Editorial

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Welcome to the tipping point in oral contraception prescribing

It's time to reduce our prescribing of 21-7 short-cycle, estrogen–progestin OCs and move to alternative formulations

No question: The estrogen–progestin oral contraceptive (OC) developed by physician John Rock and biologist Gregory Pincus was one of the great inventions of the 20th century. Their 21-7 short-cycle OC regimen recapitulated the idealized 28-day menstrual cycle.

But, over the past 10 years, contraceptive experts have increasingly, and more fiercely, questioned the soundness of a formulation that contains only 21 hormone pills and produces a monthly withdrawal bleed. Now, we are at a tipping point in OC prescribing practice, where use of the classic 21-7 formulation is likely to decline, significantly. Why? And what will come next for our patients?

21-7 formulations can cause problems

The standard OC formulation, with 21 low-dose estrogen–progestin hormone pills and 7 inert pills, contains too few hormone pills and too many inert pills. The serum follicle-stimulating hormone (FSH) level rises significantly during the 7-day hormone-free interval—an effect that may stimulate follicle growth.

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For example, in two studies, the serum FSH level rose from approximately 1.0 mIU/mL during the hormone interval to 5 to 8 mIU/mL during the hormone-free interval.[1,2] Of even greater concern, at least one study[3] reported that the rise in FSH and stimulation of ovarian follicles during the hormone-free interval are sufficient to result in intermittent luteinization of a follicle, demonstrated by a rise in a urinary progesterone metabolite.

These findings suggest that intermittent ovulation occurs in women who take the standard 21-7 regimen. Compounding this problem is the fact that, if a woman forgets to restart the hormone pills at the end of the 7-day hormone-free interval, ovarian follicle growth progresses and ovulation occurs more frequently. The 7-day pill-free interval, combined with a delay in restarting the next phase of the pill regimen, is the likely cause of some of the unintended pregnancies reported in pill users.

24-4 formulations carry advantages…

Some OC users strongly prefer to have a monthly withdrawal bleed. For them, the main OC formulations are 21-7, 24-4, and 21-2-5 (**TABLE,** page 8).

The 24-4 formulation (24 estrogen–progestin pills and 4 inert pills) results in greater suppression of FSH, luteinizing hormone, and estradiol than does a standard 21-7 formulation. This indicates more complete pituitary–ovarian suppression that, likely, results in fewer episodes of ovulation.[4]

In addition, some 24-4 formulations have been reported effective in treating acne and premenstrual dysphoric disorder.[5,6]

…and so do extended-cycle formulations

Many women are willing to consider using an extended-cycle OC regimen that is designed to reduce the frequency of withdrawal bleeding.[7] With an 84-7I formulation, which contains 7 inert (I) pills, there are only 7 hormone-free days during 91 days of therapy. The 84-7I formulation is associated with fewer intervals during which the FSH level rises and follicle growth resumes. Furthermore, the 84-7I formulation may also be associated with fewer days of heavy menstrual bleeding than are 21-7 regimens.[3,8]

A further evolution in extended-cycle formulations is to provide zero hormone-free days by following 84 days of estrogen–progestin with 7 days of ethinyl estradiol (EE). The 84-7EE regimen continually suppresses FSH and estradiol levels during the 7 days between estrogen–progestin pills, and may help reduce the risk of breakthrough bleeding.

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TABLE Sorting among the short-cycle 21-7 OC formulation and its alternatives

Regimen	Pill tally	Comments on formulation
21-7 (SHORT-CYCLE) FORMULATION		
Standard 21-day estrogen–progestin (EP)–7-day inert (I) formulations	21 EP pills 7 I pills	
28-DAY FORMULATIONS WITH REDUCED HORMONE-FREE INTERVAL		
Use any standard 21-7 OC; take 3 additional EP pills and 3 fewer I pills to extend cycle to 24-4	24 EP pills 4 I pills	
Lo Estrin 24 Fe	24 EP pills 4 iron pills	EP pills contain 20 µg ethinyl estradiol (EE) and 1 mg norethindrone acetate; iron (Fe) pill contains ferrous fumarate
Yaz	24 EP pills 4 I pills	EP pills contain 20 µg EE and 3 mg drospirenone
Mircette, Kariva	21 EP pills 2 I pills 5 EE pills	EP pills contain 20 µg EE and 0.15 mg desogestrel; EE pills contain 10 µg EE
49-DAY CYCLES		
Use any standard 21-7 OC and combine the EP pills from two packs; take as 42 EP pills followed by 7 I pills	42 EP pills 7 I pills	
84-7 FORMULATIONS		
Use any standard 21-7 OC and combine the EP pills from four packs; take as 84 EP pills followed by 7 I pills	84 EP pills 7 I pills	
Seasonale	84 EP pills 7 I pills	EP pills contain 30 µg EE and 0.15 mg levonorgestrel
Seasonique	84 EP pills 7 EE pills	EP pills contain 30 µg EE and 0.15 mg levonorgestrel; EE pills contain 10 µg
CONTINUOUS FORMULATIONS		
Use any standard 21-7 OC continuously; take hormone pills only	Daily EP pills	
Lybrel	Daily EP pills	EP pills contain 20 µg EE and 0.09 mg levonorgestrel

