CLINICAL UPDATE

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Extended Regimen Oral Contraceptives—Practical Management

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A roundtable discussion among key thought leaders in the area of hormonal contraception was held on October 20, 2006, in New Orleans, Louisiana. These experts addressed the critical questions regarding the practical management of extended regimen oral contraceptives based on information in the medical literature.

Oral contraceptives (OCs) have been available in the United States for nearly 50 years. It is easy to forget that the introduction of reliable oral contraception—a widely available method that allows women control of their fertility—was revolutionary at that time. The decision to use a 28-day pill regimen was not a response to a physiologic need for 13 cycles per year but was dictated by the social norms and pregnancy testing technology of the day. At a time when pregnancy testing was neither easy to perform nor highly sensitive, the 7-day hormone free interval (HFI) provided a monthly reassurance to the OC user that she was not pregnant. Over the ensuing years numerous improvements in oral contraception have taken place—lowering of estrogen content due to safety concerns, confirmation of the efficacy of low-dose pills,

Disclosures (PRIOR 12 MONTHS)

Dr Sulak has received research grants from Barr Pharmaceuticals, Inc., Berlex Laboratories, and Organon Inc; is a consultant to Barr Pharmaceuticals, Inc., Berlex Laboratories, and Wyeth; and is a speaker for Barr Pharmaceuticals, Inc., Berlex Laboratories, Merck, and Wyeth.

Dr Kaunitz has received support for clinical trials (funding to University of Florida Research Foundation) from Berlex, Duramed Pharmaceuticals, Johnson and Johnson, and Warner Chilcott. He serves as a speaker for and/or a consultant to the American College of Obstetricians and Gynecologists, Berlex, Duramed Pharmaceuticals, Johnson and Johnson, Merck, Organon, and Pfizer. He holds stock in Barr, Noven, Procter and Gamble, Roche, and sanofi-aventis.

Dr London is a speaker for and/or consultant to Berlex, Duramed, Eli Lilly and Co, Merck, Solvay Pharmaceuticals, and Wyeth.

Ms Moore is a speaker for and/or consultant to Berlex, Duramed, Organon, Ortho, and Wyeth.

Dr Nelson has served as a speaker for Barr, Berlex, FEI Women's Health, Merck, Organon, Ortho McNeil, Pfizer, Ther-Rx, and Wyeth. She has served as an advisor for Ascend Therapeutics, Barr, Berlex, Church and Dwight, Organon, and Wyeth. She also has received research support from Berlex, Organon, Pfizer, and Wyeth.

TABLE 1

Conditions Associated With Oligomenorrhea/Amenorrhea

Polycystic ovarian syndrome	Anorexia nervosa
Premenarchal status	Athletic amenorrhea
Uterine adhesions	Cervical stenosis
Pregnancy	Ovarian failure
Perimenopause	Ovarian tumor
Emotional stress	Brain tumor
Endocrine disorders (thyroid, pituitary, adrenal)	

TABLE 2

Health Risks

Recurrent Ovulation/Bleeding	
Bleeding/anemia	Endometriosis with associated pain and infertility
Ovarian cancer	Ovarian cysts
Premenstrual syndrome	Premenstrual dysphoric disorder
Amenorrhea	
Osteoporosis	Atrophic vaginitis
Cardiac arrhythmia	
Oligomenorrhea	
Endometrial hyperplasia	Endometrial cancer
Infertility	

introduction of new progestins, and phasic regimens. These changes came about due to a large number of clinical trials and other scientific assessments of OC regimens. Now with research shifted toward reducing the HFI and maximizing ovarian follicular suppression, oral contraception is undergoing a second revolution. By altering or eliminating the HFI, the goal of reducing withdrawal bleeding and minimizing hormone withdrawal can be accomplished.

