarian follicular activity, which may induce monthly withdrawal symptoms such as bleeding, pain, breast tenderness, and bloating/swelling. Such menstrual-like symptoms lead to increased use of pain medications and may moderate/heavy bleeding days (5.2 vs 11 days, respectively; P <0.0001). A greater decline in ovarian volume occurred with the extended regimen than with the 21/7 regimen (P <0.001), and patients using the extended-regimen reported significant improvements in pain (P <0.01) and behavioral changes (P <0.04).

Dr Portman emphasized the need to educate patients about if, when, and how bleeding may occur with extended-regimen OCs. Patients are more tolerant when they understand that bleeding may occur with extended-regimen OCs but that it is less overall than with 21/7 regimens, and there is less moderate/heavy bleeding. Also, he added, physicians should explicitly explain that the 21/7 and 24/4 regimens result in 13 annual withdrawal-bleeding episodes, a single 28-day cycle with an active mono- pharmacic pill (20 µg EE1 mg mifepristone acetate)6 although no overall difference in vaginal bleeding days between regimens occurred, the extended-regimen OC was associated with significantly fewer moderate/heavy bleeding days (5.2 vs 11 days, respectively; P <0.0001). A greater decline in ovarian volume occurred with the extended regimen than with the 21/7 regimen (P <0.001), and patients using the extended-regimen reported significant improvements in pain (P <0.01) and behavioral changes (P <0.04).

Physiologic Effects of a Modified Hormone-Free Interval

During the HFI, hormonal and ovarian follicular activity suppression is interrupted and, as an ovarian follicular activity rebounds, withdrawal and/or menstrual-like symptoms may emerge.1-3 One approach to maintaining continuous ovarian follicular suppression cited by Dr Portman is the complete elimination of the HFI with a regimen of only active pills. A randomized, open-label study comparing 28 days of a combined OC with a standard 21/7 regimen over three cycles was associated with less follicular development (P <0.001) and the development of fewer follicles larger than 4 mm (P <0.006).1 In women taking the 21/7 regimen, eight dominant follicles began development during the HFI, whereas no dominant follicles were observed with the continuous OC. Overall, the continuous regimen better suppressed follicular development and break-through ovulation than the 21/7 regimen, Dr Portman explained.

Another strategy for consistent ovarian follicular and hormonal suppression is to shorten the HFI from 7 days to 4 days or less, said Dr Portman. Comparisons of standard 21/7 regimens with altered 28-day strategies have demonstrated that the shorter HFI results in greater sustained suppression of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and inhibin-B levels.7 In one analysis, all four hormones were significantly increased from baseline (P <0.001) during a 7-day HFI, whereas, among patients receiving 24/4 and 25/3 regimens, there was substantially greater and sus- tained hormone suppression (Figure 1). The findings suggest that ovarian follicle suppression is possible during a 7-day HFI and that a shorter HFI may provide more consistent hormone suppression. Adherence to extended Regimen

Adherence to extended-regimen OCs using a 21/7 HFI has been seen in many other studies.8 Overall, the most sustained hormonal suppression was achieved with the 84/7/EE regimen.

Several another strategy described by Dr Portman may provide more robust and stable hormone suppression than standard 21/7 regimens.4,5 He cited a study by Vanderweij and colleagues that compared hormone levels in women randomized to regular cycles of 21/7 levonorgestrel (LNG) plus estradiol (EE), one cycle of LNG/EE for 8 days plus a 7-day HFI (the 84/7/EE regimen), and one cycle of LNG/EE for 8 days plus 7 days of low-dose EE (the 84/7/EE regimen). Patients randomized to the 84/7/EE regimen, as compared to patients taking 21/7 and 84/7/EE regimens, had significantly lower levels of FSH and estradiol (P <0.05). There were fewer follicles with the 84/7 EE regimen than with the other regimens. Increased hormone suppression appeared to correlate to fewer bleeding days as evidenced by the lower rates of daily menstrual flow with the 84/7/EE regimen and the 84/7/EE regimen than with the 21/7/EE regimen (P <0.05). This possible benefit of extended-regimen OCs has been observed in other studies.9 Overall, the most sustained hormonal suppression was achieved with the 84/7/EE regimen.

Similarly, Legro and colleagues, in a randomized, double-blind trial, compared the number of bleeding days during six cycles of a 21/7-regimen OC with single 28-day cycle with an active monophasic pill (20 µg EE 1 mg mifepristone acetate)6 although no overall difference in vaginal bleeding days between regimens occurred, the extended-regimen OC was associated with significantly fewer moderate/heavy bleeding days (5.2 vs 11 days, respectively; P <0.0001). A greater decline in ovarian volume occurred with the extended regimen than with the 21/7 regimen (P <0.001), and patients using the extended-regimen reported significant improvements in pain (P <0.01) and behavioral changes (P <0.04).

Study Intervals

Day 1 is the last day of oral contraceptive use for all groups. In the 7-day HFI, Days 1–7 represent the HFI and Day 8 is the first day of OC use in the next cycle. In the 5-day HFI, Days 1–5 represent the HFI and Days 6–8 are on cycle in the next cycle. In the 4-day HFI, Days 1–4 represent the HFI and Days 5–8 are on cycle in the next cycle. Levels in the 28-day regimen were assessed on Days 1 and Days 3/4 of OC use (P <0.0001), which are the 5th and 4th study days, respectively. Levels in the extended regimens were assessed weekly. No statistically significant differences were observed between the 3-day and 4-day HFI groups; thus, the plot presented posits data for shortening HFI.

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