OCs, breakthrough bleeding, and patients’ need to know
Managing expectations is as important as adjusting formulations

Recommendations for practice

- Lack of adherence is a common cause of breakthrough bleeding. Focus counseling on ensuring that patients understand and can follow pill-taking instructions before switching pills or contraceptive method.
- If breakthrough bleeding extends beyond 4 cycles and a woman wishes to continue using an oral contraceptive, consider switching to a pill with a higher ethinyl estradiol:progestin ratio, either by increasing the estradiol dose or by decreasing the relative progestin dose.
- Breakthrough bleeding may be due to progestin type; switching from an estrane to a gonane may reduce it.
- Women who have breakthrough bleeding after having well-controlled menstrual cycles on an oral contraceptive should be assessed for causes not related to their birth control pills, such as pregnancy, cervicitis, smoking, or interactions with medications.

In 1982, more than 20% of women surveyed in a nationally representative sample had discontinued oral contraceptives (OCs) on their own or at the recommendation of their physician due to bleeding or spotting.1 Sadly, the percentage today has not decreased much.

Understandable concern, embarrassment, and annoyance lead these women to abandon OCs.1,2 What they often don’t know, though, is that breakthrough bleeding generally is greatest in the first 3 to 4 months after starting OCs,3 and it steadily declines and stabilizes by the end of the fourth cycle.4 Timely counsel could enable many of these women to cope with the bleeding and stick with an effective contraceptive method. Additional incentives are noncontraceptive benefits of OCs: improved menstrual regularity and decreased menstrual blood loss, dysmenorrhea, and risk of ovarian and endometrial cancer.

Women who discontinue OCs on their own switch to less effective methods of birth control or use no method.1,2 Consequences may be unexpected pregnancies and an increased abortion rate.5 With patients who are using an OC, it would be appropriate to ask periodically whether they are satisfied with OC use.

In this review, we discuss the mechanisms and management of breakthrough bleeding in women taking OCs, and provide tips for counseling that may help decrease the risk of discontinuation due to menstrual abnormalities in the initial months of use.

Breakthrough bleeding in this review refers to either unplanned spotting or bleeding, regardless of requirement for protection—unless defined otherwise by a specific study under discussion.

Patricia A. Lohr, MD, and Mitchell D. Creinin, MD
Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, Pa

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How is irregular bleeding defined?

For the purpose of performing studies, unplanned bleeding is classified by the World Health Organization into 2 categories: 1) breakthrough bleeding, which requires sanitary protection, and 2) spotting, which does not require sanitary protection. Despite this formal classification, trials have varied in their terminology and method of recording menstrual irregularities, making comparisons between studies difficult. In addition, there is wide variation among women in tolerance to bleeding abnormalities, perceptions of heavy vs light bleeding, as well as the need for protection.

Nevertheless, menstrual abnormalities are consistently cited as a common reason for discontinuing OCs. A prospective US study of 1,657 women performed in the 1990s reported that 37% of OC users had stopped taking OCs by 6 months after starting a new prescription because of side effects. Irregular bleeding was the most common cause, cited by 12% of women, followed by nausea, weight gain, and mood changes, which ranged from 5% to 7%.

Four causes of bleeding

Breakthrough bleeding may be due to any of the following variables: 1) physiologic effects of OCs on the endometrium, 2) OC-related parameters, including dose, formulation, and regimen, 3) patient behavior (including compliance, using concomitant medications, and smoking), and 4) benign or malignant pathology.

OCs and the endometrium: Estrogen-progestin balance significant

Progestin and estrogen in combination OCs have profound effects on the endometrium that, although not contributing to contraception, do lead to a predictable pattern of bleeding or such problems as breakthrough bleeding or lack of withdrawal bleed.

Normally, estrogen causes the endometrium to proliferate. Progesterone stabilizes the growing uterine lining. Since the introduction of OCs in 1960, the trend in formulation has been to use the least amount of hormone necessary to inhibit ovulation. Given that the progestin is primarily responsible for the contraceptive efficacy of OCs, the risk of pregnancy is not altered with decreases in the estrogen component. However, significantly lowering the estrogen in OCs may account for breakthrough bleeding. Unplanned bleeding, though, is not dependent solely on the estrogen component, as variations in the progestin can contribute to breakthrough bleeding.