Both spontaneous menstrual bleeding associated with ovulatory cycles and iatrogenically induced scheduled bleeding associated with OCs are due to endogenous or exogenous hormone withdrawal. However, the similarity ends abruptly, as menstrual bleeding fulfills a physiologic need to slough the secretory endometrium after ovulation in preparation for a new cycle and possible pregnancy. In contrast, there is no health-related reason to bleed while taking OCs. Monthly menstruation in reproductive-age women is necessary unless the patient is pregnant, using hormonal contraception, breastfeeding, or has undergone hysterectomy. A lack of cyclical menstrual bleeding in women not taking hormonal contraception is indicative of a pathologic state, whether it is the hypoestrogenic state of premature ovarian failure or the unopposed estrogen anovulatory state characteristic of women with polycystic ovarian syndrome (**TABLE 1**). Conversely, the recurrent ovulation and menstruation that is common among today's post-industrial women is associated with health risks (**TABLE 2**).

The focus on alteration of the HFI to further improve OC therapy began with the introduction of Mircette® in 1998.[1] This was followed by the introduction of Seasonale®, the first extended OC regimen[2] and subsequently 2 OC products, Yaz® and Loestrin® 24 Fe, that maintained the 28-day cycle with a shortened HFI.[3-5] A recently introduced OC product, Seasonique®, uses an extended 91-day regimen with low-dose ethinyl estradiol (EE) during the HFI, thus eliminating the HFI completely (**TABLE 3**).[6]

Are there specific clinical advantages to extended regimen OCs?

DR LONDON: The real advantage to the extended regimens is that they do not have the *disadvantages* known to exist with the 21/7 regimens.

DR KAUNITZ: There are 4 advantages to extended regimens:

- improvement in contraceptive success
- therapeutic use for hormone withdrawal symptoms
- treatment of gynecologic problems such as dysmenorrhea, endometriosis, and anemia
- accommodation of lifestyle preference

TABLE 3

OC Products With Extended Regimens or Altered Hormone Free Interval

Product Content	Brand	Regimen	Duration of HFI	No. Withdrawal Bleeding Episodes/Year
30 mcg EE/150 mcg LNG and 10 mcg EE	Seasonique	91 days: 84 days active + 7 days low-dose EE	No HFI	4
20 mcg EE/1 mg NETA	Loestrin 24 Fe	28 days: 24 days active + 4 days placebo	4 days	13
20 mcg EE/3 mg DRSP	Yaz	28 days: 24 days active + 4 days placebo	4 days	13
20 mcg EE/150 mcg DSG and 10 mcg EE	Mircette	28 days: 21 days active + 2 days placebo + 5 days low-dose EE	2 days	13
30 mcg EE/150 mcg LNG	Seasonale*	91 days: 84 days active + 7 days placebo	7 days	4

DRSP = drosperinone, DSG = desogestrel, EE = ethinyl estradiol, HFI = hormone-free interval, LNG = levonorgestrel, NETA = norethindrone acetate, OC = oral contraceptive.
*Seasonale is the only extended regimen OC for which there is a generic substitute.

Once women understand that extending combined hormone contraceptives is safe, most will prefer fewer cycles.

DR SULAK: While we need to acknowledge that the decision to introduce the first OCs in a 21/7 regimen was a wise choice nearly 50 years ago, research has shown us that the low doses of EE and the 7-day HFI creates problems—incomplete pituitary-ovarian suppression, endogenous estradiol formation, follicular development, ovarian cyst formation, risk of escape ovulation, and hormone withdrawal symptoms. It doesn't matter whether a pill, patch, or ring is used—a 7-day HFI is too long with today's low-dose combined hormonal contraceptives.

Spona was the first to report greater suppression of ovarian activity with a shortened HFI.[7] By increasing the number of active pills from 21 to 23 per cycle and decreasing the HFI from 7 to 5 days, there was lower residual ovarian activity and endogenous 17β-estradiol. The study also showed that 17β-estradiol levels began to rise during the HFI but the rise was earlier and greater in women assigned to the 21-day regimen.

DR KAUNITZ: Another fundamental issue focuses on the reason our patients use OCs—effective, convenient, and reversible contraception. Unfortunately, the current 21/7 paradigm may not be optimal. The "typical" failure rate with OCs—which is what applies to our patients—is 8%.[8] I don't think that is acceptable.

