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Alteration of the hormone-free interval during oral contraception

DR SULAK: The estrogen and progestin doses in oral contraceptives (OCs) have steadily decreased since the 1960s; however, until recently, we've kept the same 21/7-day regimen. Due to the high doses in the first-generation OCs, the hormones lingered into the week off. With the low-dose pills and a 7-day hormone-free interval (HFI), we have seen problems such as ovulation, estrogen withdrawal symptoms, and unscheduled bleeding (ie, breakthrough bleeding or spotting).

DR LIU: The physiology of ovarian follicle development explains why many of these problems occur. In the normal menstrual cycle, follicle-stimulating hormone (FSH) levels increase dramatically during the first 2 days of menses, driving the development of as many as 10 early (primordial) follicles. As estrogen and inhibin B levels increase and suppress FSH, only the follicle with the greatest ability to generate FSH receptors within itself survives this low-FSH environment to become the "egg of the month."

During the HFI of an OC regimen, FSH begins to rebound just as it does in a normal menstrual cycle. With very-low-dose estrogen/progestin OCs, this rebound occurs rapidly and follicles begin to develop. If the follicle develops to a critical stage—which might be as small as 14 mm—escape ovulation may occur, despite the resumption of active OC pills and dampening of FSH.[1] In fact, up to 30% of women may ovulate on OCs when the HFI is increased.[1]

DR SULAK: It is amazing how rapidly the pituitary wakes up and starts producing FSH—and how responsive the ovary is! Studies have shown that the dramatic rise in FSH occurs around the fourth day of a 7-day HFI, followed rapidly by the rise in 17-beta estradiol from the ovarian follicles.[2,3] We reported a 500% increase in estradiol, from 10 pg to almost 60 pg—and that was using a 30 mcg pill.[2]

I am amazed that more people taking OCs do not conceive. The reason failure rates are not higher is due in large part to the "backup mechanisms" of the pill, such as cervical mucous thickening and thinning of the endometrial lining.

Patricia J. Sulak, MD
Professor, Texas A&M College of Medicine
Medical Director, Division of Departmental Research
Director, Adolescent Sex Education Program
Department of Obstetrics and Gynecology
Scott and White Hospital
Temple, Texas

James H. Liu, MD
Arthur H. Bill Professor and Chair
Departments of Reproductive Biology and Obstetrics and Gynecology
Case Medical Center
MacDonald Women's Hospital
Cleveland, Ohio

Dr Sulak reports that she has received grant/research support from Duramed, Organon, and Warner Chilcott; has served as a consultant to Duramed and Warner Chilcott; and is a member of the speakers' bureau of Bayer, Duramed, Warner Chilcott, and Wyeth.

Dr Liu reports that he has received grant/research support from Barr-Duramed, Procter & Gamble, and Solvay; and has served as a consultant to Barr, Novagyn, and Solvay.

Development of extended-regimen OCs

DR LIU: Starting in 1998 with the approval of Mircette, we've begun to see a number of modifications to the 21/7 regimen.

DR SULAK: Mircette is a regimen of 21 days of 20 mcg ethinyl estradiol (EE) and 0.15 mg desogestrel, 2 placebo days, and 5 days of 10 mcg EE pills. Comparing Mircette with a 21/7 regimen of the same hormones, researchers found that women experienced greater ovarian suppression and less follicular development when a 10 mcg EE pill replaced the last 5 placebo pills.[4]

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Interestingly, even though Mircette is a 20 mcg EE pill, its bleeding profile is comparable to many OCs with 30 mcg EE.[5,6] Adding that low dose of estrogen suppresses the ovary and prevents "rebound" FSH and estrogen production; it is the production of endogenous estrogen that interferes with the next cycle and causes breakthrough bleeding.[6,7]

All of the OCs that have been approved since 2003 feature modifications of the 21/7 regimen. Seasonale extended the OC regimen to 84 days of active pills followed by 7 days off. Loestrin 24 and Yaz shortened the HFI of a 28-day regimen and demonstrated that 20 mcg EE pills can have a good bleeding profile if the HFI is decreased.

Seasonique (84 days of levonorgestrel, 0.15 mg, and EE, 30 mcg; followed by 7 days of EE, 10 mcg) was developed when it became apparent that after prolonged suppression, FSH rises very quickly and the ovary is even more responsive; a 7-day HFI could lead to escape ovulation and other problems.[2,3,8] The most recently approved OC regimen is Lybrel, a continuous ultra-low-dose regimen of EE and levonorgestrel.

DR LIU: So the modifications to the HFI have been made based on our understanding of how follicular development

can be suppressed and why escape ovulation occurs. Altering the HFI can address some of these problems. The use of a very-low-dose estrogen in place of the placebo suppresses the pituitary and attenuates the rise of FSH and inhibin B, so that a new crop of follicles does not begin to develop.[9]

Importance of correct, consistent use

DR LIU: For patients using an OC with an HFI, during which days of the regimen is missing a pill most likely to cause contraceptive failure?

DR SULAK: The first pill is the most important one in the pack! Particularly with low-dose OCs, it's especially a problem if a patient misses a pill during the first week after a 7-day HFI.

DR LIU: I tell patients that it takes several tablets to suppress FSH; no single tablet will maintain a persistent effect. Missing a pill during the first 5 days is probably more risky than missing 1 or more in the second or third week.

DR SULAK: The rise in FSH and 17-beta estradiol during the 7-day HFI continues into the first week of active pills and takes 5 to 7 days to decrease significantly.[2]

Reducing hormone withdrawal symptoms

DR LIU: Clinicians started extending OC regimens for patients with endometriosis or suspected endometriosis, whose pelvic pain flared up with the onset of bleeding.

DR SULAK: Then we realized that the benefits of extended regimens went beyond endometriosis and could help patients with menstrual migraine headaches or severe premenstrual syndrome. With extended regimens, we have shown reductions in mood swings, pain, headaches, bloating, and swelling.[6,10-12]

With a low-dose regimen and a 7-day HFI, we were actually creating estrogen-withdrawal headaches, cramps, bloating, and other symptoms.[13] In our prospective randomized trial of Seasonale vs Seasonique, we observed a tendency toward fewer headaches during the estrogen-supplemented week.[7] And we weren't even looking at headaches in that study! Adding estrogen during that typical week off may have the potential to decrease some of these withdrawal symptoms, but this needs further study.

Bleeding and spotting: Managing expectations

DR LIU: When a patient begins an extended-regimen OC, how do you manage her expectations about spotting and bleeding?

DR SULAK: Any patient on an extended-regimen OC has to be a great pill-taker, so I suggest that she put her pills somewhere she'll see them at about the same time every-day. I tell patients that particularly during that first cycle, there is a high incidence of unscheduled bleeding. When I prescribe an OC regimen that substitutes a low-dose estrogen pill for the traditional placebo week, I explain that the patient will have a progestin withdrawal bleed during the estrogen-only pills. I also mention that in subsequent packs, the unscheduled bleeding is greatly reduced.[14,15]

Conclusions

DR LIU: The modifications to the HFI that we've seen in recently approved OCs represent an incremental advance in our understanding of the physiology of ovarian follicle development. Experience and studies have shown how altering the HFI can optimize patient outcomes.

DR SULAK: We do need to see the demise of the 7-day HFI. Practitioners should realize that these changes in OCs are not arbitrary. They are substantiated by real science and will mean a true improvement in the symptoms and quality of life our patients experience. ■

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