Most OC users in the US take low-dose formulations, so designated because the estrogen component is <50 μg. This level of estrogen in combination with a progestin provides excellent contraceptive efficacy, but may be insufficient to sustain endometrial integrity in some women. Studies that have compared OCs containing 20 μg ethinyl estradiol (EE) with those containing 30 μg or 35 μg EE have not been very useful for judging breakthrough bleeding rates because the products often also vary in the phasing and type of progestin. Some studies show more breakthrough bleeding with 20 μg EE pills, but others show equal or improved cycle control with the lower EE dose.

Estrogen-progestin balance is more important than absolute level of estrogen.

Endrikat et al conducted a study to compare two 20 μg EE pills containing different progestins, and to compare 2 levonorgestrel-based formulations with differing EE amounts. An OC of 20 μg EE/100 μg levonorgestrel was compared with a preparation of 20 μg EE/500 μg norethisterone. A 30 μg EE/150 μg levonorgestrel pill was used as a standard reference preparation.

Overall, the 30 μg EE preparation showed a lower cumulative incidence of breakthrough bleeding compared with the 20 μg EE/100 μg levonorgestrel and 20 μg EE/500 μg norethisterone pills over 13 cycles (1.0% vs 4.1% and 11.7%, respectively). However, the 20 μg EE/500 μg norethisterone pills consistently had a higher breakthrough bleeding rate than the 20 μg EE/100 μg levonorgestrel pill. This suggests that, although the higher EE component in the 30 μg pill was important when comparing 2 formulations with the same progestin, the difference in

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Low-level estrogen in combination with a progestin is excellent for contraception but may not sustain endometrial integrity in some women.
Regardless of the type of progestin or amount of estrogen, breakthrough bleeding generally decreases with successive cycles.
## TABLE 1