> "There is no medical or physiologic reason for us to force patients taking OCs to have a monthly withdrawal bleed."
>
> **A. NELSON**

The HFI and the first few days of a new pill pack are the time at which women are at greatest risk for contraceptive failure and unintended pregnancy. By extending the overall duration of active pills and decreasing the duration of the HFI, we are setting our patients up for better contraceptive success.

DR SULAK: There is also the issue of symptoms during the HFI. We all recognize that menstrual symptoms—breast tenderness, headache, bloating, and cramping—increase during the HFI.[9] Although our data reported significant hormone withdrawal symptoms in women taking OCs, women experience these symptoms with all forms of combined estrogen-progestin hormonal contraceptives regardless of route of administration.

"Data regarding health benefits of extended regimens are being published every month—they're just impossible to ignore."

P. SULAK

"We need to set our patients up for contraceptive success—the 21/7 regimen and difficulty our patients face in just getting their OCs do not make it easy for them."

A. MOORE

Importantly, the study showed that the symptoms occurred consistently not only in the new start patients, but also in the established users—the women who had been on the pill for more than a year. There is a reason why so many women stop their OCs in less than a year—it's not because they are feeling wonderful. They may stop because they feel terrible during the HFI.

DR NELSON: The symptoms are real and it is astonishing how many women experience them. Women have become so accustomed to feeling lousy once a month, whether it's due to menstrual symptoms or hormone withdrawal, that they will not mention it.

Another advantage to extended use of combination estrogen-progestin contraception is the prolonged suppression of ovulation and menstruation, like that produced by the progestin-only regimens, without the negative effects on bone. Given the multitude of problems caused by recurrent ovulation and menstruation, it may be healthier for some women not to have periods every month.

DR KAUNITZ: There are also therapeutic uses for extended regimen OCs that we should not overlook. Decreased dysmenorrhea and menorrhagia are both included in the prescribing information for all OCs. Women suffering from these disorders will likely have additive benefit from extended regimens. In the same vein, the value of extended regimens in managing endometriosis has been known for years.[10]

DR SULAK: A very recent paper showed that extending the regimen can improve premenstrual symptoms.[11] When symptomatology was compared with that recorded during a 21/7 cycle, there was a significant improvement that was especially apparent in the women who had the greatest variability in their cycles.

Another important finding was that the greatest improvement was detected in the sixth month. That is a key counseling point—you need to stick with the regimen to see the benefits.

What practical advantages does an extended regimen offer to the patient?

DR LONDON: Convenience, convenience, convenience.

MS MOORE: The worst pill to miss in any cycle is the one that is still at the pharmacy. Once your patient has already had 7 hormone-free days, her risk of pregnancy increases with each day of delay in starting a new pack of pills.

DR LONDON: With an extended regimen, that risk occurs fewer times per year. Just as the change from 50-mcg pills to low-dose pills was an improvement, the extension of the regimen beyond 28 days is a real improvement in OC therapy.

DR NELSON: Access to pills is a real issue—it's more than having to go to the pharmacy every few weeks. A recent paper from the California Family PACT (Planning, Access, Care and Treatment) Program showed that women who were dispensed a year's supply of OCs at their first visit were more likely to continue therapy, were more likely to receive Papanicolaou tests and *Chlamydia* tests, and actually had a lower annual women's health care–related costs than women who were dispensed 3 cycles.[12]

We recently presented data that support this conclusion—hormonal method continuation rates were higher among women who received 3 pill packs than in those who received only 1. Having the supply of pills available is one more way of promoting contraceptive success.

Are there side effects that are specific to the extended regimen OCs?

DR SULAK: We are in consensus that there are no side effects that are specific to the extended regimen OCs. The only side effect found to be increased with extended regimen is unscheduled bleeding, but some studies have shown less bleeding overall.[13] Studies have shown a decrease in many typical side effects seen with 21/7 OCs such as premenstrual syndrome and headaches.[14]

DR KAUNITZ: I agree. We should, however, address unscheduled bleeding and spotting. It's something that we see with every OC, but extending the regimen changes the pattern.

