

Placebo-Free OC May Improve Bleeding Pattern

BY NANCY WALSH
New York Bureau

MINNEAPOLIS — A newer extended-regimen oral contraceptive that includes 7 days of low-dose estrogen rather than a week of placebo pills is associated with an improved bleeding pattern.

The newer formulation, known as Seasonique, was shown in a cross-study analysis of two phase III trials to be associated with fewer scheduled bleeding days and a reduction in breakthrough bleeding, compared with an older formulation called Seasonale, Dr. Andrew N. Kaunitz said at the annual meeting of the Association of Reproductive Health Professionals.

Both regimens include 84 days of 30 mcg ethinyl estradiol and 150 mcg of levonorgestrel, but Seasonique substitutes 7 days of 10 mcg ethinyl estradiol monotherapy for the 7 days of placebo in the Seasonale regimen. The two drugs are manufactured by Duramed Pharmaceuticals, and Dr. Kaunitz is a speaker or consultant for Duramed Pharmaceuticals and various others.

In the first of the two pivotal 1-year trials, 682 patients from 47 sites throughout the United States were randomized to receive Seasonale or the conventional 28-day oral contraceptive (OC) Nordette, which contains the same daily dose of hormones. The incidence of unscheduled bleeding initially was higher among patients on the extended-cycle regimen, but decreased throughout the study, said Dr. Kaunitz of the University of Florida, Jacksonville, who was one of the investigators in this trial.

By the end of the trial, the incidence of unscheduled bleeding in the extended-cycle regimen was comparable, at a median of 3.6% of days, to that in the conventional group, at 2.9% of days.

In the second study, Seasonique was evaluated in an open-label fashion among 1,006 women being treated at 36 U.S. sites. In this study, the median number of days of unscheduled bleeding in the first extended cycle was similar to that reported in the first trial, but decreased sharply in subsequent cycles. By cycle four, the median number of days of unscheduled bleeding was 0.3 on a per-patient-month basis.

Analysis of the data from these two studies showed that unscheduled bleeding and spotting decreased more quickly with the 91-day regimen that included low-dose estrogen, approaching significance in the second cycle and achieving significance in the third cycle, Dr. Kaunitz said.

Moreover, there were consistent differences in length of scheduled withdrawal bleeding episodes, with a median of 3 days for Seasonique and 4 days for Seasonale, he said.

"This was not a head-to-head study," he cautioned. Nonetheless, the patient populations were comparable in baseline characteristics, race, age, prior OC use, smoking, and body mass index, and the pattern of unscheduled bleeding seen during the first 3-month cycle was identical across the two studies. Only after the first placebo or low-dose estrogen week was there a dif-

ference in bleeding pattern, so observations across the two studies should be valid, he said.

Previous research has found that there is a correlation between the amount of breakthrough bleeding and both higher endogenous 17- β estradiol levels and larger follicle size.

In a meta-analysis of seven prospective trials of various combination OC formulations, the pills that were associated with greater follicular suppression were also

those that had improved bleeding profiles.

"Endrikat in Germany [lead author of this meta-analysis] speculated that a biologic mechanism explaining why better follicular suppression was associated with less intermenstrual bleeding might be that the endometrium of women on the pill is not only responsive to exogenous estrogen, as we traditionally thought, but also to the endogenous 17- β estradiol made by follicles during OC use," he said.

In another study that compared follicu-

lar suppression by means of manipulation of the hormone-free interval with three different OC regimens, women receiving supplementation with 5 days of 10 mcg ethinyl estradiol had fewer and smaller follicles than women who had a 7-day hormone-free interval.

"I believe that my data add to Endrikat's hypothesis, that OCs that result in better follicular suppression can help women achieve better bleeding profiles," Dr. Kaunitz said. ■



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