### Available OCs by formulation and regimen

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>GENERIC NAME(S)</th>
<th>ESTROGEN (DOSE)</th>
<th>PROGESTIN (DOSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MONOPHASIC</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Alesse, Levlite</td>
<td>Avisane, Lessina</td>
<td>Ethinyl estradiol (20 μg)</td>
<td>Levonorgestrel (0.1 mg)</td>
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<td>Micelle</td>
<td>Kariva</td>
<td>Ethinyl estradiol (20 μg)</td>
<td>Desogestrel (0.15 mg)</td>
</tr>
<tr>
<td>Loestrin FE</td>
<td>Microgestin FE 1/20, June FE 1/20</td>
<td>Ethinyl estradiol (20 μg)</td>
<td>Norethindrone acetate (1 mg)</td>
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<tr>
<td>Yaz</td>
<td>Levora, Portia</td>
<td>Ethinyl estradiol (20 μg)</td>
<td>Drospirenone (3 mg)</td>
</tr>
<tr>
<td>Lo/Ovar</td>
<td>Low-ogestrel, Crysellie</td>
<td>Ethinyl estradiol (30 μg)</td>
<td>Levonorgestrel (0.15 mg)</td>
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<tr>
<td>Desogen, Ortho-cept</td>
<td>Apri</td>
<td>Ethinyl estradiol (30 μg)</td>
<td>Norgestrel (0.3 mg)</td>
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<tr>
<td>Loestrin 21 1/5/30</td>
<td>Microgestin, Junel Fe</td>
<td>Ethinyl estradiol (30 μg)</td>
<td>Desogestrel (0.15 mg)</td>
</tr>
<tr>
<td>Yasmin</td>
<td></td>
<td>Ethinyl estradiol (30 μg)</td>
<td>Norethindrone acetate (1.5 mg)</td>
</tr>
<tr>
<td>Occon 35</td>
<td></td>
<td>Ethinyl estradiol (35 μg)</td>
<td>Drospirenone (3 mg)</td>
</tr>
<tr>
<td>Ortho-Cyclen</td>
<td>Mononesessa, Sprintec</td>
<td>Ethinyl estradiol (35 μg)</td>
<td>Norethindrone (0.4 mg)</td>
</tr>
<tr>
<td>Brevicon, Modicon</td>
<td>Nortrel, Necon 0.5/35</td>
<td>Ethinyl estradiol (35 μg)</td>
<td>Norgestimate (0.25 mg)</td>
</tr>
<tr>
<td>Demulen 1/35</td>
<td>Zovia 1/35</td>
<td>Ethinyl estradiol (35 μg)</td>
<td>Norethindrone (0.5 mg)</td>
</tr>
<tr>
<td>Ortho-Novum 1/35, Norinyl 1+35</td>
<td>Necon 1/35, Nortrel</td>
<td>Ethinyl estradiol (35 μg)</td>
<td>Ethynodiol diacetate (1 mg)</td>
</tr>
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<td>Ortho-Novum 1/50</td>
<td>Necon 1/50</td>
<td>Ethinyl estradiol (50 μg)</td>
<td>Norethindrone (1 mg)</td>
</tr>
<tr>
<td>Ovral</td>
<td>Ogestrel</td>
<td>Ethinyl estradiol (50 μg)</td>
<td>Norgestrel (0.5 mg)</td>
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<td>Occon 50</td>
<td></td>
<td>Ethinyl estradiol (50 μg)</td>
<td>Norethindrone (1 mg)</td>
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<tr>
<td>Demulen 1/50</td>
<td>Zovia 1/50</td>
<td>Ethinyl estradiol (50 μg)</td>
<td>Ethynodiol diacetate (1 mg)</td>
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<tr>
<td>Norinyl 1/50</td>
<td></td>
<td>Mestranol (50 μg)</td>
<td>Norethindrone (1 mg)</td>
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<tr>
<td><strong>BIPHASIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortho-Novum 10/11, Jenest</td>
<td>Necon 10/11, Nelova 10/11</td>
<td>Ethinyl estradiol (35 μg)</td>
<td>Norethindrone (0.5 mg x 10 days, 1 mg x 11 days)</td>
</tr>
<tr>
<td><strong>TRIPHASIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortho Tri-Cyclen Lo</td>
<td>Velivet</td>
<td>Ethinyl estradiol (25 μg)</td>
<td>Norgestimate (0.18 mg x 7 days, 0.215 mg x 7 days, 0.25 mg x 7 days)</td>
</tr>
<tr>
<td>Triphasil, Tri-Levlen</td>
<td>Trivora, Enpresse</td>
<td>Ethinyl estradiol (30 μg x 6 days, 40 μg x 5 days, 30 μg x 10 days)</td>
<td>Desogestrel (0.1 mg x 7 days, 0.125 mg x 7 days, 0.15 mg x 7 days)</td>
</tr>
<tr>
<td>Tri-Norinyl</td>
<td></td>
<td>Ethinyl estradiol (35 μg)</td>
<td>Levonorgestrel (0.05 mg x 6 days, 0.075 mg x 5 days, 0.125 mg x 10 days)</td>
</tr>
<tr>
<td>Ortho Tri-Cyclen</td>
<td>Tri-Sprintec, TriNessa</td>
<td>Ethinyl estradiol (35 μg)</td>
<td>Norgestrel (0.5 mg x 7 days, 1 mg x 9 days, 0.5 mg x 5 days)</td>
</tr>
<tr>
<td>Ortho-Novum 7/7/7</td>
<td>Nortrel 7/7/7, Necon 7/7/7</td>
<td>Ethinyl estradiol (35 μg)</td>
<td>Norethindrone (0.5 mg x 7 days, 0.75 mg x 7 days, 1 mg x 7 days)</td>
</tr>
<tr>
<td>Estrostep FE</td>
<td></td>
<td>Ethinyl estradiol (20 μg x 5 days, 30 μg x 7 days, 35 μg x 9 days)</td>
<td>Norethindrone acetate (1 mg)</td>
</tr>
<tr>
<td><strong>EXTENDED CYCLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seasonale</td>
<td></td>
<td>Ethinyl estradiol (30 μg x 84 days followed by 7 placebo pills)</td>
<td>Levonorgestrel (0.15 mg)</td>
</tr>
<tr>
<td>Seasonique</td>
<td></td>
<td>Ethinyl estradiol (30 μg x 84 days followed by 10 μg x 7 days)</td>
<td>Levonorgestrel (0.15 mg)</td>
</tr>
</tbody>
</table>
in bleeding.