A number of years ago, a randomized trial showed that addition of low-dose estrogen to the HFI provided superior cycle control to that of a 20-mcg EE OC and similar to that reported with a 35-mcg pill.[15] There are more recent data that suggest that once you have passed the first cycle, addition of low-dose estrogen to the HFI also improves unscheduled bleeding in 91-day regimens.[6]

MS MOORE: Patients must understand there will be some unscheduled bleeding/spotting as their endometrium transitions from a monthly cycle or withdrawal bleed to more complete ovarian suppression, but it is manageable.

DR LONDON: Some clinicians have concerns about estrogen exposure—specifically the risk of venous thromboembolism and breast cancer. When the published data regarding extended regimens are examined in total, the safety profile is virtually the same as for 21/7. The safety of 91-day regimens have been demonstrated in both 1-year trials as well as longer-term 2-year studies.[2,6,16]

The Women's CARE (Contraceptive and Reproductive Experiences) study really put concerns about the association of OC use and breast cancer to rest.[17] There was no evidence of increased risk of breast cancer in either current or past users of OCs. Given that the study included women who had taken high-dose 50-mcg EE pills, it's very reasonable to conclude that extended OC use poses no increased risk of breast cancer.

"I think every woman who is on a birth control method should have the option of eliminating or reducing the number of her periods. Don't assume that she's not having problems, just because she hasn't told you about them."

A. NELSON

What can be done to ensure that an extended regimen is offered to all OC-appropriate patients regardless of age or pathology?

DR KAUNITZ: We still need to work on overcoming common misconceptions. Despite more than 45 years of use, a fundamental lack of understanding of how OCs work persists among patients and health care professionals outside the field of women's health.

MS MOORE: Many of my students are incredulous when they realize that there is no physiologic reason for the 7-day HFI and cyclical bleeding for women taking OCs.

DR LONDON: We also need to dispel the myth that women taking OCs are having periods. Remember that no women taking an OC has a period. They have withdrawal bleeding.

DR SULAK: Extended regimens set my patients up for contraceptive success and should be considered for all women who are candidates for OCs. The advantages—avoidance of monthly withdrawal symptoms, less follicular development, and, overall, less bleeding—outweigh the issues of unscheduled bleeding and spotting.

DR NELSON: We should discuss bleeding with our patients and, perhaps, it is time to turn the tables and ask her why she feels the need to bleed every month. For women considering use of OCs, it opens up the conversation to use of regimens other than 21/7. For women who are established users of OCs, asking whether they are having symptoms every month will open up the same conversation.

DR KAUNITZ: We're not here to suggest that women should no longer menstruate or that women should no longer experience monthly bleeding.

TABLE 4

Recommendations for Initiating Extended Regimens

New starts: Begin your pack according to the directions provided by your clinician. You may be able to begin your pack on the same day or on the first day of menstruation.

Transition patients: Begin the extended pack as soon as the withdrawal bleeding from your prior cycle ends and you have a hormone free interval that lasts no more than 4 days.

It's all about choice. Using hormones not only to provide safe, effective contraception but also to allow women the option of choosing when to bleed is a second revolution in contraception.

With regard to symptoms, I ask about grouchiness. "Do you get headaches or feel grouchy or down during your HFI?" If the answer is yes, it moves the conversation in the direction of extended regimens.

MS MOORE: I agree. The extended regimen has become mainstream over the past couple of years—the only reason I can see for using 21/7 is if the patient demands it or if reimbursement drives the issue.

How important is breakthrough bleeding in OC product selection?

DR KAUNITZ: Breakthrough bleeding occurs with all OC products—it's importance becomes a matter of how well you have prepared patients for it.

MS MOORE: I like to tell my patients that it is likely they will experience some breakthrough bleeding in the early cycles. Then they are prepared and those who do not have any are pleasantly surprised.

DR SULAK: It's inevitable and it can be managed—to me, it's more important to focus on eliminating hormone withdrawal symptoms.

Are all combined hormonal contraceptive products appropriate for use in extended regimens?

DR NELSON: At this time there are insufficient data regarding the safety and pharmacokinetics of extended regimen use of the transdermal patch. Until studies evaluating its use in multiple extended cycles become available, we cannot recommend its use in extended regimens.[18]

DR KAUNITZ: Traditional 21/7 pill packs can be used in extended regimens but I find this approach often poses challenges for the patient—from remembering not to take placebo pills to reimbursement to trips to the pharmacy every 3 weeks for a new pill pack.