Are even longer cycles feasible?

Given the success of 84-7I and 84-7EE regimens, investigators have studied the clinical effects of 168- and 365-day cycles.

Recently, a randomized clinical trial compared the reproductive endocrine effects of six cycles of a classic 21-7 formulation against a 168-day continuous active pill regimen.[3] Sixty-two women were randomized to treatment for six cycles with either the 21-7 regimen with 7 days of inert pills at the end of each cycle or 168 consecutive days of estrogen–progestin pills (ethinyl estradiol, 20 µg, plus norethindrone acetate, 1 mg).

Vaginal bleeding was the primary outcome measured; secondary outcomes were endogenous hormone production, pelvic ultrasonographic

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(US) measures of the ovary, and quality-of-life measures. Days of vaginal bleeding were similar in both groups. Over the 168 days of the study, the mean number of reported days of bleeding was 35 in the 28-day cyclic regimen group and 32 in the 168-day continuous regimen group. Reported days of moderate and heavy bleeding were greater in the cyclic regimen group (11 days) than in the continuous regimen group (5 days) ($P < .005$). Breakthrough bleeding was reported by more women in the continuous treatment group (13%) than in the cyclic group (7%) ($P = .03$).

Other findings are also noteworthy:

- Overall, subjects on continuous therapy reported less severe menstrual pain
- A decrease in the urinary estrone glucuronide level with continuous treatment was, overall, 51% greater than it was with cyclic treatment
- Pelvic US demonstrated that continuous treatment was associated with fewer ovarian follicles and a smaller ovarian volume
- Pregnanediol glucuronide measurements indicated that "escape" ovulation occurred more often in the 21-7 cyclic group.

Taken together, these findings indicate that continuous therapy produced more pronounced ovarian suppression than 21-7 cyclic therapy.

Leave the work of Rock and Pincus behind?

One of the acknowledged great inventions of the 20th century isn't making the leap into the 21st century. The time has come to ask: "Why do we continue to prescribe 21-7 OCs?" For women who desire a monthly withdrawal bleed, it's likely preferable to have our prescribing practices evolve to make greater use of 24-4 formulations. For all others, consider an extended-cycle regimen.

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Instant Poll Results

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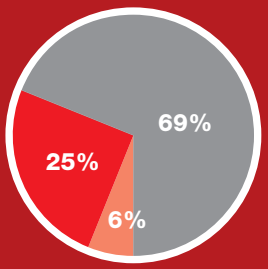
There's been an error—now what?

Postoperatively, a woman is administered extra doses of her diabetes medication. She develops hypoglycemia, has a seizure, falls out of bed, and fractures a hip.

All members of the care team confirm the causal set of events—inappropriate administration of medication, hypoglycemia, seizure, fall, fracture. The hospital focuses its efforts at improvement on 1) greater standardization of the treatment of patients who have diabetes and 2) fall-prevention strategies.

Your task is to speak with the patient. What would you say?



69% "There was an error in the way your diabetes medication was ordered and administered, and you received an extra dose. That caused you to develop low blood sugar, which caused you to have a seizure. Because of the seizure, you fell out of bed and fractured your hip. I'm sorry all this happened."

25% "You had a seizure. We'll do more tests to determine why, but it might have happened because your blood sugar was low—remember, you were postop and not eating. The seizure caused you to fall out of bed and fracture your hip."

6% "I'm sorry you had a seizure. We need to get you to surgery so that we can fix the fractured hip. We'll keep close watch on your other medical problems."

ZERO "Your diabetic condition caused you to have a seizure. The seizure caused you to fall out of bed and fracture your hip."