**Type of progestin may affect breakthrough bleeding.** All combination OCs contain either EE or mestranol. However, a variety of progestins have come into use. The 2 most common contraceptive progestins are derived from 19-nortestosterone, and are classified as gonanes.

 Estranes include norethindrone and its derivatives, norethindrone acetate and ethinyloestradiol diacetate. Gonanes include levonorgestrel, norgestrel, desogestrel, gestodene, and norgestimate.

 Each progestin differs in half-life, estrogenic, progestogenic, and androgenic properties, and these variations may explain differing rates of breakthrough bleeding among formulations. As shown by Endrikat et al,12 pills with the same quantity of EE but different progestins can have marked differences in breakthrough bleeding rates.

 Although gonanes have greater progestational activity, no trial has determined which progestin has the best bleeding profile. A recent Cochrane review comparing different progestins did find that, compared with pills containing levonorgestrel, those containing gestodene may be associated with less intermenstrual bleeding.

 Regardless of the progestin used or the quantity of EE, breakthrough bleeding generally decreases with each successive cycle. One study that compared 2 combination OCs composed of EE/norgestimate and EE/norgestrel demonstrated bleeding rates of 11.3% and 10.6% during the first 6 cycles, which decreased to 5.1% and 6.3% in cycles 13 to 24, respectively. Additionally, all women using OCs can experience some cycles without a withdrawal bleed—a menstrual abnormality that may be concerning to those who desire a menstrual period as confirmation that they are not pregnant.

**Comparing regimens.** OC regimens are available as biphasic, triphasic, extended-cycle, and continuous use. Women using extended-cycle contraceptives may experience more breakthrough bleeding than those using a standard 28-day pill. However, in a 3-month cycle, there are only 7 days of planned bleeding. This is in contrast to 28-day cycles during 3 months in which there are 21 days of planned bleeding.

 Though women on extended-cycle regimens may initially experience more breakthrough bleeding than women using 28-day regimens, the total number of planned and unplanned bleeding days may still decrease. Women using a 3-month cycle OC (30 μg EE/150 μg levonorgestrel) experienced more unscheduled bleeding than women using a standard 28-day cycle OC of the same formulation and dose. The number of bleeding days decreased with each cycle. Another study examined continuous OC use (20 μg EE/100 μg levonorgestrel) over a period of 1 year, and reported a decreasing number of bleeding days over time. In the case of continuous use, all bleeding is unscheduled, and any bleeding is considered breakthrough bleeding.

 Multiphasic OC regimens were developed with the intention of decreasing breakthrough bleeding by mimicking the rising and falling pattern of estrogen and progesterone in the normal menstrual cycle. After the introduction of the biphasic pill, an increase in breakthrough bleeding was noted, which led to the development of the triphasic pill. Though the multiphasic hypothesis is physiologically plausible, recent reviews of the literature have found the evidence for its efficacy too limited and methodologically flawed to draw any definitive conclusions about a decrease in breakthrough bleeding.

**Patient behaviors are contributory**

**Skipping a pill** is a common cause of breakthrough bleeding. Compliance with any OC regimen is crucial to achieving a regular and predictable bleeding pattern. Of 6,676 women surveyed retrospectively, 19% reported missing 1 or more pills per cycle, and 10% reported missing 2 or more pills per cycle.
TABLE 2

What to review with patients who are starting a combination OC

- Breakthrough bleeding is common in the initial months after starting OCs
- Breakthrough bleeding, if experienced, usually diminishes over the first 3 months of OC use and abates by the 4th cycle
- Skipping even 1 pill can result in breakthrough bleeding
- Avoidance of breakthrough bleeding can be aided by taking your pill at the same time every day; you may find it helpful to make pill-taking part of another daily routine such as tooth brushing
- Tell me about other medications you are taking, including over-the-counter preparations and herbal supplements
- If you smoke, the chances of breakthrough bleeding are increased
- If bleeding continues beyond the 4th cycle, there are diagnostic tests available to explore possible underlying causes
- If bleeding continues without adequate explanation and despite adherence to the regimen, we can try switching you to a different formulation to see if that helps

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Skipping pills, smoking, and taking certain medications and herbal supplements are common causes of breakthrough bleeding

perspective studies have found even higher rates of inconsistent use.