DR LONDON: It seems intuitive that the multiphasic pills would not be optimal for use in extended regimens. Given the paucity of data supporting their use, I would not recommend initiating an extended regimen with a mutiphasic pill. I certainly would allow a patient who is using them successfully to continue.

What are practical options to manage breakthrough bleeding in patients taking extended regimen OCs?

DR SULAK: We find that patients usually don't begin to have unscheduled bleeding until week 4 or later. In our prospective study, we found that women who had heavier daily flow ratings during the 21/7 lead-in cycle tended to have greater daily flow ratings and earlier occurrence of unscheduled bleeding when taking an extended regimen.[13] We also showed that a 3-day pill holiday was helpful in managing breakthrough bleeding and/or spotting that had persisted for 7 consecutive days (**TABLE 4**).

MS MOORE: Essentially patients have 2 options: endure the bleeding or take a brief pill holiday. I let my patients decide—some are very bothered by even the slightest amount of breakthrough bleeding while others have no issue with it. The worse thing a patient can do is to stop taking pills without a back-up plan for contraception. It is critical that they take at least 3 weeks of active pills between drug holidays.

DR LONDON: It's also important to remember that you cannot use a 3-day pill holiday to manage breakthrough bleeding/spotting with 21/7 regimens as the increased number of hormone-free days per cycle could lead to a greater chance of escape ovulation.

DR KAUNITZ: Let's not forget the value of counseling. Just letting women know what to expect and what to do has certainly been proven to be valuable in improving continuation rates among women on other forms of long-term contraception[19,20] and would without doubt be beneficial for women receiving extended regimens (**SIDEBAR**).

DR SULAK: With the low-dose OCs, it is especially important to let the patient know at the time you write the prescription that she has to take her pills at about the same time each day. I have had patients tell me that they experience bleeding if they take their pills even a few hours late.

DR NELSON: There will be patients with breakthrough bleeding/spotting who need to be examined, such as a long-term pill user who reports it for the first time. If you can establish a history of good pill taking with no illnesses or medication interaction which might alter hormone absorption, this woman should be evaluated for infection and anatomic changes like cervical or endometrial polyps.

Summary

DR SULAK: We are finally seeing the demise of 21/7 contraceptive regimens. Numerous studies of these regimens over the past decade have documented hormone withdrawal symptoms, inadequate pituitary-ovarian suppression, follicular development, and even ovulation. Regimens which shorten or eliminate the 7-day HFI by adding estrogen and providing greater duration of active pills will improve the side effect profile and efficacy.

Oral contraceptives first gave women control over their fertility; now, regimens that extend the cycle and eliminate the HFI give women the option of having fewer hormone withdrawal symptoms. In addition to the convenience of fewer cycles per year, women may experience further benefit from prolonged suppression of ovulation and menstruation.

While breakthrough bleeding and spotting occur with all OCs, the pattern seen with extended regimens differs. It can be managed with patient counseling and brief pill holidays. Additional strategies to manage breakthrough bleeding that should be evaluated in the future include additional estrogen only, nonsteroidal anti-inflammatory drugs, and changing the estrogen dose of the formulation (ie, increasing the dose from 20 mcg EE to 30-35 mcg EE).

Guidelines and Recommendations for Unscheduled Bleeding

Counseling Guidelines

- When prescribing, provide counseling regarding the possibility of unscheduled bleeding/spotting.
- When the patient complains of unscheduled bleeding ask about
  - Pill-taking habits
    - Did you start the most recent pill pack on time?
    - Are you taking the pills at approximately the same time each day?
    - Have you skipped any pills recently?
    - Have you had any recent illnesses?
    - Are you using other medications?
  - Characteristics of the unscheduled bleeding episode
    - How long did you experience breakthrough bleeding?
    - How severe was the bleeding?
    - At what point in the cycle did it occur?
  - Any lifestyle changes or habits that might
    - Predispose her to sexually transmitted disease (change in partners)
    - Alter the metabolism of active hormone components (use of St. John's Wort, smoking)

Management Recommendations

- With a 91-day regimen, bleeding may occur before the 7-day ethinyl estradiol period at the end of the pill pack.
- If bleeding/spotting is bothersome during the 84 combination pills, it is possible to take a 3-day hormone-free interval and immediately restart.
- Always take a minimum of 3 weeks of active pills before taking a 3-day break.
- Do not take a break during the first 3 weeks or during the last 3 weeks of the 84 combination active pills.

