

6 PRACTICE POINTS

Hormonal contraception in women with medical conditions

An interview with Dr. Andrew M. Kaunitz, who assisted in the preparation of the new ACOG Practice Bulletin

Decisive new data on risks and benefits of hormonal contraception will change how we manage many patients. These findings prompted the American College of Obstetricians and Gynecologists (ACOG) to update its practice bulletin (released in June) on hormonal contraception in women with coexisting medical conditions.¹ Among the most notable areas of change:

- 1. Family history of breast cancer or BRCA1 or 2 mutations.** Combination oral contraceptives (OCs) do not appear to increase the risk of breast cancer in these women, and do help prevent ovarian cancer.
- 2. Concomitant medications.** More women are using enzyme-inducing anti-convulsants for conditions other than seizure disorders; some affect steroid levels.
- 3. Obesity.** Progestin-only and intrauterine methods may be better for obese women older than 35 years, who face an elevated baseline risk of venous thromboembolism.
- 4. Lupus.** Combination OCs are safe in women with stable, mild disease who are seronegative for antiphospholipid antibodies.
- 5. Depot medroxyprogesterone acetate (DMPA).** Although bone density declines in women using DMPA, it recovers within 3 years after the drug is discontinued.

6. Patch and ring. Until method-specific data come in, assume that the patch and ring have the same contraindications as combination OCs.

For the fine points on these and other findings, we talked with Dr. Andrew M. Kaunitz, who assisted ACOG with preparation of the new bulletin.¹

1. Breast cancer risk

OCs do not add to existing high risk

OBG MANAGEMENT: Women who have a family history of breast cancer have a higher-than-average risk of developing the cancer themselves, and it is widely assumed that estrogen further heightens that risk. Should these women avoid combination OCs?

KAUNITZ: No. Although these women have been reluctant to use hormonal contraceptives (as have many caregivers), we now have several lines of reassuring evidence.

Among the studies demonstrating safety of hormonal methods in this population is the 2002 Women's CARE study, conducted by the Centers for Disease Control and Prevention and sponsored by the National Institute of Child Health and Human Development, which found no elevated risk of breast cancer in women currently or formerly



Andrew M. Kaunitz, MD

**OBG MANAGEMENT
Board of Editors**

Professor and Assistant Chairman
Department of Obstetrics
and Gynecology
University of Florida College
of Medicine—Jacksonville
Jacksonville, Fla

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using OCs, compared with women who had never used them.

This study compared 4,575 women who had breast cancer with 4,682 controls. The relative risk of breast cancer was 1.0 (95% confidence interval 0.8–1.3) among current OC users and 0.9 (0.8–1.0) among women who had previously used OCs. The relative risk did not increase consistently with higher doses or longer use.² Nor did use of OCs add risk in women with a family history of breast cancer.²

OBG MANAGEMENT: An editorial accompanying that study said: “The importance of this finding for public health is enormous, because more than 75% of the women in the study had used oral contraceptives.”³

KAUNITZ: Yes, but this does not mean that women with a positive family history have *no* increased risk of breast cancer—they do. Rather, the use of hormonal contraceptives does not *augment* that risk further.

OBG MANAGEMENT: What about women with other high-risk factors, such as germline mutations? Do OCs increase their risk of breast cancer?

KAUNITZ: No. In the largest study to date of breast cancer risk associated with prior or current OC use in women 35 to 64 years of age with BRCA1 and 2 mutations, low-dose OC formulations did not increase it.⁴ In fact, OC use was associated with a significantly reduced risk of breast cancer in BRCA1 mutation carriers (odds ratio 0.22; 95% confidence interval 0.10–0.49).⁴

■ Pill reduces risk of ovarian cancer in BRCA carriers

KAUNITZ: It is also important to remember the higher risk of ovarian cancer in women with BRCA mutations. We now know that use of the Pill reduces ovarian

cancer risk in BRCA-positive women, just as it does in the general population. In a study involving 451 women with BRCA1 or 2 mutations, who self-reported their lifetime history of OC use (or nonuse), the odds ratio for ovarian cancer associated with OC use for a minimum of 1 year was 0.85 (95% confidence interval 0.53–1.36) and declined by 5% (1%–9%) with each additional year of use (*P* for trend = .01). Use for 6 years or more carried an odds ratio of 0.62 (0.35–1.09).⁵

The bottom line: Women with a family history of breast cancer in general or BRCA1 or BRCA2 mutations more specifically, who have not completed childbearing or who want to avoid prophylactic mastectomy/oophorectomy, can use the Pill to prevent ovarian cancer without increasing their risk of breast cancer.^{5,6}