When an electronic device was used to monitor pill ingestion, as many as 81% of women were found to miss at least 1 pill per cycle and up to 51% missed 3 or more pills per cycle.33

Other side effects also undermine adherence. For example, women experiencing nausea may skip pills, which leads to breakthrough bleeding and, ultimately, discontinuation.34 Patients need to understand the impact of skipping pills. Women who report irregular bleeding are 1.6 to 1.7 times more likely than those not reporting this side effect to miss 2 or more pills per cycle.5 Even 1 missed pill can increase the risk of bleeding irregularities.35

Failure to take the pill at the same time every day and poor comprehension of pill-taking instructions are other strong predictors of inconsistent use and breakthrough bleeding.32

Taking some prescription and over-the-counter medications, as well as herbal supplements, may interfere with the activity of OCs to alter bleeding patterns and contraceptive efficacy.36 Medications that induce the cytochrome P-450 system (CYP450) in the liver increase the metabolism of OCs. Anticonvulsants, the antituberculosis agent rifampin, and antifungals such as griseofulvin can increase the clearance of steroid hormones and thus lead to breakthrough bleeding. The herbal supplement St. John’s wort, commonly used for mild or moderate depression, is associated with CYP450 induction. It has been shown to increase the incidence of breakthrough bleeding and probably ovulation in women taking an OC.37

Smoking is associated with such anti-estrogenic effects as early menopause, osteoporosis, and menstrual abnormalities.38 These effects may be related to induction of hepatic estrogen and progesterone metabolism by smoking.39,40

Before receiving OCs, women are made aware of the relationship between smoking, OCs, and an increased risk of myocardial infarction, stroke, and venous thromboembolism.41 They should also understand that the anti-estrogenic effect of smoking may lower estrogen levels and lead to breakthrough bleeding, even in women who are reliable pill-takers.42,43

Smoking appears to have a dose-response relationship with breakthrough bleeding. Increasing levels of smoking have been associated with an increased risk of spotting or bleeding in each cycle.44 The difference in cycle control between smokers and nonsmokers appears to be more pronounced with each cycle. Smokers demonstrate a 30% elevation in the risk of bleeding irregularities compared with nonsmokers in the first cycle of use, which rises to an 86% increased risk by the sixth cycle.

Reports conflict regarding the relationship between smoking and contraceptive efficacy, suggesting that confounding factors like compliance may be more important than the antihormonal effect of cigarettes.44 Nevertheless, women who smoke should be informed of this potential complicating factor to OC
use and as yet another reason to encourage smoking cessation.

**Bleeding is sometimes pathologic**
When a woman experiences difficult cycle control after the first 3 to 4 months of OC use, consider the possibility of benign and malignant growths, including endometrial polyps, submucous myomas, and cervical or endometrial cancer. Additionally, contraceptive failure must always be a consideration, and what appears to be breakthrough bleeding may actually represent bleeding in early pregnancy.

Cervicitis is an important but largely unrecognized source of unplanned bleeding in women using OCs. Causative organisms include *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis*. Intermenstrual bleeding in women previously well controlled on OCs is particularly suggestive of asymptomatic chlamydial cervicitis.

Krettek et al found that 29.2% of women who had been taking OCs for more than 3 months and presented with intermenstrual spotting had a positive test for *C. trachomatis*. By comparison, chlamydial cervicitis was found in 10.7% of matched controls taking OCs without spotting who were screened for symptoms of vaginitis or high-risk sexual behavior, and in just 6.1% of women undergoing routine screening before the initiation of contraception.