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Articles of Interest

Anderson FD, Gibbons W, Portman D. Safety and efficacy of an extended-regimen oral contraceptive utilizing continuous low-dose ethinyl estradiol. *Contraception*. 2006;73:229-234.

Prospective trial of 1006 sexually active adult women of childbearing potential who received a 91-day extended regimen OC (30 mcg EE/150 mcg LNG) with continuous low-dose EE (10 mcg) during the hormone free interval. Cycle control and safety of the regimen were comparable to that reported for other OCs.

Anderson FD, Gibbons W, Portman D. Long-term safety of an extended-cycle oral contraceptive (Seasonale): a 2-year multicenter open-label extension trial. *Am J Obstet Gynecol*. 2006;195:92-96.

Long-term safety study of a 91-day extended cycle OC regimen. Overall rates of study discontinuation and incidence of adverse events were similar to those of an earlier Phase 3 clinical trial. The regimen was well tolerated and the numbers of reported bleeding and/or spotting days diminished during the study.

Foster DG, Parvataneni R, de Bocanegra HT, Lewis C, Bradsberry M, Darney P. Number of oral contraceptive pill packages dispensed, method continuation, and costs. *Obstet Gynecol*. 2006;108:1107-1114.

Evaluation of the effect of the number of cycles of OC pill packages dispensed on the method continuation, pill wastage, use of services, and health care costs among 82,319 women enrolled in the California Family PACT system. Dispensing a year's supply of OCs during first visits was associated with a higher method continuation and lower health care costs than dispensing fewer cycles per visit.

Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. *N Engl J Med*. 2002;346:2025-2032.

A population-based, case-control study of 4575 women with breast cancer and 4682 controls to determine the risk of breast cancer among former and current users of OCs. The relative risk of breast cancer was 1.0 (95% CI, 0.8-1.3) for women who were currently using OCs and 0.9 (95% CI, 0.8-1.0) for those who had previously used them. The relative risk did not increase consistently with longer periods of use or with higher doses of estrogen. Use of OCs by women with a family history of breast cancer was not associated with an increased risk of breast cancer nor was the initiation of OC use at a young age.

Spona J, Elstein M, Feichtinger W, et al. Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception*. 1996;54:71-77.

Double-blind, randomized trial to determine the suppressive effect on ovarian activity of OCs administered for 21 or 23 days. Observed differences in 17β-estradiol levels and follicular development between a 21-day and 23-day preparation suggest that shortening the pill-free interval in combined OCs may increase the contraceptive safety margin in women on low-dose formulations.

Sulak PJ, Scow RD, Preece C, Riggs MW, Kuehl TJ. Hormone withdrawal symptoms in oral contraceptive users. *Obstet Gynecol*. 2000;95:261-266.

Prospective evaluation to measure the timing, frequency, and severity of hormone-related symptoms in OC users. Pelvic pain, headaches, use of pain medication, bloating or swelling, and breast tenderness occurred significantly more frequently during the 7-day hormone free interval among both current users and new start users of OCs.

Sulak PJ, Kuehl TJ, Coffee A, Willis S. Prospective analysis of occurrence and management of breakthrough bleeding during an extended oral contraceptive regimen. *Am J Obstet Gynecol*. 2006;195:935-941.

Single-center, prospective analysis of self-rated menstrual flow during a 21/7 regimen versus a 168-day extended OC regimen. Subjects with a heavier daily flow rating during the 21/7 day cycle tended to have greater daily flow ratings and earlier breakthrough bleeding during the 168-day extension cycle. The 168-day extended regimen had an acceptable bleeding profile with bleeding during the active pill interval effectively managed with institution of a 3-day hormone free interval.