2. Concomitant medications

■ Some drugs decrease steroid levels

Anticonvulsants

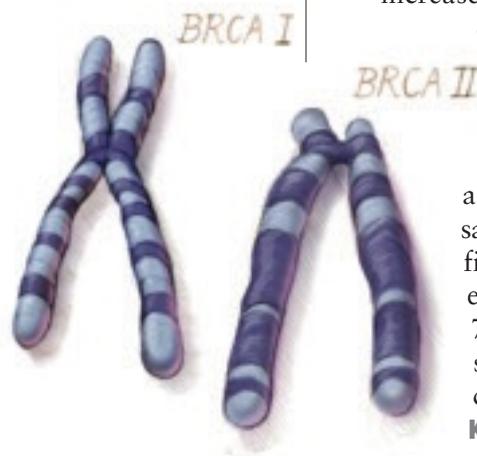
OBG MANAGEMENT: Many, perhaps most, women with medical conditions are already taking some kind of medication. What do ObGyns need to know about interactions between hormonal contraceptives and other medications, such as anticonvulsants and antibiotics?

KAUNITZ: We regularly encounter patients who are using anticonvulsants, both older and newer formulations.

Off-label use of anticonvulsants for indications other than seizure disorders (eg, bipolar disease) is increasing.

Levetiracetam and zonisamide. The revised practice bulletin includes pharmacokinetic data on 2 new anticonvulsants—levetiracetam⁷ and zonisamide.⁸ Fortunately, neither appears to reduce contraceptive steroid levels in women who are also taking combination OCs.

Which dosage, which method? Some widely



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Women with a family history of breast cancer or BRCA1 or 2 can use the Pill to prevent ovarian cancer without adding to their breast cancer risk

Some anticonvulsants reduce steroid levels in women taking OCs, and some do not

TABLE 1

| Interaction of anticonvulsants and combination OCs | |
|--|---------------|
| Anticonvulsants that decrease steroid levels in women taking oral contraceptives (OCs) | |
| Barbiturates (including phenobarbital and primidone) | |
| Carbamazepine and oxcarbazepine | |
| Felbamate | |
| Phenytoin | |
| Topiramate | |
| Vigabatrin | |
| Anticonvulsants that do not decrease steroid levels in women taking combination OCs | |
| Ethosuximide* | Tiagabine† |
| Gabapentin† | Valproic acid |
| Lamotrigine† | Zonisamide |
| Levetiracetam | |
| *No pharmacokinetic data available. | |
| †Pharmacokinetic study used anticonvulsant dose lower than that used in clinical practice. | |
| Source: American College of Obstetricians and Gynecologists. ¹ Reprinted by permission. | |

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Rifampin is the only antibiotic for which we have solid evidence of substantially lower steroid levels

Rifampin decreases steroid levels in women taking combination OCs; other anti-infectives do not

TABLE 2

| Interaction of anti-infective agents and combination OCs | |
|--|-----------------------|
| Anti-infective that decreases steroid levels in women taking OCs | |
| Rifampin | |
| Anti-infectives that do not decrease steroid levels in women taking OCs | |
| Ampicillin | Miconazole* |
| Doxycycline | Quinolone antibiotics |
| Fluconazole | Tetracycline |
| Metronidazole | |
| *Vaginal administration does not lower steroid levels in women using the contraceptive vaginal ring. | |
| Source: American College of Obstetricians and Gynecologists. ¹ Reprinted by permission. | |

used anticonvulsants do decrease steroid levels (TABLE 1); although some clinicians prescribe OCs containing 50 µg of ethinyl estradiol to offset the reduction, there is no evidence that this strategy is effective. The ObGyn may consider prescribing pills containing 30 to 35 µg of estradiol rather than lower doses, although again, we lack data to support this recommendation.

Another important point: Because serum steroid levels of women using progestin-only OCs and implants are lower than for combination OCs, low-dose progestin-only methods (progestin-only minipills and progestin implants) do not represent by themselves optimal contraceptives for women taking drugs (eg, anticonvulsants) that increase liver enzymes.^{9,10}

This recommendation does not include the levonorgestrel-releasing intrauterine system. Contraceptive effects remain high with its use, even when anticonvulsants or other liver enzyme-inducing drugs are taken.¹¹

DMPA, a high-dose progestin contraceptive, has not been formally studied in this regard; the efficacy of this injectable contraceptive does not appear to be reduced by concomitant use of enzyme inducers.³⁰ Interestingly enough, DMPA has anticonvulsant effects itself and therefore may represent a particularly attractive contraceptive for women taking anticonvulsants.¹²

Antibiotics

KAUNITZ: As for antibiotics, we have often been taught that many drugs lower the efficacy of combination OCs, but in fact it is not clear that they do.