**Three-pronged management**
Managing breakthrough bleeding involves effective pretreatment; ongoing counseling and reassurance; and timely and appropriate testing (TABLE 2). In some cases, pill-switching or other forms of medical management may be helpful, but these options are largely unproven.

Counseling reduces anxiety, improves satisfaction, and adherence
In a recent survey, 649 Canadian women who were picking up prescriptions for OCs were asked to complete a questionnaire at the pharmacy while they waited. Over one third (34.5%) reported they had not received counseling from their healthcare provider about breakthrough bleeding. Furthermore, only 28.3% of women who were counseled, and 26.1% of women who were not counseled, gave the optimal response to breakthrough bleeding as defined in this study (“continue taking pill and not call my doctor”).

Lack of counseling can lead to poor method satisfaction and significant cost expenditures because of visits and phone calls by women experiencing unexpected bothersome side effects. Compared with women who reported the highest satisfaction with the care they received from their provider, those reporting the lowest scores were 1.6 to 2.2 times as likely to be dissatisfied with the pill.

Inform women that breakthrough bleeding is common in the first 3 or 4 cycles of OC use, that bleeding irregularities tend to decline with each successive cycle, and that they should not discontinue pill use without discussing their concerns with you. Remind women to keep sanitary protection with them during the first few months.

The impact of poor counseling was underscored in a study of women enrolled in clinical trials of OCs, contraceptive vaginal rings, and Depo-Provera. Women taking an OC were the least likely to have been warned of menstrual irregularities and thus tended to stop using that method more often than those using a ring or Depo-Provera. Of women who discontinue OCs, 47% use a less effective method and 19% use no method at all.

**Give specific instructions for specific regimens.** Given the array of OC regimens available, make sure women know how to take them properly. This will help ensure contraceptive efficacy and cycle control. Women who do not understand pill-package instructions are up to 2.8 times more likely to miss pills, which increases the risk of breakthrough bleeding.
bleeding and impacts contraceptive efficacy. Among women who were counseled about the consequences of missed pills, 76% reported knowing what to do in response (“use another form of birth control that month”). Of women who received no such counseling, only 48% gave the appropriate response \( (P<.001) \).

To improve adherence, advise women to establish a routine for pill-taking: taking the pill at the same time each day or linking pill ingestion with another daily activity, such as tooth brushing. Women without an established routine were 3.6 times more likely to miss 2 or more pills per cycle than women with a routine.

**Reassurance regarding efficacy**

Reassure users who take their pills routinely that breakthrough bleeding and contraceptive efficacy are not linked. \(^ {30} \) Breakthrough bleeding is not a sign that OCs are not working. \(^ {4} \) On the other hand, approximately 1 million unintended pregnancies in the United States each year are associated with misuse or discontinuation of OCs. \(^ {51} \)

**When to consider diagnostic testing**

For OC users who continue to experience breakthrough bleeding beyond 3 to 4 cycles, other potential causes must be ruled out using appropriate diagnostic tests. A pregnancy test, appropriate testing for cervical infection, pelvic ultrasonography, Pap smear, or endometrial biopsy may be warranted, depending on clinical circumstances.

**Fall-back options**

If breakthrough bleeding continues beyond 3 months, and other reasons, including poor adherence and pathologic processes, are excluded, one option would be to provide the patient with estrogen or switch her to a different pill, though no clinical trials support definitive recommendations.

Aside from changing from a multiphasic to a monophasic formulation, altering the progestin component is often a first step in trying to control breakthrough bleeding. \(^ {46} \) An OC with a gonane rather than an estrane progestin may be beneficial as this class of progestins may provide more consistent hormonal effects on the endometrium.

Choosing an OC with a higher quantity of EE may also help, particularly for women using 20 μg pills. When possible, the same progestin should be used.

You may want to start a trial of conjugated estrogen, 1.25 mg, or estradiol, 2 mg, administered for 7 days when bleeding occurs. This can be repeated if necessary; however, if breakthrough bleeding continues despite this treatment, consideration of a different pill or method should be undertaken.

**References**


