BEST PRACTICES IN: Extended-Regimen Oral Contraception: Modifying the Hormone-Free Interval

This supplement is the first of three on oral contraception. The content is based on the proceedings of an experts' roundtable held on November 4, 2010, in Miami, Florida, with panelists:

- David J. Portman, MD
- Mandy Gittler, MD
- Christopher Estes, MD
- Versie Johnson-Mallard, PhD, RN

David J. Portman, MD
Director and Principal Investigator
Columbus Center for Women's Health Research
Columbus, Ohio

Introduction

"Extended-regimen oral contraception may be one of contemporary medicine's best-kept secrets," declared 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 OC effectiveness—would induce anxiety about OC failure rather than foster confidence in its efficacy. Thus, the 28-day cycle was designed to mimic monthly 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 adversely affect OC adherence, said Dr Portman.[1-3] Current OC research and development, he continued, is focused on strategies for modifying the HFI by shortening its duration, eliminating it completely, or replacing placebo pills with low-dose estrogen.

Physiologic Effects of a Modified Hormone-Free Interval

During the HFI, hormonal and ovarian follicular activity suppression is released and, as 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.[1] Overall, the continuous regimen provided better suppression of dominant follicle development and breakthrough 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 HFIs result in greater sustained suppression of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and inhibin-B levels.[2] In one analysis, all hormone levels 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 sustained hormone suppression (**Figure 1**).[2] The findings suggest that ovarian follicle recovery is possible during a 7-day HFI and that a shorter HFI may provide more consistent hormone suppression.

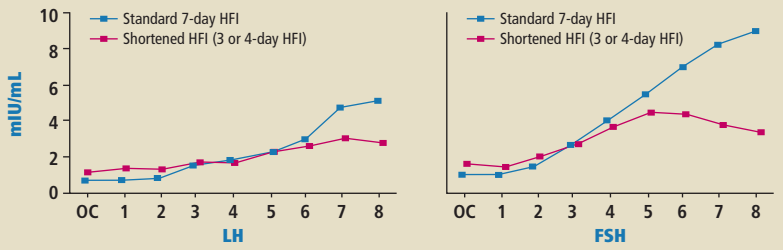
Administration of low-dose estrogen during the HFI is another strategy described by Dr Portman that may provide more robust and stable hormone suppression than standard 21/7 regimens.[4,5] He cited a study by Vandever and colleagues that compared hormone levels in women randomized to three cycles of 21/7 levonorgestrel (LNG)/ethinyl estradiol (EE), one cycle of LNG/EE for 84 days plus a 7-day HFI (the 84/7 regimen), and one cycle of LNG/EE for 84 days plus 7 days of low-dose EE (the 84/7 EE regimen).[5] Patients randomized to the 84/7 EE regimen, as compared to patients taking 21/7 and 84/7 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 regimen and the 84/7 EE regimen than with the 21/7 regimen ($P=0.03$). This possible benefit of extended-regimen OCs has been observed in other studies.[4,5] 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 and a single 168-day cycle with an active monophasic pill (20 µg EE/1 mg norethindrone 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; $P=0.005$). 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 to heavy bleeding. Also, he added, physicians should explicitly explain that the 21/7 and 24/4 regimens result in 13 annual withdrawal-bleeding episodes, whereas extended-regimen OCs induce substantially fewer annual episodes. Dr Christopher Estes, another panelist, added that, when discussing extended-regimen OC–related bleeding with patients, it is helpful to explain that bleeding is a sign of endometrial atrophy, a thin uterine lining, and OC efficacy.