Rifampin. The only antibiotic for which we have pharmacokinetic evidence of substantially lower steroid levels is rifampin¹³ (although anecdotal reports of OC failure in women taking other antibiotics have been noted). Therefore, any woman who is taking rifampin should be advised that OCs (combination or progestin-only), transdermal or vaginal contraceptives, and hormonal implants are inadequate birth control (TABLE 2).

CONTINUED

Antiretrovirals

KAUNITZ: Several small trials suggest that contraceptive steroid levels in OC users may be affected by antiretroviral medications (TABLE 3), but we lack clinical outcome studies.

St. John's wort

KAUNITZ: Another medication I want to mention is St. John's wort, an over-the-counter hepatic enzyme inducer that many women take for depression. One clinical trial found elevated progestin and estrogen metabolism in women taking combination OCs and St. John's wort concomitantly, as well as increased likelihood of breakthrough bleeding and ovulation.

St. John's wort (300 mg thrice daily) was associated with a 13% to 15% reduction in the dose exposure of combination OCs containing 20 µg of ethinyl estradiol.¹⁴ So it is important to ask about St. John's wort when counseling a woman about contraception.

3. Obesity

■ In obese women over 35, avoid combination OCs

OBG MANAGEMENT: ObGyns are seeing increasing numbers of overweight and obese women. Has selection of hormonal contraception for these women changed?

KAUNITZ: Yes. We now have a recognized obesity epidemic on our hands—and obesity, age over 35 years, and use of combination OCs all represent independent risk factors for thrombosis—prompting the question: Are there safer alternatives to combination OCs for obese women older than 35?

Tenfold risk for thromboembolism. Among the evidence addressing this question, a 2003 Dutch study found that women with a body mass index (BMI) greater than 25 who used combination OCs had 10 times the risk of venous thromboembolism of lean controls who did not use the Pill.¹⁵

Antiretrovirals may affect steroid levels in women taking OCs

TABLE 3

Pharmacokinetic interactions between combination OCs and antiretroviral drugs

| ANTIRETROVIRAL | CONTRACEPTIVE STEROID LEVELS | ANTIRETROVIRAL LEVELS |
|---|------------------------------|-----------------------|
| PROTEASE INHIBITORS | | |
| Nelfinavir | ↓ | No data |
| Ritonavir | ↓ | No data |
| Lopinavir/ritonavir | ↓ | No data |
| Atazanavir | ↑ | No data |
| Amprenavir | ↑ | ↓ |
| Indinavir | ↑ | No data |
| Saquinavir | No data | No change |
| NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS | | |
| Nevirapine | ↓ | No change |
| Efavirenz | ↑ | No change |
| Delavirdine | ?↑ | No data |

Source: World Health Organization.²⁰ Reprinted by permission.

Thus, progestin-only and intrauterine contraceptive methods may be more appropriate for older obese women. This language about obesity and combination contraceptives was not in the earlier version of the practice bulletin.

No need to rule out the patch

OBG MANAGEMENT: Aren't some hormonal contraceptives less effective in obese women?

KAUNITZ: In a 2002 analysis of pooled data, women in the highest weight category (≥90 kg) who were using the contraceptive patch had a higher pregnancy rate than lower-weight women.¹⁶ However, this finding does not rule out use of the patch in overweight women who prefer it to less effective methods. Rather, it should be kept in mind when counseling these patients about their options.

Although the new ACOG bulletin cites data from Holt et al¹⁷ suggesting a higher failure rate in obese women using



St. John's wort raised progestin and estrogen metabolism and increased breakthrough bleeding and ovulation in women taking OCs

combination OCs, other OC clinical trials have not confirmed this association.^{18,19} In a study by Anderson and colleagues,¹⁸ which found no pregnancies among the heaviest women, the mean weight was 155.9 lb, but ranged from 91.0 to 360.0 lb, and the mean BMI was 26.0, but ranged from 15.2 to an extreme of 56.5! **What about DMPA?** We also lack evidence of higher pregnancy rates among overweight women using DMPA (150-mg intramuscular or 104-mg subcutaneous formulations).^{20,21}

4. Lupus

■ OCs are an option in some women with lupus

OBG MANAGEMENT: As *The New England Journal of Medicine* observed last year, there has been an “implicit moratorium” on prescribing combination hormonal contraceptives in women with systemic lupus erythematosus (SLE) because clinicians have feared that exogenous estrogens might exacerbate disease.²² This moratorium derives from data suggesting that estrogens worsen SLE, while androgens appear to protect against the condition.