Improvements in premenstrual-type symptoms and mood changes with extended-regimen OCs have been observed and are important factors to explain to patients, continued Dr Portman. Coffee and colleagues compared mood changes in women who took a 21/7 regimen followed by an extended 168-day regimen (drospirenone/EE).[7] Mood changes occurred throughout the 21/7 regimen and reached their most extreme during the HFI. Symptoms decreased with the 168-day regimen ($P<0.001$), with the greatest improvement seen in the sixth month of treatment ($P<0.003$) (**Figure 2**).[7]

Figure 1. Gonadotropin Levels With Standard Error Comparing the 7-Day Hormone-Free Interval (HFI) With the 3-Day or the 4-Day HFI in 12 Patients

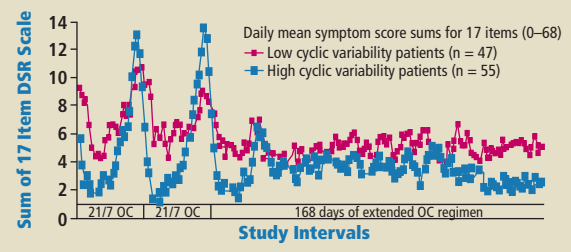


*$P<0.05$. **$P<0.01$ indicates days where gonadotropin levels differ within patients between cycles.

Day 0 is the last day of oral contraceptive (OC) use for all groups. In the 7-day HFI, Days 1–7 represent the HFI and Day 8 the first day of OC use in the next cycle. In the 3-day HFI, Days 1–3 represent the HFI and Days 4–8 OC use in the next cycle. In the 4-day HFI, Days 1–4 represent the HFI and Days 5–8 OC use in the next cycle. Gonadotropin levels did not vary ($P=0.44$) between the 3- and 4-day HFIs, so this plot presents pooled data for shortened HFI.

Source: Willis et al.[2]

Figure 2. Comparison of 17-Item Penn State Daily Symptom Report (DSR17) scores for Two 21/7 Oral Contraceptive (OC) Cycles Followed by a 168-Day Regimen for Patients With High and Low Cyclic Variations in Mood



Groups differ ($P<0.0001$), treatment days differ ($P<0.0001$), and group by treatment day interactions are significant ($P=0.042$)

Source: Coffee et al.[7]

Another panelist, Dr Mandy Gittler, pointed out that premenstrual-like symptoms often go unreported by patients taking 28-day regimens unless patients are specifically asked. These symptoms, Dr Gittler said, are often accepted with resignation; although a patient may be dissatisfied, she may not complain because she believes nothing can be done. A few questions, Dr Gittler continued, may reveal a patient's level of satisfaction and provide an opportunity to introduce an extended-regimen OC. When introducing extended-regimen OC, in addition to safety and efficacy, physicians must also consider convenience, Dr Gittler added. Some extended-regimen OCs, such as 24/4 regimens, require monthly prescription pick-up, which may prove inconvenient for some patients. Although one would hope that contraception decisions were primarily based on a patient's medical needs, said Dr Gittler, convenience, as well as cost, is an important factor for many.

Safety and Efficacy of Extended-Regimen Oral Contraception

Extended-regimen OCs containing low-dose estrogen are safe and effective. In a multicenter, open-label, phase III trial with 1,006 patients, a 91-day regimen of 30 µg EE/150 µg LNG for 84 days plus 10 µg EE for 7 days was associated with a 1-year method failure rate of 0.78 (Pearl index) and 0.64% (life table analysis). Adverse events occurred in 16.3% of patients, a rate comparable to other OC regimens.[8] A total of 116 women completed a 3-year extension of the study with a total exposure comparable to 8,292 cycles of 28 days.[9] During the follow-up period, no thromboembolic events occurred, and 9.7% of these women discontinued treatment because of an adverse event, which is a rate also consistent with other OCs. The safety of extended regimens has been confirmed in many other studies.[9-13]

Conclusion

The HFI in standard 28-day OC regimens once served to assure women of OC efficacy. However, with more than 50 years of proven OC safety and efficacy data, as well as several studies linking the HFI with withdrawal symptoms, the 28-day regimen is increasingly recognized as a strategy of the past. Emerging studies on extended-regimen OCs with and without estrogen have demonstrated comparable efficacy and safety, and sustained hormone and ovarian follicular suppression. This more robust effect may translate into reduced withdrawal and premenstrual-like symptoms, as well as to improve overall long-term OC adherence. Emphasizing these potential benefits is the key to improving acceptance among physicians and long-term OC adherence among patients, Dr Portman concluded.

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