The new practice bulletin now indicates that oral contraceptives are an option for this population. What is behind the change?

KAUNITZ: We now have data from 2 randomized clinical trials^{23,24} indicating that women can safely use combination OCs if they:

- have stable, mild disease
- are seronegative for antiphospholipid antibodies
- have no history of thrombosis

Disease remained stable. In the first trial,²⁴ 162 women with mild, stable SLE were randomized to combination OCs, progestin-only pills, or the copper IUD. Their disease level was established at baseline and over 12 months, using the Systemic Lupus Erythematosus Disease Activity Index. Disease remained stable in all 3 groups.

Estrogen did not increase severity of SLE. In the second trial,²³ 183 women with inactive or stable active SLE were randomized to combination OCs or placebo. The primary endpoint for this trial was severe lupus flare: 7 of 91 women (7.7%) in the OC group experienced a flare, compared with 7 of 92 women (7.6%) taking placebo. Thus, estrogen does not appear to increase the severity of SLE.

OBG MANAGEMENT: Isn't another concern about patients with SLE the substantial risk of thrombosis?

KAUNITZ: Yes. In the first study,²⁴ 2 thromboses occurred in women taking OCs, and 2 occurred in women using the progestin-only pill. All the women with thromboses were seropositive for antiphospholipid antibodies. Hence, we need to exclude the presence of these antibodies in women with SLE prior to prescribing combination estrogen-progestin contraception. In women with lupus and a history of thrombosis, as with all women with a history of thrombosis, we should avoid combination hormonal contraception.

In the second study,²³ which compared women on combination OCs to a placebo group, the OC group experienced 1 case of deep venous thrombosis (DVT) and 1 clotted graft. The placebo group experienced 1 case of DVT, 1 ocular thrombosis, 1 superficial thrombophlebitis, and 1 death (after the trial ended).

5. DMPA and bone density

■ DMPA does not appear to have long-term impact

OBG MANAGEMENT: There has been some furor over DMPA's effect on bone mineral density (BMD). What are the latest findings in this area?

KAUNITZ: Studies assessing BMD in former DMPA users, including postmenopausal women, show that prior use of DMPA does not appear to have any long-term impact on BMD.^{25,26} In addition, more

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Combination OCs are safe in lupus patients with stable, mild disease, who are seronegative for antiphospholipid antibodies, with no prior thrombosis

recent longitudinal data indicate that after DMPA is discontinued BMD fully recovers, which appears to take about 3 years in adults and as little as 1 year in teens.^{27,28}

One population-based prospective cohort study followed 457 nongravid women aged 18 to 39 years. These women had bone density measured every 6 months for 3 years using dual-energy x-ray absorptiometry. Although bone density decreased among DMPA users at the spine and total hip compared with nonusers, there was no difference in bone density 30 months after discontinuation of birth control injections.²⁷

In a study of 170 adolescent women 14 to 18 years of age, 80 were DMPA users and 90 were nonusers. Bone density was measured every 6 months for 24 or 36 months, and declined significantly at the hip and spine in DMPA users. Sixty-one women discontinued DMPA during the course of the study. After discontinuation, bone density increased at all anatomical sites, recovering completely over the course of 1 year.²⁸

Although the US Food and Drug Administration issued a black box warning in the fall of 2004 that use of DMPA should be reconsidered after 2 years, particularly in teens, the studies I just mentioned suggest there should be no routine restrictions on the use of DMPA in terms of skeletal health, and that DMPA use by itself is not an indication for bone density measurement.

6. Patch and ring

■ Assume contraindications are the same as for OCs

OBG MANAGEMENT: What about newer forms of combination contraceptives such as the patch and ring?

KAUNITZ: The new practice bulletin contains information on the patch, the ring, and the levonorgestrel-releasing IUD,

which were not available when the earlier bulletin was prepared. In that version we talked about combination pills only.

Even so, we continue to have much more data on the Pill than the ring or patch. For that reason, until more data become available, the patch and the ring should be assumed to have the same contraindications as combination OCs. We have very little data—if any—on the use of newer combination contraceptives in high-risk women or those with medical problems. ■

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DMPA use by itself is not an indication for bone density measurement

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